Urinary tract infection (recurrent): antimicrobial prescribing

NICE guideline

Draft for consultation, May 2018

This guideline sets out an antimicrobial prescribing strategy for recurrent urinary tract infections. It aims to optimise antibiotic use and reduce antibiotic resistance.

See a 2-page visual summary of the recommendations, including tables to support prescribing decisions.

Who is it for?

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

The guideline contains:

- the draft recommendations
- summary of the evidence.

Information about how the guideline was developed is on the guideline's page on the NICE website. This includes the full evidence review, details of the committee and any declarations of interest.

Recommendations

The recommendations in this guideline are for preventing urinary tract infections (UTI) in adults, young people and children with recurrent UTI who do not have a catheter.

1.1 Preventing recurrent urinary tract infections

1.1.1 Manage an acute UTI as outlined in the NICE guidelines on lower UTI (cystitis), acute pyelonephritis or catheter-associated UTI.

1.1.2 Be aware that recurrent UTI:

- includes lower UTI (cystitis) 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.

Referring for specialist assessment and investigations

1.1.3 Refer the following people with recurrent UTI for specialist assessment and investigations because there may be underlying anatomical or functional abnormalities:

- men (taking an individualised approach that takes account of factors such as multimorbidity)
- people aged 16 years and over with recurrent upper UTI (acute pyelonephritis).

1.1.4 Refer pregnant women (aged 16 years and over) to an obstetrician for specialist assessment and investigations if recurrent UTI is diagnosed during pregnancy.

1.1.5 Refer children and young people under 16 years to a paediatric specialist for assessment and investigations, in line with the NICE guideline on urinary tract infection in under 16s: diagnosis and management.

See the evidence and committee discussion on antibiotic prophylaxis.

Treatment for women with recurrent UTI who are not pregnant

D-mannose and vaginal oestrogen

1.1.6 Consider D-mannose[1] as a self-care treatment for women with recurrent UTI who are not pregnant and have had no improvement after behavioural and personal hygiene measures. Take account of:

- the severity and frequency of previous symptoms
- the risk of developing complications
- the woman's preferences for self-care treatments.

1.1.7 Consider the lowest effective dose of vaginal oestrogen[2] (for example, estriol cream) for postmenopausal women with recurrent UTI and no improvement after behavioural and personal hygiene measures. Discuss the following with the woman to ensure shared decision-making:

- the severity and frequency of previous symptoms
- the possible benefits of treatment, including for other related symptoms, such as vaginal dryness
- the risk of developing complications from recurrent UTIs
- 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.

[1] D-mannose used in the study was a 1% solution. D-mannose is a sugar that is available to buy as powder or tablets; it is not a medicine.

[2] Vaginal oestrogen formulations used in the studies were topical cream, vaginal ring and pessary. These 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. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing and managing medicines and devices for further information.

Review treatment at least every 6 months, or earlier if agreed with the woman.

1.1.8 Do not offer oral oestrogens (hormone replacement therapy) specifically to prevent recurrent UTI in postmenopausal women.

See the evidence and committee discussion on self-care and oestrogens.

Antibiotic prophylaxis

1.1.9 For women with recurrent UTI who are not pregnant and have had no improvement after the management options in recommendations 1.1.6 and 1.1.7, consider single-dose antibiotic prophylaxis when exposed to triggers (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 woman's preferences for antibiotic use.

1.1.10 When single-dose antibiotic prophylaxis is given, give advice about:

- how to use the antibiotic (not exceeding the maximum prophylactic dose per day)
- possible adverse effects of antibiotics, particularly diarrhoea and nausea
- returning for review after 3 months, or other agreed time
- seeking medical help if there are symptoms of an acute UTI.

See the evidence and committee discussion on antibiotic prophylaxis and antibiotic dosing and course length.

1.1.11 For women with recurrent UTI who are not pregnant and have had no improvement after single-dose antibiotic prophylaxis or have no identifiable triggers, consider continuous antibiotic prophylaxis (see

the recommendations on choice of antibiotic prophylaxis). Take account of:

- any further investigations (for example, ultrasound) that may be needed to identify an underlying cause
- 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
- the woman's preferences for antibiotic use.

1.1.12 When continuous antibiotic prophylaxis is given, 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 after 3 months, or other agreed time
- seeking medical help if there are symptoms of an acute UTI.

See the evidence and committee discussion on antibiotic prophylaxis.

Treatment for men and pregnant women with recurrent UTI

1.1.13 For men and pregnant women with recurrent lower UTI who have had no improvement after behavioural and personal hygiene measures, consider continuous antibiotic prophylaxis (see the recommendations on choice of antibiotic prophylaxis) with specialist advice. Take account of:

- any further investigations (for example, ultrasound) that may be needed to identify an underlying cause
- 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
- the person's preferences for antibiotic use.

Give advice in line with recommendation 1.1.12.

See the evidence and committee discussion on antibiotic prophylaxis.

Treatment for children and young people under 16 years with recurrent UTI

1.1.14 For children and young people under 16 years with recurrent lower UTI and no improvement after behavioural and personal hygiene measures, consider continuous antibiotic prophylaxis (see the recommendations on choice of antibiotic prophylaxis) with specialist advice. Take account of:

- underlying causes following specialist assessment and investigations
- the uncertain benefit of antibiotic prophylaxis for reducing the risk of recurrent UTI and the rate of deterioration of renal scars
- 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
- preferences for antibiotic use.

Give advice in line with recommendation 1.1.12.

See the evidence and committee discussion on antibiotic prophylaxis.

1.2 Self-care

1.2.1 Give verbal and written advice about behavioural and personal hygiene measures to people with recurrent UTI that may help to reduce the risk of UTI.

1.2.2 Consider D-mannose in non-pregnant women with recurrent UTI as in recommendation 1.1.7.

1.2.3 Explain that evidence is inconclusive about whether cranberry products or probiotics (lactobacillus) reduce the risk of UTI in people with recurrent UTI.

See the evidence and committee discussion on self-care.

1.3 Choice of antibiotic prophylaxis

1.3.1 When prescribing antibiotic prophylaxis for recurrent UTI:

- 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.

1.3.2 Review treatment success with the person every 3 months (or other agreed time) and discuss a trial of stopping antibiotic prophylaxis as appropriate.

Table 1. Adults and young people aged 16 years and over

Antibiotic prophylaxis[1,2]	**Dosage and course length[3]**
First choice	
Trimethoprim[4]	100 mg single dose or 100 mg at night continuously
Nitrofurantoin – if eGFR ≥45 ml/minute[5]	50 to 100 mg single dose or 50 to 100 mg at night continuously
Second choice	
Amoxicillin	250 mg single dose or 250 mg at night continuously
Cefalexin	125 mg single dose or 125 mg at night continuously

Pivmecillinam[6]	200 mg single dose or 200 mg at night continuously
[1]See BNF for appropriate use and dosing in specific populations, for example, hepatic impairment, renal impairment, pregnancy and breast feeding. [2]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. [3]Doses given are by mouth using immediate release medicines, unless otherwise stated. [4]Teratogenic risk in first trimester of pregnancy (folate antagonist; BNF, April 2018). Manufacturers advise contraindicated in pregnancy (trimethoprim summary of product characteristics). [5]Avoid at term in pregnancy; may produce neonatal haemolysis (BNF, April 2018). [6]Not known to be harmful in pregnancy, but manufacturer advises avoid (BNF, April 2018).	
Abbreviations: eGFR, estimated glomerular filtration rate; SPC, summary of product characteristics	

Table 2. Children and young people under 16 years

Antibiotic prophylaxis[1,2]	**Dosage and course length[3]**
Children under 3 months	
Refer to paediatric specialist	
Children aged 3 months and over (specialist advice only)	
First choice	
Trimethoprim	3 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 to 11 years, 2 mg/kg at night (maximum 100 mg per dose) or 50 mg at night 12 to 17 years, 100 mg at night
Nitrofurantoin – if eGFR ≥45 ml/minute	3 months to 11 years, 1 mg/kg at night 12 to 17 years, 50 mg to 100 mg at night
Second choice	
Cefalexin	12.5 mg/kg at night (maximum 125 mg per dose)
Amoxicillin	1 to 11 months, 62.5 mg at night 1 to 4 years, 125 mg at night 5 to 17 years, 250 mg at night
[1]See BNF for children for appropriate use and dosing in specific populations, for example hepatic and renal impairment. [2]Choose antibiotics according to recent culture and susceptibility results where possible. If 2 or more antibiotics are appropriate, choose the antibiotic with the lowest acquisition cost. [3]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. Doses given are by mouth using immediate release medicines, unless otherwise stated.
Abbreviations: eGFR, estimated glomerular filtration rate.

See the evidence and committee discussion on choice of antibiotic prophylaxis and antibiotic dosing and course length.

Terms used in the guideline

Recurrent urinary tract infection

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. The diagnosis of recurrent UTI should be confirmed by urine culture (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 the NICE guideline on urinary tract infection in under 16s.

Triggers

Some people (mainly women) 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.

Summary of the evidence

Self-care

Probiotics (lactobacillus)

- Lactobacillus did not significantly reduce the risk of recurrent infection in premenopusal women with a history of previous urinary tract infection (UTI; 1 or more episode in the last 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 postmenopausal women with 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.

- In adults with recurrent UTI or a previous history of UTI, cranberry products used for up to 12 months did not significantly reduce the risk of recurrent infection in non-pregnant women (19.9% versus 22.8%) or elderly adults (men and women; 9.7% versus 12.6%), compared with placebo or no treatment (very low to moderate quality evidence). This was based on a systematic review and meta-analysis of RCTs (Jepson et al. 2012).
- There was no significant difference between cranberry products and antibiotics (trimethoprim or co-trimoxazole) in reducing the risk of recurrent infection in women (51.1% versus 40.4%; moderate quality evidence; 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%), and when compared with antibiotics (trimethoprim; 10.7% versus 15.4%; Jepson et al. 2012; low quality evidence).
- Evidence for cranberry products reducing the risk of antimicrobial resistance compared with antibiotics was conflicting. Cranberry products reduced the risk in premenopausal women 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).
- 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 non-pregnant women 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 non-pregnant women 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 non-pregnant women (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 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:
  - the adequate intake of fluids
  - 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. However, the evidence showed that these products were not effective in reducing the risk of recurrent UTI in different populations (non-pregnant women, pregnant women, elderly men and women, and children). However, some studies may not have been able to show any benefit for cranberry products due to their design, for example, the duration of the study was too short or a population of women at lower risk of recurrence had been selected.
- The committee also noted the conflicting evidence for cranberry products in reducing the risk of antimicrobial resistance.

- Based on evidence, their experience and resistance data, the committee agreed that people should be advised that there is inconclusive evidence to recommend the use of cranberry products to prevent recurrent UTIs.

D-mannose

- The committee was aware of the mechanism of action of D-mannose, which is also in cranberry products. Based on their experience, the committee agreed that D-mannose may be easier to use than cranberry products (once a day).
- Based on evidence, the committee agreed that D-mannose was effective in reducing the risk of recurrent UTI in non-pregnant women, and noted the low 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 to consider its use as a self-care intervention in non-pregnant women with recurrent UTI.

Oestrogens

- Oral oestrogens (with or without progestogens) taken for up to 4 years did not significantly reduce the risk of recurrent infection in postmenopausal women 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 last 12 months or 2 or more episodes in the last 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 postmenopausal women compared with placebo (16.0% versus 62.8%, 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 postmenopausal women 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 postmenopausal women 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 and vaginal oestrogens increased adverse events (such as breast tenderness and vaginal bleeding) in postmenopausal women compared with placebo, no treatment or oral antibiotics. The NNH was 5 [range 3 to 14] for oral oestrogens (high quality evidence) and 5 [range 3 to 11] for vaginal oestrogens (Perrotta et al. 2008; low to high quality evidence).
- Oestrogens (hormone replacement therapy [HRT]) increase the risk of venous thromboembolism, 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 (MHRA Drug Safety Update, September 2007; British National Formulary [BNF], April 2018). Before prescribing HRT, health professionals should consider carefully the potential benefits and risks for every woman. See the NICE guideline on menopause: diagnosis and management for more information on using vagainal oestrogen for urogenital atrophy.
- Vaginal oestrogens should be used in the smallest effective amount, for the shortest duration to minimise systemic effects. The endometrial safety of long-term or repeated use of topical vaginal oestrogens is uncertain; treatment should be reviewed at least annually, with special consideration given to any symptoms of endometrial hyperplasia or carcinoma (MHRA Drug Safety Update, September 2007; BNF, April 2018). The NICE guideline on menopause: diagnosis and management recommends that women using vaginal oestrogen should report unscheduled vaginal bleeding to their GP.

Committee discussion on oestrogens

- Based on evidence of a lack of effectiveness and taking account of MHRA safety advice, the committee agreed to not recommend oral oestrogens (hormone replacement therapy) specifically to prevent recurrent UTI in postmenopausal women.
- Based on evidence, the committee agreed that vaginal oestrogens were effective in reducing the risk of recurrent UTI in postmenopausal women, although this was based on small numbers of women and appears to diminish when the treatment is stopped. They noted the low 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.
- Based on evidence and their experience, the committee recognised the adverse effects of vaginal oestrogens (such as breast tenderness and vaginal bleeding), which may require additional investigations. They noted the rate of adverse events appeared high in the studies (NNH 5 [range 3 to 11]) for vaginal oestrogens.
- The committee was aware of MHRA safety advice on the use of vaginal oestrogens; they agreed this was important for women and prescribers to discuss, but that it should not prevent the safe use of an effective treatment for recurrent UTI.
- Vaginal oestrogens are not licensed for preventing recurrent UTI, although oestrogen deficiency is a known risk factor. The committee noted that there do not appear to be any effective, licensed, non-antimicrobial alternatives for preventing recurrent UTI in postmenopausal women.
- Based on evidence, their experience and data on antimicrobial resistance, the committee agreed that vaginal oestrogens could be considered for postmenopausal women with recurrent UTI, with

review at least every 6 months, or other agreed time. The committee recognised that this was a preference-sensitive decision and the benefits and harms of vaginal oestrogens need to be discussed with the woman, taking account of other symptoms the woman may want to address, such as vaginal dryness. The committee agreed that, before vaginal oestrogen is given, women should be asked about their preferences and give advice about the possible risks and benefits, returning for review and reporting unscheduled vaginal bleeding.

- 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 with the woman on an individual basis.

Antibiotic prophylaxis

- 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 foetal 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, 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, 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 non-pregnant women with recurrent UTI (2 or more 'uncomplicated' episodes in the last 12 months) compared with placebo (12.3% versus 65.5%, 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 at least 3 months significantly reduced the risk of recurrent infection in a mixed population of adults (including non-pregnant women and men) and children (mainly females) 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 three 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 pre-term 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 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 vesicoureteral

reflux (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 [CKS]: diarrhoea – antibiotic associated).
- Allergic reactions to penicillins occur in 1 to 10% of people and anaphylactic reactions occur in less than 0.05%. People with a history of atopic allergy (for example, asthma, eczema, and hay fever) have a higher risk of anaphylactic reactions to penicillins. People with a history of immediate hypersensitivity to penicillins may also react to cephalosporins and other beta-lactam antibiotics (BNF, April 2018). See the NICE guideline on drug allergy: diagnosis and management for more information.
- Nitrofurantoin should be used with caution in those with renal impairment. It should be avoided at term in pregnancy because it may produce neonatal haemolysis. Adults (especially the elderly) and children on long-term therapy should be monitored for liver function and pulmonary symptoms (BNF, April 2018).
- Trimethoprim has a teratogenic risk in the first trimester of pregnancy (folate antagonist; BNF, April 2018). Manufacturers advise contraindicated in pregnancy (trimethoprim summary of product characteristics).
- In non-pregnant women, 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 (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 2010; 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 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 non-pregnant women, although this benefit was not seen after the treatment is stopped. They noted the low 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 pre- and postmenopausal women, 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 pre-term 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 foetal 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 every 3 months (or other agreed time) was reasonable based on possible adverse effects of antibiotics, the risk of resistance with long-term antibiotics, and the possible need for any further investigations if recurrence of UTIs continues. People should also know to seek medical help if they experience symptoms of an acute infection despite taking prophylaxis.

- 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 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 also recognised the equality considerations for managing recurrent UTI in transgender people, due to anatomical differences between women and men.

Children and young people under 16 years with recurrent UTI

- The committee was aware that the NICE guideline on urinary tract infection in under 16s: diagnosis and management makes recommendations on referring children and young people with recurrent UTI to a paediatric specialist for assessment and investigations.
- The committee was also aware of the recommendation in this guideline that antibiotic prophylaxis could be considered for children and young people with recurrent UTI.
- 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 abnormaility of the urinary tract.
- Taking account of the uncertainly 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 under 16 years, but only under specialist advice when other management options had 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 3 months (or other agreed time) was reasonable based on possible adverse effects of antibiotics, the risk of resistance with long-term antibiotics, and the possible need for any further investigations if recurrence of UTIs continues. People should also know to seek medical help if they experience symptoms of an acute infection despite taking prophylaxis.

Choice of antibiotic prophylaxis

- Antibiotic prophylaxis with nitrofurantoin (various doses: 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 non-pregnant women and men) and children (mainly females) compared with methenamine hippurate (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 (1–1.5 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 (2–3 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 2010).

- 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%; 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 2010).
- No systematic reviews or RCTs were identified that included data on the choice of antibiotic in pregnant women.

Committee discussion 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*. For infections that are not life threatening, broad-spectrum antibiotics need to be reserved for second-choice treatment 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 imprortant 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 last 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 eGFR <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. Pivmecillinam is an alternative in people aged 16 years and over (but manufacturer advises avoid in pregnant women).
  - Amoxicillin and cefalexin are broad spectrum antibiotics that have a similar spectrum of activity and can be used if bacteria are susceptible.
  - Pivmecillinam has less effect on the normal intestinal microflora in gastrointestinal tract.

Antibiotic dosing and course length

- Single-dose antibiotic prophylaxis (used when exposed to conditions that may trigger a UTI) was not significantly different to continuous antibiotic prophylaxis in the number of women with at least 1 recurrent infection over a 12-month study period in postmenopausal women with recurrent UTI (3 or more episodes in the last 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 continuous daily dose in non-pregnant women 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 continuous antibiotic prophylaxis (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 on antibiotic dosing and course length

- Based on evidence, the committee was aware that a range of doses and course lengths were used for continuous antibiotic prophylaxis. The committee agreed that usual daily doses for continuous prophylaxis should be used. The duration of treatment needs to be determined on an individual basis with a review of treatment success every 3 months (or other agreed time), 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 non-pregnant women. 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 non-pregnant women with an identifiable trigger, and should be considered as the first option for antibiotic prophylaxis in this group of women. Prophylaxis needs to be tailored to individual woman's personal triggers, and advice given about how to use the antibiotic (not exceeding the maximum prophylactic dose per day). Antibiotics for single-dose prophylaxis would be kept at home to avoid uneccessary 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 committee recognised that they may have a role in some specialist cases, but was not able to make a recommendation on their use.

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 the NICE guideline on medicines adherence.

Resource implications

- Recommended antibiotics (nitrofurantoin, trimethoprim, amoxicillin and cefalexin) are available as generic formulations, but there is currently no generic formulation of pivmecillinam, although the cost is comparable to other generic antibiotics, see Drug Tariff for costs.
- Nitrofurantoin 25mg/5ml oral suspension is more expensive than other oral suspensions, such as trimethoprim 50mg/5ml. The cost of a 300 ml bottle of nitrofurantoin is £446.95 compared with £2.30 for a 100 ml bottle of trimethoprim (Drug Tariff, April 2018).