Urinary Tract Infections & Treatment

Chapter 2

Recurrent urinary tract infections and management

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1. Introduction

Urinary tract infection(UTI) is a condition in which one or more parts of the urinary system (the kidneys, ureters, bladder, and urethra) become infected. UTIs are the most common of all bacterial infections and can occur at any time in the life of an individual. Nearly 95% of cases of UTIs are caused by bacteria that typically multiply at the opening of the urethra and travel up to the bladder. Much less often, bacteria spread to the kidney from the bloodstream.

Normally, the urinary tract is sterile, but urinary tract infections can be caused by a variety of conditions They can cause complicated or uncomplicated, symptomatic or asymptomatic infections. Anatomically can be divided into upper and lower tract infections [1,2].

When it affects the lower urinary tract it is known as a simple cystitis (a bladder infection) and when it affects the upper urinary tract it is known as pyelonephritis (a kidney infection) UTI can be symptomatic or asymptomatic subclinical infection, urinary tract infection encompasses various clinical entities like acute cystitis, acute pyelonephritis, prostitis [3-6].

UTIs are classified into 6 categories.

- The first category is an *uncomplicated infection*; this is when the urinary tract is normal, both structurally and physiologically, and there is no associated disorder that impairs the

host defense mechanisms.

- The second category is an *complicated infection*; this is when infection occurs within an abnormal urinary tract, such as when there is ureteric obstruction, renal calculi, or vesicoureteric reflux.

- The third category, an *isolated infection*, is when it is the first episode of UTI, or the episodes are 6 months apart. Isolated infections affect 25–40% of young females.

- The fourth category, an *unresolved infection*, is when therapy fails because of bacterial resistance or due to infection by two different bacteria with equally limited susceptibilities.

- The fifth category, *reinfection*, occurs where there has been no growth after a treated infection, but then the same organism regrows two weeks after therapy, or when a different microorganism grows during any period of time. This accounts for 95% of RUTIs in women. Bacterial persistence happens when therapy is impaired by the accumulation of bacteria in a location that cannot be reached by antibiotics, such as infected stones, urethral diverticula and infected paraurethral glands.

- The sixth category, *relapse*, is when the same microorganism causes a UTI within two weeks of therapy; however, it is usually difficult to distinguish a reinfection from a relapse [7,8].

This text is focused on the management of recurrent urinary tract infections, because it has not been perceived as a major clinical problem by the urology community inspite of its prevalence, which bears a financial load of more than one billion dollar on USA [9].

2. Recurrent infection

Recurrent UTI is defined as 2 uncomplicated UTIs in 6 months or, more traditionally, as 3 positive cultures within the preceding 12 months, it affects 25% of women with a history of UTI [10].

When there is recurrent infection with the same organism despite adequate therapy, it is considered a relapse. Reinfection is defined as recurrent UTI caused by a different bacterial isolate, or by the previously isolated bacteria after a negative intervening culture or an adequate time period (2 weeks) between infections [11].

Reinfection is more common than relapse. Most recurrences occur within the first 3 months after the primary infection, and there can often be clustering of infections. When the initial infection is caused by *E. coli,* there is a higher risk of reinfection within the first 6 months [12-14].

Unlike relapse, reinfection does not represent failure to eradicate infection from urinary tract but is due to reinvasion of the system. Relapse is a return of infection due to the same micro-organism which is often drug resistant. Relapse implies that there has been a failure to eradicate the infection. This most often occurs in association with renal scars, stones, cystic disease or prostatitis and in patients with chronic interstitial disease or in those who are immune compromised [15].

3. Epidemiology

UTIs account for more than 8 million visits to physician's offices, 1.5 million emergency room visits, and 300,000 hospitals admission in the United States annually. UTIs are the second most common infection of any organ system and the most common urological diseases in the United States, with a total annual cost of more than $3.5 billion [16].

These infections are common in females than in males. In the female population, these infections occur in 1-3 % of school girls and then increases markedly in incidence with the onset of sexual activity in adolescence. Incidence in women , in the age group of 20- 40 years, ranges from 25 to 30% whereas in older women , above 60 year s of age it ranges from 4 to 43% [16].

4. Risk factors and Pathophysiology

Despite the presence of several antibacterial factors such as the pH, urea concentration, osmolarity, various organic acids, salt content of the urine, urinary inhibitors to bacterial adherence e.g. Tamm-Horsfall protein (THP), bladder mucopolysaccharide, low-molecular-weight oligosaccharides, secretory IgA and lactoferrin, the uropathogenic bacteria are able to adhere, grow and resist against host defenses that finally resulting in colonization and infection of the urinary tract [17-21].

The main causative pathogen involved in recurrent UTI in women is Escherichia coli (*E. coli),* which is responsible for approximately 80% of all episodes of infection. Other significant pathogens include *Staphylococcus saprophyticus, Klebsiella pneumoniae,* and *Proteus mirabilus,* which each cause approximately 4% of all episodes of acute cystitis. *Citrobacter* and *Enterococci* are less likely causes of UTI in women.Infection with organisms that do not usually cause UTIs may be an indicator of underlying structural abnormalities or renal calculi [11].

5. Clinical Sympatology of UTI

Infections confined to lower urinary tract commonly cause dysuria, frequency and urgency. Pyelonephritis (inflammation of the renal parenchyma) is a clinical syndrome

characterized by chills and fever, flank pain and constitutional symptoms caused by bacterial invasion of the kidney. The localization of the site of infection on the basis of symptoms and signs can be inaccurate.

Response to treatment is now used to distinguish between the two upper versus lower urinary tract infections. This is based on the observation that many women with symptoms of cystitis shown by localization studies to be confined to bladder can be cured by a single dose of antibiotic.Recurrence of bacteriuria with the same organism within seven days of single dose therapy was reported to be most often associated with upper tract infection [22,23].

Risk factors in

1) Premenopausal Women:

These include increased frequency of intercourse, use of a spermicide, and new sexual partners. Intercourse and spermicide exposure increase the rate of vaginal and periurethral colonization with E. coli. When a first UTI is caused by E. coli, the risk of a second infection within 6 months is greater than when a first infection is cause by another uropathogen.11 Dysfunctional voiding patterns in which there is increased tone of the external sphincter during micturition can also be associated with recurrent UTI in otherwise urologically normal women. There are also some non-behavioural risk factors for recurrent UTI in young women. These include a history of UTI before age 15 and a maternal history of UTI. This suggests that there are also anatomic and genetic factors involved.20 Most women with recurrent UTI do not have any functional or anatomic abnormalities of the urinary tract, and extensive radiologic and cystoscopic examination is not indicated [24-27].

2) In Postmenopausal Women

In premenopausal women, 90% of the vaginal flora are lactobacilli, which protects against colonization with uropathogens such as *E. coli*. Estrogen loss at menopause results in thinning of the vaginal epithelium and decreased amounts of glycogen. The resulting environment is hostile to lactobacilli, and the numbers decrease. The vaginal pH increases, and there is an increased propensity for colonization with uropathogens.Women who are non-secretors of histocompatibility blood-group antigens are at increased risk of recurrent UTI. This is thought to be a result of attachment of P-fimbriated *E. coli* to glycolipids on vaginal and uroepithelial cells. Non-secretor status is a more significant risk factor in postmenopausal than in premenopausal women. Postmenopausal women who suffer from incontinence and who have significant pelvic floor prolapse and elevated post-void residual volumes are at increased risk for recurrent UTI. Other significant factors for recurrent UTI in postmenopausal woman is diabetes mellitus [28].

7. Evaluation of Recurrent UTI

7.1. Significant bacteriuria

It is defined as the presence of 100,000 or more colony forming units (CFU) per ml of urine. This Kass criteria has been questioned and bacterial counts of 102 or more organism per ml particularly when accompanied by pyuria (>10 wbc/mm3) provide impressive evidence of urinary tract infection in symptomatic young women. The Infectious Disease Society of America (IDSA) gave a slightly more relaxed consensus definition requiring 103 organisms per ml to diagnose cystitis and 104 per ml for pyelonephritis [29-34].

7.1.1.Urinalysis

Microscopy is a valuable diagnostic tool for patients with urinary symptoms.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.

7.1.2. Urine Culture

Urine culture is a standard criterion for the diagnosis of UTI, Urine must be collected properly (midstream or catheterized specimen) and cultured quickly or refrigerated. Traditionally, significant bacteriuria is noted when the bacterial colony-forming unit counts reach 105/ml.

7.1.3. Other Investigations

Many patients with recurrent UTIs are referred for urologic opinion and subsequently undergo both radiologic investigations and cystoscopy. However, further investigations are import Similarly, investigations are required in patients who do not respond to appropriate antimicrobial therapy after 5 to 6 days of treatment. ant if a patient is believed to have any of the following: hematuria, a complicated UTI. 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 always be the most appropriate screening procedures [32].

Table 1: Indications for further investigation of recurrent urinary tract infection [33,34].

1. Prior urinary tract surgery or trauma
2. Gross hematuria after resolution of infection
3. Previous bladder or renal calculi
4. Obstructive symptoms (straining, weak stream, intermittency, hesitancy), low uroflowmetry or high PVR
5. Urea-splitting bacteria on culture (e.g., Proteus, Yersinia)
6. Bacterial persistence after sensitivity-based therapy
7. Prior abdominopelvic malignancy
8. Diabetes or otherwise immunocompromised
9. Pneumaturia, fecaluria, anaerobic bacteria or a history of diverticulitis
10. Repeated pyelonephritis

8. Indications for specialist referral

Specialist referral is recommended for investigation of women with risk factors for complicated UTI , surgical correction of a cause of UTI , or when the diagnosis of recurrent uncomplicated UTI is uncertain.

Table 2: Host factors that classify a urinary tract infection as complicated [33].

Complication	Examples
Anatomic abnormality	Cystocele, diverticulum, fistula
Iatrogenic	Indwelling catheter, nosocomial infection, surgery
Voiding dysfunction	Vesicoureteric reflux, neurologic disease, pelvic floor dysfunction, high post void residual, incontinence
Urinary tract obstruction	Bladder outlet obstruction, ureteral stricture, ureteropelvic junction obstruction
Other	Pregnancy, urolithiasis, diabetes or other immunosuppression

9. Management of recurrent UTI

9.1 Prophylaxis: Prevention of Recurrent Urinary Tract Infections

Table 3: Prevention strategies for Recurrent Urinary tract infection [35].

1	life style changes
2	prophylactic antimicrobial therapy
3	cranberry juice extract prophylactic therapy

1) **Conservative Approach to Prevention**: 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. Attempting to change the vaginal flora by douching with lactobacilli has been suggested but not proven [36,37].

2) **Cranberries:** Cranberries (particularly in the form of cranberry juice) have been touted as an effective home remedy for the prevention and treatment of UTIs for several decades. So far, no definite mechanism of action has been established. The main suggestion is that cranberries prevent bacteria (particularly *E. coli*) from adhering to uroepithelial cells.Without adhesion, the bacteria cannot infect the mucosal surface [38,39].

3) **Probiotics :** The instillation of *Lactobacillus* into the vagina is believed to stop the ascension of uropathogens into the bladder. Available studies suggest that probiotics can be beneficial, and most authors consider this approach promising, but further research is needed before probiotics can be recommended for prevention of UTI [40-44].

4) **Estrogen:** Vaginal estrogen may be an effective prophylaxis measure for UTI in postmenopausal women [45]. The mechanism of action is thought to be the reappearance of vaginal lactobacilli which, unlike placebo, decrease the vaginal pH. This results from maturation and thickening of the vaginal epithelium with increased cellular glycogen, a main substrate for lactobacilli. This process prevents overgrowth and colonization of Enterobacteriaceae in the vagina. It can take at least 12 weeks for the vaginal ring to be effective in reducing the occurrence of UTIs [46,47].

Antimicrobial Strategy

There are as many options for prevention and management of recurrent UTI Choice of antibiotic should rely on community patterns of resistance, adverse events, and local costs. Three main management strategies generally considered are continuous antimicrobial prophylaxis, post-coital prophylaxis, and patient-administered self-treatment. For patients with two UTIs per year, the acute self-treatment may be useful. Patients with three infections annually should be offered a regimen of continuous, low-dose prophylaxis or post-coital prophylaxis [48].

9.2 Antimicrobial Prophylaxis

The two 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 pretreatment rates when prophylaxis is stopped. Long-term

antibiotics do not appear to alter the patient's basic susceptibility to infections [49,50,51].

a**) 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.

b) Acute cystitis is more common in sexually active women and a number of studies have shown that **post intercourse therapy** with antimicrobials such as nitrofurantoin, cephalexin, and TMP-SMX taken as a single dose effectively reduces the incidence of reinfection. The rationale behind post intercourse therapy 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 infection in a susceptible individual [52,53].

c) **Patient-Directed Self-Treatment of Recurrent UTIs:** 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. The patient would then self-start a 3-day course of empiric full-dose antimicrobial therapy immediately after performing the culture. The same investigators believed that fluoroquinolones are the ideal medication for self-start therapy because of their broad spectrum of activity compared to other potential alternatives. 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 [54,55].

Table 4: Treatment Regimens for Uncomplicated Acute Bacterial Cystitis

Antimicrobial Agent	Dose	Adverse Events
Trimethoprim–sulfamethoxazole	One tablet (160 mg trimethoprim–800 mg sulfamethoxazole), twice daily for 3 days	Fever, rash, photosensitivity, neutropenia, thrombocytopenia, anorexia, nausea and vomiting, pruritus, headache, urticaria, Stevens–Johnson syndrome, and toxic epidermal necrosis
Trimethoprim	100 mg, twice daily for 3 days	Rash, pruritus, photosensitivity, exfoliative dermatitis, Stevens–Johnson syndrome, toxic epidermal necrosis, and aseptic meningitis
Ciprofloxacin	250 mg, twice daily for 3 days	Rash, confusion, seizures, restlessness, headache, severe hypersensitivity, hypoglycemia, hyperglycemia, and Achilles tendon rupture (in patients older than 60 years)
Levofloxacin	250 mg, once daily for 3 days	Same as for ciprofloxacin
Norfloxacin	400 mg, twice daily for 3 days	Same as for ciprofloxacin

Antimicrobial Agent	Dose	Adverse Events
Gatifloxacin	200 mg, once daily for 3 days	Same as for ciprofloxacin
Nitrofurantoin macrocrystals	50 to 100 mg, four times daily for 7 days	Anorexia, nausea, vomiting, hypersensitivity, peripheral neuropathy, hepatitis, hemolytic anemia, and pulmonary reactions
Nitrofurantoin monohydrate crystals	100 mg, twice daily for 7 days	Same as for nitrofurantoin macrocrystals
Fosfomycin tromethamine	3 g dose (powder) single dose	Diarrhea, nausea, vomiting, rash, and hypersensitivity

Table 5: Antimicrobial prophylaxis regimens for women with recurrent urinary tract infections [28].

Oral regimens	
Continuous prophylaxis	
• TMP-SMX	40/200 mg daily
• TMP-SMX	40/200 mg 3/week
• TMP	100 mg daily
• Nitrofurantoin monohydrate/macrocrystals	50–100 mg daily
• Nitrofurantoin macrocrystal	50–100 mg daily
• Cephalexin	125–250 mg daily
• Cefaclor	250 mg daily
• Norfloxacin	200 mg daily
• Ciprofloxacin	125 mg daily
• Cinoxacin	250–500 mg daily
Post-coital prophylaxis (single dose)	
• TMP-SMX	40/200 mg
• TMP-SMX	80/400 mg
• Nitrofurantoin macrocrystal	50–100 mg
• Cephalexin	125–250 mg
• Cinoxacin	250 mg
• Ciprofloxacin	125 mg
• Norfloxacin	200 mg
• Ofloxacin	100 mg
Acute self-treatment	
• TMP-SMX	160/800 mg twice daily × 3 days
• Ciprofloxacin	250 mg twice daily × 3 days
• Norfloxacin	200 mg twice daily × 3 days

10. Pregnancy and Recurrent Utis

For pregnant women with symptomatic or asymptomatic bacteriuria, the risk of a preterm delivery and low birth weight infant is significantly increased. Indications for prophylaxis are

(1) all women with a pre-pregnancy history of recurrent UTIs,

(2) persistent symptomatic or asymptomatic bacteriuria after two antibiotic treatments,

(3) after only one UTI for a woman who has other conditions that potentially increase the risk of urinary complications during the episode of UTI (e.g., diabetes or sickle cell trait).

Both continuous and post-coital prophylaxis regimens have been shown be effective, and agents of choice are nitrofurantoin (50 mg) and cephalexin (250 mg) [57-61].

11. Adjuvant Measures

- Sufficient fluid intake (at least two liters per day) and regular voiding is commonly believed to have a 'flushing' effect on the urinary tract; bacterial proliferation might be hindered, owing to a shorter retention of urine in the patient's bladder
- Micturition after sexual intercourse is supposed to rinse bacteria from the bladder and thus prevent UTI [62].
- Since damage to the physiological vaginal flora facilitates UTI, exaggerated genital 'hygiene' (deodorant sprays, vaginal lotions or douching, etc) should be avoided [63].
- Methenamine salts act via the production of formaldehyde from hexamine, which in turn acts as a bacteriostatic agent [64].
- Methenamine hippurate appears to be ineffective when used in spinal cord injured patients with neuropathic bladder [65] the rate of adverse events reported by the studies was low, which suggests that current usage is unlikely to be causing significant harm [66].
- Cooling of the feet has been shown to promote an acute episode in patients prone to recurrent UTI, they should try to avoid getting cold [67].
- Acupuncture has been shown to be successful in preventing frequent UTI episodes [68].

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