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Review Article

Best Practices for Recurrent Urinary Tract Infections in Females

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ABSTRACT

Recurrent Urinary Tract Infection (RUTI) is a common plight among adult women. The cause of RUTI is multifactorial, with many host and pathogenic features acting as risk factors for development. When a patient develops a pattern of recurrent urinary tract infections, prompt recognition allows for accurate diagnosis, appropriate treatment, and effective preventive measures. Diagnosis of RUTI requires occurrence of 2 culture-proven UTIs in 6 months, or 3 in 12 months. When RUTI is recognized, evaluation with a thorough history and examination is indicated. On occasion, other diagnostic testing is warranted. Current guidelines for treatment of acute uncomplicated cystitis propose first-line antibiotic regimens, which are applied to women with RUTI, with certain exceptions due to resistance, medical conditions, or allergies. Prevention may involve topical estrogen treatment for women in a hypo estrogenic state, antibiotic prophylaxis, or use of other antibacterial tools. Further research is ongoing to find novel strategies to prevent RUTI.

Keywords: Recurrent Urinary Tract Infection (RUTI); Cystitis; Urine culture; Antibiotic Prophylaxis; Estrogen

INTRODUCTION

Recurrent Urinary Tract Infection (RUTI) is a challenging, and often complicated, condition encountered by the providers of women at many levels of care. In females, urinary tract infection represents a common cause of ambulatory and emergency department visits, and affects an estimated 50%-60% of adult women in their lifetime [1]. One of those who develop a UTI, 30%-44% will go on to develop RUTI [2]. Once a pattern of recurrence develops, care should be taken both to confirm the accuracy of the RUTI diagnosis and appropriateness of antibiotic use. The goal of this commentary is to discuss terminology and diagnostic criteria surrounding RUTI, to outline relevant pathophysiology, and to present current recommendations for treatment and prevention.

LITERATURE REVIEW

Terminology

Urinary Tract Infection (UTI) occurs when both the presence of a pathogen within the urinary tract and appropriate lower urinary tract symptoms coexist. When bacteria and even puree are present in the absence of symptoms, it is not sufficient to diagnose UTI, and is termed Asymptomatic Bacteriuria (ASB) [3]. Conversely, an irritative lower urinary tract symptom in the absence of culture proven infection requires careful documentation and additional evaluation. The designation of RUTI is given when a patient has at least 2 culture-proven UTIs in a 6 month span, or 3 within 12 months [2]. Relapse of a UTI, which is unique from a recurrence, occurs when the same uropathogen causes symptomatic UTI within 2 weeks of completion of treatment from the initial infection [4].

Pathophysiology

The pathophysiology of recurrent UTI is multifactorial. Common uropathogen, in particular E. coli, often exhibit features that engender attachment to the urothelium. The formation of biofilms likely contributes to RUTI, as bacteria may persist within intracellular reservoirs and replicate until they become present in numbers significant enough to cause a UTI. Characteristics specific to the host can also affect occurrence of RUTI. Anatomy, hormonal status, as well as functional and behavior status play a part in occurrence of RUTI [4]. Estrogenic status plays significant role in RUTI. This is attributable the loss

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of normal microbiome supported by well-estrogenized genitourinary tissue and thereby a loss of the tissues' natural defense against uropathogens [5]. Among urogynecology patients, RUTI is associated with urinary incontinence, patients who have an abnormal post-void residual of greater than 50 ml and a history of surgical intervention for SUI. Genetic factors play a role as well, as non-secretors of anti-B blood group substances are at a greater than 3-fold risk of RUTI. There is also a recognized association between recurrent UTI and low levels of secretory IgA [6].

Diagnosis

Symptoms associated with UTI can vary, but dysuria is the most recognizable symptom. Frequency, urgency, hematuria, and suprapubic pain are also common complaints in the young to middle age range. Older patients specifically may have new onset urinary incontinence as a herald of UTI. The presence of malodorous urine, alteration in mentation, and urinary appearance are not reliable for identifying a UTI, however report of dysuria has a 90% pre-test probability of UTI diagnosis in young women also denying vaginal discharge or irritation [4,7].

The gold standard for diagnosis of UTI is urine culture. Urine dip is sometimes used to aid in diagnosis, but its greatest utility is in its ability to rule out UTI, with a negative predictive value thought to be as high as 93% when combining negative nitrites and leukocyte esterase [8]. Particularly in the setting of patients with recurrent UTI, who typically have had multiple treatment regimens and therefore are more likely to demonstrate antibiotic resistance, dipstick is not recommended for diagnosis of UTI [9]. In this scenario, even if the urine dip is positive, UTI is not confirmed, and if an infection does exist, the pathogens are not identified nor are sensitivities elucidated. Similarly, urinalysis is not necessary for diagnosis of UTI, but microscopic findings may provide more details that allow providers to gauge the possibility that the organism in the culture is a contaminant, colonization, or infection.

While urine culture is generally agreed-upon as the most reliable means of diagnosis for UTI, some propose the use of urine PCR for complicated patients. While a standard urine culture detects pathogens such as E. coli, proteus, kelbsiella, staph, strep, and Enterococcus, other uropathogens that may go unidentified on culture could be detected by PCR [4]. At this time, such information is difficult to clinically correlate, and for this reason is not routinely used. Urine culture for 'test of cure' is also not routinely recommended if symptoms resolve after treatment of UTI, as remaining colonization of the urogenital tract may lead providers to offer antibiotic treatment outside of the scope of a symptomatic infection [9].

Evaluation

With a new diagnosis of RUTI, patients should undergo a workup including thorough history and pelvic examination. Examination will allow for identification of abnormalities such as pelvic organ prolapse, urethral diverticula, abnormal discharge, presence of foreign bodies, or other anatomic abnormalities that could be contributory or confounding in the setting of RUTI. An assessment of post-void residual urine volume is also recommended to identify urinary retention if present. Obtaining imaging of the upper urinary tract and performing cystoscopy are not routinely necessary in uncomplicated RUTI, as this is generally thought to be low yield. When there are unusual presenting symptoms or rapid recurrence, such imaging may become useful. For instance, cystoscopy is indicated when there is concern for foreign body. Imaging or cystoscopy may also be of use in complicated cases such as infections resistant to treatment or scenarios where altered urologic anatomy is known or suspected [4,9].

Treatment

The antimicrobial agents considered first-line therapy for acute uncomplicated UTI treatment includes nitrofurantoin, Trimethoprim-Sulfamethoxazole (TMP-SMX), and fosfomycin [10]. These recommendations have been set forth by the Infectious Disease Society of America as guidelines for treatment of acute uncomplicated cystitis in premenopausal women without urologic abnormalities or other complicating factors, but their usage has been applied in the treatment of older women, women with urogynecologic disorders, and women with RUTI [4].

Complicating factors including abnormal genitourinary anatomy, immunosuppression, chronic intermittent self-catheterization, and concern for pyelonephritis lead to diversion of empiric treatment recommendations. In these cases, none of these three antibiotics are recommended for use prior to culture and sensitivities [9].

Choice of antibiotic should take into account the limitations unique to each agent. For instance, nitrofurantoin is only therapeutically active within the lower urinary tract, so it should be avoided if there is concern for early pyelonephritis. While effective against *E. coli* and many other uropathogens, it is not sufficient for treatment of UTI caused by Proteus, Enterobacter, or Klebsiella species [4]. Nitrofurantoin 100 mg twice daily is a bacteriostatic agent, and recommended duration of treatment is typically between 5-10 days [9,10].

TMP-SMX 160/80 mg twice daily for 3-10 days is also an appropriate choice for the first line treatment of UTI [10]. This broad-spectrum antibiotic has the advantage of coverage of gram positive bacteria, MRSA included, as well as most gram negative bacteria. If there is concern for infection with pseudomonas, a different agent is recommended. Furthermore, if TMP-SMX has been used within the preceding 3-6 month, it should not be reused due to the high likelihood of resistance [4,9].

Fosfomycin is another effective antibiotic in treatment of UTI, with unique single dose treatment regimen due to the production of high concentration within the urine. Given this mechanism of action, Fosfomycin is recommended for lower urinary tract infections only where there is no concern for early pyelonephritis. The drug has low levels of resistance and is active against gram-positive and gram-negative bacteria. It is not sufficient for treatment of Klebsiella species. In addition to the

features particular to each agent, patient specific considerations affect treatment strategies [4,9,10].

DISCUSSION

Medical comorbidities may also affect choice of treatment. In the case of reported drug allergies, a thorough history of previous reactions should be gathered. If multiple patient allergies preclude reasonable treatment regimens, allergy testing and desensitization may be considered. In patients with altered renal function, the efficacy and safety of certain antibiotics can be lower than the general population. For example, in patients with a Creatinine Clearance (CrCl) of less than 30 mL/min, nitrofurantoin does not reach necessary urine concentrations and is therefore ineffective [4].

When use of the first-line agents (nitrofurantoin, TMP-SMX, fosfomycin) are not possible due to allergy, resistance, or other contraindication, second-line agents (β-lactams and fluoroquinolones) can be used. These second-line regimens are not preferred due to a combination of decreased efficacy, increased resistance, inferior adverse event profile, and higher cost [10]. An alternative treatment modality sometimes employed is gentamicin bladder instillation, where gentamicin mixed in a normal saline solution is introduced into the bladder and held over a period of time. This is available for both acute treatment and prophylaxis in the setting of RUTI, and may be useful when systemic treatment options fail or when multi-drug resistant pathogens are present. While evidence for gentamicin bladder instillation is limited, initial studies are supportive [11-13].

In women who are able to recognize symptoms reliably, prompt initiation of treatment with appearance of symptoms can be self-directed with standing physician orders for urine culture and suitable empiric antibiotic based on the patient's history. This is often called "self-start therapy" and can be helpful in the setting of RUTI. Culture results should be reviewed to confirm that treatment prescribed is appropriate [4,9].

Prevention

Preventative measures against acute episodes of symptomatic UTI in women with RUTI include antibiotic regimens, as well as other modes of prophylaxis of varying degrees of efficacy and supporting evidence. Daily antibiotic prophylaxis has been studied extensively and current recommendations support offering this option to women with RUTI to decrease the likelihood of UTI recurrence. The regimen is continued for months at a time, but recurrence is often seen only a few months after completion of treatment and resistance may occur at increased rates.

Exogenous vaginal estrogen can prevent RUTI by reversing genitourinary mucosal atrophy and restoring normal vaginal flora in women affected by RUTI who are also hypoestrogenic [5]. This vaginal topical treatment may be administered as a tablet, cream or ring, and is associated with a significant reduction in RUTI [9].

Methanamine salts are an alternative strategy for the prevention of UTI. In the urine, the salts are converted to ammonia and formaldehyde, thus providing a bacteriostatic environment in the bladder. Though data are somewhat limited regarding efficacy, Methanamine salts do not create bacterial resistance and are relatively low risk [4]. The routine use of D-Mannose, a simple sugar thought to impede the ability of *E. coli* to bind to the urothelium, also has limited evidence that is promising for its prevention of RUTI. Providers and patients alike may find the idea of benign preventative treatments such as probiotics, cranberry products, and vitamin C to be enticing, but there is conflicting evidence in support of these treatments for prevention of RUTI [9]. Currently in development are immunostimulant and immunizations for RUTI that may one day be added to the arsenal of RUTI management, but do not yet show sufficient efficacy [4, 9]. Further investigation will be required to determine the appropriate application for these agents, and in developing new ways to manage and prevent RUTI.

CONCLUSION

Recurrent UTI is a common medical problem for women throughout their lifetime. It is important to evaluate all patients with a thorough history and physical examination to uncover underlying abnormalities or modifiable risk factors. Clinicians must be cognizant of the differing pathogens of RUTI that commonly affect the female population. Antimicrobials continue to be the most effective form of treatment and prophylaxis but are associated with troublesome side effects. Vaginal estrogens are safe and effective therapies that reduce the number of RUTIs in the hypoestrogenic population. Although the evidence supporting other forms of RUTI prophylaxis is inconsistent; however, for those who wish to try nonantimicrobial prophylaxis, cranberry, vitamin C and methenamine salts are sensible alternatives.

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