How to investigate recurrent urinary tract infections

In this series, we present authoritative advice on the investigation of a common clinical problem, specially commissioned for family doctors by the Board of Continuing Medical Education of the Royal Australasian College of Physicians.

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Urinary tract infections (UTIs) are common and account for about 17 per 1000 GP consultations.[1] Recurrences are frequent: 27% of college students with a first UTI will have at least one recurrence in the subsequent six months.[2] Similar organisms cause recurrent urinary tract infections (RUTIs) as cause sporadic cases of infection. Up to 80% of infections are caused by *Escherichia coli*, with most of the remainder caused by other Gram-negative organisms. Most RUTIs are ably managed by GPs in an outpatient setting.

The investigation of RUTIs is aimed at identifying and reversing predisposing factors and avoiding complications. This includes a midstream urine culture, measurement of urea, electrolytes, creatinine and blood glucose levels and a renal tract ultrasound. Additional investigations are considered when history or examination suggest an underlying cause and in high-risk demographics, such as in children and men.

Diagnosis of UTI and RUTI

Typical symptoms and signs of UTIs are described in Table 1. A UTI is diagnosed by a count of more than 10^5 colony-forming units (CFU)/mL in the presence of significant pyuria (more than 10^5 white blood cells [WBC]/mL) in a midstream urine specimen. However, in women with symptoms of cystitis and pyuria, counts of 10^3 CFU/mL or higher indicate UTI. Consequently, laboratories may proceed to identify a potential uropathogen and provide an antibiotic susceptibility result when the colony count is 10^3 CFU/mL or greater.

RUTI is defined as three or more such infections within 12 months, or two or more infections within six months. Most recurrences are due to reinfection

IN SUMMARY

- **Most patients with recurrent urinary tract infections (RUTIs) will be adult women with anatomically normal urinary tracts who have no adverse renal outcomes and do not require extensive or repeated investigation.**
- **An underlying cause for RUTIs is more likely in men and children, and additional investigation is therefore required in these patients.**
- **All patients presenting with RUTIs should be screened for type 2 diabetes.**
- **Asymptomatic bacteriuria does not require investigation or treatment unless the patient is pregnant or undergoing urinary tract instrumentation or surgery.**
- **Management involves behavioural strategies, reversal of underlying causes where possible, and judicious use of antibiotic strategies.**

Table 1. Symptoms and signs of UTIs

History

Dysuria
Urinary frequency
Urgency
Fever/rigors
Suprapubic/loin pain
Macroscopic haematuria
Nonspecifically unwell

Examination

Blood pressure
Pulse
Temperature
Volume state
Suprapubic/loin tenderness
Palpable bladder

Also consider

Rectal exam, digital – enlarged or tender prostate
Pelvic examination – vaginitis

rather than relapse (in which the infection recurs within two weeks of treatment of the initial infection). Relapse most commonly reflects inadequate initial treatment or drug resistance, but may signal an underlying urinary tract abnormality.

Differential diagnoses

The situations described below are not typical of RUTIs and may indicate severe alternate pathology.

- A patient with pyuria and haematuria who has rapidly deteriorating renal function may have a rapidly progressive glomerulonephritis or vasculitis (especially when there is no documented growth of organisms) – an urgent renal consultation is required.
- Persistent haematuria following resolution of infections may be the only indicator of either urological abnormality (carcinoma or calculi) or glomerulonephritis. This should always be investigated with phase-contrast microscopy to determine glomerular versus non-glomerular origin of bleeding, urine cytology (usually performed on three separate early morning midstream specimens) and renal tract ultrasound. (A renal biopsy with or without cystoscopy may also be required, the latter particularly in older patients.)
- Dysuria with negative urine cultures may suggest a sexually transmitted infection or vaginitis (when dysuria is accompanied by symptoms of dyspareunia, vaginal discharge, odour or itch) – a pelvic examination and swabs are indicated.
- Sterile pyuria may signal interstitial nephritis, renal stone disease, uroepithelial tumours or infection by atypical organisms (e.g. *Chlamydia trachomatis, Ureaplasma* and *Mycobacterium tuberculosis*); however, prior antibiotic treatment and contamination of the urine specimen by vaginal leucocytes are more common causes. A midstream urine specimen should be collected (with meticulous attention to avoiding contamination) when the patient is not taking antibiotics; if sterile pyuria persists, further investigation for the above causes is indicated.

Asymptomatic bacteriuria

Asymptomatic bacteriuria is diagnosed in women by a count of at least 10^5 CFU/mL in two consecutive midstream urine specimens in the absence of infective symptoms. In men, a single positive specimen suffices.

Asymptomatic bacteriuria is a common finding, particularly in patients with indwelling catheters. Prevalence of this condition increases with age. It is found in 20% of women over 80 years of age living independently, and in a higher percentage of those in residential care. Further investigation is not required, especially if there is no significant pyuria. Treatment of asymptomatic bacteriuria with antibiotics can lead to resistance and has not been shown to reduce the incidence of urinary tract infections.

However, patients with asymptomatic bacteriuria who are about to undergo urinary tract instrumentation or surgery or who are pregnant (40% of whom will develop cystitis or pyelonephritis if untreated) should be treated as for a UTI. In the former group, treatment reduces the incidence of bacteriuria and septicaemia postoperatively; in pregnant women, it reduces the incidence of pyelonephritis and is associated with a reduction in the number of low birthweight infants.

Table 2. Risk factors for RUTI

Female sex
Frequent sexual intercourse
Postmenopausal state (low oestrogen level)
Abnormal urinary tract – e.g. urethral stricture, neurogenic bladder, obstruction (all leading to urine stasis) and vesicoureteric reflux
Foreign bodies – e.g. indwelling urinary catheter, ureteric stent, nephrostomy
Infective nidus – e.g. prostatitis, calculi, polycystic kidney disease
Incontinence (urinary and faecal)
Immunosuppression
Long-term indwelling catheters
Type 2 diabetes

Risk factors for RUTI

The shorter length of the female urethra and its closer proximity to the anus make women more susceptible to RUTI. In premenopausal women, frequent sexual intercourse is the strongest predictor of recurrence. Age under 15 years at first UTI, having a mother with a history of UTIs and use of spermicidal contraception are also risk factors. In postmenopausal

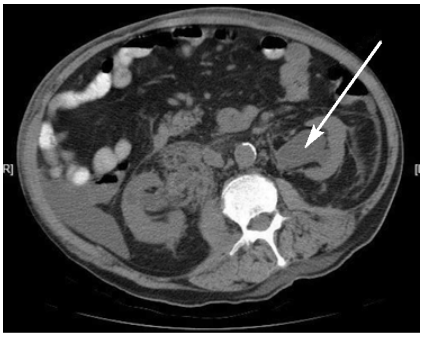


Figure 1. Non-contrast axial CT image demonstrating irregular soft tissue stranding with a small amount of fluid surrounding the dilated left renal pelvis in keeping with a developing perinephric collection (arrow).

(IMAGE COURTESY OF DR KEN LAU, DEPARTMENT OF RADIOLOGY, MONASH MEDICAL CENTRE, MELBOURNE.)

women, low oestrogen production leads to atrophy of the urethral epithelium and alterations in vaginal flora, with reduced lactobacilli and increased prevalence of uropathogens. Other risk factors in this demographic include urinary incontinence, urinary retention and bladder prolapse (Table 2).

Urinary tract abnormalities such as obstruction, urethral stricture, neurogenic bladder, vesicoureteric reflux and vesicocolic fistula also predispose to RUTIs. Obstruction, urethral stricture and neurogenic bladder all cause urine stasis, and vesicocolic fistula may lead to direct faecal contamination of the urinary tract. Renal tract (including prostatic) calculi may create a nidus for recurrent infection, as can cysts in polycystic kidney disease and foreign bodies such as urinary catheters, nephrostomies or ureteric stents.

In addition to long-term urinary catheters, chronic constipation and incontinence are potentially modifiable risk factors for RUTI in patients in residential care facilities. Patients with type 2 diabetes, particularly those requiring insulin and having disease of long duration, have an increased likelihood of complicated bacterial infection (such as pyelonephritis or renal abscess) and fungal infection (Figure 1). All patients with RUTIs should be screened, as about 50% of patients with this condition are undiagnosed. Immunosuppression also predisposes to RUTIs.

Basic investigations

RUTIs should be investigated with a midstream urine culture to confirm diagnosis and guide antibiotic choice. The diagnosing of UTIs in children is summarised in Table 3, including the collection of urine specimens. Other minimum investigations include measurement of urea, electrolytes and creatinine levels to assess renal function, measurement of blood glucose level to test for diabetes, and a renal tract ultrasound to confirm structural normality (Table 4). Additional investigations are undertaken when an underlying cause is suspected after taking a history or carrying out an examination, or in demographics at high risk of an underlying cause such as in children and men.

RUTIs are a common complaint in women, most of whom have anatomically normal urinary tracts. Although leading to significant morbidity, these infections are not associated with adverse renal outcomes in adult women, such as renal impairment or hypertension. If the above investigations are normal, and none of the above modifiable risk factors, such as urinary incontinence, are identified, the focus can shift to management strategies.

Table 3. Diagnosing UTI in children

Children who can void on request

- Perform a midstream urine culture

Children who cannot void on request

- Collect a bagged specimen of urine and perform a dipstick test for leucocytes and nitrites – a negative result does not exclude a UTI
- If the dipstick test is positive, or there is a negative result but clinical suspicion, obtain a definitive urine specimen, preferably by superpubic aspirate, and send for culture
- If a suprapubic aspirate cannot be obtained, collect a catheter specimen of urine discarding the first few millilitres, then send for culture

Table 4. Investigations for RUTIs

- Midstream urine culture – to confirm diagnosis of UTI and determine antibiotic sensitivities
- Creatinine level/eGFR – to identify renal impairment
- Blood glucose level – to test for diabetes
- Renal tract ultrasound – to identify obstruction, pyelonephritis or abscess, and determine prostate size
- Ultrasound with pre- and post-void residual volume – to identify urinary retention
- CT urogram/plain abdominal x-ray – to identify renal tract stones
- Contrast CT – to detect complex cysts or renal abscess
- Micturating cystourethrogram – to identify vesicoureteric reflux
- DMSA scan – to identify renal scars
- Urodynamic studies – to identify bladder dysfunction with or without outflow obstruction
- Cystoscopy with or without ureteroscopy – to detect a carcinoma
- Expressed prostatic secretions – to localise infection to the prostate and determine antibiotic sensitivities

Management

Behavioural and pharmacological measures can be employed to reduce recurrences of UTIs. Management is guided by the severity and frequency of episodes, the patient's ability to detect symptoms early and patient preference.

Behavioural measures

Many women find double voiding and/or voiding post intercourse useful, although there is no trial evidence to support this. The simple measure of wiping the perineum from front to back, thus reducing the risk of faecal contamination, is of unproven benefit but may be helpful. Maintaining a reasonable fluid intake to increase urinary frequency is important in those with low urine volume.

Pharmacological measures

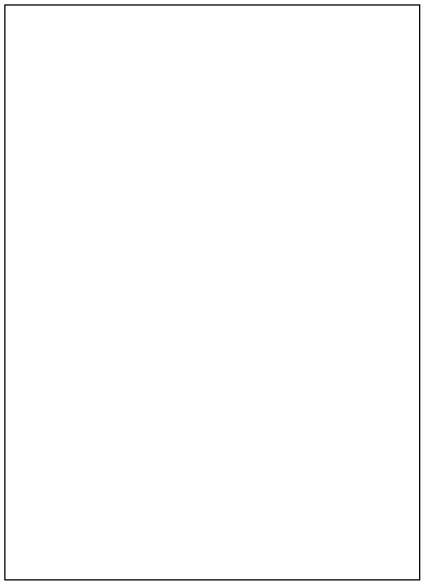
Topical oestrogen replacement

In postmenopausal women, intravaginal (but not oral) oestrogen therapy significantly reduces the incidence of RUTI.[3] Some women will find this preferable to antibiotic therapy. Intravaginal oestrogen therapy may also have a role when pathogen resistance to antibiotics make prophylaxis difficult.

Antibiotic strategies

Antibiotic strategies should always be accompanied by ongoing reinforcement of behavioural measures and identification and reversal where possible of precipitating factors. Several methods of antibiotic use are employed, as described below.

- **Intermittent patient-initiated treatment.** This consists of a three-day course of antibiotic therapy commenced at the onset of symptoms, and is most appropriate if the patient is able to detect symptoms early. Advantages include improved patient compliance and less risk of developing antibiotic resistance. Consequently, patient-initiated treatment may be a preferable strategy in many patients, even though they may have significantly more than three infections per year (the usual threshold at which continuous prophylaxis is considered), particularly if symptoms are relatively mild. Patients should be advised to seek medical attention if significant improvement in symptoms has not occurred within 24 to 48 hours of commencing antibiotics.



- **Postcoital prophylaxis.** A single dose of an appropriate antibiotic is given within two hours of intercourse. In patients in whom sexual intercourse is a clear precipitant, postcoital prophylaxis is as effective as continuous therapy.[4]
- **Continuous nocte prophylaxis.** Taking an appropriate antibiotic every night is effective at reducing both clinical and microbial recurrences. However, protection against RUTIs is only conferred during the prophylaxis period. Side effects include, but are not limited to, candidiasis, gastrointestinal tract upset and an increase in the likelihood of antibiotic resistance.[4] Continuous prophylaxis should be reserved for patients who experience frequent recurrences and are sufficiently motivated to comply with therapy during asymptomatic periods. In patients whose recurrences are severe (e.g. requiring hospitalisation or significant time off work) or complicated (e.g. known abnormal urinary tract, ascending infection or septicaemia), prophylaxis may be required even when recurrences occur less often than three per year. Typical regimens are listed in the box on page 58.
- **Antibiotic rotation.** This approach usually involves alternating two antibiotics at monthly intervals. Although there is no trial evidence to support this strategy in patients with RUTIs, it may be an option in patients who have ongoing recurrences while taking single agent continuous prophylaxis.

Cranberry products

A 2008 Cochrane review demonstrated that cranberry products significantly reduce the risk of RUTI at 12 months (relative risk, 0.65; 95% confidence interval, 0.46–0.90), and that women were more likely to benefit than men.[5] However, only one study showed a statistically significant reduction in symptomatic UTI.[6] Many patients in the reviewed trials discontinued therapy and the optimal dose and form of administration of cranberry is unknown. However, the usual recommended dose of cranberry products for UTI is the equivalent of one large glass (250 to 300 mL) of juice per day.

RUTIs in men

RUTIs are uncommon in men, so an underlying cause should always be suspected. Loin pain, a positive family history or the isolation of urease-splitting organisms such as *Proteus mirabilis* suggest calculi, warranting a CT urogram. Obstructive symptoms should be sought, and prostate size and pre- and post-void residual volumes assessed on ultrasound. A prior history of urethral trauma or instrumentation may suggest urethral stricture and require urological consultation. A sexual history should be taken and urethral

Regimens for continuous nocte prophylaxis against RUTIs

Initial antibiotic treatment will usually be given every night for a period of three to six months. If cessation of prophylaxis is accompanied by further recurrences, consideration should be given to a longer course, or even lifelong therapy in severe cases.

Typical regimens for continuous nocte prophylaxis include:

- cephalexin 250 mg orally at night (for children, 12.5 mg/kg; maximum 250 mg daily)
- trimethoprim (Alprim, Triprim) 150 mg orally at night (for children, 4 mg/kg; maximum 150 mg daily)
- nitrofurantoin (Macrodantin) 50 mg orally at night (for children aged over 3 months, 1 mg/kg; maximum 50 mg daily); avoid in patients with GFR below 60 mL/min.

swabs performed for sexually transmitted infections, if appropriate. Digital rectal examination may reveal acute prostatitis or prostatic hypertrophy. Prostatic massage in the setting of acute infection should be avoided due to the risk of precipitating septicaemia.

RUTIs in men often indicate chronic prostatitis, which is difficult to diagnose (the gland may be normal on examination) and treat because few antibiotics penetrate the noninflamed prostate. Prostatic massage to obtain expressed prostatic secretions may help confirm the diagnosis and guide antibiotic choice. An antibiotic drug with good prostatic penetration, such as a fluoroquinolone, should be used for four weeks.

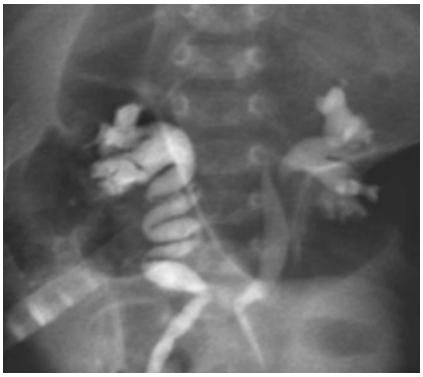


Figure 2. Micturating cystourethrogram showing reflux of contrast into bilateral ureters and dilated pelvicalyceal systems, with intra-renal reflux in keeping with grade IV vesicoureteric reflux.

(IMAGE COURTESY OF DR KEN LAU, DEPARTMENT OF RADIOLOGY, MONASH MEDICAL CENTRE, MELBOURNE.)

RUTIs in children

The underlying conditions associated with RUTIs in children include vesicoureteric reflux and dysfunctional voiding. Vesicoureteric reflux, which affects about 1% of newborns, is thought to cause renal scarring as a result of recurrent episodes of pyelonephritis. However, vesicoureteric reflux also signifies abnormal renal development, which itself predisposes to adverse renal outcomes such as hypertension and renal impairment. Children with RUTIs require paediatric review. Most cases will proceed to a micturating cystourethrogram to identify vesicoureteric reflux and a technetium-99m dimercaptosuccinic acid (DMSA) scan to identify renal scarring. A micturating cystourethrogram is a distressing investigation for both child and parents (Figure 2).

The management of vesicoureteric reflux is hampered by the lack of data comparing an observational approach versus medical or surgical therapy. This is particularly so with low grade (I or II) disease, where about 80% of cases will remit spontaneously. However, an observational approach is not recommended in children with grade III or higher vesicoureteric reflux. 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.

Management of dysfunctional voiding, initially with timed toileting and treatment of constipation, also reduces RUTIs. The role of prophylaxis in recurrent febrile UTIs in the absence of vesicoureteric reflux is less well defined in children than in adults, but is usually considered in children with three episodes or more per year when other treatment options have been ineffective.

Patients with long-term indwelling catheters

Patients with indwelling catheters are at an increased risk of RUTIs, with female and diabetic patients being particularly susceptible. As there is a clear cause, additional investigation is usually not required, with the focus instead on management strategies. When infection is suspected clinically, the catheter should be changed and a urine specimen taken via the new catheter. If ongoing catheterisation is required, intermittent or suprapubic catheterisation should be considered. Wherever possible, the catheter should be removed. Infections can be minimised by maintaining a closed drainage system and avoiding catheter blockage and trauma. Prophylaxis has not been shown to reduce the incidence of symptomatic episodes, but is associated with the development of resistant organisms and is therefore best avoided.

Candiduria is commonly isolated in patients with long-term catheters. In asymptomatic patients, this most often represents colonisation and does not require investigation or treatment. However, therapy should be considered in patients who are symptomatic or neutropenic, or who are about to undergo urological instrumentation or surgery.

Immunosuppressed patients

RUTIs in immunosuppressed patients should prompt a review of immunosuppression by the prescribing physician, and dose reduction if possible.

Immunosuppressed patients can become critically ill very quickly. In a septic patient, inflammatory marker measurement, blood culture and renal tract imaging are mandatory. Prompt admission is required for intravenous antibiotic administration and hydration. In renal transplant recipients, this should occur in consultation with the treating physician in the transplantation unit. Nephrotoxins, including aminoglycosides, NSAIDs and contrast, should also be avoided in renal transplant recipients.

Antibiotic resistance

Antibiotic resistance is an ever-increasing problem, particularly the emergence of an extended spectrum of beta-lactamases in organisms causing community-acquired infections. The opinion of an infectious diseases expert should be sought. Avoiding prophylaxis if not indicated and in patients who are poorly compliant with this strategy may help prevent resistance occurring. Behavioural measures to minimise reinfection and reversal of risk factors where possible are paramount.

Conclusion

RUTIs are a common problem facing GPs. Basic investigation with midstream urine culture, measurement of urea, electrolytes, creatinine and blood glucose levels and a renal tract ultrasound are required in all patients with this condition. MT

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Further reading

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