NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Guideline

Urinary tract infection (recurrent): antimicrobial prescribing

Draft for consultation, August 2024

This guideline sets out an antimicrobial prescribing strategy for preventing recurrent urinary tract infections in children, young people and adults who do not have a catheter. It aims to optimise antibiotic use and reduce antibiotic resistance.

This guideline will update NICE guideline NG112 (published October 2018).

Who is it for?

- Health professionals
- People with recurrent urinary tract infection, their families and carers

What does it include?

- the recommendations
- a recommendation for research
- a summary of the evidence, which also explain why the committee made the 2024 recommendations.

Information about how the guideline was developed is on the guideline's webpage. This includes the evidence reviews, the scope, details of the committee and any declarations of interest.

New and amended recommendations

We have reviewed the evidence on methenamine hippurate for preventing recurrent UTI. We have not reviewed the evidence on referral and seeking

specialist advice, or on oestrogen, but have amended some recommendations based on committee expertise. You are invited to comment on the new and amended recommendations. These are marked as **[2024]** and **[2018, amended 2024]**.

We have not reviewed the evidence for the recommendations marked **[2018]** (shaded in grey) and cannot accept comments on them. In some cases, we have made minor wording changes for clarification or to bring the language and style up to date.

See update information for a full explanation of what is being updated.

Full details of the evidence and the committee's discussion on the 2024 recommendations are in evidence review B. Evidence for the 2018 recommendations is in the evidence review for the 2018 guideline.

Recommendations

1.1 Preventing recurrent urinary tract infections

1.1.1 Manage an acute urinary tract infection (UTI) as outlined in NICE's guidelines on UTI (lower): antimicrobial prescribing or pyelonephritis (acute): antimicrobial prescribing. **[2018]**

1.1.2 Be aware that recurrent UTI:

- includes lower UTI and upper UTI (acute pyelonephritis)
- may be due to relapse (with the same strain of organism) or reinfection (with a different strain or species of organism)
- is particularly common in women, and trans men and non-binary people with a female urinary system. **[2018]**

1.1.3 Give advice to people with recurrent UTI about behavioural and personal hygiene measures and self-care treatments (see the

recommendations on self-care) that may help to reduce the risk of UTI. **[2018]**

Referral and seeking specialist advice

1.1.4 Refer or seek specialist advice on further investigation and management for:

- men, and trans women and non-binary people with a male genitourinary system, aged 16 and over
- people with recurrent upper UTI
- people with recurrent lower UTI when the underlying cause is unknown
- pregnant women, and pregnant trans men and non-binary people
- children and young people aged under 16 years in line with NICE's guideline on urinary tract infection in under 16s
- people with suspected cancer in line with NICE's guideline on suspected cancer: recognition and referral
- anyone who has had gender reassignment surgery that involved structural alteration of the urethra. **[2018, amended 2024]**

For a short explanation of why the committee made the 2018 recommendations, see the evidence and committee discussion on antibiotic prophylaxis.

Full details of the evidence and committee's discussion are available in the evidence review.

1.2 Treatments for preventing recurrent UTI

Oestrogen

In August 2024, this was an off-label use of vaginal oestrogen products. See NICE's information on prescribing medicines.

See also the recommendations about genitourinary symptoms associated with menopause in NICE's guideline on menopause. The advice in the menopause guideline covers the use of vaginal oestrogen for people with a personal history of breast cancer, and should be read in conjunction with the recommendations in this section. (An update of the NICE guideline on menopause is in development and is due to be published in November 2024).

These recommendations are for women, and trans men and non-binary people with a female urinary system, who are experiencing perimenopause or menopause, or who have already experienced menopause.

1.2.1 Consider vaginal oestrogen for recurrent UTI if behavioural and personal hygiene measures alone are not effective or not appropriate. **[2018, amended 2024]**

1.2.2 When discussing vaginal oestrogen for preventing recurrent UTI, cover the following to ensure shared decision making:

- the severity and frequency of previous symptoms
- the risk of developing complications from recurrent UTIs
- the possible benefits of treatment, including for other related symptoms, such as vaginal dryness
- that serious side effects are very rare
- that vaginal oestrogen is absorbed locally – a minimal amount is absorbed into the bloodstream, but this is unlikely to have a significant effect throughout the body

- the person's preferred treatment option for vaginal oestrogen (for example, a cream or a ring). **[2018, amended 2024]**

1.2.3 Review treatment with vaginal oestrogen within 12 months, or earlier if agreed with the person. **[2018]**

1.2.4 Do not offer systemic hormone replacement therapy specifically to reduce the risk of recurrent UTI. **[2018, amended 2024]**

For a short explanation of why the committee made the 2018 recommendations, see the evidence and committee discussion on oestrogens.

Full details of the evidence and committee's discussion are available in the evidence review.

Single-dose antibiotic prophylaxis

These recommendations are for women, and trans men and non-binary people with a female urinary system, who are not pregnant.

1.2.5 Consider a trial of single-dose antibiotic prophylaxis for recurrent UTI only if behavioural and personal hygiene measures, and vaginal oestrogen are not effective or not appropriate. **[2018]**

1.2.6 Ensure that any current UTI has been adequately treated then consider single-dose antibiotic prophylaxis for recurrent UTI for use when there has been exposure to an identifiable trigger (see the recommendations on choice of antibiotic prophylaxis). Take account of:

- the severity and frequency of previous symptoms
- the risk of developing complications
- previous urine culture and susceptibility results
- previous antibiotic use, which may have led to resistant bacteria

- the person's preferences for antibiotic use. **[2018]**

1.2.7 When single-dose antibiotic prophylaxis is offered, give advice about:

- how to use the antibiotic
- possible adverse effects of antibiotics, particularly diarrhoea and nausea
- returning for review within 6 months
- seeking medical help if there are symptoms of an acute UTI. **[2018]**

For a short explanation of why the committee made the 2018 recommendations, see the evidence and committee discussion on antibiotic prophylaxis and antibiotic dosing and course length.

Full details of the evidence and committee's discussion are available in the evidence review.

Methenamine hippurate

1.2.8 Consider methenamine hippurate as an alternative to daily antibiotic prophylaxis (see the section on daily antibiotic prophylaxis) for recurrent UTI in women, and trans men and non-binary people with a female urinary system, who:

- are not pregnant **and**
- have recurrent UTI that has not been adequately improved by behavioural and personal hygiene measures, vaginal oestrogen or single-dose antibiotic prophylaxis (if any of these have been appropriate and are applicable).

  For those with recurrent upper UTI or complicated lower UTI, follow recommendation 1.2.9. **[2024]**

1.2.9 Seek specialist advice if considering methenamine hippurate as an alternative to daily antibiotic prophylaxis for recurrent UTI:

- during pregnancy
- in people with recurrent upper UTI or complicated lower UTI
- in men, and trans women and non-binary people with a male genitourinary system
- in children and young people. **[2024]**

In August 2024, the use of methenamine hippurate for prophylaxis of recurrent upper UTI or complicated lower UTI, and for recurrent UTI in children under 6 years, was off-label. See NICE's information on prescribing medicines.

For a short explanation of why the committee made the 2024 recommendations, see the evidence and committee discussion on methenamine hippurate.

Full details of the evidence and committee's discussion are available in evidence review B.

Daily antibiotic prophylaxis

General principles for prescribing

These recommendations are for children, young people and adults with recurrent UTI.

1.2.10 When considering a trial of daily antibiotic prophylaxis, take account of:

- the severity and frequency of previous symptoms
- the risks of long-term antibiotic use
- the risk of developing complications
- previous urine culture and susceptibility results

- previous antibiotic use, which may have led to resistant bacteria.

[2018]

1.2.11 When offering a trial of daily antibiotic prophylaxis, give advice about:

- the risk of resistance with long-term antibiotics, which means they may be less effective in the future
- possible adverse effects of long-term antibiotics
- returning for review within 6 months
- seeking medical help if there are symptoms of an acute UTI.

[2018]

For women, and trans men and non-binary people with a female urinary system, who are not pregnant

1.2.12 If there has been no improvement after single-dose antibiotic prophylaxis or methenamine hippurate (if either of these have been appropriate and are applicable), ensure that any current UTI has been adequately treated then consider a trial of daily antibiotic prophylaxis for recurrent UTI (see the recommendations on choice of antibiotic prophylaxis). Take account of the following:

- any further investigations (for example, ultrasound) that may be needed to identify an underlying cause
- the person's preferences for antibiotic use
- any other factors listed in recommendation 1.2.10 in the section on general principles for prescribing daily antibiotic prophylaxis.

[2018]

For advice to give when offering daily antibiotic prophylaxis, see the section on general principles for prescribing.

During pregnancy, or for men, and trans women and non-binary people with a male genitourinary system

1.2.13 Ensure that any current UTI has been adequately treated, then consider a trial of daily antibiotic prophylaxis for recurrent UTI (see the recommendations on choice of antibiotic prophylaxis) if behavioural and personal hygiene measures alone, or methenamine hippurate (if used in line with recommendation 1.2.9), are not effective or not appropriate, with specialist advice. Take account of the following:

- any further investigations (for example, ultrasound) that may be needed to identify an underlying cause
- the person's preferences for antibiotic use
- any other factors listed in recommendation 1.2.10 in the section on general principles for prescribing daily antibiotic prophylaxis. **[2018]**

For advice to give when offering daily antibiotic prophylaxis, see the section on general principles for prescribing.

For children and young people under 16 years

1.2.14 Ensure that any current UTI has been adequately treated then consider a trial of daily antibiotic prophylaxis for recurrent UTI (see the recommendations on choice of antibiotic prophylaxis) if behavioural and personal hygiene measures alone, or methenamine hippurate (if used in line with recommendation 1.2.9), are not effective or not appropriate, with specialist advice. Take account of the following:

- underlying causes following specialist assessment and investigations

- the uncertain evidence of benefit of antibiotic prophylaxis for reducing the risk of recurrent UTI and the rate of deterioration of renal scars
- preferences for antibiotic use
- any other factors listed in recommendation 1.2.10 in the section on general principles for prescribing daily antibiotic prophylaxis. **[2018]**

For advice to give when offering daily antibiotic prophylaxis, see the section on general principles for prescribing.

Reassessing the use of daily antibiotic prophylaxis in all people

1.2.15 Review daily antibiotic prophylaxis for recurrent UTI at least every 6 months, with the review to include:

- assessing the success of prophylaxis
- discussion of continuing, stopping or changing prophylaxis (taking into account the person's preferences for antibiotic use and the risk of antimicrobial resistance)
- a reminder about behavioural and personal hygiene measures and self-care treatments (see the recommendations on self-care).

If antibiotic prophylaxis is stopped, ensure that people have rapid access to treatment if they have an acute UTI. **[2018]**

For a short explanation of why the committee made the 2018 recommendations, see the evidence and committee discussion on antibiotic prophylaxis.

Full details of the evidence and committee's discussion are available in the evidence review.

1.3 Self-care

1.3.1 Be aware that some women, and trans men and non-binary people with a female urinary system, who have recurrent UTI and are not pregnant may wish to try:

- D-mannose (the evidence for D-mannose was based on a study in which it was taken as 200 ml of 1% solution once daily in the evening); D-mannose is a sugar that is available to buy as powder or tablets – it is not a medicine
- cranberry products (evidence of benefit is uncertain and there is no evidence of benefit for older women, or older trans men or non-binary people with a female urinary system). **[2018]**

1.3.2 Be aware that some children and young people under 16 years with recurrent UTI may wish to try cranberry products with the advice of a paediatric specialist (evidence of benefit is uncertain). **[2018]**

1.3.3 Advise people taking cranberry products or D-mannose about the sugar content of these products, which should be considered as part of the person's daily sugar intake. **[2018]**

1.3.4 Be aware that evidence is inconclusive about whether probiotics (lactobacillus) reduce the risk of UTI in people with recurrent UTI. **[2018]**

For a short explanation of why the committee made the 2018 recommendations, see the evidence and committee discussion on self-care.

Full details of the evidence and committee's discussion are available in the evidence review.

1.4 Choice of antibiotic prophylaxis

1.4.1 When prescribing antibiotic prophylaxis for recurrent UTI, take account of local antimicrobial resistance (AMR) data from the UK Health Security Agency and:

- follow the recommendations in table 1 for people aged 16 years and over
- follow the recommendations in table 2 for children and young people under 16 years. **[2018]**

Table 1 People aged 16 years and over

Treatment	Antibiotic prophylaxis and dosage
First-choice oral antibiotics	**Trimethoprim**: 200 mg as a single dose when exposed to a trigger, or 100 mg at night There is a teratogenic risk in first trimester of pregnancy (folate antagonist; BNF information on trimpethoprim). The companies advise that it is contraindicated in pregnancy See also the summary of product characteristics for trimethoprim 50 mg/5 ml suspension **Nitrofurantoin** (if estimated glomerular filtration rate is 45 ml/minute or more): 100 mg as a single dose when exposed to a trigger, or 50 mg to 100 mg at night Avoid at term in pregnancy; may produce neonatal haemolysis (BNF information on nitrofurantoin) In August 2024, use of nitrofurantoin for recurrent upper UTI or complicated lower UTI was off-label. See NICE's information on prescribing medicines.
Second-choice oral antibiotics	**Amoxicillin** (off-label use): 500 mg as a single dose when exposed to a trigger, or 250 mg at night **Cefalexin**: 500 mg as a single dose when exposed to a trigger, or 125 mg at night

See the BNF for appropriate use and dosing in specific populations, for example, in people who have hepatic or renal impairment, or during pregnancy or breastfeeding.

Choose antibiotics according to recent culture and susceptibility results where possible, with rotational use based on local policies. Select a different antibiotic for prophylaxis if treating an acute UTI.

For off-label use, see NICE's information on prescribing medicines.

Table 2 Children and young people under 16 years

Treatment	Antibiotic prophylaxis and dosage
Choice for children under 3 months	Refer to paediatric specialist
First-choice oral antibiotics for children aged 3 months and over (specialist advice only)	**Trimethoprim**: 3 months to 5 months, 2 mg/kg at night (maximum 100 mg per dose) or 12.5 mg at night 6 months to 5 years, 2 mg/kg at night (maximum 100 mg per dose) or 25 mg at night 6 years to 11 years, 2 mg/kg at night (maximum 100 mg per dose) or 50 mg at night 12 years to 15 years, 100 mg at night There is a teratogenic risk in first trimester of pregnancy (folate antagonist; BNFC information on trimpethoprim). The companies advise that it is contraindicated in pregnancy (see also the summary of product characteristics for trimethoprim) **Nitrofurantoin** (if estimated glomerular filtration rate is 45 ml/minute or more): 3 months to 11 years, 1 mg/kg at night 12 years to 15 years, 50 mg to 100 mg at night Avoid at term in pregnancy; may produce neonatal haemolysis (BNFC information on nitrofurantoin) In August 2024, use of nitrofurantoin for recurrent upper UTI or complicated lower UTI was off-label. See NICE's information on prescribing medicines.
Second-choice oral antibiotics for children aged 3 months and over	**Cefalexin**: 3 months to 15 years, 12.5 mg/kg at night (maximum 125 mg per dose) **Amoxicillin** (off-label use): 3 months to 11 months, 62.5 mg at night 1 year to 4 years, 125 mg at night 5 years to 15 years, 250 mg at night

See the BNF for children (BNFC) for appropriate use and dosing in specific populations, for example, in children or young people with hepatic or renal impairment.

Choose antibiotics according to recent culture and susceptibility results where possible, with rotational use based on local policies. Select a different antibiotic for prophylaxis if treating an acute UTI. If 2 or more antibiotics are appropriate, choose the antibiotic with the lowest acquisition cost.

The age bands apply to children of average size and, in practice, the prescriber will use the age bands in conjunction with other factors such as the severity of the condition and the child's size in relation to the average size of children of the same age.

For off-label use, see NICE's information on prescribing medicines.

> For a short explanation of why the committee made this 2018 recommendation, see the evidence and committee discussion on choice of antibiotic prophylaxis and antibiotic dosing and course length.
>
> Full details of the evidence and committee's discussions are available in the evidence review.

Terms used in the guideline

Complicated lower UTI

Lower UTI where 1 or more factors predispose a person to persistent or recurrent infection, or may make treatment ineffective. These factors can include abnormalities of the urinary tract, a virulent organism that is causing infection, a weakened immune system (for example, caused by diabetes mellitus) or impaired renal function (source: clinical knowledge summary).

Recurrent UTI

Recurrent UTI in adults is defined as repeated UTI with a frequency of 2 or more UTIs in the last 6 months or 3 or more UTIs in the last 12 months (European Association of Urology [EAU] guidelines on urological infections [2017]).

Recurrent UTI is diagnosed in children and young people under 16 years if they have:

- 2 or more episodes of UTI with acute pyelonephritis/upper UTI **or**
- 1 episode of UTI with acute pyelonephritis plus 1 or more episode of UTI with cystitis/lower UTI **or**
- 3 or more episodes of UTI with cystitis/lower UTI.

See NICE's guideline on urinary tract infection in under 16s.

Systemic hormone replacement therapy (HRT)

HRT that is absorbed into the bloodstream and can have an effect throughout the body.

Trigger

Some people (mainly women, and trans men and non-binary people with a female urinary system) may be able to identify 1 or more triggers (for example, sexual intercourse) that often brings on a UTI. These triggers may vary for different people.

Recommendations for research

The guideline committee has made the following recommendation for research.

1 Methenamine hippurate use in other populations

What is the clinical and cost-effectiveness of methenamine hippurate when compared to antibiotics in the prevention of recurrent UTIs for men, pregnant

women, older people and people with upper UTI or complicated lower UTI? **[2024]**

For a short explanation of why the committee made the recommendation for research, see the summary of the evidence on methenamine hippurate.

Summary of the evidence

This is a summary of the evidence and the committee's discussions. Sections marked:

- (2024) are part of the 2024 evidence review
- (2018, amended 2024) have been amended without an evidence review, based on the expertise of the committee for the 2024 update
- (2018) are part of the 2018 evidence review.

Oestrogens (2018)

- Oral oestrogens (with or without progestogens) taken for up to 4 years did not significantly reduce the risk of recurrent infection in women after the menopause with recurrent UTI compared with placebo (moderate quality evidence). This was based on a systematic review and meta-analysis of RCTs (Perrotta et al. 2008). Recurrent UTI was defined as 3 or more episodes in the past 12 months or 2 or more episodes in the past 6 months.
- Vaginal oestrogen cream (estriol cream 0.5 mg applied topically at night for 2 weeks then twice weekly) for 8 months significantly reduced the risk of recurrent infection in women after the menopause compared with placebo (16.0% versus 62.8%, number needed to treat [NNT] 3 [range 2 to 4]; high quality evidence). This was based on 1 RCT in the Perrotta et al. (2008) systematic review.
- Vaginal oestrogen cream was also significantly more effective than oral antibiotics (ofloxacin 600 mg a day) in reducing the risk of recurrent infection over a 3-month study period (7.4% versus 80.0%, NNT 2 [range 2 to 2]; low quality evidence). However, no difference was seen 2 months

after treatment was stopped (very low quality evidence). This was based on 1 RCT included in the Perrotta et al. (2008) systematic review.

- Vaginal oestrogen administered via a vaginal ring in 12-week cycles, for a total of 36 weeks significantly reduced the risk of recurrent infection in women after the menopause compared with placebo (50.9% versus 80.0%, NNT 4 [range 3 to 9]; Perrotta et al. 2008, moderate quality evidence).
- However, vaginal oestrogen administered via a pessary (used daily for 2 weeks then once every 2 weeks) significantly increased the risk of recurrent infection in women after the menopause compared with an oral antibiotic (nitrofurantoin 100 mg a day) over a 9-month study period (67.4% versus 51.8%; Perrotta et al. 2008; low quality evidence).
- Oral oestrogens increased adverse events (such as breast tenderness and vaginal bleeding) in women after the menopause compared with placebo (number needed to harm [NNH 5; range 3 to 14]; Perrotta et al. 2008; high quality evidence).
- Vaginal oestrogens did not significantly increase adverse events (such as breast tenderness and vaginal bleeding) in women after the menopause compared with placebo or no treatment (Perrotta et al. 2008; low to moderate quality evidence).
- Oestrogens (hormone replacement therapy; HRT) increase the risk of venous thromboembolism (when taken orally), stroke, endometrial cancer (reduced by a progestogen), breast cancer and ovarian cancer; there is an increased risk of coronary heart disease in women who start combined HRT more than 10 years after menopause (Medicines and Healthcare products Regulatory Agency [MHRA] Drug Safety Update on HRT, September 2007 and BNF information on sex hormones). Before prescribing HRT, health professionals should carefully consider the potential benefits and risks for every woman. NICE's guideline on menopause covers the use of vaginal oestrogen for urogenital atrophy (an update of this guideline is in development and is due to be published in November 2024).

Committee discussion on oestrogens (in 2018 and 2024)

- Based on evidence, the committee agreed that vaginal oestrogens were effective in reducing the risk of recurrent UTI in women after the menopause, although this was based on small numbers of women and appears to diminish when the treatment is stopped. They noted the low number needed to treat [NNTs] for recurrent infection compared with placebo (NNT 3 [range 2 to 4] for topical cream; NNT 4 [range 3 to 9] for vaginal ring), and also when a topical cream was compared with antibiotics (NNT 2 [range 2 to 2]). However, oestrogen administered via a pessary was less effective than antibiotics. The committee agreed that, based on their experience, vaginal oestrogen is also effective in reducing the risk of recurrent UTI in women, and trans men and non-binary people with a female urinary system, during the perimenopausal period. **(2018, amended 2024)**
- The committee was aware of the 2019 Medicines and Healthcare products Regulatory Agency drug safety update on HRT and they agreed it was important for prescribers to discuss this with people, and to reassure people that serious side effects are very rare when using vaginal oestrogen. They also highlighted the NICE guideline on menopause because this covers the use of vaginal oestrogen for those with a personal history of breast cancer and should be read in conjunction with the recommendations in this guideline. **(2018, amended 2024)**
- Vaginal oestrogens are not licensed for preventing recurrent UTI, although oestrogen deficiency is a known risk factor. Based on evidence, their experience and data on antimicrobial resistance, the committee agreed that vaginal oestrogens could be considered for anyone with recurrent UTI who is experiencing perimenopause or menopause, or who has already experienced menopause, with review within 12 months, or earlier if agreed with the person. The committee recognised that decisions about treatment options can depend on the person's

preference and that the benefits and harms of vaginal oestrogens need to be discussed, taking account of other symptoms the person may want to address, such as vaginal dryness. **(2018, amended 2024**)

- The committee could not make any firm conclusions from the evidence or their experience about different vaginal oestrogen products. They agreed that this will need to be considered on an individual basis. **(2018)**
- Based on evidence of a lack of effectiveness and taking account of MHRA safety advice, the committee agreed not to recommend systemic HRT specifically to prevent recurrent UTI. The evidence on HRT was specific to oral HRT but the committee agreed the recommendation should cover all systemic HRT (preparations containing higher doses of oestrogen that are absorbed throughout the body, compared with low-dose vaginal preparations that minimise the amount of oestrogen absorbed) because there are high-dose oestrogen products available in non-oral preparations (for example, skin patch or gel). **(2018, amended 2024)**

Methenamine hippurate (2024)

- Evidence on the effectiveness of methenamine hippurate compared to antibiotics was derived from only 2 studies and was rated as very low quality.
- Evidence was only identified in women aged 18 years or older who were not pregnant.
- Higher total numbers of UTI episodes were reported for methenamine hippurate when compared with antibiotics during prophylactic treatment and during follow-up (evidence was low quality for prophylactic treatment and very low quality for follow-up).
- Evidence on antibiotic resistance in E. coli during prophylactic treatment found fewer antimicrobial categories and fewer antibiotics to which E. coli from perineal swabs was resistant for women taking methenamine hippurate compared with antibiotics (low quality evidence).

- There was a higher number of antibiotics to which E. coli from perineal swabs was resistant at the end of the follow-up period for women taking methenamine hippurate compared with antibiotics (low quality evidence).
- A higher rate of antibiotics used for treating a recurrent UTI episode (in addition to any antibiotics used as part of the prescribed intervention) during the prophylactic treatment was evident for women taking methenamine hippurate compared to antibiotics (very low quality evidence). A higher rate of antibiotics used for other reasons than recurrent UTI was evident in women taking methenamine hippurate compared to antibiotics during the follow-up period (very low quality evidence).
- No evidence of difference between methenamine hippurate and antibiotic prophylaxis was found for serious adverse events, measures for patient satisfaction, or gastrointestinal issues. There was also no evidence of difference for the following:
  - other measures of recurrence (for example, any recurrence of UTI and time to infection)
  - antibiotic resistance (for example, at least 1 E. coli isolate from perineal swab demonstrating multidrug resistance and any resistance in any significant isolate from symptomatic urine samples)
  - antibiotic use (for example, antibiotics used for reasons other than recurrent UTI during prophylactic treatment).
- Economic evidence centred around 2 analyses. One analysis (which was model-based) showed that over a lifetime horizon, antibiotic prophylaxis dominated methenamine hippurate having a 60% probability of being cost effective at a £20,000 per QALY threshold. The other analysis (which was trial-based) showed mixed results over a time horizon of 18 months, with methenamine hippurate dominating antibiotic prophylaxis in the adjusted analysis. Although the model-based analysis showed antibiotic prophylaxis to be more cost effective, it did not include the costs of the additional monitoring and testing needed for antibiotic prophylaxis that is not needed for methenamine hippurate.

Committee discussion in 2024 on methenamine hippurate

- The committee noted that the aim of the evidence review was to determine whether methenamine hippurate is non-inferior to antibiotics rather than determining which one is more effective. That is, the aim was to determine if it works as well as antibiotics or, where antibiotics perform better, the difference is small enough that it would be unlikely to impact on someone in an important way. In turn, this would help determine if methenamine hippurate is a viable alternative to antibiotics and could aid antimicrobial stewardship.
- The evidence found no differences in most outcomes for methenamine hippurate when compared to antibiotics. The committee agreed that this indicated that methenamine hippurate can be an effective alternative to antibiotics for recurrent UTI in women, and in trans men and non-binary people with a female urinary system.
- The committee discussed the higher incidence rate of UTI during prophylactic treatment for women taking methenamine hippurate compared to those taking antibiotics but they agreed that the difference in results was not clinically important. The absolute difference in the total number of episodes between groups was approximately 0.5 more episodes of UTI per person per year in the methenamine hippurate groups. However, according to the evidence and the committee's experience, this would need to be a reduction of 1 episode or more per person per year to be deemed clinically important.
- The committee discussed that, compared to antibiotic resistance, antibiotic use other than for the prescribed intervention was a less critical outcome. They also noted that the higher use of antibiotics other than for the prescribed intervention in women using methenamine hippurate could potentially confound the results for antibiotic resistance. This is because those prescribed additional antibiotics may be more likely to develop antibiotic resistance. Additionally, the committee highlighted that

prophylactic treatment in the studies lasted for 12 months but, in reality, treatment may last much longer.

- Evidence was only available for women aged 18 years and over. However, based on their knowledge and experience, the committee agreed that the recommendation could also be extended to those aged 16 years and over because there is no clinical reason to expect any differences in a 16- or 17-year-old compared to an 18-year-old.
- Based on their knowledge and experience, the committee agreed that specialist advice should be sought if methenamine hippurate is being considered for other groups of people with recurrent UTI, including upper UTI or complicated lower UTI. This is because, in their experience, it may be an appropriate treatment but there was no evidence to inform when it may be beneficial.
- When reviewing cost effectiveness and resource use, the committee considered both the model-based and trial-based economic analyses as equally important in their decision making. They noted that use of methenamine hippurate as an alternative to antibiotic prophylaxis for people with recurrent UTI varies throughout the NHS. Its use has also increased across all regions in England since 2019. The recommendation in this guideline may further increase the use of methenamine hippurate in women, and trans men and non-binary people with a female urinary system who are not pregnant. Methenamine hippurate is more expensive than antibiotic prophylaxis, and so there is the potential for additional costs to the NHS, but these costs would vary and depend on local prescribing strategies. However, the use of methenamine hippurate may reduce the use of antibiotics and consequences such as adverse events and antibiotic resistance, giving some drug cost and other savings.

Antibiotic prophylaxis (2018)

- The main complication of lower UTIs, including recurrent infections, is ascending infection leading to pyelonephritis. Most episodes of pyelonephritis are uncomplicated and result in no residual kidney damage. However, complications can include impaired renal function or renal failure, septicaemia and preterm labour in pregnancy (NICE clinical knowledge summary on pyelonephritis).
- In pregnancy, asymptomatic bacteriuria can lead to pyelonephritis; and symptomatic UTI has been associated with developmental delay or cerebral palsy in the infant, and fetal death (NICE clinical knowledge summary on UTI [lower] – women).
- In men with UTIs, prostate involvement is common, which may lead to complications such as prostatic abscess or chronic bacterial prostatitis, and urinary stones are a possibility (NICE clinical knowledge summary on UTI [lower] – men).
- In children and young people, UTIs can lead to renal scarring, but more often this is preceded by acute pyelonephritis rather than cystitis. Renal scarring is more common in children with vesicoureteral reflux (VUR), where recurrent UTIs are more likely (NICE clinical knowledge summary on UTI – children).

Efficacy of antibiotic prophylaxis

- Antibiotic prophylaxis for 6 to 12 months significantly reduced the risk of recurrent infection (using microbiological criteria) in women who were not pregnant and had recurrent UTI (2 or more 'uncomplicated' episodes in the past 12 months) compared with placebo (12.3% versus 65.5%, number needed to treat [NNT 2; range 2 to 3]; high quality evidence). This was based on a systematic review and meta-analysis (Albert et al. 2004). However, there was no significant difference when recurrent infections were reported after the period of prophylaxis (very low quality evidence).
- Antibiotic prophylaxis with nitrofurantoin for 5 weeks to 24 months significantly reduced the risk of recurrent infection in a mixed population of adults (including women who were not pregnant, and men) and children

(mainly girls) with recurrent UTI when compared with placebo or no treatment (22.5% versus 59.0%, NNT 3 [range 3 to 4]; low quality evidence). This was based on a systematic review and meta-analysis of RCTs (Muller et al. 2017).

- Antibiotic prophylaxis with nitrofurantoin 50 mg 3 times a day for the duration of pregnancy significantly reduced the risk of recurrent asymptomatic bacteriuria in pregnant women who were admitted to hospital with acute pyelonephritis (32.6% versus 59.3%, NNT 4 [range 3 to 13]) compared with no treatment (monitoring alone; moderate quality evidence). This was based on 1 RCT (n=102) included in a systematic review (Schneeberger et al. 2015). However, antibiotic prophylaxis did not significantly reduce the risk of recurrent UTI (including pyelonephritis) in pregnant women, or birth outcomes such as preterm birth, low birthweight and miscarriage (Schneeberger et al. 2015; very low to low quality evidence).
- Antibiotic prophylaxis with nitrofurantoin or co-trimoxazole for at least 6 months (duration not reported in all studies) did not significantly reduce the risk of recurrent infection in children aged under 18 with recurrent UTI compared with placebo or no treatment (very low quality evidence). This was based on a systematic review and meta-analysis of RCTs (Williams and Craig 2011). Not all studies had clearly defined inclusion and exclusion criteria, and some had a small proportion of children with VUR. However, the result did not change when the analysis was restricted to studies that included children without VUR (very low quality evidence).
- Antibiotic prophylaxis for at least 2 months (co-trimoxazole in most studies) did not significantly reduce the rate of deteriorated renal scars in children under 18 years (with or without VUR) compared with placebo or no treatment (very low quality evidence). This was based on a systematic review and meta-analysis of RCTs (Dai et al. 2010).
- There was no significant difference in the rate of antimicrobial resistance antibiotic prophylaxis compared with placebo in children under 18 years (Williams and Craig 2011, very low quality evidence).

Safety of antibiotic prophylaxis

- Antibiotic-associated diarrhoea occurs in 2% to 25% of people taking antibiotics, depending on the antibiotic used (NICE clinical knowledge summary on diarrhoea – antibiotic associated).
- About 10% of the general population claim to have a penicillin allergy; this has often been because of a skin rash that occurred during a course of penicillin in childhood. Fewer than 10% of people who think they are allergic to penicillin are truly allergic. See NICE's guideline on drug allergy for more information.
- Nitrofurantoin should be used with caution in those with renal impairment (MHRA Drug Safety Update on nitrofurantoin, September 2014). It should be avoided at term in pregnancy because it may produce neonatal haemolysis. Adults (especially older adults) and children on long-term therapy should be monitored for liver function and pulmonary symptoms (BNF information on nitrofurantoin).
- Trimethoprim has a teratogenic risk in the first trimester of pregnancy (folate antagonist; BNF information on trimethoprim). Manufacturers advise that trimethoprim is contraindicated in pregnancy (trimethoprim summary of product characteristics).
- In women who were not pregnant, there was no significant difference in serious adverse effects with antibiotic prophylaxis compared with placebo, but there was a significant increase in the number of 'other adverse effects' (low quality evidence). This was based on a systematic review and meta-analysis of RCTs (number needed to harm [NNH 13; [range 7 to 70]; Albert et al. 2004).
- In children, there was no significant difference in the incidence of adverse effects reported or the number of withdrawals due to adverse events with antibiotic prophylaxis compared with placebo or no treatment (Williams and Craig 2011; very low quality evidence).
- No systematic reviews or RCTs were identified that assessed the adverse effects of antibiotic prophylaxis in pregnant women.

- See the summaries of product characteristics for information on contraindications, cautions and adverse effects of individual medicines.

Committee discussion in 2018 on antibiotic prophylaxis

People aged 16 years and over with recurrent UTI

- Based on evidence and their experience, the committee agreed that antibiotic prophylaxis was effective in reducing the risk of recurrent UTI in women who were not pregnant, although this benefit was not seen after the treatment is stopped. They noted the low number needed to treat figure (NNTs) for recurrent infection compared with placebo (NNT 2 [range 2 to 3]). However, they also recognised the increased risk of harms with antibiotic prophylaxis compared with placebo.
- Based on evidence, the committee agreed that antibiotic prophylaxis was also effective in a mixed population of people with recurrent UTI, including women before and after menopause, men and children (NNT 3 [3 to 4]). However, interpretation of the evidence was more difficult due to variations in the populations studied and antibiotic choice, dosage and duration.
- The committee discussed the evidence specifically in pregnant women, which found that antibiotic prophylaxis was effective in reducing the risk of recurrent asymptomatic bacteriuria in pregnant women (NNT 4 [range 3 to 13]). However, they recognised that the study had a number of limitations. The study was small and not powered to show any benefit in preterm births. The population was pregnant women who were admitted to hospital with acute pyelonephritis. The committee noted that nitrofurantoin is not an appropriate choice of antibiotic to show benefit in this population. They were also aware that UTI has been associated with developmental delay or cerebral palsy in the infant, and fetal death.
- Taking account of the benefits and harms of antibiotic prophylaxis and the need to minimise antimicrobial resistance, the committee agreed that antibiotic prophylaxis could be considered in people aged 16 years and over with recurrent UTI, but only after other management options had been unsuccessful (behavioural and personal hygiene measures,

managing any triggers and using non-antimicrobial treatments), if appropriate.

- The committee recognised the importance of reviewing antibiotic prophylaxis, and considered that up to every 6 months was reasonable based on possible adverse effects of antibiotics, the risk of resistance with long-term antibiotics, the possible need for any further investigations if recurrence of UTIs continues, and to allow time to assess treatment success. People should also know to seek medical help if they experience symptoms of an acute infection despite taking prophylaxis.
- The committee discussed the importance of the review and were aware of other conditions where a specific date is included on the prescription to prompt review within 6 months.
- To reduce the risk of antimicrobial resistance, the committee agreed that at each review women should be reminded about self-care, and consideration should be given to either stopping, continuing or changing antibiotic prophylaxis (for example, from single-dose to daily prophylaxis). However, the committee was not able to make specific recommendations about when to stop, continue or change antibiotic prophylaxis as it will depend on the circumstances of an individual person.
- Based on evidence that suggests antibiotic prophylaxis does not continue to be effective after stopping treatment, the committee agreed that if antibiotic prophylaxis was stopped, women should be able to access treatment rapidly if they have symptoms of an acute UTI.
- The committee recognised the limitations of the evidence on antibiotic prophylaxis in pregnant women and men, and the lack of evidence to support the use of non-antimicrobial treatments. Therefore, the committee agreed that it was appropriate to refer all pregnant women to an obstetrician if recurrent UTI is diagnosed during pregnancy. They also agreed that most men with recurrent UTI should be referred for further specialist urology investigation and management, taking an individualised approach that takes account of multimorbidity. The committee agreed

that any decision to prescribe antibiotic prophylaxis in pregnant women or men should be under specialist advice.

- The committee also recognised the higher risks associated with recurrent upper UTIs (pyelonephritis), and agreed that it was appropriate to refer these people for further specialist investigation and management.
- The committee agreed that further consideration should be made for women with recurrent lower UTI if the underlying cause of recurrence was unknown or required further investigation. However, due to resource implications and the lower risk of complications for this population, the committee agreed that specialist advice should be sought, rather than specialist referral.
- The committee was aware of the recommendation in NICE's guideline on suspected cancer: recognition and referral, which states that a non-urgent referral for bladder cancer should be considered for people aged over 60 with recurrent unexplained UTI.
- The committee also recognised the equality considerations for managing recurrent UTI in trans people, because of differences between the female urinary system and the male genitourinary system.

Children and young people under 16 years with recurrent UTI

- The committee was aware that NICE's guideline on urinary tract infection in under 16s makes recommendations on referring children and young people with recurrent UTI to a paediatric specialist for assessment and investigations.
- Based on evidence, the committee noted that antibiotic prophylaxis does not appear to be effective in reducing the risk of recurrent UTI in children. However, there was considerable uncertainty in the evidence (all very low quality).
- Based on their experience, the committee agreed that most cases of recurrent UTI in children and young people are due to a functional or structural abnormality of the urinary tract.

- Taking account of the uncertainty in the evidence and the need to minimise antimicrobial resistance from long-term antibiotic use, the committee agreed that antibiotic prophylaxis could be considered in children and young people aged under 16 years, but only under specialist advice when other management options have been unsuccessful. This would be an individualised decision following an assessment of underlying causes, taking into account the severity and frequency of previous symptoms and the risk of developing complications.
- The committee recognised the importance of reviewing antibiotic prophylaxis, and considered that every 6 months was reasonable. They agreed that the same principles for the review for adults apply to children and young people.

Choice of antibiotic prophylaxis (2018)

- Antibiotic prophylaxis with nitrofurantoin (various dosages: 100 mg a day, 75 mg a day, 50 mg a day or 50 mg twice a day) for at least 3 months significantly reduced the risk of recurrent infection in a mixed population of adults (including women who were not pregnant, and men) and children (mainly girls) compared with methenamine hippurate (number needed to treat [NNT 7; range 4 to 102]; low quality evidence). However, there was no significant difference between nitrofurantoin and either trimethoprim, beta-lactams or quinolones (very low to low quality evidence). This was based on a systematic review and meta-analyses of RCTs (Muller et al. 2017).
- Antibiotic prophylaxis with nitrofurantoin (1 to 1.5 mg/kg daily) for 6 months significantly reduced the risk of having a positive urine culture at the end of the study period in children with recurrent UTI compared with trimethoprim (2 to 3 mg/kg daily; NNT 3 [range 2 to 8]) and reduced the risk of having a recurrent symptomatic UTI compared with co-trimoxazole (2 mg/kg daily; NNT 6 [range 3 to 27]; very low to moderate quality evidence). However, there was no difference with nitrofurantoin compared with cefixime (2 mg/kg daily; 6 to 12 months; moderate quality evidence). This was based on a systematic review of single RCTs (Williams and Craig 2011).

- Overall, antibiotic prophylaxis with nitrofurantoin (for at least 3 months) increased the risk of mild (not defined) adverse effects compared with other antibiotics in a mixed population of adults and children (30.6% versus 11.7%; number needed to harm [NNH 5; range 4 to 6]; Muller et al. 2017; low quality evidence). When specific antibiotics were compared, there were significantly more mild adverse effects with nitrofurantoin compared with beta-lactams (NNH 7 [range 4 to 28]), trimethoprim (NNH 3 [range 2 to 4]) and methenamine (NNH 3 [range 2 to 6]), but no difference between nitrofurantoin and quinolones or co-trimoxazole (Muller et al. 2017; very low to moderate quality evidence).
- In children, there were significantly fewer adverse events with nitrofurantoin compared with trimethoprim (NNH 2 [range 1 to 8]), but significantly more adverse events with nitrofurantoin compared with cefixime (NNH 3 [range 2 to 6]; moderate quality evidence). This was based on a systematic review of single RCTs (Williams and Craig 2011).
- No systematic reviews or RCTs were identified that included data on the choice of antibiotic in pregnant women.

Committee discussion in 2018 on choice of antibiotic prophylaxis

- Based on evidence of no major differences in clinical effectiveness between classes of antibiotics, the committee agreed that the choice of antibiotic prophylaxis should largely be driven by minimising the risk of resistance. Resistant bacteria are a particular concern in UTIs and, where possible, any previous urine culture and susceptibility results, and antibiotic prescribing for UTI, should be checked and antibiotics chosen accordingly.
- Based on their experience and resistance data, the committee agreed that a different antibiotic should be selected for antibiotic prophylaxis if an acute UTI is being treated. They also recognised that rotational use of antibiotics may be needed, based on local policies.
- The committee discussed that, if antibiotic prophylaxis is needed to prevent an infection that is not life threatening, a narrow-spectrum antibiotic should generally be first choice. Indiscriminate use of broad-spectrum antibiotics creates a selective advantage for bacteria resistant even to these ‘last-line’ broad-spectrum agents, and also kills normal commensal flora leaving people susceptible to antibiotic-resistant harmful bacteria such as Clostridium difficile. Broad-spectrum antibiotics need to be reserved for second-choice treatment of non-life-threatening infections when narrow-spectrum antibiotics are ineffective.
- Based on evidence, their experience and resistance data, the committee agreed to **recommend trimethoprim or nitrofurantoin** (based on culture and susceptibility results) as first choice antibiotics for prophylaxis. These antibiotics have less effect on the normal intestinal microflora in gastrointestinal tract, which is particularly important when continuous antibiotic prophylaxis is used.
  - Trimethoprim should only be prescribed if a lower risk of resistance is likely, for example, if trimethoprim has not been used in the past

3 months, if previous urine culture results suggest trimethoprim susceptibility (but this was not used as treatment) and in younger women in areas where local epidemiology data suggest resistance is low. There is a higher risk of trimethoprim resistance with recent use and in older people in residential facilities. Trimethoprim is contraindicated in pregnant women.

  - Nitrofurantoin is not recommended for people with an estimated glomerular filtration rate (eGFR) of less than 45 ml/minute. With long-term use, there is a lower risk of resistance of nitrofurantoin compared with trimethoprim, but this needs to be balanced against the increased harms, such as pulmonary fibrosis.
  - The committee was aware that nitrofurantoin suspension is currently substantially more expensive than trimethoprim suspension and, if both antibiotics are appropriate, the one with the lowest acquisition cost should be chosen.
- Based on evidence, their experience and resistance data, the committee agreed to recommend **cefalexin** or **amoxicillin** (based on culture and susceptibility results) as second-choice antibiotics for prophylaxis. Amoxicillin and cefalexin are broad spectrum antibiotics that have a similar spectrum of activity and can be used if bacteria are susceptible.

Antibiotic dosing and course length (2018)

- Single-dose antibiotic prophylaxis (used when exposed to conditions that may trigger a UTI) was not significantly different to daily antibiotic prophylaxis in the number of women with at least 1 recurrent infection over a 12-month study period in women after menopause with recurrent UTI (3 or more episodes in the past 12 months; 80.6% versus 70.3%; moderate quality evidence). This was based on 1 RCT (Zhong et al. 2011).
- The conditions for using the single-dose antibiotic were determined by the woman's experience, such as walking for a long time or sexual intercourse. The choice of antibiotic (nitrofurantoin, amoxicillin, co-trimoxazole,

quinolones or cephalosporins) varied and was determined on a case-by-case basis, depending on the woman's previous antibiotic use and following an antibiotic susceptibility test.

- In 1 RCT (reported in a systematic review by Albert et al. 2004) single-dose ciprofloxacin (250 mg) taken immediately after sexual intercourse was as effective as a daily dose in women who were not pregnant in reducing the risk of recurrent UTI during the period of prophylaxis (Albert et al. 2004; low quality evidence).
- There were significantly fewer adverse events with single-dose antibiotic prophylaxis compared with daily antibiotic prophylaxis (number needed to harm [NNH 3; range 2 to 9]; Zhong et al. 2011; moderate quality evidence).
- There was no significant difference in the number of non-serious adverse effects between those who took a single dose of ciprofloxacin (250 mg) immediately after sexual intercourse, or daily at night (Albert et al. 2004; low quality evidence).

Committee discussions in 2018 on antibiotic dosing and course length

- Based on evidence, the committee was aware that a range of doses and course lengths were used for daily antibiotic prophylaxis. The committee agreed that usual BNF doses for daily prophylaxis should be used. The duration of treatment needs to be determined on an individual basis with a review of treatment success within 6 months, to include discussion of a trial of stopping antibiotic prophylaxis as appropriate.
- The committee discussed the evidence for using single-dose antibiotic prophylaxis (including post-coital single-dose antibiotics) in women who were not pregnant. The committee agreed that the single dose used when exposed to an identifiable trigger would be the same as a single treatment dose for a UTI.
- Based on evidence, their experience and antimicrobial resistance data, the committee agreed that single-dose prophylaxis was as effective as continuous prophylaxis, with fewer adverse effects in women who were not pregnant and had an identifiable trigger, and should be considered as the first option for antibiotic prophylaxis in this group. The committee agreed that prophylaxis needs to be tailored to individual's personal triggers, and advice given about how to use the antibiotic. Antibiotics for single-dose prophylaxis would be kept at home to avoid unnecessary GP and pharmacy visits.
- No evidence from systematic reviews and RCTs was identified for using a course of antibiotics to keep at home for treating an acute UTI in people with recurrent UTIs (also known as stand-by antibiotics). The use of stand-by antibiotics could potentially lead to inappropriate antibiotic overuse in the absence of medical supervision, which would not reflect the principles of antimicrobial stewardship. Therefore, while the committee recognised that they may have a role in some specialist cases, they were not able to make a recommendation on their use.

Self-care (2018)

Probiotics (lactobacillus)

- Lactobacillus did not significantly reduce the risk of recurrent infection in women who have not experienced menopause with a history of previous urinary tract infection (UTI; 1 or more episode in the past 12 months) compared with placebo (low quality evidence). This was based on a systematic review and meta-analysis of randomised controlled trials (RCTs; Grin et al. 2013). When the analysis was restricted to 2 RCTs with 'effective strains' of lactobacillus, there was a statistically significant difference (16.1% versus 32.3%: number needed to treat [NNT] 7 [range 4 to 64]; moderate quality evidence).
- In most studies, lactobacillus was used following a UTI treated with antibiotics until the infection resolved. Lactobacillus pessaries were used in 4 RCTs and a drink preparation was used in 1 RCT.
- Evidence for lactobacillus compared with antibiotic prophylaxis (co-trimoxazole) in women after menopause who had 1 or more previous UTI found, overall, no significant differences between treatment options (low quality evidence). This was based on 1 RCT included in a systematic review (Schwenger et al. 2015).
- No safety data were reported for lactobacillus compared with placebo. Data for lactobacillus compared with antibiotic were reported narratively, and the reason for not pooling data was unclear. One systematic review reported no significant difference in the number of people experiencing at least 1 adverse event with lactobacillus compared with antibiotics (Schwenger et al. 2015; low quality evidence).
- No systematic reviews or RCTs were identified that included data on lactobacillus in men or children.

Cranberry products

- A range of cranberry products are available; a liquid preparation (juice or syrup), tablets or capsules were used in the included studies.

- Evidence for these products was identified in different populations (women who were not pregnant, pregnant women, elderly men and women, and children), with some conflicting results.
- In women (it is unclear whether pregnant women were included) with a previous history of UTI, cranberry products used for up to 12 months did not significantly reduce the risk of recurrent infection (19.9% versus 22.8%) compared with placebo or no treatment (very low quality evidence). This was based on a systematic review and meta-analysis of RCTs (Jepson et al. 2012).
- However, a more recent systematic review and meta-analysis of RCTs (Fu et al. 2017) was identified following stakeholder consultation, which included additional data to Jepson et al. (2012). Cranberry products used for 6 to 12 months did significantly reduce the incidence of UTI in non-pregnant women with a previous history of UTI compared with placebo or no treatment (20.7% versus 26.5%; number needed to treat [NNT] 17 [range 9 to 68]; very low quality evidence). This significant reduction was not seen when UTIs were confirmed by urine culture (19.8% versus 24.0%; very low quality evidence).
- Subgroup analysis in Fu et al. (2017) found that cranberry juice used for 6 to 12 months did not reduce the incidence of UTI diagnosed by symptom presence or culture confirmation compared with placebo or no treatment (22.0% versus 26.6%; very low quality evidence); whereas cranberry tablets taken for 6 to 12 months did show a significant reduction in the incidence of UTI (13.5% versus 28.0%; NNT 7 [range 5 to 20]; low quality evidence). However, the analysis for cranberry tablets was based on much smaller numbers of participants.
- In elderly adults (men and women) with a previous history of UTI, cranberry products used for up to 12 months did not significantly reduce the risk of recurrent infection (9.7% versus 12.6%; moderate quality evidence) compared with placebo or no treatment (Jepson et al. 2012).
- In pregnant women with a previous history of UTI, cranberry products did not show a significant benefit in reducing recurrent UTI (56.6% versus

55.6%; moderate quality evidence) when compared with placebo or no treatment (Jepson et al. 2012).

- In children with a previous history of 1 or more UTIs or 'repeated symptomatic UTI', cranberry products used for up to 12 months did not significantly reduce the risk of recurrent infection compared with placebo or no treatment (16.3% versus 29.5%; low quality evidence; Jepson et al. 2012).
- However, a more recent systematic review and meta-analysis of RCTs (Roshdibonab et al. 2017) was identified following stakeholder consultation, which included additional data to Jepson et al. (2012). Cranberry products used for up to 12 months did significantly reduce the incidence of UTI in children with recurrent UTI compared with placebo (odds ratio 0.31, 95% confidence interval 0.21 to 0.46; no absolute figures stated; very low quality evidence).
- When cranberry products were compared with antibiotics (trimethoprim or co-trimoxazole), there was no significant difference between groups in reducing the risk of recurrent infection in women (51.1% versus 40.4%; moderate quality evidence; Jepson et al. 2012). There was also no significant difference between cranberry products and antibiotics (trimethoprim) in reducing the risk of recurrent infection in children (10.7% versus 15.4%; low quality evidence; Jepson et al. 2012).
- Evidence for cranberry products reducing the risk of antimicrobial resistance compared with antibiotics was conflicting. Cranberry products reduced the risk in women who have not experienced menopause compared with antibiotic prophylaxis (co-trimoxazole) during a 12-month treatment period (Beerepoot et al. 2011; moderate quality evidence). However, the risk was not reduced in children during a 12-month treatment period (including children with vesicoureteral reflux [VUR]; Uberos et al. 2012; moderate quality evidence).
- There were no significant differences in gastrointestinal adverse events in adults treated with cranberry products compared with no treatment or antibiotics (Jepson et al. 2012; low quality evidence). Two further studies

showed higher numbers of adverse events in adults given placebo compared with cranberry products and 1 further study showed similar numbers of adverse events between groups.

- No data were identified for adverse effects of cranberry products in children.

D-mannose

- D-mannose (200 ml of 1% solution once daily in the evening) used for up to 6 months significantly reduced the risk of recurrent infection in women who were not pregnant compared with no treatment (14.6% versus 60.8%, NNT 3 [range 2 to 3]; high quality evidence). This was based on 1 RCT in women who were not pregnant presenting with a current UTI and a history of recurrent UTI (Kranjcec et al. 2014). All women were treated with ciprofloxacin 500 mg twice a day for 7 days for their current infection.
- There was no significant reduction in recurrent infection when D-mannose was compared with antibiotic prophylaxis (nitrofurantoin 50 mg a day) over the 6-month study period (Kranjcec et al. 2014; low quality evidence).
- There were significantly fewer adverse events (such as diarrhoea, nausea and vaginal burning) with D-mannose compared with antibiotics in women who were not pregnant (7.8% versus 28.2%, number needed to harm [NNH] 5 [range 4 to 10]; Kranjcec et al. 2014; high quality evidence).
- No systematic reviews or RCTs were identified that included data on D-mannose in pregnant women, men or children.

Committee discussion in 2018 on self-care

- Based on their experience, and the need to minimise inappropriate use of antibiotics, the committee agreed that people should be given advice about behavioural and personal hygiene measures to reduce the risk of UTI, such as:
  - drinking enough fluids to avoid dehydration
  - not delaying habitual and post-coital urination
  - wiping from front to back after defaecation
  - not douching or wearing occlusive underwear.

Probiotics (lactobacillus)

- The committee discussed the evidence for the probiotic lactobacillus. While there was some evidence to support the use of 'effective strains', there was no information on which lactobacillus products were included in this analysis. They also noted the high drop-out rate in the study.
- Based on evidence, the committee agreed that people should be told that there is inconclusive evidence to recommend the use of lactobacillus to prevent recurrent UTIs.

Cranberry products

- The committee recognised that cranberry products are used widely and discussed the very low quality evidence showing some benefit for reducing the risk of UTIs, specifically in women who are not pregnant, and children and young people. They were also aware that there was no evidence to suggest benefit in older women. The committee also noted the conflicting evidence for cranberry products in reducing the risk of antimicrobial resistance.
- Taking account of the limitations of the evidence, and the need to minimise antimicrobial resistance, the committee agreed that some women who are not pregnant and some children and young people under 16 may wish to try cranberry products as a self-care treatment.

However, due to safety concerns with delayed treatment, particularly in children and young people, the committee agreed that cranberry products should only be considered in this population following advice from a paediatric specialist.

- The committee recognised that there was some evidence to suggest that cranberry juice was not significantly better than placebo in women who were not pregnant, while cranberry capsules showed a significant benefit. However, due to significant limitations in the evidence the committee was not able to recommend a specific cranberry product.
- The committee discussed the sugar content of cranberry products, and based on their experience, agreed that people should be advised to take account of their daily sugar intake if using cranberry products.

D-mannose

- The committee was aware of the mechanism of action of D-mannose, which is also in cranberry products.
- The committee noted evidence suggesting that D-mannose was effective in reducing the risk of recurrent UTI in women who were not pregnant, and noted the low number needed to treat [NNT of 3; range 2 to 3) over 6 months, compared with no treatment. However, this was based on 1 small RCT. The committee agreed to make a recommendation that some women who are not pregnant may wish to try D-mannose, as a self care treatment, noting the sugar content of this product which should be considered.

Other considerations

Medicines adherence

Medicines adherence may be a problem for some people with medicines that require regular dosing or longer treatment duration (for example, continuous antibiotic prophylaxis). See NICE's guideline on medicines adherence.

Resource implications

Recommended antibiotics are available as generic formulations, see the Drug Tariff for costs.

Nitrofurantoin 25 mg/5 ml oral suspension is more expensive than other oral suspensions, such as trimethoprim 50 mg/5 ml. The cost of a 300-ml bottle of nitrofurantoin is £446.95 compared with £4.87 for a 100-ml bottle of trimethoprim (Drug Tariff, September 2018).

Finding more information and committee details

To find NICE guidance on related topics, including guidance in development, see the NICE topic page on antimicrobial stewardship.

For full details of the evidence and the guideline committee's discussion, see the evidence review. You can also find information about how the guideline was developed, including details of the committee.

NICE has produced tools and resources to help you put this guideline into practice. For general help and advice on putting our guidelines into practice, see resources to help you put this guidance into practice.

Update information

November 2024

We have reviewed the evidence on methenamine hippurate for people with recurrent UTI.

Recommendations are marked **[2024]** if the evidence has been reviewed.

Recommendations that have been changed without an evidence review

For recommendations ending **[2018, amended 2024]**, we have made changes that could affect the intent without reviewing the evidence. Reasons for the changes are given in table 1.

For recommendations shaded in grey and ending **[2018]**, we have not reviewed the evidence. In some cases minor changes have been made – for example, to update links, or bring the language and style up to date – without changing the intent of the recommendation. Minor changes are listed in table 2.

See also the previous NICE guideline and supporting documents.

Table 1 Amended recommendation wording (change to intent) without an evidence review

Recommendation in 2018 guideline	Recommendation in current guideline	Reason for change
Refer or seek specialist advice on further investigation and management for: • men aged 16 years and over • people with recurrent upper UTI • people with recurrent lower UTI when the underlying cause is unknown • pregnant women • children and young people under 16 years in line with the NICE guideline on urinary tract infection in under 16s • people with suspected cancer in line with the NICE guideline on suspected cancer: recognition and referral. (1.1.4)	Refer or seek specialist advice on further investigation and management for: • men, and trans women and non-binary people with a male genitourinary system, aged 16 and over • people with recurrent upper UTI • people with recurrent lower UTI when the underlying cause is unknown • pregnant women, and pregnant trans men and non-binary people • children and young people aged under 16 years in line with NICE's guideline on urinary tract infection in under 16s • people with suspected cancer in line with NICE's guideline on suspected cancer: recognition and referral. • anyone who has had gender reassignment surgery that involved structural alteration of the urethra. (1.1.4)	Recommendations have been edited to bring the language and style up to date. During discussions about updating the language in this recommendation, the committee agreed that specialist advice should be sought for anyone who has had gender reassignment surgery that involved structural alterations of the urethra.

Consider the lowest effective dose of vaginal oestrogen (for example, estriol cream) for postmenopausal women with recurrent UTI if behavioural and personal hygiene measures alone are not effective or not appropriate. Discuss the following with the woman to ensure shared decision-making: • the severity and frequency of previous symptoms • the risk of developing complications from recurrent UTIs • the possible benefits of treatment, including for other related symptoms, such as vaginal dryness • the possible adverse effects such as breast tenderness and vaginal bleeding (which should be reported because it may require investigation) • the uncertainty of endometrial safety with long-term or repeated use • preferences of the woman for treatment with vaginal oestrogen. Review treatment within 12 months, or earlier if agreed with the woman. In October 2018, this was an off-label use of vaginal oestrogen products. See NICE's information on prescribing medicines. (1.1.5)	Consider vaginal oestrogen for recurrent UTI if behavioural and personal hygiene measures alone are not effective or not appropriate. (1.2.1) When discussing vaginal oestrogen for preventing recurrent UTI, cover the following to ensure shared decision making: • the severity and frequency of previous symptoms • the risk of developing complications from recurrent UTIs • the possible benefits of treatment, including for other related symptoms, such as vaginal dryness • that serious side effects are very rare • that vaginal oestrogen is absorbed locally – a minimal amount is absorbed into the bloodstream but this is unlikely to have a significant effect throughout the body • the person's preferred treatment option for vaginal oestrogen (for example, a cream or a ring). (1.2.2)	NICE received stakeholder feedback concerning the inclusion of 'lowest effective dose' in the 2018 guideline recommendation. As the BNF already contains information about recommended doses we have now removed the reference to lowest effective dose to avoid confusion. We have also removed the specific reference to estriol cream as an example and instead included a prompt to discuss treatment options with the person. In addition, the 2018 recommendations contained information about possible adverse events and endometrial safety. However, stakeholders raised concerns that this was based on evidence of high dose vaginal oestrogens not used in the UK. The committee agreed to revise the discussion points listed in the recommendation. The section also now refers the updated NICE guideline on menopause for use of vaginal oestrogen for people with a personal history of breast cancer (this

		update is currently in development and is due to publish in November 2024).
Do not offer oral oestrogens (hormone replacement therapy) specifically to reduce the risk of recurrent UTI in postmenopausal women. (1.1.6)	Do not offer systemic hormone replacement therapy specifically to reduce the risk of recurrent UTI. (1.2.4)	This recommendation was amended so that it refers to any type of systemic oestrogen.

Table 2 Minor changes to recommendation wording (no change to intent)

Recommendation numbers in current guideline	Comment
Recommendations 1.1.2, 1.2.3, 1.2.5 to 1.2.7, 1.2.10 to 1.3.4, and 1.4.1 all labelled [2018].	Recommendations have been edited into the direct style (in line with current NICE style for recommendations in guidelines) to bring the language and style up to date or for clarity, where possible

Minor updates since publication

February 2019: Minor corrections to one of the evidence summaries.

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