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### **Recurrent urinary tract infections in females**

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#### **Abstract**

Uncomplicated Urinary tract infections are common in adult women across the entire age spectrum, with mean annual incidence of 15% and 10% in those aged 15-39 and 40-79 years, respectively. Urinary tract infection (UTI), with its diverse clinical syndromes and affected host groups, remains one of the most common but widely misunderstood and challenging infectious diseases encountered in clinical practice. Recurrent urinary tract infections (UTIs) present a significant problem for women and a challenge for the doctors who care for them. The diagnosis of uncomplicated UTI can be achieved best by a thorough assessment of patient symptoms with or without the addition of a urine dipstick test. Treatment should be based on the most recent guidelines, taking into account resistance patterns in the local community. The patient who suffers from recurrent UTIs can be treated safely and effectively with continuous antibiotic prophylaxis, post-coital therapy, or self-initiated treatment. This review article covers the latest trends in the management of recurrent UTI among women. Further research is needed regarding rapid diagnosis of UTI, accurate presumptive identification of patients with resistant pathogens, and development of new antimicrobials for drug-resistant UTI.

#### **Introduction**

Treatment of recurrent urinary tract infections (UTI) in female is one of the most difficult challenges for the physicians, affecting about 25% of women with a history of isolated urinary tract infection.<sup>1</sup> It is certainly bothersome for the patient and the sequelae may not only cause morbidity but in high risk patients carries a significant risk of mortality. When bacterial virulence increases or host defense mechanisms decrease, bacterial inoculation, colonization, and infection of the urinary tract occurs. Careful diagnosis and treatment results in successful resolution of infections in most instances. Treatment of recurrent urinary tract infection requires understanding of the pathogenesis of UTI and the role of host and bacterial factors.<sup>2</sup> Only with insight into this process, we can improve our ability to identify patients at risk and reduce morbidity.

The urinary tract is normally sterile; bacteria that generally ascend from the peri-anal area reservoir may cause UTIs. Bacteria in the urinary tract may remain asymptomatic or cause irritative symptoms such as frequency and urgency. If

untreated, the infection may ascend to the upper urinary tract and produce fever, chills, and flank pain. Bacterial entry into the blood stream is associated with severe morbidity, including sepsis and death.<sup>3</sup>

An ideal antimicrobial agent should be orally administrable and able to achieve high urinary and tissue levels without producing any nephrotoxicity. Developments in pharmacology have lead to introduction of drugs which have significantly reduced the need for hospitalization for severe infection. Shorter-course therapy and prophylactic antimicrobial agents have reduced the morbidity and cost associated with recurrent UTI in women.

Although the vast majority of patients respond promptly and are cured by therapy, early identification and treatment of patients with complicated infections that place them at significant risk remains a clinical challenge.

#### **Definition:**

Recurrent urinary tract infection (RUTI) is defined as three episodes of urinary tract infection (UTI) with 3 positive urine cultures in the previous 12 months or two episodes in the last six months.<sup>4</sup>

#### **Risk Factors:**

According to Cohort and case controlled studies by Hooton et al risk factors associated with recurrent UTI in sexually active premenopausal women are the symptom proximity to sexual intercourse, use of spermicides, the age of first UTI (less than 15 years of age indicates a greater risk of RUTI) and history of UTI in the mother is suggesting that genetic /long term environmental exposures might predispose to this condition.<sup>5</sup> In postmenopausal women Utero-vaginal prolapse, urinary incontinence and post void residual urine are important risk factors.

Infection with multi-resistant pathogens is more likely to occur in complicated UTI. The risk is increased with obstruction or any factor that causes urinary stasis, for example urolithiasis, malignancy, renal cyst, neurogenic bladder, or urethral diverticulum. The most common factors include an indwelling catheter, ureteric stent, or nephrostomy tube. Some medical conditions e.g. diabetes mellitus, pregnancy, renal failure, renal transplantation, and immunosuppression facilitates entry of uropathogens by bypassing normal host defenses. Diabetes mellitus has been

shown to have a two- to threefold increase in frequency of RUTI.<sup>6</sup>

### Diagnosis:

Diagnosis is usually made with the history and 3 positive urinary cultures within the preceding 12 months. Irritative voiding symptoms are common among 25-30 % of women with recurrent UTI.<sup>7</sup> Among women with irritative voiding symptoms, clinical symptoms can help to identify women with recurrent urinary tract infections at the initial presentation even if urine culture reports are not available. Causes of irritative voiding symptoms include urethral syndrome, interstitial cystitis, and recurrent urinary tract infections. It is often difficult to identify women with recurrent urinary tract infections at their initial presentation in the office because urine culture reports may not be available. Generally the women with RUTI in our country are treated by general practitioners and the repeated use of antibiotics leads to resistance and a proper diagnosis is never established. A recent retrospective case controlled study differentiated between clinical symptoms predictive of recurrent UTI and irritative voiding symptoms. Women in the recurrent urinary tract infection group were significantly more likely to report symptoms after intercourse, a prior history of pyelonephritis, and prompt resolution of symptoms after taking antibiotics than women with irritative voiding symptoms (dysuria, urgency, and/or frequency).<sup>8</sup> Women in the recurrent urinary tract infection group were significantly less likely to report nocturia and persistence of symptoms between episodes of urinary tract infection than women with irritative voiding symptoms. For women reporting irritative voiding symptoms between perceived episodes of urinary tract infection or nocturia suggests a non-infectious cause to their symptoms and they may be at higher risk for voiding dysfunction or reduced bladder compliance as seen in interstitial cystitis, urethral syndrome, or detrusor overactivity. These women require cystoscopy and/or cystometrograms and in 80% of women significant abnormalities were detected during cystoscopy with most over 50 years.<sup>9</sup>

### Classification:

Uncomplicated UTIs occur in patients with urinary tracts that are normal from both a structural and functional perspective. Most women in outpatient setting present with uncomplicated UTIs and respond promptly to short term, inexpensive oral antimicrobial therapy.

Complicated or Recurrent UTIs occur in patients with any anatomic, structural or functional abnormality that compromises therapy. Fever and chills are common along with other systemic symptoms and broad spectrum therapy is required.

Infections are further characterized into the

following categories:

**Isolated infection:** Isolated infections are either initial episodes of infection or are separated by six months from other episodes of infections, 25-40% of women aged 30-40 years present with isolated infection

**Unresolved infection:** Unresolved infections occur in patients with whom therapy has been unsuccessful due to bacterial resistance to the drug selected for treatment or bacteriuria caused by two different species with mutually exclusive susceptibilities. Another less common cause is presence of giant stag horn calculi and azotaemia.

**Re-infection:** Re-infection refers to a new infection, i.e. the urine shows no growth after the previous infection, but the same organism is re-grown 2 weeks after treatment, or a different strain is grown at any time.<sup>10</sup> These represent 95% of recurrent UTIs in women. Bacterial persistence occurs when therapy is subverted by sequestration of bacteria in a site that is protected from the drug. Recognizing bacterial persistence is important because the cause must be removed to achieve sterilization. Common correctable urologic abnormalities that can cause bacterial persistence include infected stones, urethral duplication and ectopic ureters, foreign bodies, urethral diverticula and infected Para-urethral glands.

A relapse is a UTI caused by the same bacterial strain from a focus inside the urinary tract within 2 weeks of treatment. However, it is frequently impossible to distinguish a re-infection from a relapse.<sup>11</sup>

### Pathogenesis:

The pathogenesis of recurrent UTI is assumed to be the same as with sporadic infection. The infecting bacteria in both recurrent UTIs and a de novo acute infection have been thought to originate from an extra urinary location. Most uropathogens originate in the rectal flora, colonize the peri-urethral area and urethra, and ascend to the bladder. Increasing evidence suggests that alteration of the normal vaginal flora, especially loss of H<sub>2</sub>O<sub>2</sub>-producing lactobacilli, may predispose women to introital colonization with Uropathogenic Escherichia Coli (UPEC), which is responsible for 85% of infections in ambulatory patients and 50% of nosocomial infections.<sup>12</sup> Although the vast majority of UPEC are cleared by host defenses within a few days, small clusters of intracellular bacteria have occasionally been observed to persist for months in an antibiotic-insensitive state.<sup>13</sup> It has been shown in a murine model of UTI that uropathogenic Escherichia coli (UPEC) established quiescent intracellular reservoirs (QIRs) in endosomes within the urinary bladder epithelium.<sup>14</sup> Depending on the integrity of the urothelial barriers at the time of initial infection, these QIRs were established within terminally differentiated superficial facet cells and/or underlying transitional epithelial cells. Treatment

of infected bladders harbouring facet epithelial cell barrier, invading bacteria also face a chemical barrier: the complex network of proteoglycans/glycosaminoglycans (GAG layer) that is woven into the urothelium and is known to act as an antimicrobial adherence factor. Normal physiological changes in levels of GAGs may render bladders more vulnerable to invasion by bacteria. Even in healthy young women with presumably unperturbed epithelia, bladder GAG levels may vary during the normal menstrual cycle. Furthermore, certain UPEC strains may contain virulence factors that allow the bacteria to penetrate into the transitional cells and form QIRs. Establishment of QIRs throughout the underlying transitional epithelium may predispose an individual to an increased likelihood of recurrence and may account for some of the frequent same-strain recurrences that are seen clinically despite appropriate antibiotic therapy.

### **Counseling and Treatment:**

A woman suffering from uncomplicated UTI should be informed about the possible recurrences and the relationship between UTI and sexual intercourse. Asking a patient about her own conception of the illness may (as in many general practice consultations) improve mutual understanding. The basic treatment begins with antimicrobial therapy and there are many choices available but one must understand the principles of antimicrobial therapy.

### **Principles of Antimicrobial Therapy:**

The objective of antimicrobial therapy is to eliminate the bacterial growth in the urinary tract utilizing antimicrobial agent which is efficacious, safe, and cost effective. The dose duration should be patient friendly to ensure compliance and the therapy should be prescribed only for the least possible time to decrease the resistance emerging from excessive utilization

The resolution of infection is dependant on the susceptibility of the bacteria to the concentration of the antimicrobial agent achieved in the urine. Antimicrobial agent should ultimately eliminate bacterial growth in the urinary tract. This can occur within hours if the proper antimicrobial agent is used which is able to achieve levels in the urine and the duration that this level remains above the minimal inhibitory concentration of the infecting organism.<sup>15</sup> An effective antimicrobial agent usually achieves minimal inhibitory concentration both in the serum and urine of healthy adults, the urinary levels are often many folds greater than the serum levels. However the serum levels are critical in patients with uro-sepsis and urinary infections involving renal parenchyma.<sup>16</sup>

Patients with renal insufficiency and obstructive uropathy require dose modifications. Other patient factors like age, potential pregnancy or lactation should

also be considered.<sup>17</sup>

The use of prophylactic antibiotics for six to 12 months is effective in reducing the number of recurrent UTI s but no antibiotic is significantly better than others at decreasing the number of UTIs. Postcoital prophylaxis is as effective as daily prophylaxis in young women but it should be offered to women who have UTI associated with sexual intercourse. Limited evidence suggests that weekly prophylaxis is better than monthly prophylaxis.<sup>18</sup>

### **Adjuvant Measures:**

Adjuvant measures for treatment or against recurrence and prophylaxis are often asked for by patients or recommended by GPs, based on risk factors present in a patient. Most have not been evaluated in randomized trials or prospective studies.

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. However, no trials of the effect of high fluid intake on UTI could be found in literature.

Micturition after sexual intercourse is supposed to rinse bacteria from the bladder and thus prevent UTI.<sup>19</sup> Since damage to the physiological vaginal flora facilitates UTI, exaggerated genital 'hygiene' (deodorant sprays, vaginal lotions or douching, etc) should be avoided (recommendation grade A).<sup>20</sup> If possible, other methods of contraception should be used in preference to spermicidal or diaphragms (recommendation grade A). For frequently recurring UTI, different therapeutic/prophylactic regimens can be useful; if UTI episodes occur frequently after sexual intercourse, and if post-coital voiding is not successful, 100mg trimethoprim can be taken after sexual intercourse (recommendation grade A).<sup>21</sup> Otherwise, therapy with 50 mg trimethoprim daily or 50 mg nitrofurantoin daily for six months is effective and well tolerated (recommendation grade A). Should frequent UTI still occur after six months, this treatment can be continued for several years if necessary.

In postmenopausal women, local substitution of oestrogen (for example, vaginal cream containing oestrogens) improves the trophic of the vaginal mucosa and has been shown to reduce the frequency of UTI (recommendation grade A).Based on only two studies in a systemic review of Cochrane database<sup>22</sup> which compared vaginal oestrogens to placebo, it has been proved that vaginal oestrogens reduced the number of UTIs in postmenopausal women with RUTI, however this varied according to the type of oestrogen used and the treatment duration.

Cranberry products have been advocated in America. Cranberries (usually as cranberry juice) have been used to

prevent urinary tract infections (UTIs). Cranberries contain a substance that can prevent bacteria from sticking on the walls of the bladder. This may help prevent bladder and other urinary tract infections. The Cochrane systemic review shows the evidence from four RCTs (randomized controlled trials) that cranberry product can be effective in reducing UTIs.<sup>23</sup>

Methenamine salts are often used as an alternative to antibiotics for the prevention of urinary tract infection (UTI). Methenamine salts act via the production of formaldehyde from hexamine, which in turn acts as a bacteriostatic agent.<sup>24</sup> It is uncertain whether urinary acidification and the direct bacteriostatic effect of hippuric acid contribute significantly to its action.<sup>25</sup> Methenamine salts are well tolerated and adverse effects, including minor gastrointestinal upsets, dysuria, abdominal cramps, anorexia, rash and stomatitis, are generally mild. Methenamine hippurate appears to be ineffective when used in spinal cord injured patients with neuropathic bladder.<sup>26</sup> The rate of adverse events reported by the studies was low, which suggests that current usage is unlikely to be causing significant harm.<sup>27</sup>

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 (recommendation grade B).<sup>28</sup>

Acupuncture has been shown to be successful in preventing frequent UTI episodes in one randomized, single-blind controlled trial in 67 patients with recurrent UTI.<sup>29</sup>

### Physician approach for patient with recurrent urinary tract infection:

The approach in the management of recurrent urinary tract infections is outlined in the Figure. We need to adequately treat an episode of infection and after the completion should document complete eradication with a urine culture and if infection reoccurs or persists then imaging is required. An ultrasound KUB with pre and post void bladder volumes is vital and may reveal a stone or anatomical abnormality such as hydronephrosis and hydroureter which may need further evaluation by an Intravenous urogram (IVU) to look for a ureteric stone or congenital anomalies like pelviureteric junction obstruction or ureteric strictures. Some times extra mural obstruction from adjacent organs like ovarian or uterine pathologies may result in hydroureter and can present as recurrent infections. If no obstruction is seen in the IVU but hydroureter is present, a micturating cystourethrogram may be done to look for vesicoureteric reflux.

If the ultrasound does not reveal any upper tract abnormality, the bladder volumes would still help us in getting to the cause of infections. A large post void residue may be a focus of recurrent infections and if left untreated would result in damage to the kidneys. If the post void residue is more than 100 cc, a uroflowmetry is advised to rule out bladder out flow

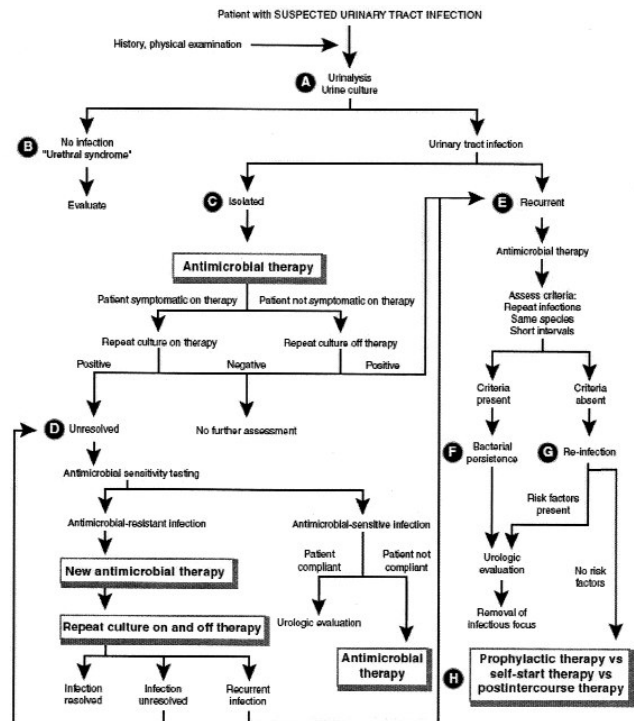


Figure: Flow chart for treating recurrent urinary tract infection by physicians.

obstruction from urethral stenosis, however if there is no obstruction on uroflowmetry, it is crucial to do urodynamic to assess the contractile capacity of the detrusor muscle and in case there is hypotonic bladder it may require clean intermittent self catheterization, a strategy often required in poorly controlled diabetic with hypotonic bladder.

If a risk factor in certain cases is not identified, a cystoscopy may be performed to rule out any mucosal lesion or foreign body in the bladder.

If no risk factors are identified and the urinary tract infections recur, prophylactic antibiotics are recommended as described earlier.<sup>30</sup>

### Conclusion

One in four women with UTI will suffer from recurrences, in healthy, young or pre-menopausal women the most common risk factor is sexual intercourse. E. coli is the most commonly isolated uropathogen and the basic treatment begins with antimicrobial therapy. Investigations must aim not only to verify the diagnosis of RUTI but also to find any possible cause of the recurrence but in the majority of women with recurrent uncomplicated cystitis there is no anatomical or functional abnormality of the urinary tract and, therefore advanced radiological imaging studies are not required. Management of most complicated infections depends on clinical experience and resources at individual institutions rather than on evidence based guidelines. Prevention include

avoiding use of deodorant sprays, vaginal lotions or douching. If possible, other methods of contraception should be used in preference to spermicidal, diaphragms or condoms. Although many approaches have not been adequately tested in studies but it is reasonable to use cranberry juice, methanamine salts and estrogen cream in postmenopausal women as a way of minimizing antibiotic exposure. The use of prophylactic antibiotics for six to 12 months is effective in reducing the number of recurrent UTIs but no antibiotic is significantly better than others at decreasing the number UTIs.

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