

# Recurrent urinary tract infections in adults: a practical guide

## Abstract

Recurrent urinary tract infections are a common problem faced by clinicians across many specialities. For the patient, recurrent urinary tract infections can be burdensome and detrimental to their quality of life. For the clinician, they can be challenging to manage, and the socioeconomic burden on healthcare systems can also be substantial. Investigations serve to rule out any underlying structural or pathological abnormalities. In conjunction with behavioural prevention methods, treatment strategies include antibiotic and non-antibiotic approaches and holistic management approaches. This article provides an overview of the investigation and treatment of urinary tract infections and includes algorithms which can be used in daily clinical practice.

**Key words:** Infection; Recurrence; Urinary tract infection

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## Introduction

Urinary tract infections are common bacterial infections in adults, encompassing a spectrum of clinical diseases from cystitis to pyelonephritis. Although they also occur in men, urinary tract infections are most common in women; one in two women will develop a urinary tract infection over their lifetime (Foxman, 2014) and up to 25% of women will suffer a further episode within 6 months. The most commonly accepted definition of a recurrent urinary tract infection is two or more episodes within a 6-month period, or three or more episodes within a 12-month period (European Association of Urology, 2021). In contrast to a persistent urinary tract infection, to diagnose recurrent urinary tract infections patients are required to be symptom free between episodes. The socioeconomic burden of urinary tract infections is an estimated \$3.5 billion per year in the USA (Flores-Mireles et al, 2015). Recurrent urinary tract infections also have a negative impact on quality of life as a result of the associated afflictive symptoms (Renard et al, 2014). Given the prevalence, hospital doctors of many specialities are likely to encounter patients with this clinical problem. Understanding and education on this topic is therefore very pertinent to all clinicians. This article provides an overview of the management of recurrent urinary tract infections.

## Pathogenesis

Women with recurrent urinary tract infections often have increased vaginal and periurethral colonisation of uropathogenic bacteria originating from the gastrointestinal flora. This is believed to act as a reservoir, allowing bacterial migration from the urethra to the bladder, which can then cause cystitis. This is supported by Gupta et al (1998) who found *Escherichia coli*, an uropathogenic bacteria originating from the gastrointestinal flora, colonisation in vaginal samples in 35% of women with recurrent urinary tract infections compared to 11% in those without recurrent urinary tract infections.

Oestrogen promotes lactobacilli colonisation, which maintains an acidic vaginal pH that is resistant to *E. coli* colonisation. However, post-menopausal women are oestrogen-deficient, hence the lactobacilli colonisation effect is lost (Lüthje et al, 2014). In premenopausal women, barrier contraceptives containing spermicides can have the collateral effect of altering the vaginal flora, which results in susceptibility to colonisation of uropathogenic organisms (Handley et al, 2002). Bacteria reaching the bladder are normally eradicated with urination, unless the bacteria can adhere to the bladder wall and/or if there is incomplete bladder emptying. Uropathogenic bacteria have numerous mechanisms of adhering to the

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bladder wall, and in recurrent urinary tract infections it is thought that the bacteria can invade urothelial cells and form intracellular bacterial communities (Rosen et al, 2007). Intracellular bacterial communities are able to evade natural host defences and antibiotic therapy, causing recurrent episodes of infections (Rosen et al, 2007).

Anatomical or functional abnormalities that promote bacterial colonisation or urinary stasis are important in recurrent urinary tract infections. Foreign bodies such as urethral catheters, urinary stones and fistulae (for example, vesico-vaginal) can precipitate infection. Similarly, impaired bladder emptying from bladder outflow obstruction (for example, because of benign enlargement of the prostate), bladder diverticula, cystocele or urethral stenosis all promote urinary stasis and predispose individuals to infection. Lesions to the neurological system, such as from cerebral infarction, spinal cord injury, multiple sclerosis or Parkinson's disease, can result in aberrant storage and dysfunctional bladder voiding, rendering, increasing the risk of developing recurrent urinary tract infections (Panicker et al, 2015).

Uropathogenic *E. coli* is the most common causative organism and is responsible for approximately 75% of urinary infections. Other common causative organisms are *Klebsiella pneumoniae*, *Proteus mirabilis*, *Enterococcus* spp. and *Pseudomonas aeruginosa* (Flores-Mireles et al, 2015).

## Risk factors

In young and pre-menopausal women sexual intercourse, spermicide use and new sexual partner(s) represent possible risk factors (Scholes et al, 2000). Additionally, an individual's first urinary tract infection occurring during childhood ( $\leq 15$  years old) and a maternal history of urinary tract infections are associated with an increased risk of developing recurrent urinary tract infections. In postmenopausal women, additional risk factors include a lack of oestrogen and atrophic vaginitis, increased post-void residuals, presence of cystocele, nursing home residency and urinary incontinence (Hu et al, 2004; Stamm and Raz, 1999).

## Clinical assessment

### History and examination

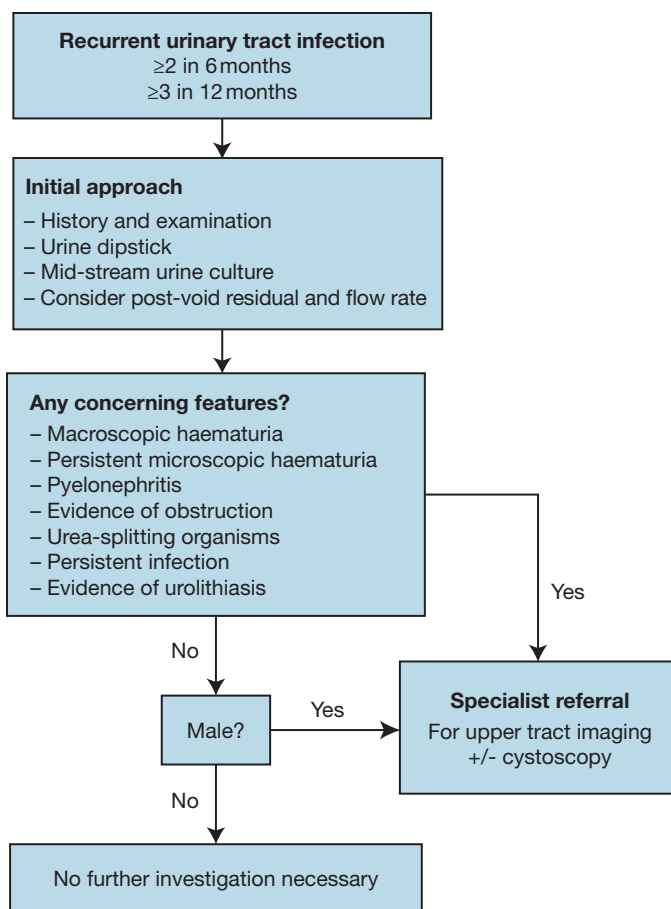
A detailed history and a physical examination should be performed in the first instance. Common symptoms are dysuria, urinary frequency, urgency and suprapubic pain. Nocturia, offensive-smelling urine and incontinence may also be reported. In elderly patients, especially those living in nursing homes, confusion may be the presenting symptom. The presence of abnormal vaginal or urethral discharge suggests an alternative diagnosis. History of fever, rigours and loin pain are indicative of pyelonephritis from ascending infection, which requires prompt management.

In men presenting with recurrent urinary tract infections, a digital rectal examination should be performed to assess prostate size, consistency and tenderness to test for signs of benign prostatic enlargement, malignancy or prostatitis. A protracted history of lower urinary tract symptoms suggests a bladder outflow obstruction. Examination in female patients should also assess for the presence of pelvic organ prolapse.

### Initial investigations

Although urinary tract infections can typically be clinically diagnosed, the European Association of Urologists recommend that in the context of recurrent urinary tract infections, diagnosis is confirmed with a urine culture consisting of a mid-stream urine sample (European Association of Urology, 2021). The sensitivity and specificity for positive nitrites and/or leucocytes on a urine dipstick for diagnosing a urinary tract infection in the general population is 75 and 70% respectively (Devillé et al, 2004). The presence of microscopic haematuria should be noted as while this may occur in infection, it could indicate an alternative pathology such as urolithiasis or malignancy (Figure 1).

It is worth noting that a urine culture reported as 'no significant growth' does not necessarily mean a case of clinically significant cystitis is not present. The widely accepted threshold of significant growth from a urine culture of  $10^5$  colony forming units per millilitre



**Figure 1.** Algorithm for the investigation of a recurrent urinary tract infection.

is derived from historical studies of young females with pyelonephritis (Kass, 1957). It is thought that a growth of  $10^3$  or even  $10^2$  colony forming units per millilitre can result in a clinically significant urinary tract infection (Hooton et al, 2013).

### Further investigations

The majority of young women with no indications of an underlying functional or structural abnormality will not require further investigation. Uncomplicated urinary tract infections are common, and the rate of further investigations is very low (European Association of Urology, 2021). Van Haarst et al (2001) reported findings from 69 women, aged 18–40 years old, presenting with recurrent urinary tract infections who underwent a cystoscopy procedure. No relevant findings were identified other than cystitis cystica. A bladder scan to measure the post-void residual volume should be obtained to rule out a high residual volume of urine. Further investigation and specialist referral is suggested in individuals who are found to have macroscopic haematuria at the point of presentation, and in those individuals where microscopic haematuria persists after the treatment of the infection, as this may indicate a malignancy.

Nickel et al (1991) proposed selection criteria to assess whether further investigation with cystoscopy and upper tract imaging is necessary. In a group of 186 women, 39 women were found to have significant detectable abnormalities, with 20 of those women requiring surgical intervention. The indications for further investigation are macroscopic haematuria, persistent microscopic haematuria between infections, pyelonephritis and atypical features (such as obstructive symptoms, infection with urea-splitting organism and clinical impression of persistent infection or urolithiasis). The National Institute for Health and Care Excellence guidelines recommend that men with recurrent urinary tract infections should be investigated further, as this may indicate the presence of an underlying structural or functional abnormality (National Institute for Health and Care Excellence, 2018).

## Management

All patients presenting with a recurrent urinary tract infection need to receive initial treatment for the acute episode. The choice of antibiotic will depend on local guidance, epidemiology and the patient's previous urine culture results (if available). A number of strategies for reducing the frequency of recurrent urinary tract infection episodes have been researched. Broadly, these can be divided as behavioural prevention, antibiotic and non-antibiotic strategies (Figure 2). While there is good evidence for the use of antimicrobials in managing recurrent urinary tract infections, the need to minimise the use of antibiotics is highly important as antimicrobial resistance is a rising issue (Wagenlehner et al, 2016). There are now several 'non-antibiotic' alternatives available in clinical practice.

### Behavioural prevention

Delayed urination following sexual intercourse, poor fluid intake and wiping from back to front post-defecation have been previously outlined as contributing to recurrent urinary tract infections. While modifications to these self-care behaviours is still recommended, this

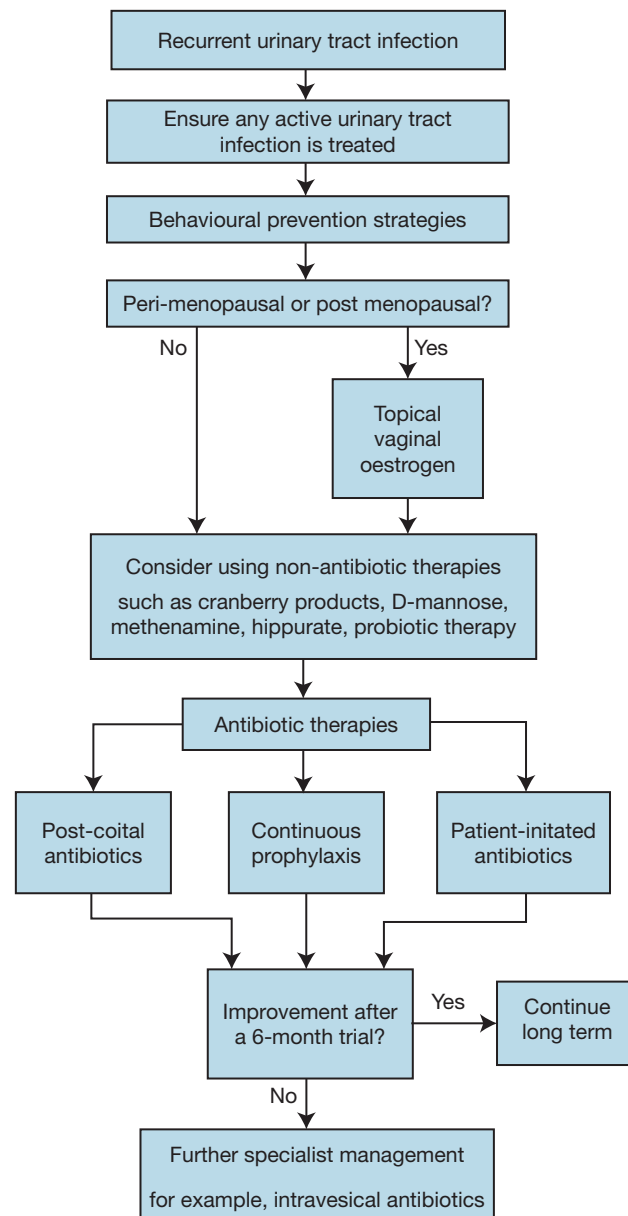


Figure 2. A treatment algorithm for the treatment of recurrent urinary tract infections.

alone may not completely eradicate the problem (Scholes et al, 2000). Patients should also be counselled regarding alternative contraceptive strategies to spermicide and diaphragm use (Handley et al, 2002).

### Antibiotic therapy

Although antibiotics are important in the management of recurrent urinary tract infections, the principles of antibiotic stewardship should be adhered to in order to be cost effective, reduce the risk of inadvertent acquisition of healthcare-associated infections and reduce the development of resistant bacterial strains (Dellit et al, 2007). The options include long-term prophylaxis, patient-initiated antibiotics and intravesical instillations.

### Long-term prophylaxis

A meta-analysis found that the use of long-term antibiotic prophylaxis in non-pregnant women with recurrent urinary tract infections reduced the risk of clinical urinary tract infections by 85% (relative risk 0.15, 95% confidence intervals 0.08–0.28) when compared to the placebo group. Additionally, the meta-analysis found that the number of patients who needed to be treated in order to prevent one recurrence was 2.2 patients (Albert et al, 2004). Adverse effects were more common in the antibiotic group, with nausea and vaginal or oral candidiasis being commonly reported. They found no difference between the different antibiotics used in prophylaxis, suggesting the choice of antibiotic should be determined by local guidance, cost and the previous microbiological sensitivities of the individual patient. Patients should be fully counselled regarding potential side effects, including antimicrobial resistance and the potential risk of contracting *Clostridioides difficile* (formerly known as *Clostridium*), before initiating long-term antibiotic prophylaxis. Current guidance for the use of prophylactic antibiotics is an initial 3–6-month course, after self-care advice and non-antibiotic therapies have been considered (European Association of Urology, 2021). If the frequency of recurrences increases after the cessation of prophylactic antibiotic treatment, the treatment course can be lengthened.

### Patient-initiated antibiotics

Where sexual intercourse has been identified as a precipitant for urinary tract infections, post-coital antibiotic administration can be used. A randomised trial found post-coital ciprofloxacin was as effective at reducing the recurrence of urinary tract infections as a daily prophylactic low-dose of ciprofloxacin, with only a third of the daily dosage required in the post-coital approach (Melekos et al, 1997).

An additional strategy that can be considered in motivated individuals that are deemed to be compliant is patient-initiated therapy. Patients can be supplied with a urine culture kit and a course of antibiotics to be started when symptoms associated with a urinary tract infection develop. In two studies, patients have been able to effectively diagnose and treat recurrent urinary tract infections, with high levels of patient satisfaction and no adverse effects (Gupta et al, 2001; Schaeffer and Stuppy, 1999). Again, choice of antibiotic could be based on previous microbiology or local epidemiology.

### Intravesical antibiotics

Gentamicin is the most used drug for intravesical antibiotic treatment. This is usually reserved as a last resort for those with multi-drug resistant bacteria or those suffering from persistent recurrent urinary tract infections. A systematic review into intravesical antibiotic treatment demonstrated a 78% reduction in symptomatic urinary tract infections and found the intravesical antibiotics to be well tolerated, with few side effects reported (Pietropaolo et al, 2018).

### Non-antibiotic therapies

Examples of non-antibiotic therapies include cranberry supplements, urinary acidification, methenamine hippurate, oestrogens, probiotics, D-mannose and vaccines. Non-antibiotic therapies are typically well tolerated with very few side effects, but there is limited high-quality evidence supporting their use in preventing the recurrence of a urinary tract infection.

### Cranberry

Cranberry (*Vaccinium macrocarpon*) tablets and drinks are commonly used in the prevention of recurrent urinary tract infections. Proanthocyanids are the active ingredients found in cranberry products, which are believed to inhibit the adherence of *E. coli* to the urothelium and prevent colonisation (Gupta et al, 2007). However, there is conflicting evidence regarding the benefits of proanthocyanids in reducing the recurrence of urinary tract infections. Cochrane meta-analysis of 24 studies involving a total of 4473 participants showed no significant reduction in the recurrence of urinary tract infections (Jepson et al, 2012). These studies also reported a large drop-out rate of participants. Conversely, another meta-analysis of similar size (4947 participants) demonstrated that cranberry products reduced the risk of recurrent urinary tract infections (Luis et al, 2017).

Owing to the conflicting evidence, the European Association of Urology (2021) does not recommend taking cranberry products to prevent the recurrence of urinary tract infections, whereas guidance from the National Institute for Health and Care Excellence (2018) suggests that patients with recurrent urinary tract infections may want to consider the use of cranberry products. Cranberry juice alone is not considered to have a high enough concentration of proanthocyanids, so cranberry tablets are the recommended form for consuming these products.

### D-mannose

D-mannose is a monosaccharide that acts as a competitive inhibitor to *E. coli* adhesion to the urothelial wall by binding to the glycoprotein receptors on the urothelium. Although the evidence is relatively scant, a meta-analysis of six studies with 695 participants reported that D-mannose administration resulted in fewer recurrent urinary tract infections, with longer periods between recurrences (Kyriakides et al, 2020). There was a lack of concordance between the dose regimen in the included studies, but D-mannose was well tolerated with minimal side effects. Further studies are required to substantiate the efficacy claims of D-mannose and establish the optimum dosing regimen. Patients have to buy it themselves and people with diabetes should factor the sugar content of D-mannose into their daily allowance.

### Methenamine hippurate

Methenamine is hydrolysed into formaldehyde in acidic urine and is bacteriostatic, so bacterial resistance does not arise (Lee et al, 2012). It can be taken at a dose of 1 g twice daily and ascorbic acid can additionally be given to lower the urinary pH. A Cochrane review of 13 studies with 2032 participants showed that in patients with anatomically normal urinary tracts, there was a reduction in the risk of urinary tract infection with few side-effects (Lee et al, 2012). However, six of the studies had a follow up period of less than 1 month and only one study specifically looked at recurrent urinary tract infections. A multicentre UK randomised controlled trial is currently ongoing, which should add some clarity to the data.

### Probiotics

As previously mentioned, the normal commensal flora colonising the vagina and perineum are thought to act as a barrier to the colonisation of uropathogenic *E. coli* and reduce the ascending infection (Lüthje et al, 2014). *Lactobacillus* spp. are the most important bacteria in the commensal flora and it is hypothesised that they reduce the rates of symptomatic bacterial urinary tract infections. A meta-analysis of nine studies with a total of 735 participants found no significant reduction in the risk of developing a recurrent urinary tract infection. Interestingly, the authors noted that this conclusion was because of the limited data obtainable from the small studies (Schwenger et al, 2015). A randomised controlled trial of 100 women demonstrated reduced risk of recurrent urinary tract infection when given an intravaginal suppository of *Lactobacillus crispatus* probiotic once a day for 5 days, and then once weekly for 10 weeks (Stapleton et al, 2011).

### Oestrogen

Oestrogen acts to promote vaginal colonisation with *Lactobacilli*, which in turn helps to maintain an acidic vaginal pH level that is more resistant to vaginal colonisation by *E. coli*

(Lüthje et al, 2014). Additionally, oestrogen has structural effects on the urogenital tract which upregulate the production of antimicrobial peptides (Lüthje et al, 2014).

A meta-analysis of two studies concluded that the administration of oral oestrogens did not reduce the rate of recurrent urinary tract infections (Perrotta et al, 2008), and had a greater tendency to result in systemic side effects. The same meta-analysis identified two randomised controlled trials which reported that local administration of vaginal oestrogen significantly reduced the number of urinary tract infections in postmenopausal women. There is some evidence from a small study of 30 women to suggest that vaginal oestrogens may contribute to a reduced recurrence of urinary tract infections in premenopausal women taking the combined oral contraceptive pill (Pinggera et al, 2005).

Both the European Association of Urology (2021) and the National Institute for Health and Care Excellence (2018) recommend that topical oestrogen should be offered to postmenopausal women presenting with a recurrent urinary tract infection.

### Immunomodulators and vaccines

A number of immunomodulators and vaccines exist with the purpose of priming the immune system to reduce the rate of urinary tract infections, without having to use antibiotic therapy. Available vaccines include the oral tablet UroVaxom (OM-89), sublingual Uromune and Solco-Urovac, which can be administered as a vaginal suppository or intramuscular injection. A systematic review has demonstrated that, overall, vaccines result in a short-term reduction in the recurrence rate of urinary tract infections, with an odds ratio of 0.17 (95% confidence intervals 0.06–0.50). However, data on long-term benefits (>12 months) are lacking (Prattley et al, 2020). The European Association of Urology recommends the use of OM-89 in women with recurrent urinary tract infections because of its efficacy and good safety profile, but it is not currently licensed in the UK. It should be noted that OM-89 contains membrane proteins of 18 strains of uropathogenic *E. coli* and is therefore unsuitable for patients with alternative urinary pathogens.

### Specific causes

In cases where a reversible cause has been identified, targeted treatment can be delivered. For example, in females with chronic urinary retention (Figure 3), intermittent self-catheterisation can be commenced. If the patient does not have satisfactory manual dexterity, for example if the individual has Parkinson's disease, an indwelling catheter may be required and referral for suprapubic catheter placement should be considered. In men, if indicated, referral should be considered for bladder outlet surgery, such as transurethral resection of



**Figure 3.** Computed tomography of chronic urinary retention in a woman.

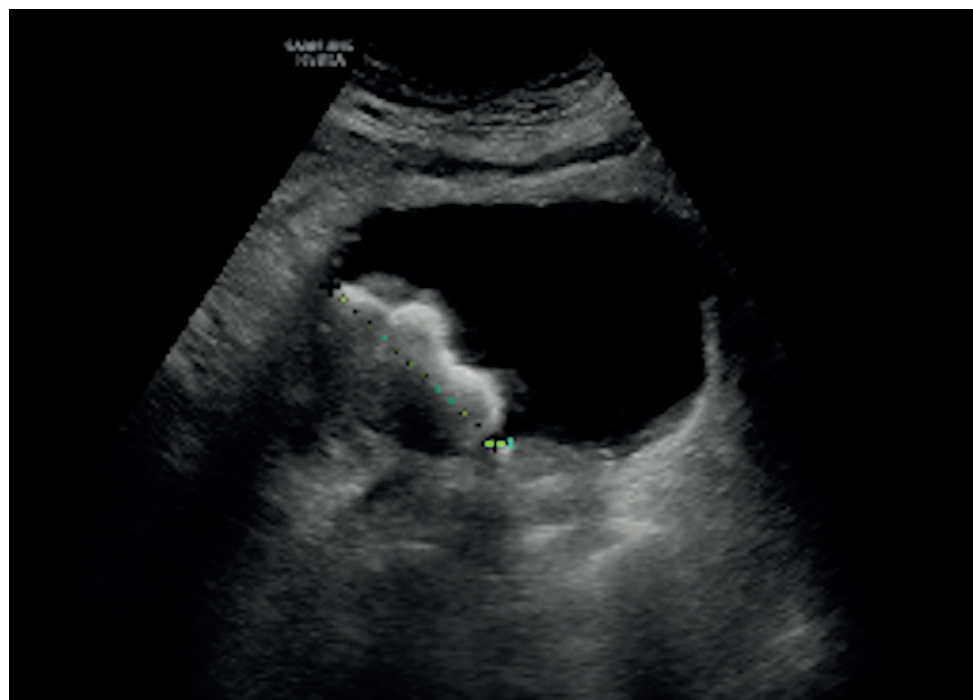
the prostate. Similarly, endoscopic fragmentation of bladder stones can be performed in the same setting if required (Figure 4). Identification of a suspected bladder tumour (Figure 5) requires urgent referral for the expedition of a transurethral resection of the bladder tumour.

## Conclusions

Recurrent urinary tract infections are a common presentation in both the community and hospital setting. Knowledge of their management is relevant for all clinicians. Investigations serve to rule out any underlying structural or pathological abnormalities. Although prophylactic antibiotics have an important role in managing recurrent urinary tract infections, in the age of antimicrobial resistance, the need for alternative therapies is



**Figure 4.** Computed tomography showing a large bladder stone.



**Figure 5.** Bladder mass found on ultrasound.

## Key points

- Three main areas of management are behavioural prevention, antibiotic and non-antibiotic strategies.
- Investigations serve to rule out any underlying structural or pathological abnormalities.
- Antimicrobial resistance is an increasing problem and alternatives, such as vaccines, represent an important area of research.

## Curriculum checklist

This article addresses the following requirements from the general internal medicine training curriculum:

- Managing an acute unselected take.
- Managing an acute speciality-related take.
- Managing medical problems in patients in other specialities and special cases.

more important than ever. Further research is warranted to determine the role of D-mannose, vaccines, probiotics and methenamine hippurate in the management of recurrent urinary tract infections.

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### Conflicts of interest

The authors declare that they have no conflicts of interest.

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