Recurrent urinary tract infections in non-pregnant adult women

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Abstract

Recurrent urinary tract infections occur in approximately 5% of adult women. It has a significant impact on the affected women's quality of life and on health care costs. It is important to be aware of the physiologically protective factors preventing urinary tract infections. The clinician should also be able to identify relevant risk factors for recurrent infection. Clinical evaluation is relatively straightforward in cases without underlying complicating factors, but urine culture ought to be readily utilised. Treatment should be according to local antibiogram patterns and prophylactic and postcoital preventative strategies can be used according to current evidence. Certain subpopulations such as HIV positive patients require a different approach compared to the general population.

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Introduction

All doctors will periodically be required to diagnose and manage a urinary tract infection (UTI). UTIs are mostly found in women, occurring in an 8:1 ratio to men and 50–60% of women report at least one UTI in their lifetime.[1,2] The majority of these women will present to their primary care physician.

The treatment of individual episodes is generally straightforward, with the more difficult challenge being the effective treatment and prevention of recurrent infection (RUTI). RUTI is defined by three or more episodes of UTI in the previous 12 months, or two episodes in the last six months. RUTIs are a significant discomfort to women and have a considerable impact on health care costs as a result of outpatient visits, diagnostic tests and prescriptions.

To have a structured approach to RUTI, one needs to understand the basics of acute UTIs. This review will therefore discuss these basic concepts and specifically highlight the aspects relevant to the management of RUTIs.

Epidemiology of UTI

UTIs can be uncomplicated or complicated. A complicated UTI is one occurring in certain clinical settings (Table I) and carries significant morbidity if not correctly treated.[3]

UTIs are more prevalent among premenopausal than postmenopausal women. Hooton et al estimated the incidence of cystitis in sexually active women in a university student population to be 0.5–0.7 episodes/person-year.[4] A second infection was shown to occur within six months after a first UTI in 21% of young women.[5] Jackson et al found the incidence of culture confirmed acute cystitis in postmenopausal women to be 0.07 episodes/person-year.[6] The peak incidence of infection occurs in young, sexually active women aged 18 to 24 years.[7] Bacteriuria is found in 2–3% of women aged 15–24 years, 20% of women 65–80 years and 25–50% of women older than 80 years.[1]

Table I: Complicated urinary tract infection

Men
Pregnant women
History of UTI in childhood
Patients with diabetes mellitus
Patients with renal insufficiency
Immunocompromised patients
Recurrent UTI
Documented relapsing UTI in the past year
History of acute pyelonephritis in the past year
Recent antimicrobial treatment (last 4 weeks)
Organism with multiple drug resistance
Functional or anatomic abnormality of the urinary tract
Recent urinary tract instrumentation
Hospital acquired UTI
Indwelling urethral catheter

The natural history of most UTIs is acute and uncomplicated and it resolves spontaneously (clinical and microbiological) in about half of women within a few days or weeks. The use of antimicrobial treatment substantially shortens the duration of symptoms.[8] UTIs are therefore mostly benign from the perspective of long-term outcomes, but each episode is associated with substantial disruption in a woman's life. Women report an average of 6.1 symptomatic days, 2 to 4 restricted activity days and 1.2 work days lost with each episode of cystitis. Also, 63% of women reported the infection had an impact on their usual activities, with a mean duration of 4.9 days.[9]

RUTIs are common among healthy women with structurally normal urinary tracts with as many as 5% of women experiencing it at some time during their life.[10] In a primary care setting, 44% of women presenting with an infection experienced a second infection within one year.[11]

Three aetiologies exist for RUTI: 1) persistence of the original organism, 2) reinfection with the original organism, or 3) reinfection with a different strain of bacteria.[12] The majority of RUTIs are the result of reinfection of the initial bacteria due to bacterial persistence in the faecal flora and subsequent recolonisation of the urethra.[13]

Protective factors

Host defences to the development of a UTI include:

- Urine that is high in osmolality and low in pH.
- Vaginal, periurethral and perineal colonisation by Gram-positive bacteria, diphtheroids and lactobacilli, and the resulting acidic vaginal pH of 4.0 inhibits migration of microorganisms from the rectum to the bladder.
- Normal periodic voiding limits the ability of bacteria to reach concentrations that are high enough in the bladder to establish a significant infection, and glycosaminoglycans of the bladder lining and Tamm-Horsfall proteins of the loop of Henle further decrease bacterial adherence.

If there is a shift or breakdown in any of these protective mechanisms, a UTI can develop.[14,15] It may be that in women prone to RUTI, the normal flora are easily altered resulting in colonisation by uropathogens.[16]

Risk factors

Ascending infection from the vagina, perineal or peri-anal areas is the most common route of infection. The risk factors for RUTI are listed in Table II.[5,9,17,18]

Table II: Risk factors associated with RUTI

Premenopausal women	Postmenopausal women
• Frequency of sexual intercourse	• Cystocele
• Spermicide use	• Urinary incontinence
• Age of first UTI (greater risk if < 15 yrs)	• Anal incontinence
• History of maternal UTI	• High post-voiding residual urine volume

One of the initial decisive events leading to an episode of UTI is the vaginal colonisation by virulent uropathogens. This is characterised by replacement of the hydrogen peroxide producing lactobacilli with *E coli* (the most prevalent uropathogen) and other organisms.

Certain biologic or genetic factors may predispose women toward UTI development and recurrence.[19] Women experiencing RUTI are more likely than those without infections to have first degree female relatives who also experience RUTI and women who express HLA-A3 and Lewis blood group LE antigens are at increased risk of RUTIs.[9,20,21] Other genetic mediators playing a role in RUTI are reduced expression of the interleukin (IL)-8 receptor and inadequate secretion of immunoglobulin A.[22,23] As genetic markers become available, it is possible that patients may be categorised into susceptibility groups, which may assist clinicians in determining optimal treatment.

Immunological defects and a persistently abnormal flora may further contribute to RUTI.[24] The immunological status of UTI-prone women has not been well characterised, but there is some indication that genetic polymorphisms related to the induction of immune responses could contribute to their susceptibility.[25]

Factors that were not associated with RUTI include voiding habits before or after intercourse, douching, wiping patterns, tub bathing, underwear type, bacterial vaginosis, sexually transmitted diseases, or number of lifetime sexual partners.[26]

Microbiology

Approximately 80% of bacteria isolated in UTIs are Gram-negative bacilli from the large family *Enterobacteriaceae.* These include *E coli*, *Klebsiella, Enterobacter, Proteus* and *Serratia.*[19] Polymicrobial infections are the exception rather than the rule and most of the time there is a solitary microbe. *E coli* virulence factors include adhesins, flagellae, haemolysins and bacterial resistance (through plasmids). *Proteus* shares many of these virulence factors with *E coli*, but it can in addition predispose to struvite stones.

Clinical presentation

The most common clinical presentation for women with uncomplicated acute cystitis is dysuria with or without any of the following: urinary frequency, urgency, suprapubic pain, lower abdominal discomfort and haematuria. New onset frequency, dysuria and urgency, together with the absence of vaginal discharge or pain, has a positive predictive value of 90% for acute cystitis.[27] The presentation is so characteristic that women with a history of RUTI are over 90% accurate in self-diagnosis of infection.[28] Because these symptoms are not just indicative of UTIs, a focused history and examination must precede any diagnosis. The frequency of UTI in women with specific combinations of these symptoms varied between 50% and 90%.

Diagnosis

The first step in the approach to these patients is an accurate history and examination. The second step is a urinalysis with dipsticks and preferably followed by a urine culture. There are three ways to obtain urine suitable for analysis: midvoid, catheterisation and suprapubic aspiration. The third step is to consider whether imaging of the urinary tract is indicated. Imaging (e.g. cystourethroscopy) would be warranted in women whose symptoms are recurrent and severe, if conventional treatment has failed, infection with unusual organisms, unexplained haematuria, history of calculi, history of non-pregnant pyelonephritis, history of childhood UTI, or if other complicating conditions (Table I) co-exist.

Treatment of RUTI

Several strategies have been proposed which allow prompt and efficient initiation of treatment for women with RUTI, while limiting costs. These include:

1. Telephone assessment and treatment by a physician or nurse practitioner following an algorithm.[29,30]
2. Use of an interactive computer by the patient.[31]

The general features of these strategies include no urine specimen collection, phone prescription without in-person assessment and follow-up only if symptoms persist or if they recur early following treatment. Approaches for antimicrobial treatment in recurrent UTI are: prescription treatment, self-treatment, continuous prophylaxis and postcoital prophylaxis.

Prescription treatment

It is always necessary to not only cover Gram-positive and Gram-negative bacteria, but also to choose the specific drugs based upon the antibiogram available in the hospital or area. Drug resistance is more common in patients with complicated UTIs, which may be caused by exposure to more antimicrobials.[32]

Antimicrobial susceptibility of *E coli* evolves continuously in response to antimicrobial pressure with recent antimicrobial therapy the most important determinant for isolation of a resistant organism.[33] Two recent international studies have looked at the antimicrobial resistance rates of primarily *E coli*. Resistance to amoxicillin was 38–58%, 21–29% to TMP/SMX, 6–9% to ciprofloxacin, 1–4% to nitrofurantoin, 4% to mecillinam and 2% to fosfomycin.[34,35]

Both a three day and a 5–10 day course of antimicrobials will provide symptomatic relief for acute UTIs. Microbiological cure rates are, however, significantly less for three day therapy (approximately 40%) compared to 5–10 day therapy.[36]

Eradication of bacteriuria is important in patients with RUTI and they should therefore receive antibiotic treatment for 5–10 days according to culture sensitivities or local antibiogram patterns. Single dose therapy is consistently less successful than more prolonged courses and although it can be used successfully for acute UTI, it cannot be recommended for women with RUTI.[37,38]

It is worthwhile to note that postmenopausal women have poorer outcomes with any duration of antimicrobial therapy compared with premenopausal women.[39]

Self-treatment

Self-treatment by women who experience recurrent infection is a strategy that is effective in 85% of cases.[28] It is particularly useful for women with infrequent recurrences, or those who are concerned they may develop infection while travelling or who are otherwise unable to access their usual health care.

Prevention of RUTI

One has to start by addressing modifiable behavioural practices. Other strategies can be antimicrobial or non-antimicrobial.

Antimicrobial prevention

Low dose antimicrobial therapy remains an effective intervention to manage recurrent, acute uncomplicated UTIs. Women receiving long term prophylactic therapy have four times less episodes of UTI compared to those without.[40] The antimicrobial may be given as continuous daily or every-other-day therapy, usually at bedtime, or as postcoital prophylaxis. First line treatments are nitrofurantoin, trimethoprim and sulphametoxazole, or fosfomycin.

Fluoroquinolone antimicrobials (e.g. ciprofloxacin or levofloxacin) are effective, but should be reserved for women who are unable to tolerate first line agents or who experience recurrent infection with resistant organisms while receiving first line regimens. The initial suggested duration of prophylaxis is six months; however, 50% of women will experience recurrence by three months after discontinuation of the prophylactic antimicrobial. When this occurs, prophylaxis may be reinstituted for as long as one or two years and remain effective.[41]

Non-antimicrobial prevention

Daily cranberry products (juice or tablets) or lingonberry juice decreases the frequency of RUTI by about 30–35% at 12 months compared to placebo.[42,43] The exact mechanism of action is not clear, but the belief is that they prevent bacteria (particularly *E coli*) from adhering to uroepithelial cells that line the wall of the bladder and that without adhesion, *E coli* cannot infect the mucosal surface of the urinary tract.

Topical vaginal oestrogen is also a potential intervention to decrease recurrent episodes for postmenopausal women. Vaginal oestrogens compared to placebo reduced the number of UTIs in postmenopausal women with RUTI.[44] The recommended treatment is to use a vaginal cream for a minimum period of six months.

Urinary alkalinisers should be reserved for uncomplicated UTIs only. It will provide temporary symptomatic relief in the short term, but are ineffective in providing cure and preventing further episodes of RUTI.

Future preventative strategies

Alternative strategies are being evaluated to combat the growing reality of antimicrobial resistance in treating UTIs and also as an alternative option for the prevention of RUTIs.

Probiotics have many established uses, with prevention of RUTI a possible further clinical use. Vaginally administered *Lactobacillus*-based probiotics have been proposed to restore normal levels of vaginal flora and show real promise in preventing RUTI.[45,46] Further research and larger studies on types of lactobacilli strains, dosage of lactobacilli, optimal route and vehicle of administration are still needed before the widespread use for this indication can be recommended.[47]

Vaccination with an *E coli* extract is currently being tested as a form of immunotherapy in patients with RUTI and shows a 34% reduction in UTIs over a one year period.[48] It remains uncertain which route of administration will be best (parenteral, oral or vaginal) and which patients will benefit most from this exciting development.[49,50]

Herbal products have also been proposed as a means of preventing RUTI and have shown promise, but larger sample sizes and confirmatory studies are needed.[51]

RUTI in HIV positive patients

Patients with HIV and AIDS are predisposed to UTI by uncommon bacteria and pathogens (fungi, parasites and viruses). Treatment for these patients should be culture-specific and long-term (5–10 days), because there is a trend towards recurrence, infection with multiple organisms and resistant isolates.[52] When the CD4 count declines to $< 200/mm^3$ the risk of opportunistic infection increases dramatically.

The reported incidence of bacterial UTI in patients with AIDS is 7–50%. They can experience the typical LUTS such as dysuria and frequency, although many patients are asymptomatic. Pyuria has been noted in up to 52% of patients, with associated UTI in only 20%.[53,54] The most common bacterial pathogens in HIV-infected patients are *E coli, Enterobacter, Pseudomonas, Proteus, Klebsiella, Acinetobacter, Staphylococcus aureus,* group D S*treptococcus, Serratia* and *Salmonella* spp.[55] Urine cultures may be negative because the patient is taking prophylactic antimicrobials against opportunistic infections. Urine should also be cultured for mycobacteria and the use of special culture media and stains, blood cultures and viral titres should be considered. Advanced

investigative testing might be necessary to establish the diagnosis of RUTI due to these unusual organisms. This last group of patients should ideally be managed by a specialist, but the diagnostic tests can also be evaluated by a general physician and referral considered if there is either no clear management plan or if the patient does not respond to therapy.

The treatment of infection in patients with AIDS should be culture-specific and broad spectrum antibiotics should be avoided.[54] Phenazopyridine may be helpful for patients with dysuria resulting from viral reactivation or urothelial damage by the metabolites of AIDS medications. Asymptomatic bacteriuria in HIV-positive patients does not require treatment.[56]

Conclusion

Caregivers treating UTIs should remain vigilant and suspicious of underlying pathology in the face of persistent or recurrent infection. Sexual intercourse and the frequency thereof is the most important risk factor in premenopausal women. Culture specific treatment for acute episodes is recommended in patients with RUTI. Equally important is knowledge about bacterial resistance within the community and to follow subsequent prescribing recommendations. The implications for the appropriate diagnostic, therapeutic and preventative approaches should be noted and this may have significant clinical and economic impact. Management should therefore continue to be evidence based. New developments for the prevention of RUTI holds much promise and these should be closely monitored.

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