

Investigation and management of recurrent urinary tract infection

Key points

- Most patients with recurrent urinary tract infections (UTIs) are women who have no anatomical abnormalities of the urinary tract and will not have adverse renal outcomes; they do not require extensive or repeated investigation and their management focuses on preventing recurrences.
- All men and children who present with a UTI require investigation for a predisposing cause.
- All patients presenting with recurrent UTI should be screened for type 2 diabetes.
- Urine culture and sensitivity testing should be performed for all patients who do not respond to empirical antibiotic therapy.
- Pregnant women should be screened with a midstream urine test at the first antenatal visit.
- Asymptomatic bacteriuria generally does not require investigation or treatment, except in pregnant women and patients undergoing urinary tract instrumentation.

HOLLY HUTTON MB BS, FRACP; LIV AMOS MB BS, FRACP; PETER G. KERR MB BS, PhD, FRACP

Recurrent urinary tract infections are common in women; after investigations to exclude common predisposing causes and complications, the focus is on strategies to prevent recurrence. In children and men, there is a higher index of suspicion for an underlying cause and further investigation is usually needed.

Urinary tract infections (UTIs) are common, especially in women, and account for about 17 per 1000 GP consultations.¹ Approximately one-third of women who have an initial UTI will have a recurrence, mostly in the absence of any anatomical abnormality of the urinary tract. Recurrences are much less common in children and men and suggest the presence of a predisposing abnormality.

Recurrent UTI is defined as three or more infections within 12 months, or two or more infections within six months. Investigations for recurrent UTI aim to identify predisposing causes and prevent long-term complications. Selection of investigations is guided by history and examination findings and patient age and

sex. Most patients are able to be managed in general practice and do not require specialist referral.

AETIOLOGY

Uncomplicated UTIs are common in nonpregnant women with no abnormality of the urinary tract. In about 80% of cases of uncomplicated UTI, the causative organism is *Escherichia coli*, with other Gram-negative organisms comprising most of the remainder. Complicated UTI occurs in the setting of abnormal anatomy, urinary catheterisation or immunosuppression, such as in diabetes or after kidney transplantation. *E. coli* is isolated in up to 50% of cases; other Gram-negative bacteria such as *Enterococcus*, *Proteus* and *Klebsiella* spp. are more common in this group.²

Dr Hutton and Dr Amos are Nephrology Fellows at Monash University and Monash Health, Melbourne.

Professor Kerr is Director of Nephrology at Monash Health, and Professor in the Department of Medicine, Monash University, Melbourne, Vic.

1. RISK FACTORS FOR MULTIDRUG-RESISTANT UTI

- Recent hospitalisation
- Recent antibiotic use
- Residence in an aged care facility
- Age over 65 years
- Travel to high-risk regions in Asia, Africa or the Middle East
- Diabetes
- Recurrent UTI
- Long-term urinary catheterisation

ABBREVIATION: UTI = urinary tract infection.

Some organisms are associated with particular conditions, and their isolation should guide further investigations. For example, recurrent *Proteus* isolation is a hallmark of renal calculi. *Staphylococcus aureus* isolation in patients who have not had recent urinary tract instrumentation may indicate haematogenous bacterial spread and should prompt a blood culture.

Recurrent UTI may be due to either relapse or reinfection. Relapse is arbitrarily defined in clinical practice as detection of the same organism within two weeks of completing treatment for an initial UTI episode.³ It may be due to inadequate antibiotic therapy or a persistent focus of infection. Relapse should prompt further investigations to exclude anatomical abnormalities and confirm the antimicrobial sensitivities of the causative bacteria.

However, most recurrences are the result of reinfection, which usually occurs within three months of the initial episode. Reinfection is caused by the migration of pathogens from a vaginal or rectal reservoir into the urinary tract, or persistence within bladder epithelial cells. In contrast to relapse, reinfection may involve a different organism to that in the initial infection. However, as reinfection with the same organism is also common, it is often impossible to distinguish reinfection from relapse clinically. Reinfection should always prompt investigation of a midstream urine specimen.

TABLE 1. COMPARISON OF FEATURES OF UTI AND NONINFECTIVE URINARY TRACT CONDITIONS*

	UTI symptoms	Bacteriuria	Pyuria
Colonisation	–	+	–
Infection: asymptomatic	–	+	+
Infection: symptomatic	+	+	+
Inflammation with no infection	–	–	+
Symptoms with no infection	+	–	–

ABBREVIATION: UTI = urinary tract infection.

*Adapted from: Stamm WE. *Infection* 1992; 20 Suppl 3: S151-S154.⁴

ANTIBIOTIC RESISTANCE

There has been a worrying increase worldwide in UTIs caused by antibiotic-resistant organisms.^{2,5} These infections are associated with worse outcomes and are a treatment challenge in outpatient settings owing to organism resistance to commonly used oral antibiotics.

The production of β -lactamase is a common mechanism of resistance in Gram-negative bacteria, with each type of β -lactamase inactivating a distinct spectrum of antibiotics. In Australia, extended spectrum β -lactamase (ESBL)-producing organisms, which are resistant to third-generation cephalosporins, have been predominantly seen in hospital settings. However, a 2010 survey of common Gram-negative organisms isolated from patients with community-acquired UTIs found a concerning trend of increasing resistance to third-generation cephalosporins (ceftriaxone 3.2%), and ciprofloxacin (5.4%).⁵ Almost half (43%) of *E. coli* isolates were resistant to ampicillin and amoxicillin, which are no longer recommended as a first-line treatment for UTI by the Australian *Therapeutic Guidelines: Antibiotic*.² Rates of *E. coli* resistance to trimethoprim, amoxicillin–clavulanate and cefazolin were 21%, 21% and 15%, respectively.

As specimens in this survey came from hospital rather than community laboratories, these figures may overestimate true resistance rates in the community. Nevertheless,

the survey highlights that antibiotic resistance in the community is a significant problem. The prevalence is likely to have increased since the survey was conducted.

Risk factors for infection with multidrug-resistant organisms are listed in Box 1. Although the rate of ESBL-producing strains among *E. coli* strains in Australia is relatively low, rates higher than 25% have been recorded in Asian and Pacific countries. Hence, returned travellers from high-risk regions, notably India and South-East Asia, are at increased risk.⁶

Enterococcus spp. are Gram-positive cocci that form part of the normal gastrointestinal flora. They commonly colonise the urinary tract and urinary catheters; colonisation does not require therapy. Enterococci are responsible for only a minority of uncomplicated UTIs but may cause serious infection in hospitalised patients, particularly those with indwelling urinary catheters, and renal transplant recipients. Enterococci are increasingly developing resistance to β -lactams, aminoglycosides and glycopeptides such as vancomycin, which can limit treatment options.

HISTORY AND EXAMINATION

Typical symptoms of UTI include:

- dysuria
- urinary frequency or urgency
- fever
- suprapubic pain
- macroscopic haematuria (occasionally).

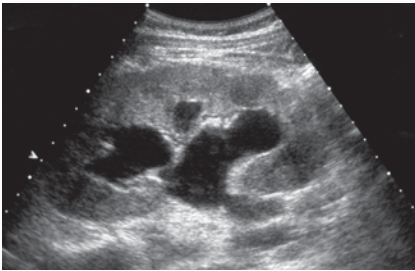


Figure. Renal ultrasound scan showing moderate hydronephrosis.

However, the presentation may be far more subtle, particularly in children, who may have nonspecific symptoms such as fever, irritability, poor feeding and vomiting.

History taking and examination may reveal patients who are unwell and therefore require further investigation, or have risk factors for complicated infection such as diabetes.

The physical examination for UTI should include at a minimum:

- measurement of blood pressure, pulse and temperature
- assessment of volume status (particularly important in children)
- abdominal examination for suprapubic and loin tenderness and a palpable bladder.

INVESTIGATIONS

Urine microscopy and culture

As a UTI can often be diagnosed based on symptoms and urinary dipstick findings, many guidelines do not recommend urine microscopy and culture for patients with an initial uncomplicated infection. However, urine microscopy and culture are imperative for patients with complicated UTI, those who do not respond to empirical antibiotic therapy and those with recurrent UTI. Furthermore, as urine culture increases diagnostic accuracy and allows more specific antimicrobial therapy, we believe that urine should be cultured in all patients with an uncomplicated UTI because of the increasing prevalence of antibiotic-resistant organisms. Empirical antibiotic therapy can be commenced while awaiting culture results.

2. CAUSES OF STERILE PYURIA

- Previous antibiotic treatment (most common)
- Contamination of specimen by vaginal leucocytes
- Interstitial nephritis (e.g. analgesic nephropathy)
- Renal stone disease
- Uroepithelial tumours
- Infection with atypical organisms (e.g. chlamydia, ureaplasma infection, tuberculosis)

The diagnosis of UTI centres on the isolation of bacteria from a midstream urine specimen. A threshold concentration of 10^8 colony forming units (cfu)/L is commonly used for diagnosis in research settings. However, a significant proportion of patients with UTI symptoms and pyuria (white cell count over 10×10^6 /L) have lower levels of bacteriuria but will still benefit from antimicrobial treatment. A lower threshold of 10^6 cfu/L has greater sensitivity and acceptable specificity for diagnosis of UTI.⁴ The finding of pyuria supports the diagnosis of UTI but does not always signal infection; other causes of pyuria are shown in Box 2.

In the presence of UTI symptoms, bacteriuria and pyuria are strongly suggestive of the diagnosis of UTI. In practice, all three of these parameters should be considered for a diagnosis of UTI (Table 1).⁴

Other investigations

Other minimum investigations for adults with recurrent UTI include:

- serum urea, electrolytes and creatinine (UEC) measurement to assess renal function
- blood sugar measurement to screen for diabetes
- a renal tract ultrasound examination to identify any structural abnormality (Figure).

Further investigations should be guided by history and examination findings and

3. ANTIBIOTICS FOR EMPIRICAL TREATMENT OF UTI*

Nonpregnant women with acute uncomplicated UTI: trimethoprim, cephalexin, amoxicillin–clavulanate, nitrofurantoin or, if resistant to these and susceptibility proven, norfloxacin

Pregnant women: cephalexin, nitrofurantoin, amoxicillin–clavulanate (consider pregnancy risk categories)

Men: trimethoprim, cephalexin, amoxicillin–clavulanate

Children: for mild UTI, amoxicillin–clavulanate, cephalexin, trimethoprim or trimethoprim–sulfamethoxazole

Prophylaxis: trimethoprim (150 mg) or cephalexin (250 mg) orally at night, continue for three to six months

*Adapted from Antibiotic Expert Group. Therapeutic guidelines: antibiotic; 2010.²

patient demographic characteristics, as discussed for specific patient groups below.

Careful consideration must be given to situations where delayed diagnosis may worsen the outcome, as follows.

- Patients with risk factors for sexually transmitted infections (STIs) should be screened with nucleic acid amplification tests for chlamydia and gonococcus. Patients with dysuria and negative urine cultures should also have the possibility of an STI considered.
- Patients with persistent haematuria following resolution of infection should always be investigated, as this may be the only indicator of a urological abnormality (e.g. carcinoma or calculi) or glomerulonephritis.
- Patients with deteriorating renal function require urgent referral to a renal specialist. Rapidly declining renal function with pyuria and haematuria, especially without documented growth of organisms on culture, may indicate rapidly progressive glomerulonephritis.

4. RISK FACTORS FOR RECURRENT UTI IN WOMEN²

Younger women

- Frequent sexual intercourse
- Age <15 years at first UTI
- Mother with history of UTIs
- Spermicide use

Older women

- Postmenopausal status
- Urinary incontinence
- Cystocele
- Postvoid residual urine

ABBREVIATION: UTI = urinary tract infection.

TREATMENT

Antibiotic selection for the treatment of UTI in different patient groups is outlined in Box 3.² Recurrent UTI is most commonly caused by the same organisms that cause sporadic infection, and empirical therapy is the same as for initial infections. Empirical therapy can be modified if necessary when culture results become available.

INVESTIGATION AND MANAGEMENT IN SPECIFIC GROUPS

Nonpregnant women

Most women with recurrent UTI have an anatomically normal urinary tract. Although these infections can cause significant morbidity, they are not associated with adverse renal outcomes such as renal impairment or hypertension in these women. Risk factors for recurrent UTI are predominantly behavioural in premenopausal women and urological in those who are postmenopausal (Box 4).

Not all dysuria is caused by a UTI. Both nonspecific urethritis and vaginitis frequently cause dysuria. If symptoms such as pelvic pain or vaginal discharge are present then a pelvic examination and swabs are appropriate.

Recurrent UTI should be investigated with microscopy and culture of a mid-stream urine specimen to confirm the diagnosis and help guide antibiotic choice. Other minimum investigations include measurement of UEC and blood sugar levels

and renal tract ultrasound examination. If results of these investigations are normal then extensive or repeated investigation is not required and the focus can shift to management strategies.

Prophylaxis for recurrent UTI

Behavioural and pharmacological measures can be used to reduce recurrences of UTI in women.

Behavioural strategies

Many women find double voiding or voiding after sexual intercourse useful, although there is no trial evidence to support this. Maintaining a reasonable fluid intake to increase urinary frequency is helpful in those with a low urine volume.

Antibiotic strategies

Use of antibiotic prophylaxis should be guided by the severity and frequency of episodes, the patient's ability to detect symptoms early and patient preference. Several strategies can be used:

- continuous prophylaxis taken at night, usually prescribed for three to six months. If further recurrences occur after cessation of antibiotics, consideration should be given to a longer course or even lifelong therapy in some cases. Typical regimens include:
 - cephalexin 250 mg (for children, 12.5 mg/kg; maximum 250 mg daily)
 - trimethoprim, 150 mg (for children, 4 mg/kg; maximum 150 mg daily)
 - nitrofurantoin, 50 mg (for children aged over 3 months, 1 mg/kg, maximum 50 mg daily); to be avoided in patients with a glomerular filtration rate less than 60 mL/min
- postcoital antibiotics – usually a single dose taken within two hours of intercourse (e.g. trimethoprim 150 mg, nitrofurantoin 50 mg, cephalexin 250mg, ciprofloxacin 125mg, norfloxacin 200 mg)
- intermittent patient-initiated treatment – a three-day course commenced at

the onset of symptoms (as per empirical treatment recommendations, guided by the sensitivities of previously cultured organisms).

In cases where sexual intercourse is a clear precipitant, postcoital and continuous prophylaxis have equal effectiveness, according to a 2004 Cochrane review.⁷ This showed that continuous prophylaxis is effective at reducing UTI recurrence but only while being taken, and has potential side effects.⁷ Further, much of the evidence for antibiotic prophylaxis is over a decade old, and it is not known whether this strategy has similar efficacy with the increase in antimicrobial resistance. The potential to increase rates of antibiotic-resistant organisms is also a consideration.

Cranberry products

Products derived from cranberry (*Vaccinium macrocarpon*) contain proanthocyanidins, which have been shown in laboratory studies to interfere with the adhesion of fimbriated *E. coli* organisms to uroepithelial cells. Despite this plausible mechanism of action, there is a lack of clinical data to clearly demonstrate the efficacy of cranberry products in reducing UTIs.

Two recent meta-analyses came to conflicting conclusions and were limited by low power, high dropout rates and variability in cranberry products used in the included trials.^{8,9} A 2008 Cochrane review showed that cranberry products significantly reduced the risk of recurrent UTI at 12 months. However, the updated Cochrane review, which included an additional 14 studies, found there was no benefit in reducing symptomatic UTI overall (relative risk [RR] 0.86, 95% CI 0.71 to 1.04) or in the subgroup of women with recurrent UTI (RR 0.74, 95% CI 0.42 to 1.31).⁸ A meta-analysis of 1175 patients in nine randomised controlled trials showed a benefit of cranberry products in decreasing the risk of UTI (RR 0.62, 95% CI 0.49 to 0.80). However, this result was obtained after excluding a negative study of 319 patients, the inclusion of

which would influence the overall analysis to show only a nonsignificant trend (RR 0.68, 95% CI 0.47 to 1.00).⁹

The optimal dose and form of cranberry products for UTI prevention are also unknown. The usual recommendation for juice consumption has been 300 mL per day. The Cochrane review noted high dropout rates and lack of compliance with juice consumption.⁸ Use of capsules and tablets may overcome compliance issues, but these products have the disadvantage of not being standardised for content of proanthocyanidins, the postulated active ingredients.

Topical oestrogen replacement

In postmenopausal women, topical intravaginal oestriol therapy over eight months significantly reduces the incidence of recurrent UTI (0.5 vs 5.9 episodes per patient-year).¹⁰ Some women find this preferable to antibiotic therapy. It may also have a role when resistance patterns make prophylaxis difficult.

Probiotics

Certain *Lactobacillus* strains have been shown to interfere with the colonisation and adherence of pathogenic bacteria to the urogenital epithelium. A randomised controlled trial in postmenopausal women with recurrent UTIs showed that 12 months of prophylaxis with oral lactobacilli was inferior to trimethoprim–sulfamethoxazole treatment in terms of time to UTI recurrence.¹¹ However, there was a relatively higher rate of discontinuation of therapy in the lactobacillus group because of adverse effects (12.2% vs 5.2%). A 10-week course of intravaginal capsules containing *Lactobacillus crispatus* was compared with placebo in premenopausal women with a history of recurrent UTI. After 10 weeks of follow up, there was a trend towards decreased rates of UTI in the lactobacillus group (15% vs 27%, RR 0.5, 95% CI 0.2 to 1.2).¹² A potential advantage of using probiotics over antibiotics is a reduced likelihood of generating resistant organisms. However, more evidence is required before probiotic therapy can be recommended in routine practice.

Antiseptic agents

Hexamine hippurate is hydrolysed in acidic urine to formaldehyde, which has antiseptic properties. Antibacterial effects are maximal when urine pH is less than 5.5. Hippurate is not effective in alkaline urine, which occurs commonly in infections caused by urea-splitting organisms. Evidence suggests hippurate is efficacious as short-term (one week or less) prophylaxis in women undergoing gynaecological procedures. However, as this group is not at high risk for UTI, there is no clear indication for prophylaxis in this setting. Hippurate is not effective in preventing UTI in patients with renal tract abnormalities or neuropathic bladder.¹³ Further studies are needed to evaluate the potential role of hippurate for long-term UTI prophylaxis in the current era of increasing antibiotic resistance.

Urinary alkalinisers

Urinary alkalinisers may relieve UTI symptoms. However, they do not have a role in prophylaxis.

Pregnant women

Around 2 to 7% of women are diagnosed with asymptomatic bacteriuria during pregnancy. Without treatment, up to 40% of these women will develop cystitis or pyelonephritis. Therefore, screening of a midstream urine specimen with microscopy and culture is recommended for all pregnant women at the first antenatal visit. Treatment of asymptomatic bacteriuria is recommended. This has been shown to decrease the risk of pyelonephritis and reduce the incidence of low birth weight.

If a symptomatic UTI develops, urine should be cultured. Treatment is commenced empirically and continued for five days.⁴ Patients with pyelonephritis in pregnancy should have a renal tract ultrasound examination and initially be managed in hospital with intravenous antibiotics. A repeat urine culture to ensure clearance is essential.

Children

UTIs are common in children, affecting 2% of boys and 8% of girls by the age of 7 years.

5. DIAGNOSING UTI IN CHILDREN

Children who can void on request

- Collect a midstream urine specimen for urine microscopy and culture

Children who cannot void on request

- Collect a bagged specimen of urine and perform a dipstick test for leucocytes and nitrites. A negative dipstick result does not exclude UTI.
- If the dipstick result is positive or there is clinical suspicion of UTI despite a negative result then a definitive urine specimen should be obtained, preferably by suprapubic aspirate, for urine microscopy and culture.
- If a suprapubic aspirate cannot be obtained then a catheter specimen of urine should be collected, discarding the first few millilitres.

ABBREVIATION: UTI = urinary tract infection.

They can be associated with long-term morbidity.¹⁴ UTIs cannot be diagnosed on symptoms alone, and features are often nonspecific, such as fever, irritability, poor feeding and vomiting.

Investigation and management

A clean-catch urine specimen is required for diagnosis. Empirical treatment should be commenced as per antibiotic guidelines and adjusted when antibiotic sensitivities are available. Although prophylactic antibiotics do slightly reduce the incidence of further UTIs, prophylaxis is no longer routinely recommended in children and should be discussed with a nephrology or urology unit.

Investigating children with recurrent UTI is aimed at identifying anatomical abnormalities, including vesicoureteric reflux (VUR). VUR is thought to cause renal scarring as a result of recurrent episodes of pyelonephritis. However, VUR also signifies abnormal renal development, which itself predisposes to adverse renal outcomes.

Methods of obtaining a urine specimen for culture in children are outlined in Box 5. In addition to urine culture, the Melbourne Royal Children's Hospital clinical practice guidelines recommend a renal tract ultrasound examination, especially in children under the age of 4 years.¹⁵ Further imaging modalities may be considered as per the UK National Institute for Health and Care Excellence (NICE) guidelines and include a micturating cystourethrogram and a renal radionuclide (DMSA) scan to identify any renal scarring.¹⁶

Management of VUR

The management of VUR is limited by the lack of data comparing an observational approach versus medical or surgical therapy, particularly in children with low grade (I or II) disease, about 80% of whom will have a spontaneous remission. However, treatment is recommended for children with VUR grade III or higher. In most cases, patients treated with medical therapy (prophylaxis plus management of dysfunctional voiding) have similar outcomes to those managed surgically. Ongoing annual surveillance in these children is advised, comprising measurements of height, weight and blood pressure, and urine dipstick testing for proteinuria.

Men

Simple UTI is uncommon in men and require further investigation. An ultrasound examination to assess prostate size and pre- and post-residual volumes is warranted. Loin pain or a positive family history suggests renal calculi, warranting a CT urogram. A history of urethral trauma or instrumentation may suggest urethral stricture and require urological consultation.

A sexual history should be taken, and investigations for STIs performed if appropriate. Digital rectal examination may reveal acute prostatitis or prostatic hypertrophy. Avoid prostatic massage in the setting of acute infection because of the risk of septicaemia. For UTI or acute prostatitis, antibiotics should be prescribed for two weeks.²

Recurrent UTI in men often indicates chronic prostatitis, which is difficult to diagnose (the gland may be normal on examination, and prostate-specific antigen is elevated in only 25% of cases) and also to treat, because few antibiotics penetrate the noninflamed prostate. Prostatic massage to obtain expressed prostatic secretions may help confirm the diagnosis and guide antibiotic choice. Antibiotics with good prostatic penetration, such as fluoroquinolones, should be used and treatment continued for four weeks.²

Renal transplant recipients

Over 9300 Australians are living with functioning renal transplants, often at some distance from their treating transplantation unit. All renal transplant recipients presenting with dysuria should be investigated with, at a minimum, a urine culture and measurement of UEC levels. Empirical antibiotic treatment should be given until culture results are available. If the patient has a past history of UTI caused by antibiotic-resistant organisms then early liaison with the transplanting unit is imperative. Patients should be advised to return to their healthcare provider in the event of deterioration, or if significant improvement has not occurred within 48 hours.

Immunosuppressed patients can become critically ill very quickly. Prompt admission is required for intravenous antibiotics (avoiding aminoglycosides) and monitoring of urine output. This should occur in consultation with the treating transplantation unit.

Patients with asymptomatic bacteriuria

Asymptomatic bacteriuria is a common finding. Further investigation is not usually required, especially if there is no significant pyuria. Treatment with antibiotics in the absence of clinical infection has not been shown to reduce the incidence of UTIs and merely promotes antibiotic resistance. Bacteriuria recurs in 50% of patients by one year after treatment.¹⁷ In addition, asymptomatic bacteriuria is not associated with long-term adverse outcomes such as chronic kidney

disease or mortality.¹⁸ However, patients who are pregnant or about to undergo urinary tract instrumentation or surgery are exceptions and should be treated as for a UTI.

CONCLUSION

Recurrent UTIs are common and should be investigated at a minimum with microscopy and culture of a midstream urine specimen, measurement of serum urea, electrolytes and creatinine and blood sugar levels and renal tract ultrasound examination. Further investigation and management should be guided by history and examination findings and patient demographic characteristics. MT

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A list of references is included in the website version (www.medicinetoday.com.au) and the iPad app version of this article.

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HOLLY HUTTON MB BS, FRACP; **LIV AMOS** MB BS, FRACP; **PETER G. KERR** MB BS, PhD, FRACP

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