Healthcare Improvement Scotland | SIGN Evidence-based clinical guidelines

SIGN 160

Management of suspected bacterial lower urinary tract infection in adult women

A national clinical guideline

September 2020

NHS SCOTLAND

Key to evidence statements and recommendations

Levels of evidence

1^{++}	High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1^{+}	Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
1^{-}	Meta-analyses, systematic reviews, or RCTs with a high risk of bias
2^{++}	High-quality systematic reviews of case-control or cohort studies High-quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2^{+}	Well-conducted case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2^{-}	Case-control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, eg case reports, case series
4	Expert opinion

Recommendations

Some recommendations can be made with more certainty than others. The wording used in the recommendations in this guideline denotes the certainty with which the recommendation is made (the 'strength' of the recommendation).

The 'strength' of a recommendation takes into account the quality (level) of the evidence. Although higher-quality evidence is more likely to be associated with strong recommendations than lower-quality evidence, a particular level of quality does not automatically lead to a particular strength of recommendation.

Other factors that are taken into account when forming recommendations include: relevance to the NHS in Scotland; applicability of published evidence to the target population; consistency of the body of evidence, and the balance of benefits and harms of the options.

R For **'strong'** recommendations on interventions that **'should'** be used, the guideline development group is confident that, for the vast majority of people, the intervention (or interventions) will do more good than harm. For **'strong'** recommendations on interventions that **'should not'** be used, the guideline development group is confident that, for the vast **majority** of people, the intervention (or interventions) will do more harm than good.

R For **'conditional'** recommendations on interventions that should be **'considered'**, the guideline development group is confident that the intervention will do more good than harm for most patients. The choice of intervention is therefore more likely to vary depending on a person's values and preferences, and so the healthcare professional should spend more time discussing the options with the patient.

Good-practice points

✓ Recommended best practice based on the clinical experience of the guideline development group.

NICE has accredited the process used by Scottish Intercollegiate Guidelines Network to produce clinical guidelines. The accreditation is applicable to guidance produced using the processes described in SIGN 50: a guideline developer's handbook, 2019 edition (https://www.sign.ac.uk/assets/sign50_2019.pdf). More information on accreditation can be viewed at www.nice.org.uk/accreditation

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Every care is taken to ensure that this publication is correct in every detail at the time of publication. However, in the event of errors or omissions corrections will be published in the web version of this document, which is the definitive version at all times. This version can be found on our web site www.sign.ac.uk

Scottish Intercollegiate Guidelines Network

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Contents

1 Introduction

1.1 The need for a guideline

Lower urinary tract infections (LUTI) are commonly-occurring and frequently self-limiting infections involving the bladder (cystitis) and urethra.[1] A population-based survey of adult women in England reported that over a third (892/2,424) reported having had at least one urinary tract infection (UTI) in their lifetime.[2]

Infections that occur in hospitals, or long-term care facilities are considered healthcare associated and contribute to the morbidity and mortality of the population, in particular the older population, leading to increased hospitalisations.[3,4] In Scotland, UTIs are the most prevalent healthcare-associated infection within inpatient adult care.[5]

Urinary tract infections are the second most commonly-reported indication for an antibiotic prescription in the community after respiratory tract infection, accounting for approximately 23% of antibiotic prescriptions where the anatomical site is specified.[6]

The majority of drug-resistant infections are acquired in the community[7] and there is a clear association between antibiotic prescribing in suspected UTI and the development of antimicrobial resistance.[8] These factors, the prevalence and burden of UTIs and variation in approaches to diagnosis and management contribute to the need for an evidence-based national guideline in this area.

1.1.1 Prevalence

Two national point prevalence surveys of healthcare-associated infection and antimicrobial prescribing carried out in long-term care facilities and in hospitals in Scotland in 2016–2017 reported on the epidemiology of infections and prevalence of antimicrobial use in different settings.[5,9] In the hospital setting, the prevalence of UTI was 1.1% in acute adult patients (95% confidence interval (CI) 1.0 to 1.2). Urinary tract infections represented 24.5% of all healthcare-associated infections in this setting. Patients with UTI had a median age of 80 years and 58.9% were female. Approximately half of these UTIs, where data relating to prior catheterisation was recorded, developed in patients who had been catheterised at some point in the seven days prior to onset of the UTI. In non-acute adult inpatients, the prevalence of UTI was 1.9% (95% CI 1.4 to 2.6) representing over half of all healthcare-acquired infections.[5]

Within long-term care facilities the prevalence of diagnosed UTI was 1.9% (95% CI 1.4 to 2.5). Urinary tract infections represented 31% of all healthcare-associated infections in this setting. Residents with UTI had a median age of 85 years and three quarters were female. The percentage of residents with indwelling urinary catheters at the time of data collection was higher in those with UTI compared with those without (23.1% *v* 8.2%, p=0.003).[9]

Lower UTI in itself is not generally associated with mortality but occasionally may be associated with subsequent bacteraemia and *Escherichia coli (E. coli)* bacteraemia in particular. During 2018, there were 4,738 cases of *E. coli* bacteraemia in Scotland which accounted for the majority of all bacteraemia (measured across the ten most commonly-reported bacteria).[10] Over a third of *E. coli* cases are caused by urinary tract infections, the highest proportion of any infection site.[11] The relationship between management of the LUTI and subsequent development of bacteraemia is unclear.

1.1.2 Antimicrobial resistance

Rationalising and limiting unnecessary antibiotic use in patient with suspected (usually self-limiting) LUTI is a crucial step in controlling antimicrobial resistance (AMR). Understanding the evidence supporting LUTI diagnosis and the subsequent appropriate use of alternative (non-antibiotic) strategies which do not compromise clinical outcome and patient well-being is important. The safe and appropriate use of antibiotics is fundamental to national antimicrobial stewardship strategies overseen by the Scottish Antimicrobial Prescribing Group (SAPG, www.sapg.scot).

In 2012, surveillance of AMR in a representative sample of all urinary isolates was introduced in Scotland to detect and characterise emergence and spread of resistance in hospital and community settings. The most common causative UTI organisms in Scotland are *E. coli* and *Klebsiella pneumoniae (K. pneumoniae)*. *Escherichia coli* accounted for the majority of isolates. Susceptibility to commonly-used antibiotics has been generally stable in recent years although non-susceptibility to trimethoprim remains high at 33.8%. The majority (98.2%) of isolates remained susceptible to nitrofurantoin. The second most common cause of UTIs was *K. pneumoniae*, accounting for <10% of all UTIs. Similar to *E. coli*, non-susceptibility was stable but remained high with 23.5% of isolates non-susceptible to trimethroprim, and 64.4% to nitrofurantoin.[10]

Unnecessary use of tests and antibiotic treatment may be minimised by developing simple decision rules, diagnostic guidelines or other educational interventions.[12–16] Prudent antibiotic prescribing is a key component of the UK's action plans for reducing AMR.[17] Unnecessary antibiotic treatment of asymptomatic bacteriuria is associated with significantly increased risk of clinical adverse events[18,19] including *Clostridioides difficile* infection (CDI) or methicillin-resistant *Staphylococcus aureus* (MRSA) infection, and the development of antibiotic-resistant UTIs.

1.1.3 Variation in practice

Healthcare practitioners regularly have to make clinical judgements about managing patients with common infections including UTI and it is essential that they recognise the importance of signs and symptoms as part of the diagnostic assessment. Criteria for the diagnosis of UTI vary across the UK, and are also dependent on the patient and the context. There is evidence of variation in practice in use of diagnostic tests, interpretation of signs or symptoms and initiation of antibiotic treatment,[20–23] with continuing debate regarding the most appropriate approach.[24,25]

Existing evidence-based guidelines tend to focus on issues of antibiotic treatment (drug selection, dose, duration and route of administration) with less emphasis on clinical diagnosis or the use of near patient tests.[26–28] This guideline includes diagnostic recommendations for UTI including the use of urinary dipsticks as near patient tests. In addition to use of antibiotics, recommendations are provided for non-antibiotic and non-pharmacological treatment options.

1.1.4 Patient perspective

Patients and healthcare professionals may have different perspectives on healthcare processes and outcomes. The involvement of patients in guideline development is important to ensure that guidelines reflect their needs and concerns and address issues that matter to them.

Common concerns raised by patient groups include:

- inconsistency in diagnostic processes in primary care
- addressing worries for patients asked to delay antimicrobial treatment
- lack of awareness of self-management and prevention strategies
- emotional and practical issues associated with UTI, in particular the management of catheterisation.

1.1.5 Definitions

The European Association of Urology categorises urinary tract infections based on the clinical presentation of the UTI, the anatomical level of the UTI, the grade of severity of the infection, the categorisation of risk factors and availability of appropriate antimicrobial therapy. Details of their classification of UTI is shown in the table below:[29]

Uncomplicated UTIs	Acute, sporadic or recurrent lower (uncomplicated cystitis) and/or upper (uncomplicated pyelonephritis) UTI, limited to non-pregnant women with no known relevant anatomical and functional abnormalities within the urinary tract or comorbidities.
Complicated UTIs	All UTIs which are not defined as uncomplicated, meaning UTIs in a patient with an increased chance of a complicated course: ie all men, pregnant women, patients with relevant anatomical or functional abnormalities of the urinary tract, indwelling urinary catheters, renal diseases, and/or with other concomitant immunocompromising diseases, for example diabetes.
Recurrent UTIs	Recurrences of uncomplicated and/or complicated UTIs, with a frequency of at least three UTIs/year or two UTIs in the last six months.
Catheter-associated UTIs	Catheter-associated urinary tract infection (CA-UTI) refers to UTIs occurring in a person whose urinary tract is currently catheterised or who has had a catheter in place within the past 48 hours.

Recurrent UTI may be due to relapse/persistence or reinfection.[30]

- Relapse or persistence is recurrent UTI with the same strain of organism. Relapse/persistence is the likely cause if UTI recurs (or fails to be eradicated) within a short period (within two weeks) after sensitivity-adjusted treatment.
- Reinfection is recurrent UTI with a different strain or species of organism or the same organism more than two weeks after treatment.

Empirical antimicrobial treatment occurs when the prescriber has not yet identified the bacteria causing the infection and does not know the suspected bacteria's susceptibility to antibiotics.

1.2 Remit of the guideline

1.2.1 Overall objectives

This guideline provides recommendations based on current evidence for best practice in the diagnosis and management of suspected bacterial lower urinary tract infection in adult women. It replaces SIGN 88: Management of suspected bacterial urinary tract infection in adults which was first published July 2006 and updated in July 2012. This guideline includes younger women aged 16–64 years, older women aged 65 years and over and women of any age using an indwelling, intermittent or suprapubic catheter. It also includes the diagnosis and management of recurrent UTI in these groups.

Based on the definitions in section 1.1.5 this guideline includes recommendations on uncomplicated LUTI, recurrent LUTI and CA-UTI in adult women.

This guideline does not cover the following:

- diagnosis and management of upper UTI
- UTI in children under 16 years of age
- UTI in pregnant women
- UTI in men
- interstitial cystitis and bladder pain syndrome.

Although the guideline excludes pregnancy, the possibility a woman of childbearing age may be unknowingly pregnant must always be considered.

The decision to focus on guidance for managing UTI symptoms in non-pregnant women of all ages was based on the burden of infection being in this population and the potential complicated nature of UTI in other populations. The National Institute for Health and Care Excellence (NICE) provides guidance on antimicrobial prescribing for prostatitis[31] and pylonephritis[32] and the European Urology Association provides guidance on both diagnosis and management of UTI across several populations.[29]

Within this guideline diagnosis and management have been considered separately to acknowledge and promote that making a diagnosis of UTI should not automatically lead to prescription of an antibiotic. This is important due to the threat of antimicrobial resistance and the need to balance risks and benefits of using antibiotics at patient and population level.

The guideline is aimed primarily at healthcare professionals in primary-care settings as the majority of non-pregnant women with symptoms of UTI will present in the community. Women with symptoms of UTI account for a significant proportion of acute presentations to GP practices and out-of-hours services and evolution of services in Scotland means a proportion will also now be managed by community pharmacists.[33]

The setting in which uncomplicated UTIs in younger women are managed has shifted towards community pharmacy in recent years to improve access for patients. The context regarding community pharmacy is dynamic and subject to continual change but the principles of management remain the same regardless of the setting.

The guideline will complement existing resources in Scotland to support management of UTI provided by the Scottish Antimicrobial Prescribing Group (SAPG),[34] NHS Education for Scotland[35] and the Scottish UTI Network.[36]

1.2.2 Comorbidities to consider when managing patients with urinary tract infections

Multimorbidity is more common in older people and is associated with an increased risk of infection and hospitalisation, increased primary-care consultation rates and increased primary-care polypharmacy.[37–40] The diagnosis of UTI can be difficult in older patients, who are more likely to have asymptomatic bacteriuria,[41] and may experience increased frailty and comorbidities. In these patients urine culture ceases to be a diagnostic test unless there are other signs of infection.[42] Frail elderly patients, particularly those with dementia in long-term care facilities, may receive unnecessary antibiotic treatment due to asymptomatic bacteriuria and non-specific symptoms with consequent risk of adverse effects and no clinical benefit.[43,44]

Common comorbidities and coexisting health issues which have been considered when reviewing the evidence for this guideline are:

- diabetes
- neurological diseases accounting for neurogenic bladder symptoms, where the diagnosis and management is similar to idiopathic UTI.

1.2.3 Target users of the guideline

This guideline will be of interest to healthcare professionals in primary and secondary care, officers in charge of residential and care homes, antibiotic policy makers, clinical effectiveness leads, carers and patients.

1.3 Statement of intent

This guideline is not intended to be construed or to serve as a standard of care. Standards of care are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge and technology advance and patterns of care evolve. Adherence to guideline recommendations will not ensure a successful outcome in every case, nor should they be construed as including all proper methods of care or excluding other acceptable methods of care aimed at the same results.

The ultimate judgement must be made by the appropriate healthcare professional(s) responsible for clinical decisions regarding a particular clinical procedure or treatment plan. This judgement should only be arrived at through a process of shared decision making with the patient, covering the diagnostic and treatment choices available. It is advised, however, that significant departures from the national guideline or any local guidelines derived from it should be documented in the patient's medical records at the time the relevant decision is taken.

1.3.1 Influence of financial and other interests

It has been recognised that financial interests in, or close working relationships with, pharmaceutical companies may have an influence on the interpretation of evidence from clinical studies.

It is not possible to completely eliminate any possible bias from this source, nor even to quantify the degree of bias with any certainty. SIGN requires that all those involved in the work of guideline development should declare all financial interests, whether direct or indirect, annually for as long as they are actively working with the organisation. By being explicit about the influences to which contributors are subjected, SIGN acknowledges the risk of bias and makes it possible for guideline users or reviewers to assess for themselves how likely it is that the conclusions and guideline recommendations are based on a biased interpretation of the evidence.

Signed copies of declaration of interests forms are retained by the SIGN Executive and a register of interests is available in the supporting material section for this guideline at www.sign.ac.uk

1.3.2 Prescribing of licensed medicines outwith their marketing authorisation

Recommendations within this guideline are based on the best clinical evidence. Some recommendations may be for medicines prescribed outwith the marketing authorisation (MA) also known as product licence. This is known as 'off-label' use.

Medicines may be prescribed 'off label' in the following circumstances:

- for an indication not specified within the marketing authorisation
- for administration via a different route
- for administration of a different dose
- for a different patient population.

An unlicensed medicine is a medicine which does not have MA for medicinal use in humans.

Generally 'off-label' prescribing of medicines becomes necessary if the clinical need cannot be met by licensed medicines within the marketing authorisation. Such use should be supported by appropriate evidence and experience.[45]

"Prescribing medicines outside the conditions of their marketing authorisation alters (and probably increases) the prescribers' professional responsibility and potential liability".[45]

The General Medical Council (GMC) recommends that when prescribing a medicine 'off label', doctors should:[46]

- be satisfied that there is no suitably licensed medicine that will meet the patient's need.
- be satisfied that there is sufficient evidence or experience of using the medicine to show its safety and efficacy
- take responsibility for prescribing the medicine and for overseeing the patient's care, including monitoring the effects of the medicine, and any follow-up treatment, or ensure that arrangements are made for another suitable doctor to do so.
- make a clear, accurate and legible record of all medicines prescribed and, when not following common practice, the reasons for prescribing an unlicensed medicine.

Non-medical prescribers should ensure that they are familiar with the legislative framework and their own professional prescribing standards.

Prior to any prescribing, the licensing status of a medication should be checked in the summary of product characteristics (www.medicines.org.uk). The prescriber must be competent, operate within the professional code of ethics of their statutory bodies and the prescribing practices of their employers.[47]

1.3.3 Health technology assessment advice for NHSScotland

Specialist teams within Healthcare Improvement Scotland issue a range of advice that focuses on the safe and effective use of medicines and technologies in NHSScotland.

The Scottish Medicines Consortium (SMC) provides advice to NHS boards and their Area Drug and Therapeutics Committees about the status of all newly-licensed medicines, all new formulations of existing medicines and new indications for established products. NHSScotland should take account of this advice and ensure that medicines accepted for use are made available to meet clinical need where appropriate.

SMC advice relevant to this guideline is summarised in section 8.4.

2 Key recommendations

The following recommendations were highlighted by the guideline development group as the key clinical recommendations that should be prioritised for implementation.

2.1 Lower urinary tract infection in women aged under 65 years

R **Diagnose a UTI in the presence of two or more urinary symptoms** (dysuria, frequency, urgency, visible haematuria or nocturia) **and a positive dipstick test result for nitrite.**

R **Consider NSAIDs as first-line treatment in women aged <65 years with suspected uncomplicated lower UTI who describe their symptoms as mild.**

✓ Consider NSAIDs as an alternative to an antibiotic following a discussion of risks and benefits in women aged <65 years with suspected uncomplicated lower UTI when symptoms are moderate to severe.

R **Use short** (3-day) **courses of antimicrobials for treatment for LUTI, as this is clinically effective and minimises the risk of adverse events.**

R **Do not treat asymptomatic bacteriuria in non-pregnant women of any age.**

3 Lower urinary tract infection in women aged under 65 years

Urinary tract infection in women causes significant distress to individuals and economic impact with days absent from work. Patients presenting with UTI symptoms commonly receive empirical antibiotics (for coverage of the most common uropathogens) *(see section 3.2.4)*. A significant risk of empirical treatment is the emergence of multidrug-resistant organisms especially among *Enterobacteriaceae* family members, such as *E. coli* and *K. pneumoniae*. Empirical therapy without accurate estimation of infection can also needlessly put patients at risk of serious infections such as CDI and MRSA.[48]

Despite reduced rates of antibiotic use in the community during the past decade in Scotland and stable resistance rates, cases of *E. coli* bacteraemia continue to increase with the primary source for the majority of cases being a UTI.[33] Trends in resistance in Scotland are stable.[49] Reduction of *E. coli* bacteraemia rate is a national target in Scotland to be achieved through enhanced surveillance programmes and targeted interventions.[11] Effective management of UTI and appropriate use of antibiotics, where required, are both important in achieving this.

3.1 Diagnosis

The current approach for diagnosing patients with suspected UTI is clinical diagnosis based on presenting complaint and medical history. It is important to take a detailed history to inform a differential diagnosis and exclude other causes, for example a sexually-transmitted disease that may present with urinary symptoms alone. It is also important in women of childbearing age to consider if the patient could be pregnant as this will influence management. As recurrent UTI is defined as repeated UTI within a given frequency *(see section 1.1.5)*, there is no difference in the diagnostic criteria used when managing recurrent UTI. It is important to consider other causes for recurrent symptoms such as interstitial cystitis, bladder pain syndrome, renal stone or underlying malignancy (particularly in the context of haematuria).

In terms of diagnostic tests, microscopy, culture and antibiotic sensitivity analysis of a midstream, clean-catch urine specimen is used to confirm the presence and identity of bacteria causing urinary infections.[50]

The European Association of Urology guideline for urological infection states that uncomplicated LUTI can be diagnosed based on a history of urinary symptoms and absence of vaginal discharge, and dipstick analysis can increase the diagnostic accuracy when diagnosis is unclear. Urine culture and sensitivity analysis is not routinely recommended other than in patients with atypical symptoms, as well as those who fail to respond to appropriate antimicrobial therapy.[29] The results of these tests are typically available within 24–72 hours after the microbiology laboratory receives the specimen, meaning that in some cases, symptoms may resolve before the result can influence diagnosis or management. Clinicians can perform a urine dipstick test to confirm the presence of bacteria, which, in the presence of signs and symptoms, may be suggestive of a UTI with 30–40% sensitivity and up to 95-98% specificity based on positive urine nitrites.[51] The test does not specify the pathogen(s) causing the infection or the antibiotic sensitivities.

Three meta-analyses were identified which investigated pretest probabilities, post-test probabilities or a combination of both to predict UTI in women.[51–53]

3.1.1 Clinical assessment

Diagnosis of a UTI requires awareness of the prevalence of the condition within the population (pretest probability) and the use of additional tests and symptoms (post-test probability). The predictive value of additional symptoms and tests are defined by the likelihood ratios. Positive likelihood ratios (LR+), or the effect of a positive test on the change of odds of disease, indicate association with disease where ratios are >1 and are most useful to rule in disease at values >10. Negative likelihood ratios (LR-), or the effect of a negative test on the change of odds of disease, indicate association with lack of disease where ratios are <1 and are most useful to rule out a disease at values <0.1 *(see Table 1)*.

Table 1: Likelihood ratios and their effect on post-test probability

Likelihood ratio (LR)	**Change in likelihood of disease after test** (post-test probability)
>40	Large increase
5–10	Moderate increase
2–5	Small increase
1–2	Minimal increase
1	**Change**
0.5–1.0	Minimal decrease
0.2–0.5	Small decrease
0.1–0.2	Moderate decrease
<0.1	Large decrease

Pre- and post-test odds can be converted to probabilities to give clinicians and patients an easily-interpreted value to help rule in or rule out disease. Symptoms or tests used to inform the diagnostic process are most useful when the pretest probability is 50%. They are unlikely to alter disease probability and may confuse the situation when pretest probability is either high or low.

The pretest probability of UTI for a woman presenting with ≥1 urinary symptom in the community can be modified by the presence or absence of specific symptom(s). Possible outcomes of applying likelihood ratios of symptoms and tests are that the post-test probability of disease is high enough to warrant treatment; the post-test probability of disease is not significantly changed, and further testing is required to inform decision making; or that post-test probability of disease is reduced to the point where the healthcare professional is confident that no treatment is warranted. Such decisions are contingent on the risks and benefits associated with treatment and withholding treatment.

No population-level data were identified for baseline prevalence of UTI in the Scottish primary-care population. Prevalence of UTI is reported for the population of each study included in the three meta-analyses providing data in this section (range: 28% to 83%).[51–53] Reasons for this variation are unclear, but are likely to be associated with demographic differences in study populations, variations in the index test descriptions and different thresholds used for definition of bacteriuria. Studies from UK populations within these meta-analyses report prevalences of 28% to 66.6%. The only meta-analysis to calculate a mean weighted prior probability of UTI at the standard threshold used for definition of UTI in the UK (10^5 colony-forming units (CFU)/ml) reported a rate of 44.8% which was endorsed by the Guideline Development Group as representative of clinical experience in Scotland.[52]

3.1.2 Urinary symptoms

The first meta-analysis included 16 studies with 3,711 women presenting to primary care.[52] The age of patients ranged from 15 to 90 years (mean age range of included studies: 26–54 years). 1++

Three urinary symptoms were identified as useful diagnostic symptoms and increased the pretest probability of a UTI with positive likelihood ratios when a threshold of ≥10^5 CFU/ml is the reference standard; dysuria (LR+ 1.22, 95% CI 1.11 to 1.34), frequency (LR+ 1.09, 95% CI 1.02 to 1.16) and urgency (LR+ 1.17, 95% CI 1.04 to 1.31) *(see Table 2)*. At the lower threshold of ≥10^3 CFU/ml, the presence of any of five urinary symptoms increased the pretest probability of UTI (dysuria, frequency, urgency, nocturia and haematuria). There was no likelihood ratio given for the presence of vaginal discharge when the threshold of ≥10^5 CFU/ml is the reference standard. At a threshold of ≥10^2 CFU/ml as the reference standard, vaginal discharge had an LR+ of 0.65 (95% CI 0.51 to 0.83) and an LR- of 1.10 (95% CI 1.01 to 1.20) for UTI. **1++**

The second meta-analysis included 11 studies carried out in primary care (total patient number not reported).[53] The age of patients ranged from 8 to 90 years. Mean age was not reported in all studies, but most patients were <50 years of age. Using pooled positive (LR+) and negative (LR-) likelihood ratios when a threshold of ≥10^5 CFU/ml is the reference standard, dysuria (LR+ 1.09, 95% CI 1.03 to 0.16)[sic], urgency (LR+ 1.18, 95% CI 1.04 to 1.34) and nocturia (LR+ 1.28, 95% CI 1.08 to 1.52) were weak diagnostic indicators of UTI, whereas vaginal discharge (LR- 1.18, 95% CI 1.08 to 1.28) and suprapubic pain (LR- 1.14, 95% CI 1.07 to 1.21) were negative predictors (ie the absence of the symptom increased the odds of a diagnosis of UTI). **1+**

The third meta-analysis included four studies with a total of 948 patients who presented to the Emergency Care Department and used history and physical examination to predict UTI.[51] The age of patients ranged from 8 to 84 years (mean age range of included studies: 23–33 years). Assuming a UTI prevalence range of between 40–60% the likelihood ratios for the individual symptoms of dysuria, urgency, frequency or haematuria considered in isolation were insufficient to significantly alter the pretest probability. **1++**

All three meta-analyses used likelihood ratios to draw conclusions from the individual studies (two meta-analyses used pooled LRs,[52,53] while the other listed individual LRs for each of the four included studies[51]). Dysuria was found to be the most useful single symptom in predicting a UTI. However one meta-analysis did not find any single urinary symptom alone to be predictive.[51] This does not mean signs and symptoms are not helpful as the presence of these variables is necessary to define the at-risk population. Haematuria was only found to have a positive predictive value in one meta-analysis.[52]

While the likelihood ratios of individual symptoms considered in isolation are generally not sufficient to rule in or out a diagnosis of UTI, the presence of multiple relevant symptoms is more predictive. Although likelihood ratios for different symptoms or tests may be applied serially to an individual (such that the post-test odds for disease after applying the LR for the first symptom can be taken as the pretest odds for the second symptom), when symptoms are not independent there is a risk of overestimating the effect on post-test probability.

One systematic review reported the pooled LR+ for the combination of dysuria and frequency as 1.53 (95% CI 0.94 to 2.50)[53] while an earlier review reported the combination of dysuria and frequency without vaginal discharge resulted in a large LR+ of 24.6.[54] **1+**

3.1.3 Dipstick testing

Normally urine should not show any trace of nitrite, but most bacterial species causing UTI reduce nitrate in the urine to nitrite. The nitrite dipstick test is an indirect measure of nitrate-reducing bacteria (including *Enterobacteriaceae* and most of the non-fermenting bacteria), provided the urine contains sufficient dietary nitrates and has been retained in the bladder for more than four hours. Dipstick tests used for the detection of significant bacteriuria pick up the sodium nitrite in concentration of as little as 0.1 micrograms/ml to give a positive result. Some human leukocytes produce proteins with esterolytic activity and their blood level increases in response to infections.

These proteins hydrolyse ester substrates, which is the basis of leukocyte esterase (LE) tests. Colour intensity read at two minutes is proportional to the number of leukocytes in a sample. Positive results are reported as trace, 1+, 2+, or 3+. A positive test result is not highly specific for UTI as many other conditions also cause pyuria.

Dipstick tests are used to increase the predictive value of urinary symptoms. While LE test results are expressed on a semiquantitative scale, the nitrite test gives a binary result, either present or absent. The three reviews identified for inclusion in the analysis of urinary symptoms also evaluated dipstick tests to increase the diagnostic probability of the pretest symptoms.

In the first meta-analysis, combining the pretest results with post-test analysis using either a nitrite dipstick test or a combination of nitrite plus LE tests increased the post-test probability.[52] The presence of nitrites on a dipstick had a LR+ of 4.42, while a negative result for nitrites had LR- of 0.53 (although these values were derived from a population which included men and pregnant women). The post-test probabilities for a UTI, when the threshold of $\geq 10^5$ CFU/ml is the reference standard, are reported in Table 2. A decision tree containing probabilities of UTI modified by the presence or absence of symptoms and test results based on data from this study is contained in Annex 2. **1++**

Table 2: Post-test probabilities of infection based on symptoms alone and with positive or negative dipstick tests (at 10^5 CFU/ml threshold)

Symptom (LR+)	**Pretest probability based on single symptom**	**Post-test probability of symptom with a positive dipstick test result** (LR+ 4.42)	**Post-test probability of symptom with a negative dipstick test result** (LR- 0.53)
Dysuria (1.22)	50%	82%	35%
Frequency (1.09)	47%	80%	32%
Urgency (1.17)	49%	81%	34%
Vaginal discharge (0.65)	<35%*	<70%*	<22%*

Note: Pretest probability on presentation (population prevalence) is 44.8%

* values reported for threshold of $\geq 10^2$ CFU/ml, therefore probabilities at higher reference standards are lower

Data extracted from Giesen LG, Cousins G, Dimitrov BD, van de Laar FA, Fahey T. Predicting acute uncomplicated urinary tract infection in women: a systematic review of the diagnostic accuracy of symptoms and signs. BMC Family Practice 2010;11:78.[52]

In the second meta-analysis, pooled likelihood ratios were also applied to pretest probability which altered post-test prediction for a UTI. The nitrite dipstick test had a pooled LR+ of 6.51 (95% CI 4.24 to 10.01) and a pooled LR- of 0.58 (95% CI 0.52 to 0.64). For the leukocyte esterase test the pooled LR+ was 1.42 (95% CI 1.23 to 1.57) and a pooled LR- of 0.44 (95% CI 0.35 to 0.56).[53] **1+**

In the third meta-analysis, the LR+ for nitrite ranged from 7.5 to 24.6 and a LR- from 0.6 to 0.7. For leukocyte esterase the LR+ ranged from 1.5 to 5.6 and LR- from 0.2 to 0.6.[51] **1++**

All studies show the benefit of dipstick testing to rule in or rule out a UTI. A positive nitrite test is helpful to rule in a UTI, however a negative test does not exclude a UTI. The presence of LE moderately increases the post-test probability of disease.

An economic evaluation which compared the cost effectiveness of 15 different diagnostic strategies found that the presence of urinary symptoms and a positive dipstick test for nitrites was the least costly strategy. Performing a dipstick test in parallel with, rather than sequentially after, a positive history of symptoms only led to a marginal increase in costs but a higher proportion of women receiving a correct diagnosis (from 0.59 sequentially to 0.73 in parallel). The authors concluded that the most cost-effective diagnostic strategy where providers were willing to pay up

to €10 per additional UTI diagnosis was a dipstick test taken after a positive history of symptoms. When the willingness-to-pay threshold was €10–17 per additional UTI diagnosis the most cost-effective strategy is to combine history and dipstick in parallel. Sequentially adding either a microscopy test or a culture after a negative history and dipstick had the highest proportions of women receiving a correct diagnosis (0.87 and 0.88, respectively), but this strategy was only cost effective at relatively high willingness-to-pay thresholds in excess of €17 per additional diagnosis.[55]

R **Do not diagnose a UTI in the presence of a combination of new onset vaginal discharge or irritation and urinary symptoms** (dysuria, frequency, urgency, visible haematuria or nocturia).

✓ In making a differential diagnosis it is important to investigate for urethritis and other causes of symptoms to rule out conditions that present in similar ways to uncomplicated UTI.

R **Do not confirm the diagnosis of a UTI in the presence of a single urinary symptom** (dysuria, frequency, urgency, visible haematuria or nocturia).

✓ Advise the patient that a UTI cannot be confirmed based on a single urinary symptom and to return if the symptom fails to improve or worsens.

R **Diagnose a UTI in the presence of two or more urinary symptoms** (dysuria, frequency, urgency, visible haematuria or nocturia) **and a positive dipstick test result for nitrite.**

✓ Before carrying out a dipstick test urine should be retained in the bladder for at least four hours to allow conversion of urinary nitrates to nitrite by pathogens. Shorter incubation times may lead to false negative results.

✓ On diagnosis of UTI in the presence of two or more urinary symptoms and a positive dipstick test result for nitrite, a urine specimen should only be sent for culture if the patient has a history of resistant urinary isolates, has taken any antibiotics in the past six months or fails to respond to empirical antibiotics.

✓ Consider sending a urine specimen for culture to inform the diagnosis in patients who present with suspected UTI and two or more urinary symptoms and a negative dipstick test result for nitrite.

The algorithm in Figure 1 describes evidence-based pathways for the diagnosis and management of suspected LUTI in non-pregnant women <65 years. It emphasises the provision of self-care advice and consideration of treatments for symptomatic relief ahead of antimicrobial therapy depending on symptom severity.

3.2 Management

Symptoms of UTI in women can vary from mild discomfort when passing urine to moderate constant pain and the need to pass urine frequently and urgently which can impact on daily activities. Decisions on how to manage UTI symptoms should take into account their impact on daily life including consideration of work, activities and any responsibilities to care for others.

In an era of increasing resistance to antibiotics and an increasing awareness of the need for shared decision making in healthcare it is important for patients presenting with UTI symptoms to have the opportunity to discuss options with their healthcare professional to determine the best approach. Some patients may prefer to avoid taking antibiotics and prefer a 'watch and wait' approach if symptoms are not severe.

All women who are symptomatic of UTI should receive appropriate verbal and/or written self-care advice at every consultation regardless of diagnosis and treatment.

Lower UTI is a self-limiting disease. If untreated, increased daytime urinary frequency lasts on average 6.3 days, dysuria 5.2 days, urgency 4.7 days, and patients report feeling generally unwell for on average 5.3 days, with moderately bad or worse symptoms for 3.8 days.[1] 1+

3.2.1 Self care

3.2.1.1 Fluid intake

Increasing fluid intake is thought to reduce UTI by dilution and flushing of bacteriuria. This reduces attachment to uroepithelial cells, reduces growth nutrients and/or improves clearance *(see section 5.1.1)*.

While no evidence was identified for benefit, increasing fluid intake with water in women with urinary symptoms is a low-cost intervention without evidence of harm that may provide symptomatic relief.

3.2.2 Pharmacological treatment: non-steroidal anti-inflammatory drugs

Whilst the majority of LUTIs are self limiting, meta-analysis of RCTs comparing placebo with antibiotic therapy in uncomplicated LUTIs in women have shown antibiotic therapy to be superior to placebo in reducing duration of symptoms and reducing bacteriuria but with increased risk of antibiotic-associated adverse effects.[56] In one large case-control study antibiotic prescription is associated with increase in the individual risk of a subsequent antibiotic-resistant urinary tract isolate.[8] 1+ 2+

Non-steroidal anti-inflammatory drugs (NSAIDs) have been investigated as an alternative strategy to antibiotics in the treatment of uncomplicated LUTI in women. The rationale is to minimise self-limiting symptoms, avoid the need for antibiotic therapy and reduce risk of subsequent antimicrobial resistance. Four RCTs (n=1,209) compared either ibuprofen or diclofenac with a variety of antibiotics in the treatment of uncomplicated LUTI in adult women *(see Table 3)*. The three larger studies[57–59] included women >18–70 years and one smaller study[60] included patients up to 85 years.

Three studies used ibuprofen as the study NSAID, with a dose of 400 mg three times per day for three days[57,60] or 600 mg three times per day.[59] Diclofenac 75 mg twice daily was used in the remaining study.[58] In the three ibuprofen studies the need for a subsequent antibiotic prescription was determined by review by the participants' general practitioner (GP) if required. In the study comparing diclofenac with pivmecillinam, participants were provided with fosfomycin 3 g to be taken if required for ongoing symptoms.[58] 1++

Speed of symptom resolution and risk of pyelonephritis

Symptom resolution was 1–3 days quicker in those who received antibiotics compared with NSAIDs (symptom duration 2–5 days compared with 4–6 days). By day 7 the majority (63–83%) of NSAID-treated participants reported symptom improvement.[57–59] Between 2% and 5% of participants receiving NSAIDs were diagnosed with pyelonephritis. 1++

3.2.2.1 Urine culture positive at follow up

Two studies reported urine culture results at 10 days[58] and 14 days.[59] Bacteriuria was reduced in those patients receiving antibiotics compared to those receiving NSAIDs (*see Table 3)*. Culture of the primary pathogen was seen in 19% of participants treated with ibuprofen and 4% of those treated with pivmecillinam.[59] 1++

Effect of NSAIDs on antimicrobial use

Use of an NSAID was associated with significant reduction in total antibiotic use with 38%, 53% and 61% of NSAID-treated patients not requiring an antibiotic in the month following study enrolment in the three larger studies *(see Table 3)*. An additional course of antibiotic was prescribed in 11–15% of patients randomised to receive antibiotics, within one month of enrolment. In one study where only 38% who received diclofenac improved without an antibiotic, participants were provided with a "rescue" antibiotic fosfomycin to be taken at their own discretion.[58] In the majority (71%) of subjects randomised to NSAIDs who took antibiotics, fosfomycin was taken within three days of enrolment, ie before symptoms were likely to have resolved. In a follow-up study the risk of recurrent UTI up to six months after the study was not predicted by non-antibiotic (NSAID) treatment.[61] 1++

3.2.2.2 Predicting patients more likely to benefit from NSAIDs rather than immediate antimicrobial therapy

In a follow-up study clinical factors associated with an antibiotic prescription within 28 days of receiving ibuprofen as symptomatic treatment of urinary tract infection were investigated.[62] Of the 235 females included in the analysis, around only one third (79 participants, 34%) subsequently required antibiotics because of persistent or recurrent UTI symptoms in the following 28 days, with the other two thirds (156 participants, (66%) recovering without any antibiotics. The final model identified five factors which predicted subsequent antibiotic prescription - moderate to severe urinary urgency/frequency (odds ratio (OR) 2.3, 95% CI 1.12 to 4.58), impairment of daily activities (OR 1.7, 95% CI 0.97 to 2.88), positive urine dipstick test results for erythrocytes (OR 4.6, 95% CI 2.05 to 10.19) or leukocytes (OR 4.8, 95% CI 1.65 to 14.22) or nitrite (OR 2.4, 95% CI 1.28 to 4.59). Scores were calculated for each factor through multivariate logistic regression analysis. Depending on where the threshold was set in the prediction model different proportions of participants would receive antibiotics at presentation or would be initially classified as not requiring antibiotic treatment. Of the latter, some would be predicted to subsequently return to the practice because of symptomatic treatment failure (false negatives). The lower the cut-off threshold, the greater the proportion of participants who would receive an antibiotic, but the smaller the proportion required to return to the GP practice after treatment failure. For example, a score of ≥210 points gives a sensitivity of 84% and specificity of 55% for subsequent antibiotic treatment. Applying this to the study cohort, 58% of all females presenting with symptoms of UTI would be advised to be treated with antibiotics (in 42% antibiotics would not be recommend). Using this score it was estimated that only 6% of the females started on symptomatic treatment would require subsequent antibiotics, however a large group of patients who could probably manage their condition without antibiotics would not be recognised. A score of ≥219 successfully predicted all of those with pyelonephritis. This proposed scoring method selects a lower-risk population who could be targeted for NSAID treatment. The model underestimates those who might improve with an NSAID and is of limited usefulness as a formal strategy to restrict antibiotic prescriptions. The principles of risk stratification by symptom severity and risk factor burden suggest that NSAID treatment is a useful strategy for management of patients with milder symptoms and promoting antimicrobial stewardship. 2+

Predictive scoring was not explored in other studies except partly in the one study which showed in a subset analysis that symptom score at day six was similar in the two groups if urine culture at baseline was negative.[59] This suggests that successfully predicting those with symptomatic bacteriuria might be useful to determine those most likely to benefit from antibiotic therapy. 1++

NSAIDs may be associated with worsening of asthma control, renal impairment, an increased risk of thrombotic events and serious gastrointestinal toxicity, particularly in the context of alcohol use. Individual drugs within the class have specific contraindications. All NSAIDs are contraindicated in those with a history of hypersensitivity to aspirin or any other NSAID, which includes those in whom attacks of asthma, angioedema, urticaria or rhinitis have been precipitated by aspirin or any other NSAID.[45]

R **Consider NSAIDs as first-line treatment in women aged <65 years with suspected uncomplicated lower UTI who describe their symptoms as mild.**

✓ Consider NSAIDs as an alternative to an antibiotic following a discussion of risks and benefits in women aged <65 years with suspected uncomplicated lower UTI when symptoms are moderate to severe.

✓ The decision to use an NSAID or antibiotic should be shared between patient and prescriber and risks and benefits should be fully discussed and considered. This is particularly important in women with comorbidities that increase renal impairment.

✓ Duration of NSAIDs should be limited to three days to minimise adverse effects.

✓ Patients receiving NSAIDs should be informed to contact their prescriber if UTI symptoms do not resolve within three days or worsen.

Table 3: RCTs of non-antibiotic pharmacological and non-pharmacological treatments ∪ antibiotic treatment of uncomplicated LUTI in women

		Study agent	Comparator antibiotic	No.	Bacteriuria at baseline (%)	Symptom duration following intervention (days)	Symptom resolution by day 3–4 (%)	Symptom resolution by day 7 (%)	Pyelonephritis (%)	Bacteriuria at follow up (%)	Follow on antibiotic within one month (%)
Study	**Bleidorm (2010)[60]**	ibuprofen 3 days	ciprofloxacin 3 days	79	86 ∪ 80	Not reported	58 ∪ 52 (NS)	75 ∪ 61 (NS)	Nil	Not reported	Not reported
	Gagyor (2015)[57]	ibuprofen 3 days	fosfomycin 3 g once	494	76 ∪ 77	5.6 ∪ 4.6 (mean) (p<0.001)	39 ∪ 56 (p<0.001)	70 ∪ 82 (p=0.004)	2.1 ∪ 0.4 NS	Not reported	35 ∪ 14 (p<0.001)
	Kronenberg (2017)[58]	diclofenac 3 days	norfloxacin 3 days	253	72 ∪ 74	4 ∪ 2 (median) (p<0.001)	54 ∪ 80 (p<0.001)	83 ∪ 96 (p=0.003)	5 ∪ 0 (p=0.031)	28 ∪ 7 (day 10) (p<0.001)	55** ∪ 15 (p<0.001)
	Vik (2018)[59]	ibuprofen 3 days	pivmecillinam 3 days	383	67 ∪ 64	6 ∪ 3 (median)	39 ∪ 74 (p<0.01)	63 ∪ 91 (p<0.01)	4 ∪ 0	28 ∪ 10 (day 14) (p<0.01)	46 ∪ 10 (p<0.01)
	Wagenlehner (2018)[63]	BNO 1045 7 days	fosfomycin 3 g once	659	79 ∪ 73	Not reported	Not reported*	Not reported◇	1.8 ∪ 0.3		16 ∪ 10

All comparisons are study drug ∪ antibiotic

NS – not significant

* values estimated from graphs 70% (BNO 1045 group) ∪ 74% (fosfomycin group)

◇ values estimated from graphs 78% (BNO 1045 group) ∪ 82% (fosfomycin group)

** 58/82 (71%) of participants who took antibiotics did so within three days of enrolment and the majority with the rescue antibiotic fosfomycin

3.2.3 Pharmacological treatment: urine alkalinising agents

Urinary alkalisers reduce the acidity of urine which may, theoretically, relieve dysuria. They are recommended by the British Association of Urological Surgeons and may reduce the need for subsequent antimicrobial treatment. These agents reduce the efficacy of nitrofurantoin and this combination should be avoided *(see section 3.2.4.1)*. A Cochrane review concluded that the safety and efficacy of urinary alkalisers for the symptomatic treatment of uncomplicated UTI is unknown.[64] Therefore no recommendations can be made about their use. 1++

3.2.4 Pharmacological treatment: antimicrobials

Antimicrobials achieve clinical and microbiological cure of disease more rapidly than placebo[56] and are able to shorten the duration of symptoms such as dysuria, frequency, and urgency by half and shorten the average period with symptoms which the patient perceives to be moderately bad or worse by a third.[1] Treating patients who have LUTI with antimicrobials does not significantly affect risk of pyelonephritis compared with treatment with placebo (OR 0.33, 95% CI 0.04 to 2.7)[56] and results in equal or lower risk compared with treatment with NSAIDs *(see Table 3)*. 1+

3.2.4.1 Choice of agent

One Cochrane review provides evidence for the use of a number of classes of antimicrobials in the treatment of LUTI, (trimethoprim-sulfamethoxazole, flurorquinolones, nitrofurantoin, and beta-lactams), and reported no statistically significant difference in short-term or long-term symptomatic cure of disease when comparing these classes with each other, with the exception of the beta-lactam agent co-amoxiclav which was found to be inferior to fluoroquinolones in achieving bacteriological cure both in the short and longer term (relative risk (RR) 1.22, 95% CI 1.13 to 1.31 and RR 1.2, 95% CI 1.07 to 1.35, respectively).[65] 1++

The beta-lactams in the included studies were amoxicillin, cefuroxime, pivmecillinam and two cephalosporins which are not available in the UK (cefadroxil and cefpodoxime). Current practice in the UK for use of beta-lactam antibiotics in UTI would be to use co-amoxiclav, cefalexin or cefuroxime, but not as first-line agents due to their broader spectrum of activity than trimethoprim and nitrofurantoin and their increased risk of CDI. Amoxicillin is rarely used except for targeted treatment due to high resistance rates.

The possible inferiority of co-amoxiclav is also seen in a network meta-analysis which included 10 studies involving different classes of antimicrobials and ranked the drug classes by order of efficacy with ciprofloxacin as the reference agent.[66] Co-amoxiclav performed poorly compared with all other agents (including ciprofloxacin, trimethoprim-sulfamethoxazole, pivmecillinam, and fosfomycin) for short-term clinical cure (OR 0.07, 95% CI 0.02 to 0.24), short-term bacteriological cure (OR 0.17, 95% CI 0.8[sic] to 0.35), and longer-term clinical cure (OR 0.31, 95% CI 0.19 to 0.53). Odds ratios were calculated relative to the reference treatment (ciprofloxacin). 1++

Fluoroquinolones, such as ciprofloxacin, are no longer used widely in the UK for treatment of LUTIs, and while effective, the class has come under increased scrutiny, both due to its role as a driver of increasing gram-negative antimicrobial resistance[67] and mounting evidence of severe and irreversible toxicity associated with its use, particularly in the elderly. The Medicines and Healthcare products Regulatory Agency (MHRA) states that fluoroquinolones should not be used for uncomplicated cystitis unless other antibiotics that are commonly recommended are considered inappropriate.[68] Individuals who are prescribed a fluoroquinolone should receive information about potential serious adverse effects and actions to take should they experience them. 1+ 4

Antimicrobial stewardship initiatives place an emphasis on the use of narrow-spectrum antimicrobials, such as nitrofurantoin and trimethoprim whenever possible. *Escherischia coli*, which is the most common cause of UTI, has low resistances rates to nitrofurantoin in Scotland (declining from 2.7% in 2014 to 1.8% in *E. coli* urinary isolates in 2018).[10]

Trimethoprim resistance in laboratory samples while higher at around 40% has been stable for several years and analysis of national data suggests that patients prescribed trimethoprim are no more likely to require a subsequent antibiotic prescription for suspected UTI within one month than those prescribed nitrofurantoin[33] (personal communication: Health Protection Scotland). Urine samples sent for culture and sensitivity in Scotland are predominantly from patients with recurrent symptoms or frequent UTIs so surveillance data are not representative of the whole population of patients with UTI symptoms. Local guidelines in Scotland mostly suggest trimethoprim as first-line treatment with nitrofurantoin as an alternative for uncomplicated lower UTI in women of all ages. Pivmecillinam and fosfomycin, while effective antibiotics in lower UTI, are generally reserved for targeted treatment to protect them from emerging resistance.

Nitrofurantoin is concentrated in the urinary bladder, rendering the antimicrobial more effective in managing LUTIs than infections at other sites. Following an oral dose of 100 mg nitrofurantoin, blood plasma concentration is typically <1 micrograms/ml while urine concentration reaches 200 micrograms/ml.[69] Urinary pH affects the activity of nitrofurantoin. The minimum inhibitory concentration (MIC), is the lowest concentration (in micrograms/ml) of an antibiotic that inhibits the growth of a given strain of bacteria. The MIC for nitrofurantoin (≤32 micrograms/ml) has been shown to increase substantially as urine pH increases, indicating that a higher concentration is required for a bactericidal effect at higher pH levels. In the context of a standard course treatment with nitrofurantoin at fixed-dose, the drug is less effective at eradicating *E. coli* infection at higher pH levels.[70,71]

Despite absence of evidence for their safety or effectiveness, urinary alkalinising agents (most commonly containing potassium citrate, sodium citrate, or sodium bicarbonate) are available over the counter and often used by women seeking symptomatic relief from LUTI *(see section 3.2.3)*.[64] Use of urinary alkalinising agents should be discussed with patients who are prescribed nitrofurantoin with a view to discontinuation.

Nitrofurantoin should be avoided during pregnancy and when breastfeeding and the manufacturer advises caution in those with hepatic or renal impairment. It should be avoided if the estimated glomerular filtration rate (eGFR) is <45 ml/minute/1.73 m². When potential benefit outweighs risk, it may be used with caution if the eGFR is 30–44 ml/minute/1.73 m² for a short course only (3–7 days), to treat uncomplicated LUTI caused by suspected or proven multidrug resistant bacteria.[45]

R **Use a narrow-spectrum antimicrobial with activity against common uropathogens** *(see Table 4)* **for empirical treatment of LUTI in suitable patients.**

R **Do not use fluroroquinolones or co-amoxiclav empirically for LUTI unless other narrow-spectrum agents are contraindicated due to comorbidity, toxicity or resistance.**

✓ Advise women with LUTI, who are prescribed nitrofurantoin, not to take alkalinising agents (such as potassium citrate, sodium citrate, or sodium bicarbonate).

Increasing resistance in urinary gram-negative isolates has recently led to a revival of the antimicrobial fosfomycin, which is given as a single oral dose of 3 g for acute uncomplicated UTI, but evidence for the effectiveness of this agent is conflicting.

A meta-analysis found the single-dose treatment to be non-inferior to 3–5 day treatment courses of other antimicrobials (10 RCTs including 1,657 patients; RR 1.0, 95% CI 0.98 to 1.03).[72] A more recent RCT which compared five days of oral nitrofurantoin with single-dose fosfomycin found the latter to be less likely to achieve clinical cure at follow up after 28 days (clinical resolution 70% and 58%, respectively, absolute difference 12%, 95% CI 4% to 21%, p=0.004), although no significant difference was found for microbiological resolution of infection (74% and 63%, respectively, absolute difference 11%, 95% CI 1 to 20%, p=0.4).[73] 1+

✓ The choice of agent for an individual patient should be based on available microbiological results, tolerability and balance of risk versus benefit.

✓ Local guidance should take local resistance patterns and risk stratification into account.

3.2.4.2 Duration of treatment

A Cochrane review reported that short antibiotic treatment courses of three days were as likely to achieve symptomatic cure in the short and longer term (RR 1.06, 95% CI 0.88 to 1.28, and RR 1.09, 95% CI 0.94 to 1.7, respectively) compared with longer durations of treatment, and were no more likely to fail in achieving microbiological cure at short-term follow up (RR 0.92, 95% CI 0.8 to 1.06, p=0.01) than 5–10 day courses. Five to seven day courses of treatment performed better than three-day courses of the same agent for bacteriological cure of infection at long-term follow up (RR=1.43, 95% CI 1.19 to 17.73, p=0.0002). All adverse effects were more common with 5–10 day treatment regimens. The risk of developing adverse effects was 17% lower in the 3-day group (RR 0.83, 95% CI 0.74 to 0.93, p=0.001), and the effect was particularly pronounced in trials comparing different durations of the same antimicrobial (RR 0.76, 95% CI 0.63 to 0.92).[74] 1++

R **Use short** (3-day) **courses of antimicrobials for treatment for LUTI, as this is clinically effective and minimises the risk of adverse events.**

3.2.4.3 Adverse events associated with antimicrobial treatment of LUTI in women aged <65 years

A meta-analysis which compared treatment with an antimicrobial with placebo concluded that adverse events were significantly more likely in individuals treated with antimicrobials (OR 1.64, 95% CI 1.1 to 2.44).[56] 1+

A further meta-analysis reported an increased risk of allergic reactions in form of a rash in patients treated with trimethoprim-sulfamethoxazole compared with fluoroquinolones and nitrofurantoin, and a higher risk of rashes associated with beta-lactams when compared to fluoroquinolones.[65] 1++

In the UK, trimethoprim on its own (rather than trimethoprim-sulfamethoxazole) is used for treatment of UTI. No studies were identified comparing trimethoprim with trimethoprim-sulfamethoxazole either for efficacy in treating UTI or for risk of adverse events.

Adverse effects to any class of antimicrobial were significantly less common with 3-day treatment courses compared with 5–7 day courses *(see section 3.2.4.2)*.

Development of resistance is a risk with any antimicrobial use, but it is an outcome not commonly examined in RCTs. The only meta-analysis identified which reports on this outcome showed no significant increase in emergence of resistance between patients treated with antimicrobials compared with placebo.[1] 1+

Table 4: Comparison of selected antimicrobial agents for treatment of LUTI

First-line / empirical agents	Comments
Nitrofurantoin	First-line treatment option. Narrow-spectrum agent with low rate of resistance. Not suitable for patients with eGFR <45 ml/min/1.73 m². Efficacy reduced when taken concurrently with over-the-counter urinary alkalinising remedies containing citrate.
Trimethoprim	First-line treatment option. Narrow-spectrum agent. Dose adjustments required in patients with renal impairment. Resistance rate for *E. coli* 33.6% in Scotland.[10]
Alternative agents	**Comments**
Amoxicillin	Second-line treatment option but high rate of resistance in *E. coli* (52.8% in 2018)[10] so only suitable for targeted treatment.
Pivmecillinam	Second-line treatment option which is useful for targeted treatment (against organisms sensitive to pivmecillinam). Narrow-spectrum agent.
Fosfomycin	Second-line treatment option which is useful for targeted treatment (against organisms sensitive to fosfomycin). Broad-spectrum agent. Single-dose treatment.
Restricted agents	**Comments**
Cefalexin	Broad-spectrum agent. 0.5–6.5% of penicillin-sensitive patients will also be allergic to the cephalosporins. If a cephalosporin is essential in patients with a history of immediate hypersensitivity to penicillin, because a suitable alternative antibacterial is not available, then cefixime, cefotaxime, ceftazidime, ceftriaxone, or cefuroxime can be used with caution; cefaclor, cefadroxil, cefalexin, cefradine, and ceftaroline fosamil should be avoided.[45] Cephalosporins are associated with an increased risk of CDI.[11,75]
Ciprofloxacin	Use only where other antibiotic choices are unsuitable· Adverse safety profile - MHRA warning; do not use for LUTI unless all other agents unsuitable.[68] Fluoroquinolones are associated with an increased risk of CDI.[11,75]
Co-amoxiclav	Restricted treatment option. Less effective in achieving cure than other classes. Broad-spectrum agent. Contraindicated in patients with history of co-amoxiclav-associated jaundice or hepatic dysfunction and those with history of penicillin-associated jaundice or hepatic dysfunction.[45] Resistance rates for *E. coli* around 25% in Scotland.[33] Co-amoxiclav is associated with an increased risk of CDI.[11,75]

Local formularies will determine the dose and duration of individual antimicrobials used for treatment of UTI.

3.2.4.4 Treatment of asymptomatic bacteriuria in non-pregnant women

A Cochrane review comparing treatment of asymptomatic bacteriuria in men and non-pregnant women with antimicrobials or placebo reported an increased risk of adverse events associated with antimicrobial treatment (RR 3.77, 95% CI 1.4 to 10.15).[76] Only three of the nine studies included in this review recruited patients under the age of 65 years. 1++

R **Do not treat asymptomatic bacteriuria in non-pregnant women of any age.**

3.2.4.5 Delayed prescription of antimicrobials

An RCT of 309 patients undertaken in general practices in south-west England compared five management strategies for adult women aged 75 years or under presenting with UTI symptoms. No information was available on the age distribution of participants in any group. There were no significant differences in symptom duration, severity of frequency symptoms or severity of unwell symptoms between the antibiotic management strategies but those who delayed antibiotics for 48 hours or more were likely to suffer a 37% longer duration of symptoms rated moderately bad (incidence rate ratio (IRR) 1.37, 95% CI 1.11 to 1.68; p<0.001). Seventy seven per cent of patients in the delayed antibiotics group did take antibiotics but fewer patients reconsulted compared with those given immediate antibiotics.[77] 1+

In the accompanying economic evaluation, delayed antibiotics was both less effective and more expensive than immediate antibiotics or antibiotics targeted to a dipstick algorithm.[78]

Insufficient evidence about the impact of delayed prescription of antimicrobials was identified to support the development of recommendations.

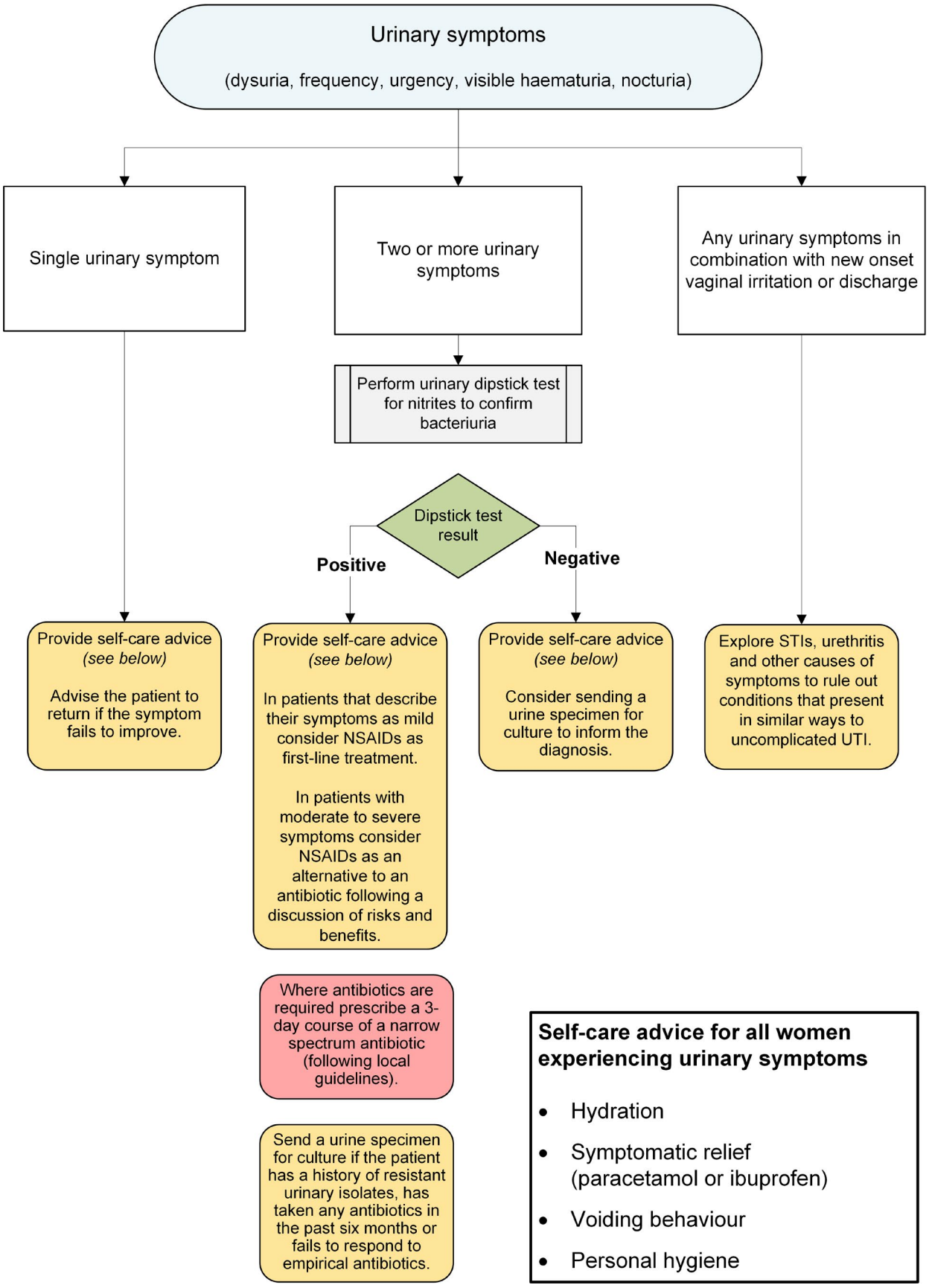
3.2.5 Non-pharmacological treatment

A single RCT was identified which investigated the herbal product BNO 1045 (Canephron®). BNO 1045 administered for seven days was compared with a single dose of 3 g fosfomycin (n=659).[63] The study was sponsored by the product manufacturer. BNO 1045 was non-inferior to antibiotic therapy. Of 325 participants randomised to BNO 1045, 83.5% improved without antibiotics by day 38 compared with 89.8% randomised to fosfomycin (rate difference: –6.26%; 95% CI -11.99 to -0.53%; 2-sided p=0.0014); the non-inferiority margin for this comparison was 15%. There were five (2%) cases of pyelonephritis in participants receiving BNO 1045 compared with one (0.2%) in those treated with fosfomycin. While overall adverse effect rates were similar in BNO 1045 and fosfomycin groups, the most commonly reported adverse effects were gastrointestinal disorders, which were reported with a higher frequency in the fosfomycin group (22 patients) than in the BNO 1045 group (13 patients). 1++

BNO 1045 is not used routinely in Scotland and cannot be supplied on prescription or purchased as an over-the-counter product. Patients can buy BNO 1045 via online retailers.

✓ Decision making should be shared between patient and prescriber and risks and benefits should be fully discussed and considered.

Figure 1: Algorithm for diagnostic and management options in non-pregnant women aged <65 years presenting with suspected LUTI



4 Lower urinary tract infection in women aged 65 years and over

4.1 Diagnosis

Urinary tract infection in older women can cause distress and a reduction in daily functioning. The incidence and mortality of sepsis and urosepsis are also higher in older people.[79] Multimorbidity is more common in older women and symptoms may be caused by other factors which, combined with an atypical symptomatology in the older adult, can make a definitive diagnosis difficult. As recurrent UTI is defined as repeated UTI within a given frequency, there is no difference in the diagnostic criteria used when managing recurrent UTI. It is important to consider other causes for recurrent symptoms such as interstitial cystitis, bladder pain syndrome, renal stone or underlying malignancy (particularly in the context of haematuria).

The incidence of asymptomatic bacteriuria (ASB) also rises with age, especially for those in long-term residential facilities, where it can be as high as 70% *(see Annex 3)*. Asymptomatic bacteriuria can lead to overdiagnosis of UTI and unnecessary antibiotic prescribing *(see section 4.2.2)* although is not directly associated with increased morbidity.[80] The frequency of antibiotic prescribing is higher in older adults, especially those in long-term care facilities, and older adults are more likely to harbour resistant bacteria.[9] Frail elderly people requiring assisted living services are assumed to be at similar risk to those in long-term care facilities.

Although the age of 65 years is used as a cut off, this is an artificial divide that does not distinguish a homogenous group. It includes fit ambulatory, self-caring older women who, on an individual basis, may be managed as those aged under 65 years, as well as older women in long-term care facilities or requiring assisted living, and it is this latter group to whom the majority of the evidence identified below applies.

4.1.1 Urinary symptoms

One meta-analysis incorporated 15 studies with a total of 12,039 participants (including men, however symptom scoring is stratified by sex), investigating 66 different symptoms and signs of UTI in individuals aged over 65 years.[81] Eight studies included individuals in residential or nursing facilities (9,500/12,039 participants) and a further four studies in a combination of home or residential settings (1,400/12,039 participants). Only 1,038/12,039 participants were reported to be at home, so the evidence is mostly applicable to the group of older women in care homes or requiring assisted living.

The meta-analysis investigated urinary symptoms and reported pooled estimates for the association between UTI and urinary continence and dysuria. Due to heterogeneity or lack of data, all other estimates were presented as individual study estimates. 2++

Both urinary incontinence and dysuria were weak predictors of UTI when considering combined data from men and women (LR+ 1.96, 95% CI 1.48 to 2.60 and LR+ 1.70, 95% CI 1.12 to 2.57, respectively). Absence of these symptoms (LR-) did not help to rule out a diagnosis of UTI. Only one of four studies which contained data from women alone recorded a significant association between urinary incontinence and UTI. Similarly, only one of four studies containing data from women on urinary frequency and one of six studies reporting on nocturia suggested a positive association. Data from all studies involving women alone showed no association between dysuria, urgency or haematuria and UTI.[81]

✓ Where incontinence is a feature, causes other than UTI should be considered, for example prolapse, voiding dysfunction or functional impairment.

4.1.2 Clinical assessment

The meta-analysis identified a single study which suggested that inability to perform a number of activities of daily living predicted UTI, for example, disability in feeding oneself (LR+ 11.8, 95% CI 5.51 to 25.2) and disability in washing one's hands and face (LR+ 6.84, 95% CI 4.08 to 11.5). The authors noted that the majority of these estimates were derived from a single study and are likely to be highly correlated with each other. Another single study suggested that constipation may be a weak predictor of UTI (LR+ 1.36, 95% CI 1.09 to 1.71; LR- 0.77, 95% CI 0.62 to 0.95).

A single, small cross-sectional study included in this meta-analysis suggested that tachycardia (heart rate >90 beats per minute) may be weakly predictive of UTI (LR+ 3.52, 95% CI 1.23 to 10.1), this study only included 65 women and confidence intervals are wide. A larger study of 551 nursing home residents (81.3% female, mean age 85.9%) showed no association between tachycardia and bacteriuria plus pyuria (RR 0.85, 95% CI 0.48 to 1.35). Neither fever (two studies) nor hypotension (one study) were predictive of UTI in men or women. 2++

A cross-sectional study of 481 women conducted in Finland in 1965 and included in this meta-analysis reported that cloudy urine was a significant predictor of UTI (LR+ 4.77, 95% CI 1.92 to 11.9, LR- 0.83, 95% CI 0.73 to 0.94), but neither foul smelling urine nor haematuria were.

In one study, abdominal pain was a significant predictor of UTI in women, but back pain and hypogastric pain were not. Results from two studies of flank pain as a predictor of UTI which included men and women were conflicting with one study showing a significant effect, while the other did not.

Two studies included in this meta-analysis reported presence of delirium to be a predictor of UTI, and absence of this symptom weakly helped to rule out UTI (LR+ 1.91, LR- 0.72 and LR+ 1.52, LR- 0.83).[81] Delirium can also be an indication for many other conditions, including dementia, other infections, 'high risk' medication use, diminished activities of daily living, immobility, sensory impairment, urinary catheterisation, urea and electrolyte imbalance and malnutrition.[82] 2++

SIGN guideline 157: Risk reduction and management of delirium recommends systematic identification and treatment for potential causes (of delirium, such as medications, acute illness etc), noting that multiple causes are common and that regulation of bladder and bowel function in people at risk of delirium should be considered to reduce the incidence.[83] 4

R

- **Be aware that women aged 65 years and over, especially those in long-term care facilities, may not display the usual symptoms and signs of UTI that are seen in younger women.**
- **Be aware that functional deterioration and/or changes to performance of activities of daily living may be indicators of infection in frail older people.**

✓ A holistic assessment is needed in the frail elderly to rule out other causes with both classical and non-classical signs of UTI. Signs and symptoms which may lead to functional decline include dehydration, constipation, electrolyte abnormality, polypharmacy, pain and urinary retention.

✓ Consider sepsis, non-urinary infections and other causes of delirium in an unwell older adult with abnormal vital signs (for example, fever, tachycardia, hypotension, respiratory rate and saturations).

4.1.3 Urinalysis and dipstick testing

A prospective observational study compared two cohorts of 100 patients at a hospital emergency department with and without non-urinary symptoms which may be associated with underlying infection (acute confusion, weakness or fever).[84] Dipstick tests and urine cultures were taken from all participants. Of the 33 positive urine culture results, 10 had negative dipstick test results. Thirteen of the 14 positive nitrite dipstick tests were culture positive for a specificity of 92.8% and a sensitivity of 36.1%. Due to the prevalence of ASB in older women, positive cultures may not imply a diagnosis of UTI. Of the 67 positive dipstick results, 41 (61.2%) were associated with negative cultures. Likelihood ratios in both groups suggested that dipsticks may not help significantly in decision making, with positive and negative LRs in the range representing small changes in post-test probability (control group: 2.8 and 0.31, symptomatic group: 2.7 and 0.46, respectively). The authors concluded that dipstick testing is an unreliable method of identifying patients with positive cultures in the elderly. Moreover, positive urine culture rates are only slightly higher in patients with vague symptoms attributable to UTI than they are in (asymptomatic) patients treated for non-urologic problems, which suggests that many positive cultures in elderly patients with symptoms of UTI are false-positive results reflecting asymptomatic bacteriuria and not UTIs. 2+

A cross-sectional study investigated the correlation between bacteriuria and a range of non-urinary symptoms in 651 individuals (74% female, mean age 86 years) at 32 nursing homes. Urine cultures provide little or no useful information when evaluating diffuse symptoms among elderly patients of nursing homes. (*E. coli* in urine had some correlation with 'not being him/herself' in the previous month, but not in previous three months).[85] 3

R **Use of dipsticks for diagnosis of UTI in women aged 65 years and above in long-term care facilities or in frail elderly people requiring assisted living services is not recommended.**

✓ In women aged 65 years and over with symptoms suggestive of UTI a positive test for nitrite in the urine is a marker for bacteriuria, and this should be assessed in the context of the background incidence of asymptomatic bacteriuria.

Insufficient evidence was identified to support a recommendation for or against use of urinary dipsticks for the prediction of UTI in non-frail women aged over 65 years.

Urine cultures will lead to false positives if used to diagnose UTI in the context of diffuse symptoms in elderly patients in residential homes and will lead to overdiagnosis.

✓ Send a urine specimen for culture to confirm the pathogen and antibiotic susceptibility in women aged 65 years and above prior to starting antibiotics for a UTI.

4.2 Management

✓ Manage suspected UTI in ambulant women aged 65 years and over who are able to look after themselves independently with no comorbidities as in those aged under 65 years, taking into account the increasing background incidence of asymptomatic bacteriuria.

For further information see section 3.2.4.4

4.2.1 Self care

There is a lack of evidence for self-care interventions to reduce UTI risk in the over 65s. Increased fluid intake in one cohort study showed a reduction in rates of asymptomatic bacteriuria (29.7% to 17.6%), although this was not statistically significant.[86] Another small cross-sectional study did not identify a significant association between daily fluid intake and UTI.[87] 2- 3

Evidence from premenopausal women and those with recurrent UTI suggests increased fluid intake can be beneficial in reducing incidence, and represents a low-cost, no-harm intervention *(see sections 3.2.1.1 and 5.1.1)*.[88] 1+

In the older population factors such as poor mobility, cognitive impairment, and medication are likely to impact on an individual's ability to ensure adequate hydration. Incontinence is also more prevalent in this population, and a cross-sectional study in nursing homes found an association between increased UTI incidence and the use of absorbent pads.[87] 3

The Scottish Urinary Tract Infection Network (SUTIN) leads a National Hydration Campaign which aims to convey the public health benefits of good hydration in terms of UTI prevention.[89] Materials to support promotion of continence are available from the Care Inspectorate.[90,91]

✓ Exercise caution in women who are on fluid restriction for medical reasons (for example, those with chronic heart failure or on renal dialysis).

✓ The Care Inspectorate document *Eating and Drinking Well in Care* provides best practice guidance on older people's dietary needs and related food and fluid requirements.[92]

4.2.2 Pharmacological treatment: antimicrobials

In women over 65 antimicrobials remain an effective way to achieve clinical cure of LUTI.[56] No evidence was identified that describes specifically the risks inherent to antimicrobial treatment of acute UTI in women aged over 65 years, but the risks described for women aged under 65 are likely to be similar. In addition, older people are more likely to be affected by multimorbidity and be subject to polypharmacy and the resulting higher risk of drug interactions which can be associated with preventable harm.[93,94]

Due to the difficulties in diagnosing UTI in older women, particularly frail elderly women in long-term care facilities, decisions on how to manage symptoms should be made on an individual patient basis taking account of the risks and benefits of various treatment options.

To support health and care staff in managing urinary symptoms in older people a decision aid developed by SAPG is available for use in long-term care facilities (https://www.sapg.scot/media/4092/uti-in-older-people.pdf).

4.2.2.1 Choice of agent

No studies were identified which examined choice of antimicrobial agents for treatment of LUTI in this age group. The following recommendation is extrapolated from evidence in women aged under 65 years *(see section 3.2.4.1)*.

R **Consider use of a narrow-spectrum antimicrobial with activity against common uropathogens for treatment of LUTI in women aged 65 years and over. Consider individual patient factors such as impaired renal function, polypharmacy and adverse effects, such as CDI and antimicrobial resistance** *(see Table 4).*

4.2.2.2 Duration of treatment

One RCT was identified which provides data on the effectiveness of different durations of treatment for LUTI in older women, suggesting that 3-day courses are as effective as 7-day courses in controlling most symptoms of LUTI, apart from urgency, and are less likely to cause side effects.[95] 1++

4.2.2.3 Adverse events

A cohort study which included 178,222 people aged 65 years or over treated with an antibiotic for UTI showed that trimethoprim was significantly associated with hyperkalaemia within 14 days of antibiotic initiation (OR 2.27, 95% CI 1.49 to 3.45) compared with amoxicillin, irrespective of use of renin-angiotensin system blockers or potassium-sparing diuretics.[96]

Adverse events caused by prophylactic antimicrobials for prevention of recurrent UTI are common, and a systematic review of three RCTs involving 491 postmenopausal women reports them to be particularly frequent with trimethoprim-sulfamethoxazole (any side effect 54%, rash 14.8%, nausea 15.7%, vaginal symptoms 16.5%) and nitrofurantoin (total side effects 16%, pneumonitis 1.1%, thrombocytopenia 2.3%).[97] 1+

A systematic review of long-term antibiotics for prevention of recurrent UTI in older adults found that resistance to trimethoprim-sulfamethoxazole increased to >90% after only one month of continuous prophylaxis. While resistance levels were seen to decrease after prophylaxis was stopped, levels at 15 month follow up remained above baseline prior to prophylaxis.[98] 1++

4.2.2.4 Treatment of asymptomatic bacteriuria

A Cochrane review comparing treatment of asymptomatic bacteriuria in men and non-pregnant women with antimicrobials or placebo reported an increased risk of adverse events associated with antimicrobial treatment (RR 3.77, 95% CI 1.4 to 10.15).[76] Six of the nine studies included in this review recruited patients over the age of 65 years. 1++

R **Do not treat asymptomatic bacteriuria in non-pregnant women of any age.**

4.2.3 Pharmacological treatment: non-steroidal anti-inflammatory drugs

No evidence was identified on the use of NSAIDs specifically in women aged 65 years and over.

4.2.4 Non-pharmacological treatment

No evidence was identified on the use of non-pharmacological treatment for UTI specifically in women aged 65 years and over. Non-pharmacological treatment in women with recurrent UTI, including those aged 65 years and over, is covered in section 5.1.5.

5 Recurrent lower urinary tract infection in women

Recurrent UTI is a common condition in women of all ages with significant effects on the quality of life of affected individuals. It may be associated with a range of lifestyle and concurrent medical conditions. As recurrent UTI is defined as recurrences of uncomplicated and/or complicated UTIs, with a frequency of at least three UTIs per year, or two UTIs in the last six months, diagnosis is made using the same criteria as an acute UTI and consideration of the previous history of UTI.

5.1 Management

5.1.1 Self care

Fluid intake

One RCT suggested that increasing fluid intake by 1.5 L/day in lower volume drinkers (mean 1.1 L/day) with recurrent UTI significantly reduces the number of UTIs (mean reduction of 1.5 over 12 months; p<0.001); increases time between episodes (mean 58.4 days; p<0.001) and reduces antimicrobial regimen use (mean reduction 1.7, 95% CI 1.3 to 2.1; p<0.001).[88] 1+

A small case-control study identified an increased incidence of UTI in those who restricted their fluid intake.[99] 2+

R **Women with a history of recurrent UTI should be advised to aim for a fluid intake of around 2.5 L a day of which at least 1.5 L is water.**

To help achieve a fluid intake of around 2.5 L a day, it may be useful to express total fluid intake as 6 to 8 mugs a day (with a mug expected to hold around 350 ml).

✓ Materials to support public awareness of the importance of hydration are available from Health Protection Scotland.[89]

✓ Exercise caution in women who are on fluid restriction for medical reasons (for example, those with chronic heart failure or on renal dialysis).

Spermicidal contraception

Spermicides are thought to increase the risk of UTI by eradicating protective bacteria in the vagina which prevent colonisation with uropathogens allowing overgrowth of those that cause infection.

Evidence of the association between spermicides and risk of UTI is limited. Based on two studies a Canadian guideline recommends offering women using spermicide-containing products an alternative form of contraception.[100,101] 2+ 4

R **Consider offering women who are experiencing recurrent UTI an alternative to spermicide-containing contraceptives.**

Voiding behaviours and hygiene

Two case-control studies found that postponing voiding can lead to an increased incidence of urinary tract infection.[99,100] Other voiding and hygiene factors associated with increased risk of UTI are wiping genitals back to front, not urinating and not drinking water within 15 minutes of sexual intercourse, and avoidance of washing genitals with soap after urinating.[100] 2+

5.1.2 Pharmacological treatment: antimicrobials

A Cochrane review of 19 studies which included 1,120 non-pregnant women, most of whom were premenopausal, reported that long-term antimicrobial treatment, usually with single daily doses given at night time, is effective at reducing the number of recurrent episodes while prophylaxis is ongoing, with a number needed to treat (NNT) of 1.85 to prevent 1 microbiological recurrence, and 2.2 to prevent 1 clinical recurrence. Compared with placebo, prophylactic antimicrobials reduce the number of microbiological recurrences from 0.8–3.6 per year to 0.0–0.9 per year, and the number of clinical recurrences from 1.12–3.6 per year to 0.0–0.27 per year.[102] 1++

Two RCTs comparing a daily dose of 480 mg trimethoprim-sulfamethoxazole with a preparation containing 500 mg of cranberry extract taken twice daily in premenopausal women with recurrent UTI found antimicrobials to be more effective[103] and cheaper[104] than cranberry products in this setting. 1++

As in any prophylactic antimicrobial use, the potential beneficial effects must be weighed up against an increase in antimicrobial resistance (both on an individual and population level). Few studies examine this issue.

One RCT, in which participants received prophylaxis with trimethoprim-sulfamethoxazole, reported the development of resistance not only to this agent, but also to beta-lactams with and without beta-lactamase-inhibitor (increase by 10% and 70% respectively), and fluoroquinolones (increase by 10%). Resistance rates returned to baseline levels three months after prophylaxis was stopped.[103] 1++

A systematic review with meta-analysis, which included three RCTs comparing long-term antimicrobials with vaginal oestrogens, oral *lactobacilli*, and D-Mannose reported that prophylactic antimicrobials are effective in preventing recurrent UTI in women aged over 65 years, reducing the risk of recurrent UTI by 24% while prophylaxis is ongoing (RR 0.76, 95% CI 0.61 to 0.95).[98] However the NNT is almost fourfold higher than in females under 65 years (8.5 *υ* 2.2).[102] 1++

R **Consider prophylactic antimicrobials for women experiencing recurrent UTI after discussion of self-care approaches and the risks and benefits of antimicrobial treatment involved.**

R **Long-term prophylactic antimicrobials for prevention of recurrent UTI should be used with caution in women aged 65 years and over, and careful consideration given to the risks and benefits involved.**

Choice of agent for long-term prophylaxis of recurrent UTI

The narrow-spectrum agent nitrofurantoin is excreted efficiently by the kidneys and in individuals with normal renal function this results in high levels of the agent in the urine without any detectable serum or systemic levels. In the context of long-term prophylaxis, this lack of systemic effect makes it an attractive option.

Nitrofurantoin has been shown to be as effective as other classes of antimicrobials in preventing recurrent UTI for microbiological success (RR 1.06, 95% CI 0.89 to 1.27) and for clinical cure (RR 1.06, 95% CI 0.89 to 1.27).[105] 1++

In an economic model based on a cohort of patients experiencing a mean of three UTIs per year, prophylaxis using nitrofurantoin (100 mg) was projected to result in a large reduction in UTI incidence (mean of 0.4 per year) with only a marginal increase in cost relative to a no-treatment strategy. The simulation also showed a greater number of quality-adjusted life-days gained per year (9.8) compared with alternative strategies such as oestrogen use, cranberry pills and acupuncture.[106]

There is a risk of significant adverse events associated with long-term use of nitrofurantoin. One meta-analysis reported thrombocytopenia in 2.3% of participants and pneumonitis in 1.1% of participants using nitrofurantoin.[97] Other meta-analyses report an increased risk of adverse effects severe enough to lead to discontinuation of treatment when comparing nitrofurantoin with other classes of agents (RR 1.58, 95% CI 0.47 to 5.28), and an increased risk of adverse effects overall (RR 1.83, 95% CI 1.18 to 2.84).[102] 1+ 1++

The BNF recommends monitoring of liver function and pulmonary function in any individual treated with nitrofurantoin for prophylaxis, and that the agent be discontinued if any deterioration in pulmonary function is found.[45]

Duration of antimicrobial prophylaxis for prevention of recurrent UTI

A meta-analysis of RCTs which recruited women with recurrent UTI who were treated prophylactically with nitrofurantoin compared with any other treatment showed no additional benefit when prophylaxis was given for more than six months compared with cessation of prophylaxis after six months. Studies included women of all ages, but based on mean age values for individual studies, most were in the premenopausal range.[105] 1++

✓ To minimise the development of resistance antimicrobial prophylaxis should be used as a fixed course of three to six months in women with recurrent UTI.

5.1.3 Pharmacological treatment: methenamine hippurate

A Cochrane review of methenamine hippurate for preventing urinary tract infection incorporated studies involving men and women of all ages, including those with renal tract abnormalities and postsurgical procedures. The overall quality of evidence was reduced by limitations in individual study quality, variation in doses used, variation in length of treatment and other factors. Although six of the eight studies suggested a trend in favour of treatment with methenamine hippurate, it was concluded that due to the significant methodological problems and inclusion criteria this evidence should be treated cautiously.[107] Therefore no recommendations for use of methenamine hippurate in recurrent UTI can be made. 1++

5.1.4 Pharmacological treatment: non-antimicrobials

Antimicrobials are more effective than non-antimicrobial agents such as oral *lactobacilli*, and vaginal application of topical oestrogens, but there is some evidence that the non-metabolised sugar D-Mannose may perform similarly to daily prophylaxis with nitrofurantoin in preventing recurrent UTI without a statistically significant rise in adverse events.[98] 1++

The risk of recurrent UTI is increased in postmenopausal women and this may be due to falling oestrogen levels triggering both a rise in vaginal pH and decrease in vaginal *Lactobacillus* which allows gram negative bacteria to proliferate. The use of vaginal or oral oestrogens has been proposed as a preventative strategy.

A systematic review of pharmacological agents to decrease new episodes of recurrent LUTI in postmenopausal women identified five studies involving a total of 596 patients using various vaginal oestrogen products. All preparations of vaginal oestrogen decreased the number of UTIs compared with placebo or compared with baseline recurrence rate. Local adverse reactions such as itching or burning occurred in 0–36% across treatment and placebo groups. The authors note that most of the side effects of these medications are minimal and well tolerated. Two studies of oral oestrogens showed no significant reduction in episodes of UTIs compared with placebo.[97] 1+

A Cochrane review of oestrogens for preventing recurrent urinary tract infection in postmenopausal women included nine studies of 3,345 women and concluded that, based on two studies, vaginal oestrogens reduced the proportion of women with UTI at the end of the treatment period compared with placebo. Study results were not pooled due to heterogeneity arising from the different application methods. Oral oestrogens did not reduce UTIs compared with placebo (RR 1.08, 95% CI 0.88 to 1.33).[108] 1++

The licensed indication for use of oestrogen vaginal products is to treat symptoms of vaginal atrophy in postmenopausal women. Use of these products for prevention of UTI is an unlicensed indication. In 2019 European Medicines Agency advice recommended that high-strength oestradiol creams containing 100 micrograms/gram (0.01%) should only be used for a single treatment period of a maximum of four weeks due to the risk of cardiovascular adverse effects and certain types of cancer.[109]

5.1.5 Non-pharmacological treatment

Cranberry

Cranberry products have been used as a possible non-antimicrobial method for UTI prevention for decades. Amongst the constituents of cranberry are proanthocyanidins (PAC) and other polyphenols which disrupt the adhesion of *E. coli*, the most common cause of UTIs, to the epithelium of the urinary tract, and may prevent infection.[110] Processing raw cranberry affects the PAC composition of various cranberry formulations. The measurement of PAC content is complex and can be erroneous and non-reproducible which complicates the comparison of studies. Most studies did not report the amount of type A proanthocyanidin in the product which was used. Unlike antimicrobials which have a pharmacological effect on the bacteria, cranberry's effect is physicochemical, meaning that it is likely to work in similar ways for both sensitive and resistant strains of bacteria.[103,111]

Evidence for the effectiveness of cranberry products in preventing UTI is conflicting. Three systematic reviews and the body of evidence which these include report inconsistent results on the incidence of new UTIs across a range of populations.[111–113]

A Cochrane review of 24 studies with a total of 4,473 participants suggested that cranberry products were not effective in preventing UTIs either overall (RR 0.86, 95% CI 0.71, 1.04) or for the subgroup of women with recurrent UTIs (RR 0.74, 95% CI 0.42 to 1.31).[111] The studies used various forms of cranberry (juice or concentrate, capsules, tablets) and the control arm used either placebo, no treatment, water, methenamine hippurate, antibiotics or *Lactobacillus*. Study design was robust but a significant number of randomised patients were not analysed (lost to follow up) and intention to treat analysis was only performed in six studies. Most studies were not sufficiently powered to detect differences, even when combined. The fluid intake associated with each intervention was not routinely recorded. 1++

Another meta-analysis reported that cranberry-containing products were more effective than placebo or non-placebo controls in preventing incidence of UTI (RR 0.62, 95% CI 0.49 to 0.80) and more effective in a subgroup of women with recurrent UTIs (RR 0.53, 95% CI 0.33 to 0.83). The authors note that one RCT was removed from the analysis as an outlier due to high levels of heterogeneity.[114] Although lowering heterogeneity, this also had a major impact on risk estimates, moving the overall result from absence of significant effect of cranberry to significance. 1++

A further systematic review and meta-analysis of 7 RCTs involving 1,498 healthy women over 18 years of age who were at risk of recurrent UTIs was sponsored by manufacturers of cranberry products. There was a high rate of loss to follow up and selective outcome reporting. Many of the studies were small with only two having more than 300 participants. The review reported a 26% reduction in the risk of UTI recurrence for healthy women who received cranberry than for those who did not (RR 0.74, 95% CI 0.55 to 0.98). In a subgroup of women who were enrolled with confirmation of an active UTI episode and then treated with antibiotics before UTI recurrence assessment, there was no significant effect of cranberry and a large degree of heterogeneity (RR 0.84, 95% CI 0.47 to 1.50; I^2=73%; n=3 studies).[113] 1+

Methodological differences that may be related to the conflicting findings of these studies include variations between the systematic reviews in methods used to select literature for inclusion, the populations of included studies, data extraction techniques and the handling of heterogeneity.[115]

There is evidence that cranberry may be more effective in prevention of uncomplicated UTI than UTIs caused by structural or functional complications, or catheterisation.[116,117] The first systematic review, which reported no overall effect of cranberry on prevention of UTI, combined studies with complicated and uncomplicated UTIs in the calculation of their risk estimates without making allowances for the weighting of these.[111]

Two systematic reviews noted that the inclusion of one RCT[114] introduced substantial heterogeneity. However one review[111] did not exclude this study, mainly because of its large sample size (the only study powered sufficiently to detect a difference), whereas the second review conducted a sensitivity analysis that identified the RCT as an outlier and excluded this study from their analysis.[112] The third review[113] included this RCT, however, it received approximately average weighting (15.12% as one of seven RCTs). Considerable heterogeneity was noted in the subgroup analysis which included this study, however authors did not exclude it and, despite its negative findings, the overall results were in favour of cranberry.

An RCT published after the Cochrane review included 928 patients in long-term care facilities, (median age 84), and compared cranberry capsules (500 mg with 1.8% PAC, equivalent to 9 mg) with placebo in patients at high risk (n=516) and low risk (n=412) of UTI. Participants with long-term catheterisation (>1 month), diabetes mellitus, or at least one UTI in the preceding year were considered to be at high UTI risk. There was a high dropout rate in this study. Results were stratified according to both a clinical and a scientific definition of UTI.[118] Cranberry capsules did not reduce the incidence of UTI in high-risk patients if UTI was given a scientific definition (25.3 *υ* 24.6 per 100 patient-years at risk, p=0.91; treatment effect 1.02, 95% CI 0.68 to 1.55). However, cranberry did reduce the incidence of clinically-defined UTI compared with placebo in high-risk patients (62.8 *υ* 84.8 per 100 patient-years at risk, p=0.04; treatment effect 0.74, 95% CI 0.57 to 0.97). The reason for this difference is unclear, but may suggest that not all clinical diagnoses of UTI reflected genuine infections. Cranberry capsules did not reduce the incidence of UTI in patients at low risk of UTI according to either definition. The authors noted that the daily use of 18 mg of PAC as used in this study may not have been high enough, given that in vitro studies had previously noted antiadherent effects at around 72 mg PAC per day. 1++

A further RCT investigated the effect of cranberry capsules (72 mg PAC per day) on bacteriuria and pyuria in older women in nursing homes (mean age 86.4 years). The trial showed no significant decrease in pyuria or bacteriuria with cranberry compared with placebo (29.1% *υ* 29.0%; OR 1.01, 95% CI 0.61 to 1.66; p=0.98).[119] 1++

It should be noted that the antiadhesion properties of cranberry juice on *E. coli* lasts for approximately eight hours after ingestion, therefore optimal exposure to maximise potential preventative effects on infection would require more than twice daily consumption.[116] The relatively strong flavour of cranberry juice may be difficult to tolerate in large daily volumes, especially for care home residents affected by swallowing disorders, exacerbation of incontinence, or reduced thirst.

Due to methodological inconsistencies between meta-analyses, it is not possible to form a recommendation on cranberry for the prevention of recurrent UTI. Further reviews are required using stricter criteria for study eligibility (focusing on populations, outcomes and interventions) and management of heterogeneity in order to provide clearer advice on the discrete population of women with recurrent uncomplicated UTI.

Herbal products

One RCT randomised patients with acute UTI to treatment with either a herbal product containing 80 mg horseradish root *(Armoraciae rusticanae radix)* and 200 mg nasturtium *(Tropaeoli majoris herba)* or placebo. Of the 174 participants, four were male and the mean age was 54 years). In the per-protocol population, the mean number of UTI recurrences in 180 days was 0.43 for the herbal product group and 0.75 for the placebo group (p=0.039). Intention to treat population results differ from the per-protocol results as 28 patients did not enter the treatment phase following complete healing after antibiotic treatment.[120] 1++

Probiotics

Probiotics are live micro-organisms which are thought to confer a health benefit on the host. The hypothesis is that they work by preventing other harmful bacteria from colonising the urinary tract and causing infection.

A meta-analysis of six studies that involved 352 women and children demonstrated no significant difference in recurrent symptomatic bacterial UTI between participants receiving probiotics and placebo (RR 0.82, 95% CI 0.60 to 1.12). The data were few and derived from small studies with poor methodological reporting.[121] 1++

A further meta-analysis of RCTs involving use of *Lactobacillus* probiotics for prophylaxis of recurrent UTIs did not show a significant effect from the probiotic compared with placebo (RR 0.85, 95% CI 0.58 to 1.25). When studies using *Lactobacillus* strains which have not been shown to be effective or to establish vaginal colonisation with the delivery methods used in the trials were excluded, a sensitivity analysis reported that use of *Lactobacillus* was associated with a significant reduction in risk of recurrent UTI (RR 0.51, 95% CI 0.26 to 0.99; n=2 studies).[122] 1+

Acupuncture

Based on two small RCTs, a Canadian guideline recommended that acupuncture may be considered as an alternative intervention in the prevention of recurrent UTI in women who are unresponsive or intolerant to antibiotic prophylaxis.[101] 4

While acupuncture is not routinely used in Scotland for this indication its use could be considered by individual patients.

6 Catheter-associated lower urinary tract infection in women

Urinary catheters are used to enable bladder drainage in the short or long term and are commonly-used invasive devices in both acute and community settings. The presence of a catheter increases the risk of bacteriuria. The urinary catheter provides a portal of bacterial entry into the bladder, either during catheter insertion or along the catheter urethral interface, increasing the risk of UTI. Two NHSScotland national point prevalence surveys of healthcare associated infection and antimicrobial prescribing *(see section 1.1.1)* reported that UTIs were the most common type of healthcare-associated infection in acute hospital inpatients (24.5%) and within non-acute settings (58.8%). The surveys also found 20.8% of inpatients had an indwelling urinary catheter in place, most commonly in intensive care, geriatric medicine and surgical specialities.[5,9]

The National Catheter Passport serves as an education tool for individuals using a catheter when there are no appropriate alternatives and supports effective care of the catheter in order to reduce the risk of infection. It also works as a communication tool for health and social care staff to explain the purpose of the catheter, when it was inserted and future plans, including trials without the catheter. There is also a catheter maintenance section which includes an evidence-based care bundle which can be completed by the health or social care professional, carer or patient themselves.[123]

The duration of catheterisation is the most important risk factor for the development of a CA-UTI. Urinary catheterisation perturbs host defence mechanisms and provides easier access of uropathogens to the bladder.[29]

A retrospective cohort study of 47,926 patients in the USA with indwelling catheterisations of more than 3 days' duration, which included men, women and children, examined risk factors for CA-UTI. Infection rates increased with each additional day of catheterisation and patients who were female along with those with cerebrovascular disease or paraplegia were at higher risk of CA-UTI. This supports regular review of the need for a urinary catheter to minimise UTI in this population.

- ✓ Use a catheter passport to provide education for patients and families and to facilitate communication between hospital and community healthcare teams.
- ✓ Patients with indwelling catheters should have regular review to assess the ongoing need for catheterisation, including consideration of alternatives to catheterisation and trial without catheter.

6.1 Diagnosis

6.1.1 Clinical assessment

The shared aetiology among all people with CA-UTI may allow greater overlap in diagnostic and management strategies between the sexes. Most signs and symptoms in catheterised patients with bacteriuria are non-specific and to prevent unnecessary antibiotic use, patients should be thoroughly evaluated for the source of signs and symptoms before attributing them to the urinary tract. The presence of bacteria in the urine of catheterised patients is common and inevitable but ASB does not necessarily indicate presence of infection.

The following statements are reproduced, with permission, from The Infectious Diseases Society of America (IDSA) guideline which provides useful advice to support diagnosis of CA-UTI in women and men.[124] 4

- CA-UTI in patients with indwelling urethral, indwelling suprapubic, or intermittent catheterisation is defined by the presence of symptoms or signs compatible with UTI with no other identified source of infection along with ≥10^3 CFU/mL of ≥1 bacterial species in a single catheter urine specimen or in a midstream voided urine specimen from a patient whose urethral, suprapubic, or condom catheter has been removed within the previous 48 hours.
- Signs and symptoms compatible with CA-UTI include new onset or worsening of fever, rigors, altered mental status, malaise, or lethargy with no other identified cause; flank pain; costovertebral angle tenderness; acute haematuria; pelvic discomfort; and in those whose catheters have been removed, dysuria, urgent or frequent urination, or suprapubic pain or tenderness.
- In catheterised patients, pyuria (presence of pus in the urine) is not diagnostic of CA-bacteriuria or CA-UTI.
  - The presence, absence, or degree of pyuria should not be used to differentiate catheter-associated asymptomatic bacteriuria (CA-ASB) from CA-UTI.
  - Pyuria accompanying CA-ASB should not be interpreted as an indication for antimicrobial treatment.
  - The absence of pyuria in a symptomatic patient suggests a diagnosis other than CA-UTI.
- In the catheterised patient, the presence or absence of odorous or cloudy urine alone should not be used to differentiate CA-ASB from CA-UTI or as an indication for urine culture or antimicrobial therapy.

Urine culture in symptomatic catheterised patients and use of clinical criteria-based decision-aid tools are common in clinical practice in Scotland. A specific decision aid for diagnosis and management of suspected UTI in people with indwelling catheters is available from SAPG (https://www.sapg.scot/media/4570/decision-aid-for-management-of-cauti.pdf).

R **Clinical signs and symptoms compatible with CA-UTI should be used to diagnose infection in catheterised patients with urine culture and sensitivity testing employed to confirm the diagnosis and pathogen.**

✓ Clinical scoring tools and decision aids may be considered to aid assessment of clinical signs and symptoms.

6.1.2 Dipstick testing

All patients with a long-term indwelling catheter will have bacteria in their urine and will test positive for nitrite and leucocytes even in the absence of CA-UTI, rendering dipstick testing less sensitive to the detection of clinically significant bacteriuria. No evidence was identified for or against use of dipstick testing in patients with indwelling catheters and symptoms suggestive of CA-UTI.

✓ Urinary dipsticks should not be used as part of the diagnostic assessment for UTI in patients with indwelling catheters.

6.2 Management

6.2.1 Non-pharmacological treatment

A cohort study undertaken in Israel in older hospitalised adults with an indwelling catheter in situ for longer than 7 days showed no association between catheter replacement and clinical failure of CA-UTI treatment.[125] 2+

In contrast, an RCT which included 21 male and 33 female care home residents (mean age 72.6 years) also in Israel suggested that clinical and bacteriological outcomes are improved when long-term indwelling catheters are replaced before initiating antibiotics for CA-UTI.[126] 1+

Both studies showed similar rates of resolution of the acute symptoms with antibiotic treatment, but conflicting results with respect to longer-term clinical outcomes. In the RCT, patients having catheter replacement before antimicrobial treatment had a decreased duration of fever, were significantly more likely to be cured or improved after 3 days of treatment and were less likely to have symptomatic recurrence at post-treatment follow up. In the cohort study, there was no significant advantage of catheter replacement (propensity score-matched participants: clinical failure on day 7, OR 0.90, 95% CI 0.50 to 1.63; 30-day all-cause mortality, OR 0.76, 95% CI 0.40 to 1.44). Catheter replacement was not significantly associated with duration of febrile illness for participants discharged alive in the matched population (intervention group: median 2 days (interquartile range (IQR) 1–5 days) *υ* control group: median 1.5 days (IQR 0.75–4 days); p=0.50).

There is insufficient evidence to support a recommendation either in favour of or against the replacement of catheters before antimicrobial treatment as a strategy to prevent CA-UTI. However, while evidence is lacking, this is acknowledged to be current practice and there are theoretical reasons for doing so.

6.2.2 Pharmacological treatment: antimicrobials

Management of CA-UTI with antibiotics is the approach currently used in clinical practice with antibiotic choice informed by local guidelines that are based on guidance from NICE[27] and IDSA.[124] 4

For patients with catheters, broader-spectrum treatment is recommended in local health board guidelines and these patients would routinely have a urine sample taken for culture and sensitivity testing to ensure empirical treatment is appropriate.

6.2.2.1 Prevention of recurrent UTI

An RCT of 404 patients (43% female) using intermittent self catheterisation for bladder emptying randomised participants to receive antibiotic prophylaxis or no prophylaxis. Over 12 months, the incidence of symptomatic antibiotic-treated UTIs in the prophylaxis group was 1.3 cases per person-year and 2.5 cases per person-year for no prophylaxis. The IRR was 0.52 (95% CI 0.44 to 0.61; p<0.0001) in favour of prophylaxis, which indicated a 48% reduction in the incidence of UTIs associated with prophylaxis treatment. These data suggest that 5.3 individuals who are able to use clean intermittent self catheterisation have to be treated with a daily low-dose prophylactic antibiotic for one year to prevent one episode of symptomatic UTI. There was no significant difference in incidence of asymptomatic bacteriuria or incidence of febrile UTI between groups.[127] 1+

At baseline, there were no significant differences between groups in frequency of antimicrobial resistance to oral antibiotics commonly used for UTI treatment. During the 12-month trial, resistance was more common in urine cultures submitted during symptomatic UTIs by participants in the prophylaxis group than those in the control group. In addition, an increase in resistance to most of the antibiotics used was found in the prophylaxis group from asymptomatic samples taken from three months onwards, while there was no evidence of an increase in resistance in the control group. By 9 to 12 months, resistance to nitrofurantoin, trimethoprim and co-trimoxazole had significantly increased in the prophylaxis group. 1+

The economic analyses based on this RCT found antibiotic prophylaxis to be a more costly but also more effective strategy compared to no prophylaxis with an incremental cost of £99 per UTI avoided based on observed data. There was a 66% chance that prophylaxis would be cost effective should society be willing to pay in excess of £200 to avoid a UTI. The incremental cost per quality-adjusted life year (QALY) over 12 months was £5,059 and there was 64% likelihood that prophylaxis use would be cost effective at a threshold value of £20,000 per QALY.

It should be noted that this group of patients makes up a small proportion of all patients with catheters and that there are concerns about the balance of harms and risks. While individuals taking prophylactic low-dose antibiotics reduced the incidence of symptomatic UTIs by around a half, all participants experienced a low rate of infections meaning that, on average, individuals only experienced one fewer UTI per year at a cost of increased individual and societal resistance to antimicrobials.

In patients with an indwelling urethral catheter, antibiotics do not generally eradicate asymptomatic bacteriuria.[80] 4

R **Do not routinely prescribe antibiotics to prevent UTI in patients using intermittent self catheterisation for bladder emptying. Consider only after full discussion of the benefits and harms likely to apply to the individual.**

6.2.3 Pharmacological treatment: non-antimicrobials

No evidence was identified on pharmacological non-antimicrobial management of CA-UTI.

7 Provision of information

This section reflects the issues likely to be of most concern to patients and their carers. These points are provided for use by healthcare professionals when discussing urinary tract infection with patients and carers and in guiding the development of locally-produced information materials.

7.1 Checklist for provision of information

This section gives examples of the information patients/carers may find helpful at the key stages of the patient journey. The checklist was designed by members of the guideline development group based on their experience and their understanding of the evidence base. The checklist is neither exhaustive nor exclusive.

Diagnosis

- Explain the symptoms of UTI, how to tell a UTI might be present and when to seek medical advice, eg from GP or pharmacist.
- Inform women of the cause of UTIs and the effect UTIs have on the body.
- Discuss with women how having other conditions can make them more susceptible to UTIs, eg diabetes. Offer time to answer questions women may have.
- Discuss the implications of recurring UTIs on health in general, including the bladder.
- Discuss with women aged under 65 years how to provide a urine sample for dipstick testing, including advice around ensuring the bladder has not been emptied for at least four hours before taking the sample.
- Provide women with the SIGN patient version of this guideline to help them understand and manage UTIs.
- Explain the rationale for not prescribing and delayed prescribing.

Treatment

- Explain the difference between a 3-day and a 7-day course of antibiotics and the reasons for using one or the other.
- Ensure women understand the need to finish the course of antibiotics.
- Advise women how long it will be before they start to feel better after starting treatment.
- Inform women of common side effects associated with treatment and advise them not to be concerned and not to stop treatment without discussion with a healthcare professional.
- Discuss potential drug interactions with other prescribed medicines they may be taking.
- Advise women to return to their GP or NHS24 (at weekends or evenings) if symptoms don't improve with treatment, get worse or come back after treatment.
- Explain the long-term effects that can occur when taking long-term prophylactic antibiotics.
- Discuss steps women can take to reduce the chances of having further UTIs, including:
  - drinking plenty of fluid.
  - avoidance of spermicide containing contraceptives.
  - personal hygiene.
  - voiding behaviours.

7.2 Publications from SIGN

SIGN 157: Risk reduction and management of delirium
www.sign.ac.uk/sign-157-delirium

This guideline provides recommendations based on current evidence for best practice in the detection, assessment, treatment and follow up of adults with delirium, as well as reducing the risk of delirium. The guideline applies to all settings: home, long-term care, hospital, and hospice and includes recommendations on the regulation of bladder and bowel function.

SIGN patient versions of guidelines are documents that 'translate' guideline recommendations and their rationales, originally developed for healthcare professionals, into a form that is more easily understood and used by patients and the public. They are intended to:

- help patients and carers understand what the latest evidence supports around diagnosis, treatment and self care
- empower patients to participate fully in decisions around management of their condition in discussion with healthcare professionals
- highlight for patients where there are areas of uncertainty.

Delirium
www.sign.ac.uk/pat157-delirium

This booklet describes recommendations from SIGN 157: Risk reduction and management of delirium and explains for patients and carers:

- what delirium is
- how to reduce the risk of experiencing delirium
- what it is like to have delirium
- how it is identified
- how it is treated, and
- the care provided.

7.3 Sources of further information

Bladder Health
bladderhealthuk.org/cystitis-utis-fowlerssyndrome

Bladder Health UK gives support to people with all forms of cystitis, overactive bladder and continence issues together with their families and friends.

British Association of Urological Surgeons
www.baus.org.uk/patients/conditions/14/urinary_infection_a

The British Association of Urological Surgeons is a registered charity which promotes the highest standards of practice in urology, for the benefit of patients.

The Cystitis & Overactive Bladder Foundation
www.cobfoundation.org/bacterial-cystitis

The Cystitis and Overactive Bladder Foundation is the largest bladder patient support charity in the UK. It gives support to people with all forms of cystitis, overactive bladder and continence issues together with their families and friends.

Healthcare Improvement Scotland
ihub.scot/improvement-programmes/acute-care-portfolio/older-people-in-acute-care/delirium

In collaboration with the Scottish Delirium Association, NHS Education for Scotland and colleagues across NHSScotland, Healthcare Improvement Scotland has developed a range of tools and resources to support improvements in the identification and immediate management of delirium. A THINK Delirium toolkit has been produced to provide easy access to all of these tools and resources.

National Urinary Catheter Passport
www.hps.scot.nhs.uk/web-resources-container/urinary-catheter-care-passport

The National Urinary Catheter Care Passport was developed by Health Protection Scotland and the Scottish Urinary Tract Infection Network. It is a patient-held record which provides information to support individuals to effectively manage their catheters and allows for revisions to clinical management plans, the history of catheter changes and a record of catheter maintenance to be recorded.

NHS
www.nhs.uk/conditions/urinary-tract-infections-utis

The NHS website is the UK's biggest health website and contains thousands of freely available articles, videos, tools and apps to help people make the best choices about their health and wellbeing.

NHS Inform
www.nhsinform.scot/illnesses-and-conditions/kidneys-bladder-and-prostate/urinary-tract-infection-uti

NHS Inform is a patient access website providing health advice across a wide range of topics.

Patient
patient.info/womens-health/lower-urinary-tract-symptoms-in-women-luts/cystitis-in-women

Patient is a health information website which contains patient advice reviewed by doctors and other health professionals.

8 Implementing the guideline

This section provides advice on the resource implications associated with implementing the key clinical recommendations, and advice on audit as a tool to aid implementation.

8.1 Implementation strategy

Implementation of national clinical guidelines is the responsibility of each NHS board, including health and social care partnerships, and is an essential part of clinical governance. Mechanisms should be in place to review care provided against the guideline recommendations. The reasons for any differences should be assessed and addressed where appropriate. Local arrangements should then be made to implement the national guideline in individual hospitals, units and practices.

Implementation of this guideline will be encouraged and supported by SIGN. The implementation strategy for this guideline encompasses the following tools and activities.

8.2 Resource implications of key recommendations

A budget impact assessment (BIA) provides a comparison of expected expenditure in a healthcare system before and after the adoption of a new intervention or change in practice. It takes into account both the expenditure, for example acquisition and implementation costs, as well as potential savings, for example displaced medicines and procedures avoided which are associated with a change.

In this guideline, a BIA was considered to estimate the costs associated with an anticipated increase in urinary dipstick usage, and to quantify the potential decrease in the number of patients prescribed antibiotics for UTI. It was not feasible to conduct a BIA in this instance as the results would be highly uncertain and of limited utility due to the issues outlined below.

8.2.1 Procurement

There is no managed procurement of dipstick tests in Scotland. Hospitals, community pharmacies and GP surgeries are individually responsible for purchasing tests from a range of suppliers in the open market. Purchasing costs for providers are highly variable as there are no established unit prices for dipstick tests across NHSScotland. Given the ad hoc nature of procurement and supply of dipstick tests, BIA estimates would be highly uncertain.

8.2.2 Market share/comparators

A large variety of dipstick tests is available for purchase through different supply chains. There is no preferred manufacturer or brand of dipstick test. Tests not only vary in price, but also in other attributes such as complexity of urinalysis (ie the number of reagents being tested), diagnostic accuracy and shelf life. It is difficult to estimate the number of brands to include in a BIA and assigning respective proportional market share to each brand included would not have been based on any usage statistics.

8.2.3 Eligible population

There is no existing data source on the number of patients for whom a dipstick test is used to inform diagnosis of UTI. The size of the eligible population (to predict usage) would require to be estimated using epidemiological or prescription data for other conditions/indications as proxies. Coupled with the uncertainty surrounding other parameters, this would have resulted in an insufficiently robust BIA.

8.2.4 Impact of reduced antibiotic use

The predicted increase in dipstick testing as a result of the guideline recommendations could lead to a decrease in the number of patients prescribed antibiotics for UTI. Whilst the cost savings associated with displaced antibiotic use may have been of some use for budgetary planning, it is less suitable as an indicator of the wider, more significant benefit of preventing antimicrobial resistance at patient and population level.

8.3 Auditing current practice

A first step in implementing a clinical practice guideline is to gain an understanding of current clinical practice. Audit tools designed around guideline recommendations can assist in this process. Audit tools should be comprehensive but not time consuming to use. Successful implementation and audit of guideline recommendations requires good communication between staff and multidisciplinary team working.

The Scottish Antimicrobial Prescribing Group has developed an audit tool to support primary-care teams in managing UTI. The results will facilitate reflective learning on the processes leading up to the decision to prescribe antibiotics in patients with an acute UTI. The tool allows prescribers to compare their prescribing decisions with local guidance and supports identification of areas for quality improvement.[128]

The guideline development group has identified the following as key points to audit to assist with the implementation of this guideline:

8.3.1 Diagnosis

- The proportion of women who receive a diagnosis of UTI who have ≥2 urinary symptoms and a positive dipstick test result for nitrite
- The proportion of women who receive a diagnosis of UTI who have ≥2 urinary symptoms and a negative dipstick test result for nitrite
- The proportion of women aged 65 years and over in residential care who are not catheterised for whom a urine culture is sent to confirm diagnosis. (Note that this is NOT recommended, and the audit point is to establish non-compliance with recommended practice)
- The proportion of women using catheters for whom a urine culture is sent to confirm diagnosis.

8.3.2 Management

- The proportion of women with a history of recurrent LUTI consuming 2.5 L of fluids per day
- The proportion of women at risk of recurrent LUTI using contraception which does not include spermacides
- The proportion of women with suspected LUTI who are treated empirically who are prescribed a first-line antimicrobial (nitrofurantoin or trimethoprim)
- The proportion of antimicrobial courses prescribed for a 3-day duration
- The proportion of women using intermittent self catheterisation for bladder emptying who are prescribed antimicrobials for prevention of UTI (Note that this is NOT recommended, and the audit point is to establish non-compliance with recommended practice).

8.4 Health technology assessment advice for NHSScotland

In September 2016, SMC advised that fosfomycin trometamol is accepted for use within NHSScotland for the treatment of acute lower uncomplicated urinary tract infections, caused by pathogens sensitive to fosfomycin in adult and adolescent females.

9 The evidence base

9.1 Systematic literature review

The evidence base for this guideline was synthesised in accordance with SIGN methodology. A systematic review of the literature was carried out using an explicit search strategy devised by a SIGN Evidence and Information Scientist. Databases searched include Medline, Embase, Cinahl, CENTRAL, PsycINFO and the Cochrane Library. The year range covered was 2003–2018. Internet searches were carried out on various websites for relevant guidelines. The main searches were supplemented by material identified by individual members of the development group. Each of the selected papers was evaluated by two Evidence and Information Scientists using standard SIGN methodological checklists before conclusions were considered as evidence by the guideline development group.

The search strategies are available on the SIGN website, www.sign.ac.uk at publication.

9.1.1 Literature search for patient issues

At the start of the guideline development process, a SIGN Evidence and Information Scientist conducted a literature search for qualitative and quantitative studies that addressed patient issues of relevance to diagnosis and management of suspected bacterial UTI. Databases searched include Medline, Embase, Cinahl and PsycINFO, and the results were summarised by the SIGN Patient Involvement Advisor and presented to the guideline development group.

9.1.2 Literature search for cost-effectiveness evidence

The guideline development group identified key questions with potential cost-effectiveness implications, based on the following criteria, where it was judged particularly important to gain an understanding of the additional costs and benefits of different treatment strategies:

- treatments which may have a significant resource impact
- opportunities for significant disinvestment or resource release
- the potential need for significant service redesign
- cost-effectiveness evidence could aid implementation of a recommendation.

A systematic literature search for economic evidence for these questions was carried out by a SIGN Evidence and Information Scientist covering the years 2008–2018. Databases searched include Medline, Embase and NHS Economic Evaluation Database (NHS EED). Each of the selected papers was evaluated by a Health Economist, and considered for clinical relevance by guideline group members.

Interventions are considered to be cost effective if they fall below the commonly-accepted UK threshold of £20,000 per QALY.

9.2 Recommendations for research

The guideline development group was not able to identify sufficient evidence to answer all of the key questions asked in this guideline *(see Annex 1)*. The following areas for further research have been identified:

- RCTs on antimicrobial treatment and prophylaxis of CA-UTI.
- Further evidence to confirm findings on the utility of acupuncture in women who are unable to tolerate antimicrobial therapy.
- RCTs conducted in UK populations on self-care behaviours to prevent and manage UTI.
- A meta-analysis with independent participant data of patients receiving ibuprofen +/- diclofenac for control of UTI symptoms.
- Studies using better stratification of patients to determine which characteristics are most likely to be associated with response to NSAID and reduced risk of treatment failure or pyelonephritis.
- Further studies (particularly studies not sponsored by commercial interests) of anti-inflammatory compounds (such as BNO 1045) to assess their place as alternatives to antibiotic treatment in this patient group.
- Meta-analysis of primary evidence for the use of cranberry products to prevent recurrent UTI in women with uncomplicated UTI which have used strict criteria for study selection, population and intervention eligibility and standardised concentrations of PAC used.
- Studies investigating compliance with cranberry products.
- RCTs investigating the efficacy of urine alkalinising agents.
- Further evidence to confirm initial findings on the effectiveness of *Tropaeoli majoris herba* (nasturtium) and *Amoraciae radix* (horseradish).
- Studies of effective probiotic agents that test the optimal doses and duration and examine adverse events in different populations at risk of UTI.
- Studies of the diagnostic accuracy of specific and non-specific symptoms for UTI in women over the age of 65 years stratified according to age, frailty, setting and comorbidity.
- Studies to establish the range of asymptomatic bacteriuria in women over the age of 65 years stratified according to age, frailty, setting and comorbidity.
- RCT of self-care interventions on UTI incidence in women over the age of 65 years, focusing in particular on hydration, and correlations with different methods of bladder and bowel care.
- RCTs investigating the risks inherent to antimicrobial treatment of acute UTI in women over the age of 65 years, focusing on drug interactions, impact of multimorbidity and adverse effects of antimicrobial treatment such CDI.
- Studies informing diagnosis of UTI in patients with catheters using clinical criteria scoring tools.

9.3 Review and updating

This guideline was issued in 2020 and will be considered for review in three years. The review history, and any updates to the guideline in the interim period, will be noted in the update report, which is available in the supporting material section for this guideline on the SIGN website: www.sign.ac.uk

Comments on new evidence that would update this guideline are welcome and should be sent to the SIGN Executive, Gyle Square, 1 South Gyle Crescent, Edinburgh, EH12 9EB (email: sign@sign.ac.uk).

10 Development of the guideline

10.1 Introduction

SIGN is a collaborative network of clinicians, other healthcare professionals and patient organisations and is part of Healthcare Improvement Scotland. SIGN guidelines are developed by multidisciplinary groups of practising healthcare professionals using a standard methodology based on a systematic review of the evidence. Further details about SIGN and the guideline development methodology are contained in 'SIGN 50: A Guideline Developer's Handbook', available at www.sign.ac.uk

This guideline was developed according to the 2015 edition of SIGN 50

10.2 The Guideline Development Group

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Dr Carolyn Sleith	Evidence and Information Scientist, Healthcare Improvement Scotland
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Ms Anne Thomson	Lead Clinical Pharmacist, Prescribing, Glasgow City Health and Social Care Partnership
Mrs Pauline Warsop	Patient Representative, Gauldry, Fife
Mrs Heather Wilson	Patient Representative, Auchterarder, Perthshire

The membership of the guideline development group was confirmed following consultation with the member organisations of SIGN. All members of the guideline development group made declarations of interest. A register of interests is available in the supporting material section for this guideline at www.sign.ac.uk

Guideline development and literature review expertise, support and facilitation were provided by SIGN Executive and Healthcare Improvement Scotland staff. All members of the SIGN Executive make yearly declarations of interest. A register of interests is available on the contacts page of the SIGN website www.sign.ac.uk

Kirsty Allan	Administration Officer
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Juliet Brown	Evidence and Information Scientist, Healthcare Improvement Scotland
Karen Graham	Patient and Public Involvement Advisor
Kelly Humphrey	Project Officer
Domenico Romano	Publications Designer
Gaynor Rattray	Guideline Co-ordinator
Lynne Smith	Evidence and Information Scientist, Healthcare Improvement Scotland

10.2.1 Acknowledgements

SIGN is grateful to the following former members of the guideline development group and others who have contributed to the development of the guideline.

Ms Jacqueline Dennis	Improvement Adviser, Care Inspectorate, Paisley
Ms Keaton Fletcher	Graphic Designer, NHS Education for Scotland
Mr Daniel Jenks	Care Home Manager, Glasgow

10.3 Consultation and peer review

This guideline was reviewed in draft form by the following independent expert referees, who were asked to comment primarily on the comprehensiveness and accuracy of interpretation of the evidence base supporting the recommendations in the guideline. The guideline group addresses every comment made by an external reviewer, and must justify any disagreement with the reviewers' comments. A report of the peer review comments and responses is available in the supporting material section for this guideline on the SIGN website. All expert referees made declarations of interest and further details of these are available on request from the SIGN Executive.

10.3.1 Specialist review

SIGN is very grateful to all of these experts for their contribution to the guideline.

Ms Clare Colligan	Clinical Governance and Lead Antimicrobial Pharmacist, NHS Forth Valley
Dr Jennifer Dow	General Practitioner, Ballieston, Glasgow
Dr Victoria Henderson	Consultant Physician in Medicine for Elderly, Gray's Hospital, Elgin

Ms Pamela Innes	Advanced Prescribing Support Pharmacist, Glasgow City Health and Social Care Partnership
Ms Sheila McGhee	Patient representative, Alloa
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Dr Cliodna McNulty	Consultant Medical Microbiologist and Honorary Visiting Professor, National Infection Service, Public Health England, Primary Care Unit
Dr Ewan Olson	Consultant Medical Microbiologist, NHS Lothian
Mrs Stacey Reid	Charge Nurse, Dalmellington Care Centre, Dalmellington
Ms Ashley Williamson	Advanced Prescribing Support Pharmacist, Glasgow City Health and Social Care Partnership

10.3.2 Public consultation

The draft guideline was also available on the SIGN website for a month to allow all interested parties to comment.

10.3.3 SIGN editorial group

As a final quality control check, the guideline is reviewed by an editorial group comprising the relevant specialty representatives on SIGN Council to ensure that the specialist reviewers' comments have been addressed adequately and that any risk of bias in the guideline development process as a whole has been minimised. The editorial group for this guideline was as follows. All members of SIGN Council make yearly declarations of interest. A register of interests is available on the SIGN Council Membership page of the SIGN website www.sign.ac.uk

Dr Roberta James	SIGN Programme Lead; Co-Editor
Professor Angela Timoney	Chair of SIGN; Co-Editor
Dr Jenny Bennison	Vice-Chair of SIGN; Royal College of General Practitioners
Dr Safia Qureshi	Director of Evidence, Healthcare Improvement Scotland

Abbreviations

AMR	antimicrobial resistance
ASB	asymptomatic bacteriuria
BIA	budget impact assessment
CA-ASB	catheter-associated asymptomatic bacteriuria
CA-UTI	catheter-associated urinary tract infection
CDI	*Clostridioides difficile* infection
CFU	colony-forming unit
CI	confidence interval
E. coli	*Escherichia coli*
eGFR	estimated glomerular filtration rate
GMC	General Medical Council
GP	general practitioner
IDSA	Infectious Diseases Society of America
IQR	interquartile range
IRR	incidence rate ratio
K. pneumoniae	*Klebsiella pneumoniae*
LE	leukocyte esterase
LR-	negative likelihood ratio
LR+	positive likelihood ratio
LUTI	lower urinary tract infection
MA	marketing authorisation
MHRA	Medicines and Healthcare Products Regulatory Agency
MIC	minimum inhibitory concentration
MRSA	methicillin-resistant *Staphylococcus aureus*
NHS	National Health Service
NHS EED	NHS Economic Evaluation Database
NICE	National Institute for Health and Care Excellence
NNT	number needed to treat
NS	not significant
NSAID	non-steroidal anti-inflammatory drug
OR	odds ratio
PAC	proanthocyanidin
QALY	quality-adjusted life year
RCT	randomised controlled trial
RR	relative risk
SAPG	Scottish Antimicrobial Prescribing Group
SIGN	Scottish Intercollegiate Guidelines Network
SMC	Scottish Medicines Consortium
SUTIN	Scottish Urinary Tract Infection Network
UTI	urinary tract infection

Annex 1

Key questions used to develop the guideline

This guideline is based on a series of structured key questions that define the target population, the intervention, diagnostic test, or exposure under investigation, the comparison(s) used and the outcomes used to measure efficacy, effectiveness, or risk. These questions form the basis of the systematic literature search.

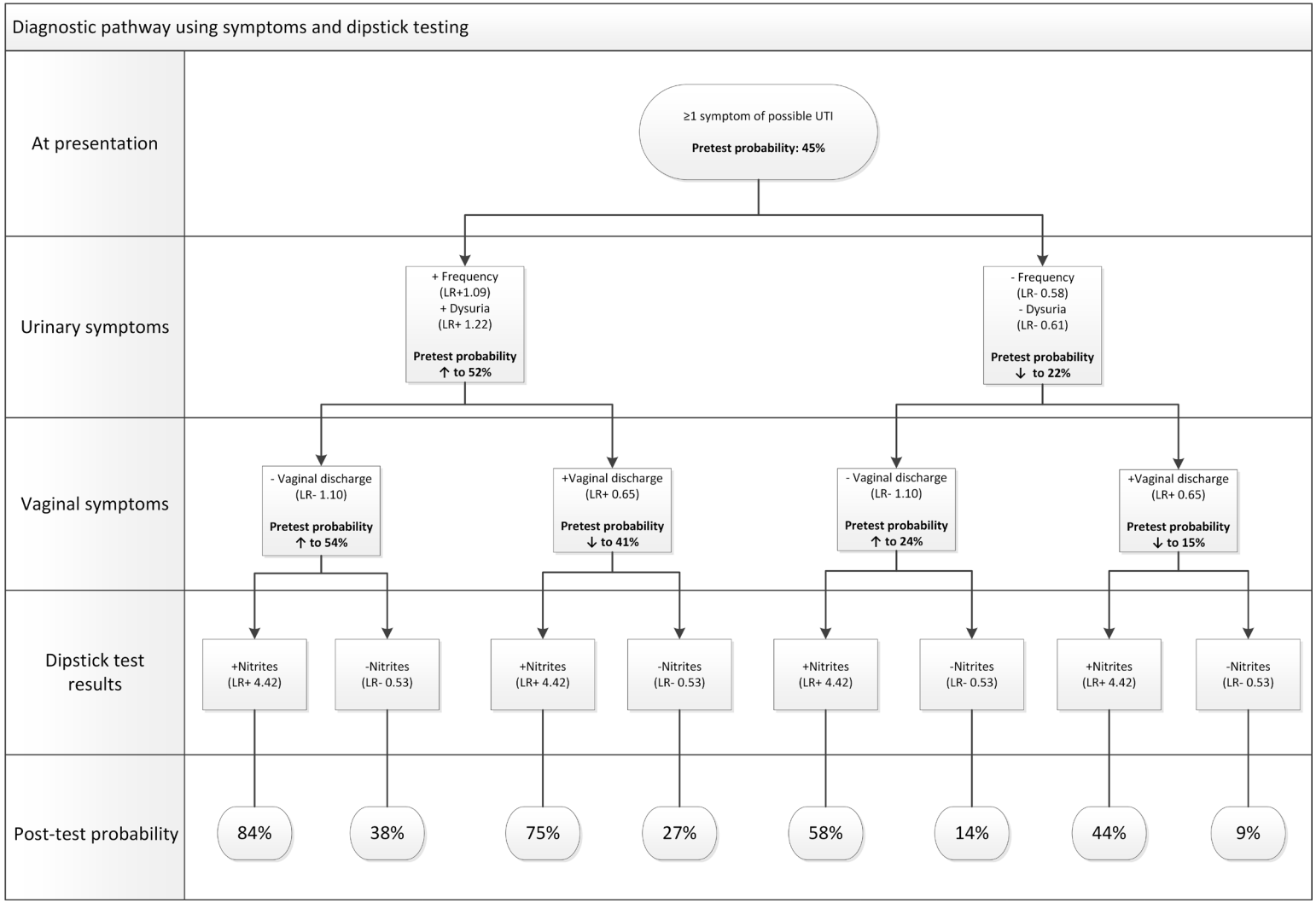
Section(s)	Key question
3.1	**1. How should uncomplicated lower UTI be diagnosed in women aged under 65 years?**
	Population: adult women aged 16–64 years Interventions: • clinical assessment • urinary symptoms (dysuria, urgency, frequency, cloudy urine) • dipstick testing (nitrite, leucocyte esterase, haematuria) Comparisons: laboratory culture of urine samples Outcomes: sensitivity, specificity, likelihood ratio, positive predictive value, negative predictive value, cost effectiveness
3.2	**2. How should uncomplicated lower UTI be managed in women aged under 65 years?**
	Population: adult women aged 16–64 years with: • recurrent UTI • non-recurrent UTI Interventions: • Self-care (personal hygiene, fluid intake, appropriate contraception) • Antibiotic treatment (amoxicillin, cefalexin, pivemecillinam, trimethoprim, fosfomycin, nitrofurantoin, ciprofloxacin, levofloxacin, moxifloxacin, nalidixic acid, norfloxacin, ofloxacin) • Non-antibiotic treatment (cranberry products, D-mannose, potassium citrate mixture, acidification, increased fluid intake, oestrogen, analgesia, diuretics, methenamine hippurate) • Delayed treatment strategies Comparisons: • antibiotic *υ* non-antibiotic treatment • any intervention *υ* no treatment Outcomes: bacteriological cure rate, time to symptomatic relief, symptom recurrence, development of antimicrobial resistance, adverse effects, cost effectiveness

4.1	**3. How should uncomplicated lower UTI be diagnosed in women aged 65 years or over?**
	Population: adult women aged ≥65 years Interventions: • clinical assessment • urinary symptoms (dysuria, urgency, frequency, cloudy urine) • non-specific symptoms (eg new or worsening confusion or delirium, raised temperature, loss of diabetic control) Comparisons: laboratory culture of urine samples Outcomes: sensitivity, specificity, likelihood ratio, positive predictive value, negative predictive value, cost effectiveness
4.2	**4. How should uncomplicated lower UTI be managed in women aged 65 years or over?**
	Population: adult women aged ≤64 years with: • recurrent UTI • non-recurrent UTI Interventions: • self-care (personal hygiene, fluid intake) • antibiotic treatment (amoxicillin, cefalexin, pivemecillinam, trimethoprim, fosfomycin, nitrofurantoin, ciprofloxacin, levofloxacin, moxifloxacin, nalidixic acid, norfloxacin, ofloxacin) • non-antibiotic treatment (cranberry products, D-mannose, potassium citrate mixture, acidification, increased fluid intake, oestrogen, analgesia, diuretics, methenamine hippurate) • delayed treatment strategies Comparisons: • antibiotic *v* non-antibiotic treatment • any intervention *v* no treatment Outcomes: bacteriological cure rate, time to symptomatic relief, symptom recurrence, development of antimicrobial resistance, adverse effects, cost effectiveness

6.1	**5. How should catheter-associated UTI be diagnosed in women?**
	Population: adult women aged 16 years and over with: • an indwelling urinary catheter, or • an intermittent urinary catheter, or • a suprapubic catheter Interventions: • self-care (personal hygiene, fluid intake, appropriate contraception) • antibiotic treatment (amoxicillin, cefalexin, pivemecillinam, trimethoprim, fosfomycin, nitrofurantoin, ciprofloxacin, levofloxacin, moxifloxacin, nalidixic acid, norfloxacin, ofloxacin) • non-antibiotic treatment (cranberry products, D-mannose, potassium citrate mixture, acidification, increased fluid intake, oestrogen, analgesia, diuretics, methenamine hippurate) • delayed treatment strategies Comparisons: • antibiotic *υ* non-antibiotic treatment • any intervention *υ* no treatment Outcomes: Bacteriological cure rate, time to symptomatic relief, symptom recurrence, development of antimicrobial resistance, adverse effects, cost effectiveness
6.2	**6. How should catheter-associated UTI be managed in women?**
	Population: adult women aged 16 years and over with: • an indwelling urinary catheter, or • an intermittent urinary catheter, or • a suprapubic catheter. Interventions: • self-care (personal hygiene, fluid intake, appropriate contraception) • antibiotic treatment (amoxicillin, cefalexin, pivemecillinam, trimethoprim, fosfomycin, nitrofurantoin, ciprofloxacin, levofloxacin, moxifloxacin, nalidixic acid, norfloxacin, ofloxacin) • non-antibiotic treatment (cranberry products, D-mannose, potassium citrate mixture, acidification, increased fluid intake, oestrogen, analgesia, diuretics, methenamine hippurate) • delayed treatment strategies Comparisons: • antibiotic *υ* non-antibiotic treatment • any intervention *υ* no treatment Outcomes: Bacteriological cure rate, time to symptomatic relief, symptom recurrence, development of antimicrobial resistance, adverse effects, cost effectiveness

Annex 2

Decision tree for urinary symptoms and tests in women aged <65 years



This sample decision tree displays changes in probability of UTI associated with urinary symptoms (presence or absence of frequency and dysuria), vaginal symptoms (presence or absence of vaginal discharge) and dipstick test result (presence or absence of positive nitrite test).

As frequency and urgency have a higher sensitivity than specificity they are more useful for ruling out UTI when absent than ruling in when present. The reverse is true for positive dipstick results which strongly increase the probability of infection where present.

Likelihood ratios for urinary symptoms are based on a diagnostic threshold of 10^5 CFU/ml. Likelihood ratio for vaginal symptoms is based on a diagnostic threshold of 10^2 CFU/ml.

Data adapted from: *Giesen LG, Cousins G, Dimitrov BD, van de Laar FA, Fahey T. Predicting acute uncomplicated urinary tract infection in women: a systematic review of the diagnostic accuracy of symptoms and signs. BMC Family Practice 2010;11:78.*

Annex 3

Asymptomatic bacteriuria

Asymptomatic bacteriuria refers to the isolation of bacteria in significant counts (>10^5 bacteria/mL) of a single bacterial species from a clean catch urine specimen of an individual who has no acute signs or symptoms. Long-term ASB may be described as a persistent infection of more than three weeks of duration resulting from an organism being sufficiently adapted to urine to survive host defences. Estimates of ASB prevalence vary between studies due to participant-related factors (for example, gender, age and the extent of multimorbidity) and methodological factors (for example, differences in threshold for definition of ASB in different populations and differences in sampling affecting the mix of comorbidities in people included in each study). A range of estimates for different populations is presented in the table below.

Premenopausal women resident in the community

Age range (years)	**Characteristics of sample**	**Country**	**Prevalence of ASB** (%)
15–24		Jamaica[129]	1.3
18–40	university students	USA[130]	5
18–40	health maintenance organisation	USA[130]	6
20–29		Japan[131]	1
24–44	nuns	USA[132]	0.7
24–44	married women	USA[132]	4.6
25–34		Jamaica[129]	2.3
30–39		Japan[131]	1.8
35–44		Jamaica[129]	3.3
38		Sweden[133]	3.5
40–49		Japan[131]	3.1
46		Sweden[133]	4.8
<50	healthy premenopausal	USA[134]	1–5

Postmenopausal women resident in the community

Age range (years)	**Characteristics of sample**	**Country**	**Prevalence of ASB** (%)
50–59		Japan[131]	2.8
50–59		Finland[135]	4.4
55–64	nuns	USA[132]	2.7
55–64	married	USA[132]	6.3
55–64		Jamaica[129]	8.6
60–64		Finland[135]	6.6
60		Sweden[133]	8.6
60–69		Japan[131]	7.4
>65	nuns	USA[132]	5.8
>65	married	USA[132]	6.5
65–74		Scotland[136]	16
68–103		USA[137]	12.1
>70		Japan[131]	10.8
>70		Various[134]	3.9–50
72		Sweden[138]	16
>75		Scotland[136]	17
79		Sweden[138]	14

Postmenopausal women in long-term care facilities

Age range (years)	**Characteristics of sample**	**Country**	**Prevalence of ASB** (%)
Unknown		USA[139]	29
Unknown		USA[140]	57
>65		Various[141]	23–27
67–104		Belgium[142]	40
68–103		USA[137]	23.5
>70		Greece[143]	27
>70		Various[134]	25–70

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