

# Recurrent Urinary Tract Infections

## Management conundrums

by Dr Arthur Tseng



The inconvenience, discomfort and incapacitation that women feel when a urinary tract infection (UTI) strikes is all too common to general practitioners and specialists alike. Uropathogenic bacteria originating from the gut system can easily spread to cause infection. The belief that simply giving antibiotics is all that is required is still in force. Unfortunately, with the rampant overuse of antibiotics, bacterial resistance has developed rapidly.

UTIs are especially common in females, requiring over six million visits to physicians per year in the United States alone. UTIs are commonly termed cystitis and represent the majority of renal tract infections. Rarer but more severe infections include pyelonephritis,

where there is upper urinary tract involvement by contiguous infective spread. Asymptomatic bacteriuria, which describes bacteria in the urine in an asymptomatic patient, is significant in pregnant women for risk of significant urosepsis and pregnancy-related complications.

Unfortunately, one in four (25%) women with acute cystitis will progress to have recurrent UTI (RUTI), which is defined as two or more infections in a six-month period. These infections tend to cluster in time, and are due to colonisation in faecal, peri-urethral and bladder reservoirs.<sup>1</sup>

### Signs and Symptoms

The classical symptoms of a UTI are that of dysuria, urinary frequency and urgency, suprapubic pain, possible flank and costo-vertebral pain, foul-smelling and/or bloody urine, and voiding difficulties. The addition of fever, chills and rigors are often associated with pyelonephritis.

There is growing appreciation that voiding dysfunction is the earliest symptom to herald a UTI, where there is difficulty initiating urination, hesitancy and poor stream, from urethral spasm secondary to bacterial irritation. This may be a crucial indicator of when to start treatment for patients prone to RUTIs.

### Pathophysiology

*Escherichia coli* causes the majority (70%-95% prevalence) of UTIs. Other pathogens responsible include *Staphylococcus saprophyticus*, *Proteus mirabilis*, *Klebsiella pneumoniae* and *Enterococcus faecalis*.

The urinary tract is sterile under normal circumstances, due to the regular emptying of stale urine, thus reducing the potential for bacterial multiplication and bladder mucosal invasion.<sup>2</sup>

Uropathogenic bacteria cause UTIs by peri-genital spread, with colonisation, ascending contiguous spread, and the unique ability to adhere to bladder mucosa, thereafter invading between cells to form bio-films that evade local host immune systems and antibiotic attack.

Thus, in women, the shorter urethra predisposes to UTIs. Sexual intercourse, dehydration with urinary volume depletion, obstruction, bladder instrumentation, vesico-ureteric reflux, poor catheter care and drainage are other risk factors for UTIs.



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In post-menopausal women, the lack of *Lactobacilli* species in the vagina prevent competitive inhibition of uropathogens. Pregnancy, pre-existing urinary tract abnormalities and obstruction (from pelvic organ prolapse), diabetes mellitus and other immunocompromised states all predispose to complicated UTIs and recurrent infection.<sup>3,4</sup>

## Diagnostic Tools

### Urine Dipstick

With acute UTIs, many doctors rely on dipsticks to look for positive leukocyte esterase, and nitrite positive status. "Leukocyte esterase positive" status has only a 57%-96% sensitivity, but is 94%-98% specific. The wide ranging sensitivity reduces accuracy of diagnosis. Moreover, only 25% of patients with UTI are "nitrite positive".

Hence, for women with a risk of complicated acute and recurrent UTIs, it is useful to do a urine microscopy and culture. More so if the patient is immunosuppressed in any way, had recent antibiotic exposure, recent bladder instrumentation, known obstruction, post-menopausal, and is of advanced age.<sup>5</sup>

### Urine Microscopy

A WBC count greater than 10/ml in a fresh unspun sample is abnormal, and has a sensitivity of 80%-95%, but with a specificity of 50%-75% only for UTI detection. As such, in symptomatic women with a negative urine dipstick, a urine microscopy should be performed, as levels as low as 2-5 WBC/ml can be significant.<sup>6</sup>

Gram staining for the presence of bacteria during urine microscopy is highly sensitive and specific for UTI (90% and 88% respectively).

### Urine Culture

The current definitions of UTI, based on culture reporting are:<sup>7</sup>

**Cystitis** – more than 1000 CFU/mL

**Pyelonephritis** – more than 10,000 CFU/mL

**Asymptomatic bacteriuria** – more than 100,000 CFU/mL

The reduced CFU numbers for cystitis are in recognition that lower counts in symptomatic patients is significant and ought to be treated. Due to emergent antibiotic resistance, empirical antibiotic treatment should be based on knowledge of local sensitivity and resistance patterns, but the eventual culture sensitivities for particular bacterial strains allows for targeted treatment, with higher symptomatic and bacteriologic cure rates and reduced re-infection rates.<sup>8</sup> This however, does predispose to antibiotic resistance in uropathogenic bacteria and adversely affects beneficial gut and vaginal flora.<sup>9</sup>

In patients with RUTIs, further investigations are required, and include investigating for diabetes mellitus where there is clinical suspicion. Urine cytology is a useful screen for malignancy. An ultrasound of the renal tract is required to exclude stones, obstruction, or malignancy. Cystoscopy with possible biopsy is required for full assessment of the lower renal tract. CT urography has largely superseded ultrasound in sensitivity and specificity for upper tract abnormalities.<sup>10</sup>

## Treatment

In patients with an uncomplicated acute UTI, international guidelines for antibiotics usage are recommended, with first-line antibiotics including

nitrofurantoin, fosfomycin, and the beta-lactam antibiotic or cephalosporin group. Bactrim (trimethoprim-sulfamethoxazole) should be less often used as resistance patterns are high in various localities and limited usage will maintain effectiveness for certain serious infections. Fluoroquinolones, as second-line agents, should be reserved for complicated UTIs. Treatment duration should range between three to seven days.<sup>11</sup> Fosfomycin, in a single 3g dose, is particularly effective due to minimal resistance patterns and collateral damage to gut and vaginal flora when compared to other antibiotic types and is better tolerated in pregnancy.<sup>12</sup>

With such treatment, women can expect symptom relief after the third day of antibiotic use, and complete resolution by one week. It is not necessary to do a "test-of-cure" urine culture in uncomplicated cases, unless patients have a risk of recurrence or have a complicated UTI, wherein treatment regimens can be up to two weeks with an appropriate antibiotic.<sup>13</sup>

Urinary alkalinisers are used concomitantly to reduce dysuria and burning discomfort and pain.

In patients with RUTIs, low-dose suppressive antibiotics are used, on a monthly rotational basis, for a minimum duration of three to six months to eradicate the bacteria(e) present in the bladder. Rotational antibiotic use again reduces the risk of antibiotic resistance emerging in uropathogenic bacteria(e).

In patients with a risk of recurrent complicated UTI, long-term prophylactic treatment between six to twelve months may be attempted with Bactrim (one tablet), nitrofurantoin (100mg), norfloxacin (200mg) or trimethoprim (100mg) as a

nightly dose; with a drug break after an extended symptom-free period, as 30% of women will be UTI-free for a prolonged period of time. Long-term suppression has been evaluated to be safe and effective even after five years of continuous usage.

An alternative therapeutic mode for RUTI is self-initiated antibiotic therapy. Once a woman suspects herself to have a UTI, she initiates treatment using ofloxacin 200mg BD or levofloxacin 250mg OM for three days, with a clinical cure rate of 95% efficacy.<sup>14</sup>

## Adjunctive Measures

In sexually active women, drinking adequate amounts of fluids, cleansing the perineum before intercourse, and voiding after intercourse reduces the risk of "honeymoon cystitis". The use of single-dose suppressive antibiotics post-coitally is particularly effective in preventing infection. Spermicides should be avoided, as they kill normal vaginal flora that keep uropathogenic bacteria in check.

The use of cranberry juice (300ml/day) or extract appears to be useful in preventing RUTI, by reducing bacterial adherence due to the active ingredient type A proanthocyanidins and bactericidal effects of hippuric acid.<sup>15,16</sup> Recent meta-analysis has proven that cranberry is beneficial if used twice daily at requisite doses.<sup>17</sup>

It has been found that oral administration of probiotics restored vaginal lactobacilli flora and reduced colonisation of uropathogenic bacteria, as did intra-vaginal probiotic suppository usage. In both methods, reduction in recurrence was comparable to antibiotic suppression, with less adverse effects and less resistance build-up to bacteria species. Currently, evidence is accruing that may support the widespread use of probiotic therapy in pre- and post-menopausal women with RUTIs, as a reasonable alternative for women wishing to avoid long-term antibiotic use and minimise antimicrobial resistance.<sup>18,19</sup>

In menopausal women with RUTI, topical oestrogen therapy bolsters vaginal, peri-urethral and bladder local defences by restoring lactobacilli that resist uropathogenic infection.<sup>20,21</sup>

Perineal hygiene is important in preventing contiguous spread. The use of tampons during periods reduces menstrual blood contamination of the perineum and infective risk. The use of breathable cotton undergarments to prevent moisture accumulation and perineal skin maceration reduces infective risk.

There is some research suggesting intravesical chondroitin sulphate and hyaluronic acid instillation, compared to prophylactic antibiotics, significantly reduces RUTI recurrence rates, with improved quality of life and urodynamic parameters over a 12-month study period.<sup>22</sup>

## Conclusion

With the onset of antibiotic resistance, gone are the days where simply throwing any antibiotic at a patient was guaranteed a cure for what was considered a minor, albeit troublesome and unpleasant, infection by most doctors. The need to be aware of local antibiotic sensitivities and resistance patterns makes UTIs, RUTIs and complicated UTIs more challenging. Hence, there is a need to educate our patients on good perineal hygiene habits. We should also consider the possibility of instituting non-antibiotic modalities of treatment and novel therapeutic methods that are on the horizon.

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