RECURRENT URINARY TRACT INFECTIONS

In this comprehensive overview of urinary tract infections, the author looks at common causes, ways to diagnose and potential treatments

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Urinary tract infections (UTIs) are among the most common bacterial infectious diseases encountered in clinical practice, and account for significant morbidity and high medical costs. Sexually active women aged 20 to 40 years and postmenopausal women older than 60 years are the two populations at greatest risk for UTI.

A UTI occurs when the normal flora of the periurethral area are replaced by uropathogenic bacteria, which then ascend to cause a bacterial cystitis. Sometimes this infection ascends to the kidney to cause a bacterial pyelonephritis. Ascending infection is thought to be caused by bacterial virulence factors allowing for improved adherence, infection and colonisation by uropathogens.

The usual uropathogens include *Escherichia coli, Staphylococcus saprophyticus, Klebsiella pneumoniae* and *Proteus mirabilis*. *Escherichia coli* is the most predominant pathogen causing 80-90% of community-acquired UTIs.[1]

In England and Wales, consulting rates in general practice for cystitis and other urinary infections were found to be of approximately 315 per 10,000 persons.[2]

Recurrent UTIs are frequently defined as >2 episodes in the last six months or >3 episodes in the last 12 months. In a primary care setting, 53% of women above the age of 55 years and 36% of younger women report a recurrence within one year.[3]

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There are currently no NICE guidelines in the UK for UTIs in adults, however there are developments in guidance for this underway due at some point in 2015. There are other guidelines and publications regarding recurrent UTIs in women from other countries or urological/gynaecological associations which are helpful.[4,5,6]

Increasing antimicrobial resistance has stimulated interest in non-antibiotic prophylaxis for recurrent UTIs. This paper is a review for assessment for recurrent UTIs and treatment strategies with antimicrobial and non-antimicrobial intervention which will help guide practice.

Diagnosis of UTI

The diagnosis of symptomatic UTI is made when a patient has both clinical features and laboratory evidence of a urinary infection.

BOX 1: PATIENTS PRESENTING WITH ANY 2 OF THE FOLLOWING MEET THE CLINICAL DIAGNOSTIC CRITERIA FOR SYMPTOMATIC UTI:

- Fever
- Worsened urinary urgency or frequency
- Acute dysuria
- Suprapubic tenderness
- Flank/renal angle pain or tenderness

Women who have one of the symptoms of UTI listed in Box 1 have a 50% likelihood of having and infection. If they have a combination of symptoms, e.g. frequency and dysuria, this increases the likelihood to >90%.

The presence of vaginal discharge decreases likelihood of UTI to 20%.[7]

Urine dipstick

Urine dipstick is recommended in young healthy women under the age of 65 years with mild symptoms, or two or less of the symptoms listed in Box 1 to help aid diagnosis.[4]

Positive nitrite +leucocyte +/blood - positive predictive value 92% (in women with uncomplicated UTI).[8]

Nitrites are a surrogate marker for bacteriuria. Presence indicates bacterial reduction of dietary nitrates to nitrites by some gram negative uropathogens such as *E. coli* and Proteus. For nitrites to be present, urine should have been in the bladder for at least one hour to allow conversion of nitrate to nitrite; i.e. first void of the day is best. Also adequate dietary nitrates are necessary.

It generally requires more than 10,000 bacteria per ml to turn the dipstick positive, making it a specific but not a very sensitive test.

It is important to remember that some organisms, such as enterococci and staphylococci, do not reduce nitrate to nitrite and therefore will not be detected and could produce a false negative. Also if there are low colony counts, there may be false negative results.

In most patient populations, treatment of asymptomatic bacteriuria is not clinically beneficial, and consequently, screening for it is not recommended

Urine culture

A urine culture is used to identify the bacteria or funghi that may be causing the UTI. Urine in the bladder is usually sterile but if bacteria enter the urethra they can cause infection. A culture can be helpful if the diagnosis is in question or the UTI is recurrent.

Normally the presence of a single type of bacteria growing at high colony counts is considered a positive urine culture. With a well collected clean catch, mid-stream urine, the diagnostic feature is the presence of $>10^5$ colony forming units CFU/ml of bacteria.

In some cases there may not be a significantly high number of bacteria even though an infection is present. Sometimes, lower numbers (1,000 up to 100,000CFU/mL) may indicate infection, especially if symptoms are present. Also, in samples collected with a catheter, results of 1,000 to 100,000CFU/mL may be considered significant if in the context of symptoms.

Asymptomatic bacteriuria

Asymptomatic bacteriuria is isolation of 105CFU/ml bacteria in an appropriately collected urine specimen obtained from a person without symptoms or signs referable to urinary infection on 2 consecutive voids.

For the diagnosis of asymptomatic bacteriuria in a catheterised urine specimen, the laboratory criterion is a single bacterial species isolated in a quantitative count of at least 100CFU/mL.

There is a similar prevalence of asymptomatic bacteriuria among pregnant women and healthy premenopausal women (5-9%) but this rises in post menopausal women (20-25%) and is very high in elderly women (up to 50%) in long-term care facilities.[9]

In most patient populations, treatment of asymptomatic bacteriuria is not clinically beneficial, and, consequently, screening for it is not recommended.

The consensus is that antibiotic prescription is not indicated in elderly asymptomatic bacteriuria patients, in healthy young women, in diabetic women, and in patients who have indwelling catheters or undergo intermittent urinary catheterization.

Pregnant women should be screened for bacteriuria by urine culture at least once in early pregnancy because there is a 20-30 fold increased risk of developing pyelonephritis during pregnancy compared with women without bacteriuria.[10]

As a result the best course of action may be as follows:

- Do not send urine for culture in elderly asymptomatic women with positive dipsticks
- Only send catheter specimen urine for culture if there are features of systemic infection
- Pregnant women should be screened for asymptomatic bacteriuria at least once due to risk of pyelonephritis being increased.

Recurrent UTIs

Recurrent UTIs are symptomatic UTIs that follow resolution of an earlier episode, usually after appropriate treatment.[11]

They can occur secondary to:

- **Persistance/relapse** – i.e. same organism not eradicated following adequate sensitivity adjusted therapy. This occurs from persistent colonisation by the same organism of the vagina, periurethral area, or rectum, and each recurrent episode is caused by repeated "reinfection" of the urinary tract by ascendance of the same bacterium.
  Most relapsing infections occur within two to four weeks after short-course therapy with antibiotics has been completed. For a subgroup of women, the cause of repeated relapses is the presence of unrecognised clinical pyelonephritis. Because many patients who develop recurrent infection have "silent" pyelonephritis, antibiotic treatment should be directed toward curing the kidney infection, i.e. a longer course (14 days) of antibiotics.
- **Reinfection** – i.e. with a different organism or a recurrence of the same organism following a negative urine culture. If the organism is the same one, then the main feature differentiating reinfection from relapse is that individual episodes are usually separated by a symptom-free interval of at least a month after antibiotics are stopped and the urine has shown no bacterial growth.
  Recurrent UTIs are common among women with normal anatomical and physiological urinary tracts.

Risk factors for recurrent UTIs

There are risk factors for recurrent urinary tract infections in younger women (see Box 2).[12]

There are also groups of women who have underlying medical conditions which put them them at increased risk of UTIs. These are considered 'complicated' UTIs as the underlying anatomy or physiology is not considered 'normal' (see Box 3).

Assessment of a woman with recurrent symptomatic UTI

Women who have >2 infections within six months or >3 episodes within the last year meet the definition of recurrent UTIs. In these circumstances management and prevention of UTI is significant. Fortunately, most recurrent UTIs in young women are uncomplicated infections caused by different organisms. These infections are not usually associated with underlying anatomical or physiological issues and therefore do not need a work up of the urinary tract. Suspected complicated UTIs often need further work up to find the underlying issues and help plan management and prevention strategies.

History

- Document symptoms which patients say are their 'UTI' symptoms (in elderly patients, confusion may be the only presenting feature with recurrent UTIs)
- Look at previous responses to treatment
- Check culture positive events – is there recurrence or relapse (consider 'silent' pyelonephritis)
- If cultures show proteus spp. consider the presence of stones
- Look for red flags or indications which may warrant further investigations (see Box 4).

Pregnant women should be screened for asymptomatic bacteriuria at least once due to risk of pyelonephritis being increased

Examination

- General observations - pulse, BP, temp
- Abdominal and flank examination (palpable bladder and renal palpation/tenderness)
- Pelvic examination including external genitalia +/- vaginal examination if necessary, e.g. suspected prolapse or atrophic vaginitis (in older postmenopausal women)
- Neurological examination if appropriate (if associated limb weakness).

BOX 2: RISK FACTORS FOR RECURRENT UTIS IN YOUNG WOMEN

- Sexual intercourse (the more frequent the more likely)
- New sexual partner in the past year
- Age at first UTI<15
- Any spermicide use in the past year (the pathogenesis of this is not completely understood but it is postulated that spermicides reduce normal 'good' vaginal flora allowing increased susceptibility to pathogens during intercourse)
- Maternal history of UTIs (postulating genetic factors in recurrent UTIs)

BOX 3: RISK FACTORS FOR COMPLICATED UTIS

- Diabetes Mellitus
- Neurological conditions, e.g. multiple sclerosis, Parkinson's disease
- Spinal cord injuries (neurogenic bladder)
- Indwelling catheters or intermittent self-catheterisation
- Urinary incontinence/faecal incontinence
- Cystocele (prolapse)
- Increased post void residual (any cause)
- Chronic renal insufficiency
- Renal stones
- Renal transplant
- Polycystic kidney disease
- Ureteral/urethral stricture

BOX 4: RED FLAG SYMPTOMS

- Persistent haematuria
- Faeces in urine (faecaluria)
- Air in urine (Pneumaturia)
- Repeated pyelonephritis
- Prior abdominal/pelvic malignancy
- Previous bladder or renal calculi
- Prior urinary tract surgery or trauma
- Obstructive urinary symptoms (such as hesitancy, straining, poor stream)
- Immunocompromised patients

Laboratory

- Urine dipstick
- Urine culture
- Consider renal function tests if suspected acute pyelonephritis or chronic pyelonephritis
- Glucose test (in recurrent infections to diagnose diabetes).

Imaging

Routine imaging for younger women with recurrent UTIs is not necessary. If there is clinical suspicion with recurrent infections of structural or functional

abnormalities then ultrasound may be warranted. This may be the case in older women.

If there is ongoing haematuria after infection has been eradicated a more complete urological evaluation should be conducted in secondary care with ultrasound scan and, if necessary, a cystoscopy.

Management strategies

Conservative measures

- Encourage better hydration to ensure more frequent urination
- Encourage post-coital voiding (poor evidence of efficacy but does no harm)
- Advise sexually active women that diaphragm and spermicide use are risk factors for cystitis and discuss alternative contraception.

Some patients may not wish to take longer-term antibiotics and are very good at recognising their UTI symptoms

Non antimicrobial prevention

Cranberry products: Cranberry juice has been used to prevent UTIs for many years. There is some laboratory evidence that cranberry juice prevents adherence of uropathogens to uroepithelial cells.[13]

The evidence for cranberries preventing recurrent UTIs is not so clear and a relatively recent Cochrane review showed no conferred benefit.[14] Another meta-analyses showed a benefit with a halving of events.[15] Unfortunately, the evidence base is not really present as none of the trials conducted are robust enough and therefore cranberry containing products cannot be recommended but women are at liberty to try them.

Methenamine Hippurate: These salts are hydrolysed to formaldehyde and ammonia in acidified urine and thus have antibacterial activity. A small number of studies have been conducted in healthy pre- and post-menopausal women and there is weak evidence that they may be effective at reducing recurrences at 12 months.[16] In addition, a Cochrane review on methenamine showed it effective in preventing recurrent UTIs with short-term use in women with no urinary tract abnormalities or neuropathic bladder.[17] Side effects of methenamine are uncommon but can include nausea, vomiting and diarrhoea. Rarely, it can cause lower back pain and haematuria. In the case of the rarer side effects a doctor should be contacted.

Topical Oestrogen Therapy (in post-menopausal women): Topical oestrogen normalises the vaginal flora and reduces the risk of UTI in post-menopausal women.[18,19] Advised usage based on these studies suggests use of vaginal oestriol cream every night for two weeks and then twice a week for several months.

D Mannose: This is a sugar which is thought to work by inhibiting bacteria from adhering to urothelial cells. In a randomised controlled trial in women >18 years with acute UTI and a history of recurrent UTIs, three groups received either D Mannose daily for six months, nitrofurantoin prophylaxis for six months or nothing. The group receiving nothing had a higher rate of recurrence (60%) vs D-mannose (15%) vs nitrofurantoin (20%).[20] Further clinical trials are needed to provide further evidence of effectiveness.

Vaccines: Urovac is a vaginal suppository vaccine. It is made from 10 uropathogenic strains of bacteria including six *E. coli* strains, and *Proteus, Mirabilis, Morganella Moraganii, K. Pneumoniae* and *Enterococcus faecalis*. So far, in a trial with 91 women, primary immunisation comprising three vaginal vaccine suppositories at weekly intervals was compared with placebo. There was no significant difference in the proportion of women with at least one UTI and the mean number of UTIs in 20 weeks of follow up. In further studies, there was a trial of additional booster vaccines, i.e. three additional vaccine suppositories at monthly intervals. In these studies, results were more promising with the time until reinfection, the proportion of women experiencing UTI and the mean number of UTIs all in favour of booster immunisation versus placebo or primary vaccination only.[21,22,23]

Antibiotic prophylaxis

This has been shown to be highly effective in reducing the risk of recurrent UTIs in women.

Continuous: Studies have shown that continuous prophylaxis decreases recurrence of UTI in pre- and post-menopausal women when compared with placebo.[24] Public Health England has recommended low dose prophylaxis with either Trimethoprim 100mg or Nitrofurantoin 50-100mg nightly for women with frequent symptomatic recurrent infections.[25]

There are no guidelines on how long prophylaxis should continue, although six months is considered a 'reasonable recommendation'. In addition there are no randomised controlled trials or meta-analyses to show any superiority of individual antibiotic classes.

NB: consider carefully the use of longer-term Nitrofurantoin as it can be hepato-toxic (therefore check LFTs regularly) and pulmonary toxic causing pneumonitis. It is also contraindicated in patients with renal failure GFR<45 in longer-term use and it can only be used with caution for short three to seven day courses with GFR >30 (https://www.gov.uk/drug-safety-update/nitrofurantoin)

Patient initiated therapy: Some patients may not wish to take longer-term antibiotics and are very good at recognising their UTI symptoms. In these cases, they can perform a urine dipstick and start their own three-day course of antibiotics. There are studies which show that UTI can be accurately diagnosed by women >85% of the time and that short course antibiotics are effective in cure.[26,27]

Post-coital prophylaxis: A Cochrane review found that post-coital prophylaxis was equally effective as low-dose continuous antibiotic prophylaxis in prevention of recurrent UTIs. This comprises single dose of antibiotics following sexual activity.[11]

Treatment of recurrent UTIs

Treatment of complicated UTIs should begin with broad-spectrum antibiotic coverage, with adjustment of antimicrobial coverage guided by culture results. There is usually local guidance on antibiotic choice.

There are no clear guidelines for referral of patients with recurrent or complicated UTIs. Most patients with recurrent uncomplicated UTIs can be treated in the community by GPs. Patients with complicated UTIs may require consultation from subspecialists in urology or renal medicine if further investigation is warranted.

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SUMMARY OF KEY POINTS

1. Recurrent UTIs are common
2. Recurrent UTIs are frequently defined as >2 episodes in the last six months or >3 episodes in the last 12 months
3. The most common uropathogen is *E. Coli*
4. Asymptomatic bacteriuria is common particularly in post-menopausal women and great care must be taken not to treat this condition inappropriately
5. Complicated UTIs occur when anatomy or physiology of the urogenital tract is not normal and under these circumstances further investigation may be required by specialists
6. Always consider red flags when considering the diagnosis of recurrent UTIs (see history)
7. Management strategies can involve antibiotic strategies and non-microbial strategies
8. It may be important to consider antibiotic resistance in future guidelines for recurrent urinary tract infections
9. There are a number of useful agents to consider in prophylaxis against recurrent urinary tract infections including D-mannose, methanamine hippurate and urovac

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