

The diagnosis and management of uncomplicated recurrent urinary tract infection

Guidelines

summarising clinical guidelines for primary care

MGP Ltd identified a need for clinical guidance in this area and approached Aspire Pharma Ltd for an educational grant to support the development of a working party guideline.

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The diagnosis and management of uncomplicated recurrent urinary tract infection

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Introduction

Urinary tract infection (UTI) usually results from ascending infection of uropathogenic bacteria via the urethra, and typically results in dysuria, urinary frequency, suprapubic tenderness, urinary urgency, and haematuria.^{1,2} About 150 million people worldwide are believed to experience a UTI every year.³ Women are significantly more likely to experience a UTI than men,⁴ with an annual incidence of 12.6% in women and 3% in men.⁵ At least one in three women have one episode of UTI requiring antimicrobial therapy by the age of 24 years, and almost 50% of all women experience one UTI during their lifetime.⁴

Patients, particularly women, can develop recurrent UTI in the form of cystitis (lower UTI) or pyelonephritis (upper UTI), both of which may be due to relapse with the same organism or reinfection with a different strain or species of organism.⁶ Recurrent infections become a problem in up to 25–30% of women who experience an initial infection,³ with 44% of all women,⁷ 53% of women older than 55 years,⁸ and 36% of younger women⁸ experiencing a further infection within 12 months. Furthermore, 2.7% of patients experience a second recurrence.⁹ Although recurrent UTI is not usually life-threatening, the high incidence significantly increases healthcare costs and has a negative impact on patients' quality of life.^{10,11}

If recurrent UTIs are not treated appropriately, they can occasionally lead to kidney damage and renal failure.⁶ Standard treatment in the UK currently consists of lifestyle modifications, antibiotic treatments, and non-antibiotic treatments;⁶ however, some patients continue to experience recurrent infections and symptoms that affect their quality of life. Furthermore, antimicrobial resistance is a concern,^{12,13} and treatment with antibiotics can increase the resistance of bacteria that cause UTIs, making antibiotics less effective for future use.¹⁴

Rationale for this guideline

NICE Clinical Guideline 54 on the diagnosis and management of UTI in under 16s was published in August 2007 and updated in October 2018,¹⁵ but limited guidance is available on the management of UTIs in adults,^{16,17} particularly recurrent UTI. Guidance from NICE on antimicrobial prescribing for recurrent UTI was published in October 2018,⁶ but this primarily focuses

on antibiotics, offering limited advice on other available treatment options, and does not cover diagnosis.

With current concerns about antimicrobial resistance and the advent of new therapies, there is a clear need for guidance to help healthcare professionals in primary care diagnose and manage recurrent UTI appropriately and in a timely fashion. This working party guideline has been developed in line with current evidence to provide practical, evidence-based recommendations for patients with uncomplicated recurrent UTI and an algorithm to support the diagnostic and treatment pathway.

Guideline for the diagnosis and management of recurrent UTI

Figure 1 provides an algorithm summarising the working party group's consensus guideline on the diagnosis and management of uncomplicated recurrent UTI.

This guideline does not cover patients with acute UTI, who should be managed with a standard, 3-day course of narrow-spectrum antibiotics where possible, provided that their infection is uncomplicated.^{16,18} This guideline also does not cover patients with complicated recurrent UTI,¹⁸ so specialist referral should be considered for the following according to local pathways:

- › pregnant women
- › men
- › patients with recurrent or severe pyelonephritis
- › patients infected with resistant bacteria
- › patients with recurrent UTI associated with structural or functional abnormalities of the urinary tract
- › patients with recurrent UTI associated with atypical infections, such as tuberculosis or schistosomiasis
- › catheterised patients, in whom misdiagnosis is common because of colonisation (treat only when symptomatic)
- › patients with immunity compromised as a result of drugs or

diseases

- › patients with chronic renal failure with oliguria, who should be seen by the renal team because of the risk of renal deterioration

Defining and diagnosing recurrent UTI

- › Recurrent UTI is defined as two UTIs within 6 months or three UTIs within 12 months¹⁷
- › Diagnosis of UTI should be based on a combination of:
 - clinical diagnosis based on typical symptoms (Box 1)
 - microbiological diagnosis by appropriate use of urine dipsticks and urine culture
 - past response to antibiotic treatment of isolated episodes of acute of UTI
- › A diagnosis of UTI can be considered if the patient has a strong symptom profile, even in the absence of culture-positive urine or dipstick confirmation
 - fever can be useful to differentiate inflammatory and infective causes
 - previous response to antibiotics for similar symptoms also supports this diagnosis
- › A diagnosis of UTI should not be made in asymptomatic patients with a positive urine sample (asymptomatic bacteriuria)
 - dipsticks have a poor predictive value due to a high rate of false positives and false negatives; they may be useful in making a diagnosis when a combination of positive results including nitrites are detected in patients with classical symptoms, but a negative dipstick result, while making UTI less likely as a diagnosis, does not rule out UTI and thus must be interpreted in the light of symptoms/previous response to antibiotics^{19–21}
 - do not use dipsticks for asymptomatic or catheterised patients¹⁶
 - diagnosis in elderly patients should not be based on positive microbiology alone, because asymptomatic bacteriuria is increasingly common with advancing age²²
 - use of urine dipsticks in elderly patients is associated with a high false-positive rate²³
 - elderly patients are often unable to provide a history of acute urinary symptoms for reasons such as delirium or dementia²⁴

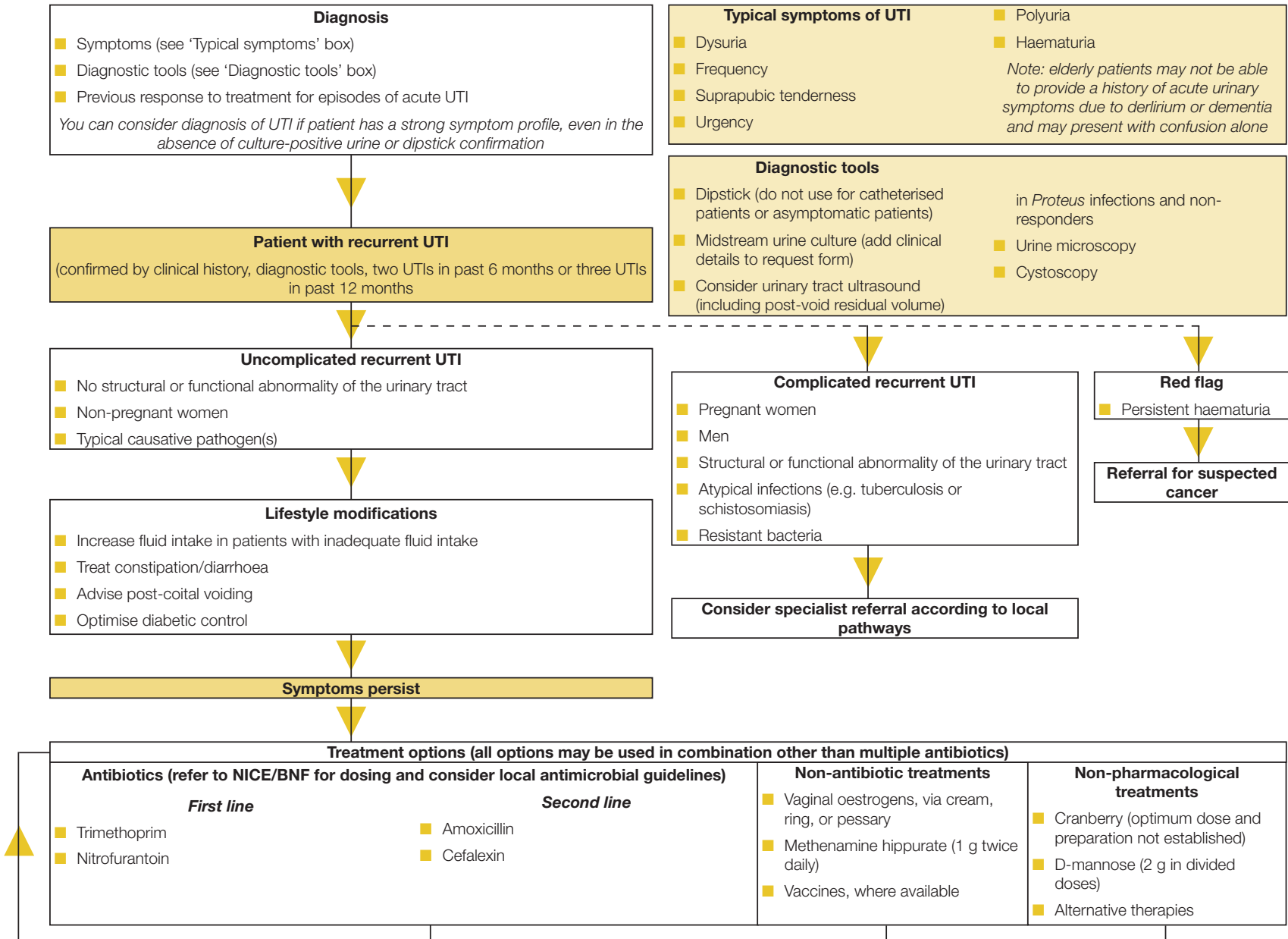
Box 1: Typical symptoms of UTI²

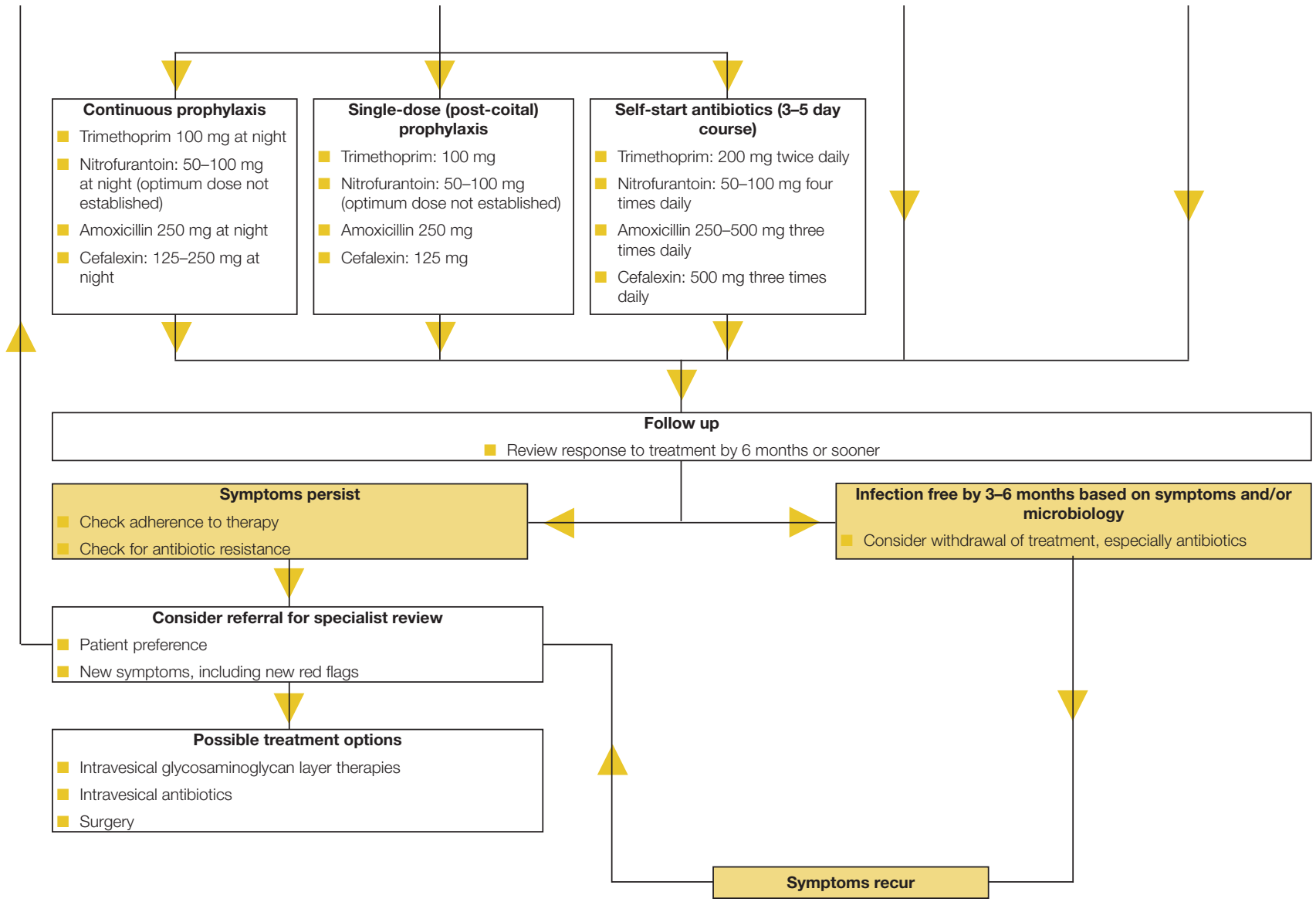
- › Dysuria
- › Frequency
- › Suprapubic tenderness
- › Urgency
- › Haematuria

Box 2: Urine dipsticks and cultures

- › Urine samples should ideally be taken in the early morning, because these samples will have a higher yield
- › Samples should be taken midstream to avoid urethral contamination
 - patients should be instructed on how to collect a midstream sample (see 'Useful resources' on p.10)
 - consider whether patients are physically able to take a sample, especially elderly patients
- › Overhydration can impact dipstick results by diluting urine, leading to false-negative results
- › Please refer to manufacturer's advice on appropriate storage for urine dipsticks, because incorrect storage and use may result in inaccurate results, such as false-positive results following prolonged exposure to air
- › The presence of leucocytes and nitrites in combination has a higher predictive value of UTI than leucocytes alone²⁰
- › Provide full and accurate clinical details and antibiotic choice on request forms
- › Do not dipstick test the urine of asymptomatic elderly and catheterised patients¹⁶
 - UTIs are overdiagnosed in elderly patients²⁴
 - urinary catheters are also commonly colonised, resulting in asymptomatic bacteriuria
 - asymptomatic bacteriuria is present in 3.6–19% of elderly patients and 15–50% of elderly individuals in long-term care²⁴
 - elderly institutionalised patients frequently receive unnecessary antibiotic treatment for asymptomatic bacteriuria despite clear evidence of adverse effects with no compensating clinical benefit^{14,25–27}
- Box 2 offers key advice about urine samples and dipsticks
- › Consider referral for urinary tract ultrasound (including post-void residual volume) in patients:
 - with very frequent infections
 - with recurrent *Proteus* infections (due to their association with renal calculi)
 - who do not respond to treatment
 - with post-micturition symptoms, such as a sensation of incomplete emptying, or those with a palpable bladder
- › Anatomical and surgically resolvable causes of recurrent UTI should be considered, including kidney stones, anatomical abnormalities, and urethral stricture (Table 1)²⁸
- › Consider a non-urgent referral for suspected bladder cancer in people aged 60 years and over with recurrent or persistent unexplained symptoms of UTI
 - who do not respond to antibiotics
 - with new storage symptoms where UTI is not confirmed

Figure 1: Algorithm on the diagnosis and management of patients with recurrent urinary tract infection





- with rigors, systemic illness, and loin pain
- › Consider an urgent referral (within 2 weeks) for suspected bladder cancer in patients:²⁹
 - aged 45 years and over with unexplained visible haematuria without urinary tract infection or visible haematuria that persists or recurs after successful treatment of urinary tract infection
 - aged 60 years and over with unexplained non-visible haematuria and either dysuria or a raised white blood cell count

Behavioural and lifestyle modifications

- › Advise patients with inadequate fluid intake to increase their fluid intake to at least 1.5 litres per day³⁰
 - increasing fluid intake does not reduce the risk of UTIs in patients who already drink sufficient fluids,³⁰ but evidence suggests that it may reduce the frequency of recurrent infections in those who do not drink sufficiently
 - dehydration is a particular cause of recurrent UTI in elderly individuals and should be discussed with the patient
- › Optimise diabetic control³¹
- › Treat constipation and diarrhoea, particularly in elderly patients—constipation in particular is a common underlying cause of recurrent UTI in this population
- › Encourage post-coital voiding in women with intercourse-triggered UTI

Antibiotic treatment

- › Antibiotic stewardship requires careful, reasonable, and accountable use of antibiotics to preserve their value and efficacy^{14,32}

- follow the recommendations regarding choice of antibiotic when sensitivities are provided with microbiological results
- › Choice of antibiotic is based on a variety of factors, including:
 - pathogens identified from urine culture
 - local variations in resistance and susceptibility patterns
 - comorbidities; e.g. nitrofurantoin should be used cautiously in patients with renal impairment^{33,34}
 - refer to summaries of product characteristics for precautions and warnings
 - interactions with concomitant drugs; e.g. folate antagonism may occur when trimethoprim is used with methotrexate³⁵
 - refer to summaries of product characteristics for drug interactions
 - multiple antibiotics should not be combined unless on expert advice
- › A 3-day course of antibiotics is usually sufficient for most adult non-pregnant women over 16 years of age¹⁸
 - if the patient remains symptomatic at the end of this course, reassess the diagnosis and consider continuing antibiotics after obtaining an MSU for culture and sensitivities
- › Patients with recurrent UTI can be treated via three approaches:
 - self-start antibiotics³⁶
 - many patients with recurrent UTI can accurately self-diagnose new episodes; these patients can access antibiotics via repeat prescription, keeping a course at home to start when they develop the first symptoms of an infection
 - limit the number of repeats so that patients are reviewed after six courses
 - consider monitoring to ensure that patients are not

Table 1: Correctable causes of recurrent UTI²⁸

Congenital	Acquired
› Vesico-ureteric reflux	› Calculi
› Pelvi-ureteric junction obstruction	› Fistulae
› Urethral valves (prosterior or anterior)	› Foreign bodies (stents, catheters)
› Mega-ureter	› Sexual activity-related causes
› Neurogenic bladder (e.g. spina bifida)	› Neuropathic bladder dysfunction
› Phimosis	› Detrusor dysfunction (acontractile or hypocontractile bladders)
	› Dysfunctional voiding
	› Bladder outflow obstruction (bladder neck dyssynergia, prostate disease, urethral stenosis, high-tone non-relaxing sphincters)
	› Chronic renal disease (infected cysts, papillary necrosis)
	› Malignancies
	› Immune deficiency—diabetes mellitus, immune suppressant medications, acquired immune deficiency syndrome

- acquiring antibiotic-resistant organisms
- continuous antibiotic prophylaxis³⁶
 - patients take low-dose antibiotics daily to prevent recurrence
 - consider non-antibiotic prophylaxis for all patients before starting continuous antibiotic prophylaxis
 - non-antibiotic prophylaxis may be continued as combination therapy if continuous antibiotic prophylaxis is started later
 - ask the patient to try no treatment after 3–6 months without infection and restart if UTI recurs
 - a single UTI following the cessation of prophylactic treatment is not uncommon, and patients should be informed of this possibility
 - the recommencement of prophylactic treatment should not be triggered by a single UTI after completion of a period of prophylactic treatment
 - if a patient develops a breakthrough infection while on antibiotic prophylaxis:
 - stop prophylaxis
 - order urine culture to check for resistant organisms
 - use a different agent to treat the acute episode
 - restart the original prophylaxis after the acute episode is resolved if resistance has not developed
 - audit antibiotic prophylaxis regularly and review patients who have been taking prophylactic antibiotics for 6–12 months to justify their continued use and with a view to stopping prophylaxis
- single-dose antibiotic prophylaxis³⁶
 - useful in women whose UTIs are triggered by intercourse with no other triggers
 - post-coital prophylaxis should be taken within 2 hours of intercourse
 - ask the patient to try no treatment after 3 months without infection and restart if UTIs recur
 - patients with other triggers, such as runners and cyclists, may also benefit from this approach
 - there is no evidence that this approach leads to increased resistance compared with continuous antibiotic prophylaxis
 - consider monitoring to ensure that patients are not developing antibiotic-resistant organisms

Side-effects of antibiotic prophylaxis

- › Antibiotic prophylaxis can have side-effects such as gastrointestinal upset³⁷
- › Vaginal thrush is a common side-effect of antibiotic prophylaxis,³⁷ but the risk is lower than with standard treatment doses; ideally, treat the thrush, but do not stop the antibiotic
- › Pulmonary toxicity is a rare side-effect of long-term nitrofurantoin use; any patient that develops breathlessness while taking low-dose nitrofurantoin should stop treatment and seek advice from their GP^{33,34}

- › Long-term nitrofurantoin use is also associated with hepatitis; patients should be monitored for signs such as brown urine^{33,34}

Antibiotic failure

- › Antibiotic failure can be defined as no significant change in the frequency of UTIs in two comparative 6-month periods, after the suitability of the antibiotic and adherence to treatment have been taken into account
 - consider a different antibiotic in patients with antibiotic resistance
 - emphasise the importance of adherence to treatment in patients who are non-adherent to their antibiotic regimen
 - consider non-antibiotic options
 - refer to specialist care for consideration of specialist options

Non-antibiotic treatments

- › Consider non-antibiotic therapies in all eligible patients
 - choose therapies with clinical evidence supporting their use in the treatment of recurrent UTI
 - take into account availability, ease of administration, cost-effectiveness, contraindications, and patient preferences
- › Treatments may need to be used in combination; none of the non-antibiotic therapeutic options discussed are contraindicated with other non-antibiotic treatments

Topical oestrogens

- › Decreasing oestrogen levels at menopause can lead to changes in the vaginal flora and pH
 - levels of protective lactobacilli decrease, reducing the capability of beneficial bacteria to outcompete *Escherichia coli* in the vaginas of postmenopausal women³⁸
 - oestrogen deficiency is a known risk factor for recurrent UTI⁶
- › There is no evidence to support the efficacy of oral oestrogens in the treatment of recurrent UTI,³⁹ but topical oestrogens may enhance innate immune mechanisms that protect against UTI⁴⁰ and are superior to placebo for reducing UTIs³⁹
- › Public perception is that vaginal oestrogens are dangerous because of the putative association between endometrial cancer and systemic hormone replacement therapy (HRT), but current evidence suggests that local oestrogens are effective in relieving symptoms in the short and long term (up to a year) and risks are very low⁴¹
- › Use of vaginal oestrogens prior to antibiotic prophylaxis in peri/postmenopausal women with oestrogen deficiency,

particularly those with other symptoms of oestrogen deficiency such as vaginal itching and dryness, may be beneficial for recurrent UTI

- because oral HRT has no effect on recurrent UTI, consider adding vaginal oestrogen to oral HRT
 - topical oestrogens can be administered by pessary, cream, or ring according to patient preferences, but patients may not achieve good internal coverage when applying cream
 - prescribe as directed according to choice of preparation
 - topical oestrogens can be continued after the discontinuation of antibiotic prophylaxis
- Vaginal oestrogen products are not licensed for preventing recurrent UTI, so use for this indication would be off-label; the prescriber should follow relevant professional guidance, taking full responsibility for the decision, and informed consent should be obtained and documented⁶
 - Although the risk of treatment with topical vaginal oestrogens is thought to be small, it is advisable to discuss possible risks of oestrogens, in line with NICE guidance:⁶
 - breast tenderness and vaginal bleeding in postmenopausal women compared with placebo, no treatment, or oral antibiotics
 - increased risk of venous thromboembolism, stroke, endometrial cancer (reduced by a progestogen), breast cancer, and ovarian cancer
 - increased risk of coronary heart disease in women who start combined HRT more than 10 years after menopause

Methenamine hippurate

- Methenamine hippurate has antibacterial properties when present in the urine, but it is unclear whether urinary acidification and the direct bacteriostatic effect of hippuric acid contribute significantly to its mode of action⁴²
- Available evidence comes from heterogeneous studies, but some trials report reductions in symptomatic UTIs with short-term use and suggest similar efficacy to antibiotic prophylaxis⁴²
- Methenamine hippurate is well tolerated and effective⁴²
- Methenamine hippurate may be ineffective in patients with neuropathic bladder or an abnormal renal tract⁴²
- Methenamine hippurate is contraindicated in patients with gout, severe renal and liver impairment, and dehydration⁴³
- Methenamine hippurate is an option for women who prefer to avoid antibiotics, but can also be taken in addition to antibiotic treatment
 - prescribe 1 g twice a day for 6 months initially, then review
 - consider advising patients to take vitamin C to acidify the urine, although the necessity of acidic urine for the

activation of methenamine hippurate is unclear

- check liver function every 3 months
- continue methenamine hippurate as a prophylactic

Vaccines

- In this context, vaccines are immunostimulants rather than true vaccines
- OM-89 involves oral administration of 18 heat-killed uropathogenic bacterial strains of *E. coli*^{44,45}
 - several randomised controlled trials (RCTs) have shown that OM-89 is superior to placebo and has a good safety profile^{44,45}
 - OM-89 is recommended by the European Association of Urology,¹⁷ but availability is an issue in the UK
- An inactivated bacterial cell suspension of selected strains of *E. coli*, *Klebsiella pneumoniae*, *Proteus vulgaris*, and *Enterococcus faecalis* can be administered sublingually for the prevention of UTI⁴⁶
 - in a multi-centre observational study involving 319 women with recurrent UTI, prophylactic treatment with this vaccine achieved a significant reduction in the number of UTIs compared with antibiotic treatment⁴⁶
 - good-quality evidence from RCTs is currently lacking on the efficacy of this treatment
- Vaginal mucosal vaccination involves vaginal administration by pessary of 10 heat-killed uropathogenic bacterial species, including *E. coli*, *P. vulgaris*, *K. pneumoniae*, *Morganella morganii*, and *E. faecalis*⁴⁵
 - studies show a slightly reduced recurrence of UTIs and an increased time to reinfection following repeated booster immunisations^{44,45}

Non-pharmacological options

Cranberry

- Cranberry is widely used in the prevention and treatment of UTI, and is postulated to acidify urine and prevent the adherence of bacterial fimbriae to urothelial cell receptors⁴⁷
- Evidence on the efficacy of cranberry in preventing recurrent UTI is lacking, and many studies are of poor quality with high levels of heterogeneity
 - a Cochrane review in 2008⁴⁸ suggested that cranberry can reduce recurrent UTIs, but an updated Cochrane review in 2012⁴⁷ that included three new papers found that cranberry products did not significantly reduce the occurrence of symptomatic UTI overall compared with placebo, water, or non-treatment
 - NICE concludes that some patients may benefit and there is no evidence of harm⁶
 - cranberry products, including juice, syrup, capsules, and tablets, are widely available⁶

- › Cranberry-based products may have beneficial effects with a low risk of harm:
 - the optimum dose and duration of use are unclear⁴⁷
 - capsules may be better than juice and high-strength capsules may be most effective¹⁶
 - cranberry may be an option for patients who do not want to take antibiotics, although SIGN guidance recommends that patients taking warfarin should avoid taking cranberry products¹⁶

D-mannose

- › D-mannose is a sugar that is available to buy as a powder or tablets^{6,49}
 - use of D-mannose is recommended in NICE guidance on recurrent UTI⁶
 - D-mannose is not a medicine
 - during the glycosylation of certain proteins, D-mannose is thought to bind to the type 1 pili of enteric bacteria, blocking their adhesion to uroepithelial cells
 - D-mannose showed similar efficacy to nitrofurantoin in preventing recurrent UTI in a single, relatively small RCT⁴⁹
 - the dose used in this RCT was 1000 mg twice daily,⁴⁹ but the optimum dose is unclear
 - D-mannose is well tolerated, but it should be used cautiously in patients with diabetes

Alternative therapies

- › Evidence about whether probiotics (lactobacilli) reduce the risk of UTI in people with recurrent UTI is inconclusive^{6,50}
- › Acupuncture has been shown to reduce episodes of UTI compared with no treatment, but studies to date are small⁵¹

Specialist options

Intravesical GAG layer replacement

- › An intact glycosaminoglycan (GAG) layer in the bladder is essential to protect bladder cells and prevent the adhesion of bacteria to the bladder epithelium, and damage to the GAG layer or deficiencies in GAG-layer components may be aetiological in recurrent UTI^{52,53}
- › The GAGs hyaluronic acid and chondroitin sulphate, alone and in combination, can be instilled into the bladder to enhance the protective function of the urothelium^{54,55}
- › GAG layer therapies are currently a specialist option that offer an alternative to antibiotics for patients with persistent symptoms
- › GAG layer therapies are often administered by a specialist through a catheter
 - a catheter-free option is available that may facilitate administration by non-specialists
 - patients competent in self-catheterisation will be able to

self-administer GAG layer therapies following training

- › GAGs reduce the recurrence of cystitis and UTIs, pelvic pain, and urgency/frequency and have a favourable side-effect profile, but their cost-effectiveness is unclear and further studies are needed to validate these treatments^{54,55}

Intravesical antibiotics

- › Intravesical installation of antibiotics, most commonly gentamicin and amikacin, has been used in specialist centres and has been anecdotally reported to be helpful for some patients; however, this approach should only be used with expert advice⁵⁶

Patient education

- › Explain the need for good adherence to treatment
- › Reinforce lifestyle modifications at every opportunity

Follow up

- › Advise patients to return if they develop breakthrough infections or troublesome side-effects
- › If patients are free of infection by 6 months based on symptoms and/or microbiology, consider withdrawal of

Useful resources

Resources for healthcare professionals

- › Bath and North East Somerset Clinical Commissioning Group. *To dip or not to dip – a patient centred approach to improve the management of UTIs in the care home environment*. www.bathandnortheastsomersetccg.nhs.uk/assets/uploads/2016/04/To-Dip-or-Not-to-Dip.pdf
- › NICE. *Urinary tract infection (recurrent): antimicrobial prescribing*. NICE Guideline 112. www.nice.org.uk/ng112
- › Public Health England. *Diagnosis of urinary tract infections (UTIs) – quick reference guide for primary care: summary table*. www.gov.uk/government/uploads/system/uploads/attachment_data/file/619772/Urinary_tract_infection_UTI_guidance.pdf

Resources for patients

- › NHS. *How should I collect and store a urine sample?* www.nhs.uk/common-health-questions/infections/how-should-i-collect-and-store-a-urine-sample/
- › Patient.info. *Midstream specimen of urine*. <https://patient.info/health/urine-infection-in-men/midstream-specimen-of-urine-msu>

treatment, especially antibiotics

Red flag

- Refer patients with persistent haematuria for suspected cancer in line with NICE Guideline 12²⁹

Conflicts of interest

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