Management of suspected bacterial lower urinary tract infection in adult women

A national clinical guideline

Consultation draft - August 2019
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 of RCTs, or RCTs with a low risk of bias

1−
Meta-analyses, systematic reviews of RCTs, 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.
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1 Introduction

1.1 The need for a guideline

Lower urinary tract infections (UTI) are commonly-occurring infections involving the bladder (cystitis) and urethra. A population-based survey of adult women in England reported that over a third (37%, 892/2,424) of women reported having had at least one UTI in their lifetime.\(^1\)

\textit{DATA ON COMMUNITY-ACQUIRED UTI INCIDENCE AND PREVALENCE IN WOMEN <65 YEARS TO BE ADDED}

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.

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.\(^2,3\)

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. Within long-term care facilities the prevalence of 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 urinary catheters was higher in those with UTI compared with those without (23.1\% v 8.2\%, \(p=0.003\)).\(^4\)

In the hospital setting, the prevalence of UTI was 1.1\% in acute adult patients (95\% 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 UTI, 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.\(^5\)

Lower UTI in itself is not generally associated with mortality but can progress if not managed optimally to bacteraemia, in particular Escherichia coli (E. coli) bacteraemia, which is a serious infection with high mortality. During 2017, there were 4,763 cases of E. coli bacteraemia in Scotland which accounted for the majority of all bacteraemia (measured across the ten most commonly-reported bacteria).\(^6\) Over a third of E. Coli cases are caused by urinary tract infections, the highest proportion of any infection site.\(^7\)

In 2012, surveillance of antimicrobial resistance (AMR) in a representative sample of all urinary isolates was introduced in Scotland to detect and characterise emergence and spread of resistance. Each NHS board is required to provide susceptibility data in relation to 400 consecutive non-duplicate urine specimens per quarter including data from community and hospital patients. The most common causative UTI organisms in Scotland are E. coli and Klebsiella pneumoniae (K. pneumoniae). E. 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 38.6\%. The majority (97.4\%) 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 29.7\% of isolates non-susceptible to trimethoprim, and 57.9\% to nitrofurantoin.\(^6\)

Multimorbidity is particularly significant in older people and is associated with increased risk of infection and hospitalisation.\(^8,9\) In a UK cohort of 218,805 people with diabetes aged >65 years, four weeks after onset of UTI all-cause mortality was 1.6\% (1,472/91,574).\(^10\)
Healthcare practitioners regularly have to make clinical judgements about managing common infections including urinary tract infection. Criteria for the diagnosis of urinary tract infection 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, with continuing debate regarding the most appropriate approach.

The diagnosis of UTI is particularly difficult in older patients, who are more likely to have asymptomatic bacteriuria, therefore urine culture ceases to be a diagnostic test unless there are other signs of infection. 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.

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.

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.

Unnecessary use of tests and antibiotic treatment may be minimised by developing simple decision rules, diagnostic guidelines or other educational interventions. Prudent antibiotic prescribing is a key component of the UK’s action plans for reducing antimicrobial resistance. Unnecessary antibiotic treatment of asymptomatic bacteriuria is associated with significantly increased risk of clinical adverse events including Clostridioides difficile infection (CDI) or methicillin-resistant Staphylococcus aureus (MRSA) infection, and the development of antibiotic-resistant UTIs. In people aged over 65 years asymptomatic bacteriuria is common but is not associated with increased morbidity. In patients with an indwelling urethral catheter, antibiotics do not generally eradicate asymptomatic bacteriuria.

1.1.1 Patient perspective

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

Common concerns raised by patient groups and through research include:
- inconsistency in diagnostic formulation in primary care causing confusion for patients
- 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.

1.1.2 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. Specifically, it uses the following classification of UTI:
**Management of suspected bacterial lower UTI in adult women**

**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 in a narrower sense UTIs in a patient with an increased chance of a complicated course: i.e. 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 has had a catheter in place within the past 48 hours.

Recurrent UTI is defined as repeated urinary tract infections with a frequency of at least three infections in the last year or two infections in the last six months. This may be due to relapse or reinfection.

- Relapse is recurrent UTI with the same strain of organism. Relapse is the likely cause if UTI recurs within a short period (for example within two weeks) after treatment.
- Reinfection is recurrent UTI with a different strain or species of organism. Reinfection is the likely cause if UTI recurs more than two weeks after treatment.

### 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 includes younger women aged 16–64 years, older women aged 65 years and above 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. It excludes upper UTI, and any UTI in pregnant women, men and children below the age of 16 years. Interstitial cystitis and bladder pain syndrome are also excluded.

Based on the classification system included in section 1.1.2 this guideline includes recommendations on uncomplicated lower UTIs and CA-UTI in adult women.

This guideline excludes guidance on several topics that were included in SIGN 88 Management of suspected bacterial urinary tract infection in adults, namely, diagnosis and management of upper UTI, UTI in pregnant women and men. Like SIGN 88 it also excludes diagnosis and management of UTI in children below the age of 16 years and interstitial cystitis and bladder pain syndrome.

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. NICE provides guidance on antimicrobial prescribing for prostatitis and pyelonephritis and the European Urology Association provides guidance on both diagnosis and management of UTI across several populations.

The guidance 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. UTI
accounts 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.6

The guideline will complement existing resources in Scotland to support management of UTI provided by the Scottish Antimicrobial Prescribing Group (SAPG),35 NHS Education for Scotland36 and the Scottish UTI Network.37

1.2.2 Comorbidities to consider when managing patients with urinary tract infections

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, community pharmacists, 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 licenced 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.38

“Prescribing medicines outside the conditions of their marketing authorisation alters (and probably increases) the prescribers’ professional responsibility and potential liability”.

The General Medical Council (GMC) recommends that when prescribing a medicine ‘off label’, doctors should:39
- 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.40

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 7.4.
2 Key recommendations

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

NOT INCLUDED IN THIS DRAFT – WORK IN DEVELOPMENT
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. However, inappropriate use of antibiotics has a risk to the individuals with possible side effects and development of resistance in endogenous gut flora as well as an ecological risk to the population. 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. Trends in resistance in Scotland are stable while in many European countries rates are rising in several key organisms. However, reduction of E. coli bacteraemia rate is a national target in Scotland through enhanced surveillance programmes and targeted interventions. Effective management of UTI and appropriate use of antibiotics where required are therefore both important to address this increasing trend in E. coli bacteraemia.

3.1 Diagnosis

The current standard for diagnosing patients with suspected UTI is microscopy, culture and antibiotic sensitivity analysis of a midstream, clean-catch urine specimen, although this is not recommended for first-time uncomplicated UTI. The results of these tests are typically available within 24–72 hours after the microbiology laboratory receives the specimen. In routine practice, clinicians can perform a urine dipstick test which confirms the presence of a urinary tract infection with 30–40% sensitivity and 95-98% specificity based on positive urine nitrites. However, the test cannot specify the pathogen(s) causing the infection or the antibiotic sensitivities. Standard practice when patients present with UTI symptoms, is the prescription of empirical antibiotics (for broad-spectrum coverage of the most common uropathogens) or based on a positive urine dipstick test (see section 3.2).

A significant risk of empirical treatment is the emergence of multi-drug-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.

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

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).
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 high or low.

Assuming a pretest probability of around 55% for a UTI for an unselected woman complaining of ≥1 urinary symptom in the community, the probability of infection 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 therefore 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.

### Urinary symptoms

The first meta-analysis included 16 studies carried out in primary care. The age of patients ranged from 15 to 90 years (mean age range of included studies: 26–54 years). Five urinary symptoms were identified as useful diagnostic symptoms and increased the pretest probability of a UTI with positive likelihood ratios when a threshold of ≥10⁴ colony-forming units (CFU)/ml is the reference standard; dysuria (LR+ 1.31, 95% CI 1.18 to 1.45), frequency (LR+ 1.12, 95% CI 1.03 to 1.19), haematuria (LR+ 1.68, 95% CI 1.06 to 2.65), nocturia (LR+ 1.37, 95% CI 1.13 to 1.65) and urgency (LR+ 1.28, 95% CI 1.11 to 1.47) (see Table 2). There was no likelihood ratio given for the presence of vaginal discharge when then the threshold of ≥10³ CFU/ml is the reference standard. However, at a threshold of ≥10² 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.

The second meta-analysis included 11 studies carried out in primary care. 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, dysuria (LR+ 1.09, 95% CI 1.03 to 0.16) and sexual activity (LR+ 1.18, 95% CI 1.04 to 1.34) 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).

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. 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.

All three meta-analyses used likelihood ratios to draw conclusions from the individual studies (two meta-analyses used pooled LRs,\textsuperscript{44,45} while the other listed individual LRs for each of the four included studies\textsuperscript{45}). No single clinical sign or symptom can reliably predict a UTI. Dysuria was found to be the most useful single symptom in predicting a UTI. However one meta-analysis did not find any single urinary symptoms to be predictive.\textsuperscript{42} 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.\textsuperscript{44}

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)\textsuperscript{45} while an earlier review reported the combination of dysuria and frequency without vaginal discharge resulted in a large LR+ of 24.6.\textsuperscript{47} If a woman presents with a combination of new onset vaginal discharge or irritation and urinary symptoms (dysuria, frequency, urgency, visible haematuria or nocturia) do not diagnosis a UTI. \textsuperscript{1+}

\begin{itemize}
\item [\textbf{Dipstick testing}]
\end{itemize}

Dipstick tests are used to increase the predictive value of urinary symptoms, but different brands use different methods to characterise the leukocyte esterase, while the nitrite test was binary, either present or absent. The three reviews identified for inclusion in the analysis of urinary symptoms also evaluated near patient tests (dipstick tests) to increase the diagnostic probability of the pretest signs.

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. Normally urine should not show any trace of nitrite. The nitrite test is an indirect measure of nitrate-reducing bacteria, provided the urine contains sufficient dietary nitrates and has been retained in the bladder for more than 4 hours. Most bacterial species causing UTI reduce nitrate in the urine to nitrite.

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 leucocyte esterase tests increased the post-test probability.\textsuperscript{44} 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 the author notes that these values were derived from a population which included men and pregnant women). The post-test probabilities for a UTI, when the threshold of $\geq10^3$ 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.

\textsuperscript{1+}
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Table 2: Post-test probabilities of significant symptoms alone and in the context of positive and negative dipstick tests

<table>
<thead>
<tr>
<th>Symptom (LR+)</th>
<th>Pretest probability based on symptom</th>
<th>Post-test probability of symptom with a positive dipstick test result (LR+ 4.42) (95% CI)</th>
<th>Post-test probability of symptom with a negative dipstick test result (LR- 0.53) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysuria (1.31)</td>
<td>62.3% (61.0 to 63.6)</td>
<td>88.0% (86.4 to 88.5)</td>
<td>46.7% (45.3 to 48.1)</td>
</tr>
<tr>
<td>Frequency (1.12)</td>
<td>58.6% (57.5 to 59.5)</td>
<td>86.2% (85.7 to 87.0)</td>
<td>42.9 (41.8 to 43.8)</td>
</tr>
<tr>
<td>Haematuria (1.68)</td>
<td>67.4% (60.6 to 73.6)</td>
<td>90.1% (87.2 to 92.5)</td>
<td>52.3 (44.9 to 59.6)</td>
</tr>
<tr>
<td>Nocturia (1.37)</td>
<td>60.8% (58.4 to 63.3)</td>
<td>87.3% (86.1 to 88.4)</td>
<td>45.1 (42.7 to 47.8)</td>
</tr>
<tr>
<td>Urgency (1.28)</td>
<td>61.7% (59.9 to 63.6)</td>
<td>81.0% (79.7 to 82.2)</td>
<td>46.1 (44.2 to 48.1)</td>
</tr>
<tr>
<td>Vaginal discharge (0.65)</td>
<td>&lt;54.1% (48.3 to 59.9)*</td>
<td>&lt;61.6% (56.0 to 67.0)*</td>
<td>&lt;29.8 (25.2 to 35.0)*</td>
</tr>
</tbody>
</table>

Note: Pretest probability on presentation is 55.4%
* values reported for threshold of ≥10^2 CFU/ml therefore probabilities at reference standard of ≥10^3 CFU/ml are lower


In the second meta-analysis, pooled likelihood ratios were used to increase the post-test prediction for a UTI. Nitrites 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 leukocytes 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).45

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 0.6.42

All studies reaffirm 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 leukocytes moderately increases the pretest 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 sequentially rather than in parallel with a positive history of symptoms only led to a marginal increase in costs but a higher proportion of correctly classified women (from 0.59 sequentially to 0.73 in parallel). Sequentially adding either a sediment test or a dipslide after a negative history and dipstick had the highest proportions of correctly classified women (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.46

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 nitrites.

✔ On diagnosis of UTI in the presence of two or more urinary symptoms and a positive dipstick test result for nitrites, 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.

R Consider the diagnosis of a UTI in a woman with two or more urinary symptoms (dysuria, frequency, urgency, visible haematuria or nocturia) and a negative dipstick test result for nitrites.
Send a urine specimen for culture to confirm the diagnosis in patients who present with suspected UTI and two or more urinary symptoms and a negative dipstick test result for nitrites.

If a woman presents with a single urinary symptom (dysuria, frequency, urgency, visible haematuria or nocturia) with a positive dipstick test result for nitrites, do not confirm the diagnosis of a UTI.

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.

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 considering the patient’s need to work and/or to provide care for children or other dependents.

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

3.2.1 Self care

Fluid intake

Increasing fluid intake is thought to prevent UTI by dilution and flushing of bacteriuria. This reduces attachment to uroepithelial cells, reduces growth nutrients and/or improves clearance. One RCT suggested that increasing fluid intake in lower volume drinkers 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 regime use (mean 1.7; p<0.001).49

A smaller case-control study identified an increased incidence of UTI in those who restricted their fluid intake. Increasing fluid intake with water is a low cost intervention without evidence of harm.50

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.

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.51

Exercise caution in women who are on fluid restriction for medical reasons.

Spermicidal Contraception

Spermicides are thought to increase the risk of UTI by killing off protective bacteria in the vagina allowing overgrowth of those that cause infection. Although the evidence is limited, based on two studies a Canadian guideline recommends offering women using spermicide-containing products an alternative form of contraception.52,53

Women at risk of recurrent UTI should avoid the use of spermicide containing contraceptives.
Voiding behaviours and hygiene

Behavioural interventions are low cost and do not have any evidence of harm. Two case control studies found that postponing voiding can lead to an increased incidence of urinary tract infection. Additional interventions from one of these studies found a reduced incidence of UTI with wiping front to back, postcoital voiding and drinking water within 15 minutes; and avoidance of washing with soap after urination.

Acupuncture

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

R Advise women at risk of UTI where antibiotic prophylaxis has failed or is not tolerated that acupuncture may be considered as a treatment option.

3.2 Pharmacological treatment: Antimicrobials

Lower UTI (LUTI) 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.

Treating patients who have LUTI with antimicrobials does not significantly affect risk of pyelonephritis compared with treatment with placebo (odds ratio (OR) 0.33, 95% CI 0.04 to 2.7). Antimicrobials achieve clinical and microbiological cure of disease more rapidly than placebo 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.

An RCT comparing three days’ treatment with oral ciprofloxacin with three days’ treatment with a non-steroidal anti-inflammatory drug (ibuprofen) found no statistically significant difference in speed of symptom resolution between the regimens, suggesting that in selected patients antimicrobial treatment could be deferred or avoided altogether if adequate symptom control can be achieved with non-steroidal anti-inflammatory drugs (NSAIDs). However, a further trial by the same group which compared treatment with a single dose of the antimicrobial fosfomycin with three days treatment with ibuprofen for symptomatic relief was unable to reproduce this result and showed statistically significant advantages of antimicrobial treatment in terms of speed of symptom resolution (mean difference 17.4% in favour of antimicrobial therapy), symptom burden (mean difference 3% in favour of antimicrobial therapy) and impairment of usual activities (mean difference 10.8% in favour of antimicrobial therapy) (p<0.001 for each outcome).

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, fluoroquinolones, nitrofurantoin, and beta-lactams), and reported no statistically significant difference in short-term or longer-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).

It should be noted that the beta-lactams in the included studies were amoxicillin, cefuroxime, pivmecillinam and two cephalosporins which are not available in the UK (cefdroxil and cefpodoxime). Current practice in the UK for use of beta-lactam antibiotics in UTI would be to use co-amoxiclav, cephalaxin or cefuroxime, but not as first line agents due to their broader spectrum of activity than trimethoprin 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.\textsuperscript{59} 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\textsuperscript{[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). An odds ratio of 1 represents no effect relative to the reference treatment. An odds ratio >1 indicates better cure for the treatment compared with the reference treatment. An odds ratio <1 indicates worse cure for the treatment compared with the reference treatment.

Fluoroquinolones, such as ciprofloxacin, are used widely for treatment of UTIs, and while effective, the class has come under increased scrutiny, both due to its role as a driver of increasing gram-negative antimicrobial resistance\textsuperscript{60} and more recently due to 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.\textsuperscript{61} Furthermore, quinolone use is a well-described risk factor for the acquisition of CDI.\textsuperscript{62,63}

Antimicrobial stewardship initiatives place an emphasis on the use of narrow-spectrum antimicrobials, such as nitrofurantoin and trimethoprim whenever possible. Escherichia coli, which is the most common cause of UTI, has low resistances rates to nitrofurantoin in Scotland (declining from 4.2% in 2013 to 2.6% in E. coli urinary isolates in 2017).\textsuperscript{6}

Trimethoprim resistance 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 present with symptoms than those prescribed nitrofurantoin.\textsuperscript{6} (personal communication: Health Protection Scotland) It is also acknowledged that urine samples sent for culture and sensitivity in Scotland are predominantly from patients with recurrent symptoms or frequent UTIs therefore surveillance data are not representative of the whole population of patients with UTI symptoms. Current 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 urine, rendering the antimicrobial more effective in managing UTIs 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.\textsuperscript{64} 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.\textsuperscript{65}

Urinary alkalinising agents (most commonly containing potassium citrate, sodium citrate, or sodium bicarbonate) are sold at pharmacies and often used by women seeking symptomatic relief from LUTI, despite a lack of evidence for their safety or effectiveness.\textsuperscript{66}

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 estimated glomerular filtration rate (eGFR) <45 mL/minute/1.73 m\textsuperscript{2}. When potential benefit outweighs risk, it may be used with caution if eGFR 30–44 mL/minute/1.73 m\textsuperscript{2} for a short course only (3–7 days), to treat uncomplicated LUTI caused by suspected or proven multidrug resistant bacteria and only if the potential benefit outweighs risk.\textsuperscript{38}

\textbf{R} \textit{Use a narrow-spectrum antimicrobial with activity against common uropathogens (see Table 3) for empirical treatment of LUTI in suitable patients.}

\textbf{R} \textit{Advise women with LUTI, who are prescribed nitrofurantoin, not to take alkalinising agents (such as potassium citrate, sodium citrate, or sodium bicarbonate).}
Do not use fluoroquinolones or co-amoxiclav empirically for LUTI unless other narrow-spectrum agents are contraindicated due to comorbidity, toxicity or resistance.

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 contradictory.

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). However, 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).

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.

**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 1.73, 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).

**Use short (3-day) courses of antimicrobials for treatment for LUTI, as this is clinically effective and minimises the risk of adverse events.**
Table 3: Comparison of selected antimicrobial agents for treatment of LUTI

<table>
<thead>
<tr>
<th>Agent</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitrofurantoin</td>
<td>First-line treatment option. Narrow spectrum agent with low rate of resistance. Not suitable for patients with eGFR &lt;45 ml/min/1.73 m². Interacts with over-the-counter cystitis remedies containing citrate.</td>
</tr>
<tr>
<td>(100 mg modified-release twice a day for 3 days)</td>
<td></td>
</tr>
<tr>
<td>Trimethoprim</td>
<td>First-line treatment option. Narrow spectrum agent with low rate of resistance. Dose adjustments required in patients with renal impairment. Resistance rate for E. Coli &gt;37% in Scotland.6</td>
</tr>
<tr>
<td>(200 mg twice a day for 3 days)</td>
<td></td>
</tr>
<tr>
<td>Cefalexin</td>
<td>Broad spectrum agent. Main use is in pregnancy where trimethoprim and nitrofurantoin are less suitable. 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.38 Cephalosporins are associated with an increased risk of CDI.7,70</td>
</tr>
<tr>
<td>(500 mg twice a day for 7 days)</td>
<td></td>
</tr>
<tr>
<td>Pivmecillinam</td>
<td>Second-line treatment option which is useful for targeted treatment. Narrow spectrum agent.</td>
</tr>
<tr>
<td>(400 mg initial dose, then 200 mg three times a day for a total of 3 days)</td>
<td></td>
</tr>
<tr>
<td>Fosfomycin</td>
<td>Second-line treatment option which is useful for targeted treatment (against organisms sensitive to fosfomycin). Broad spectrum agent. Single dose treatment.</td>
</tr>
<tr>
<td>(3 g single-dose sachet)</td>
<td></td>
</tr>
<tr>
<td>Co-amoxiclav</td>
<td>Second-line 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.38 Resistance rates for E. Coli around 25% in Scotland.6 Co-amoxiclav is associated with an increased risk of CDI.7,70</td>
</tr>
<tr>
<td>(One tablet containing 250 mg amoxicillin trihydrate and 125 mg clavulanic acid taken three times a day for 3 days)</td>
<td></td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>Use only where other antibiotic choices are unsuitable (Adverse safety profile – MHRA warning; do not use for LUTI unless all other agents unsuitable.61) Fluoroquinolones are associated with an increased risk of CDI.7,70</td>
</tr>
<tr>
<td>(250 mg twice daily for 3 days)</td>
<td></td>
</tr>
</tbody>
</table>

Adverse events

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).71 Only four of the nine studies included in this review recruited patients under the age of 65 years. A further meta-analysis which compared treatment with an antimicrobial or placebo also concluded that adverse events were significantly more likely in individuals treated with...
antimicrobials (OR 1.64, 95% CI 1.1 to 2.44).\textsuperscript{55}

A third 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.\textsuperscript{56}

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. Trimethoprim is known to cause hyperkalaemia in patients taking renin-angiotensin system blockers or potassium-sparing diuretics.\textsuperscript{72}

Side effects to any class of antimicrobial were significantly less common with three-day treatment courses compared with 5–7 day courses (see duration of therapy section).

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.\textsuperscript{54}

**Antimicrobials for recurrent UTI**

Recurrent UTI is a condition with significant effects on the quality of life of affected individuals. A Cochrane review reported that long-term antimicrobial treatment, usually with single daily doses given at night time, is effective at reducing the number of recurrence 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/year to 0.0–0.9/year, and the number of clinical recurrences from 1.12–3.6/year to 0.0–0.27/year.\textsuperscript{73}

Two RCTs compared a daily dose of 480 mg trimethoprim-sulfamethoxazole with a preparation containing 500 mg of cranberry extract taken twice daily and showed antimicrobials to be more effective\textsuperscript{74} and cheaper\textsuperscript{76} than cranberry products in this setting.

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, observed resistance development 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 3 months after prophylaxis was stopped.\textsuperscript{74}

**Choice of agent for long-term prophylaxis of recurrent UTI**

The narrow-spectrum agent nitrofurantoin is excreted avidly 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, and 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).\textsuperscript{76}

In an economic model based on cohort of patients experiencing a mean of 3 UTIs/year, prophylaxis using nitrofurantoin (100 mg) was projected to result in a large reduction in UTI incidence (mean of 0.4/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.\textsuperscript{77}

There is however 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.\textsuperscript{78} Other meta-analyses report an increased risk of side-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 side effects overall (RR 1.83, 95% CI 1.18 to 2.84).\textsuperscript{73}

The BNF recommends monitoring of liver function and pulmonary function in any individual treated with nitrofurantoin for prophylaxis, and the agent discontinued if any deterioration in pulmonary function is found.\textsuperscript{80}

\textit{Duration of antimicrobial prophylaxis for prevention of recurrent UTI}

Evidence from one meta-analysis showed no additional benefit when prophylaxis was given for more than six months, when compared with cessation of prophylaxis after six months.\textsuperscript{76}

\textit{Treatment of asymptomatic bacteriuria in non-pregnant women}

Antimicrobial treatment of asymptomatic bacteriuria compared with placebo does not prevent development of UTI, and does not lower mortality, but is associated with an increased risk of drug-related adverse events.\textsuperscript{71}

\textbf{R} Do not treat asymptomatic bacteriuria in non-pregnant women aged <65 years.

\textit{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 (IRR 1.37, 95% CI 1.11 to 1.68; \( p < 0.001 \)). 77% of patients in the delayed antibiotics group did take antibiotics but fewer patients reconsulted compared with those given immediate antibiotics.\textsuperscript{79}

In the accompanying economic evaluation, delayed antibiotics was both less effective and more expensive than immediate antibiotics or antibiotics targeted to dipstick algorithm (nitrites or leucocytes and a trace of blood).\textsuperscript{80}

\textbf{3.2.3 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.\textsuperscript{55} In one large case-control study antibiotic prescription is associated with increase in the individual risk of a subsequent antibiotic-resistant urinary tract isolate.\textsuperscript{81}

Non-steroidal anti-inflammatory drugs 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 4). The three larger studies\textsuperscript{57,82,83} included women aged >18–65–70 years and one smaller study\textsuperscript{46} included patients up to the age 85 years.

Three studies used ibuprofen as the study NSAID, with a dose of 400 mg three times per day for three days\textsuperscript{56,57} or 600 mg three times per day.\textsuperscript{83} Diclofenac 75 mg twice daily was used in the remaining study.\textsuperscript{82} 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 diclofenac versus pivmecillinam study participants were provided with fosfomycin 3 g to be taken if required for ongoing symptoms.\textsuperscript{82}

\textit{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 subjects reported symptom improvement.\textsuperscript{57,82,83} Between 2% and 5% of subjects receiving NSAIDs were diagnosed with pyelonephritis. In the remaining study
pyelonephritis in NSAID-treated subjects was predicted by a baseline C-reactive protein level of >10 mg/l.\textsuperscript{82}

**Urine culture positive at follow up**

Two studies reported urine culture results at 10 days\textsuperscript{82} and 14 days.\textsuperscript{83} Bacteriuria was reduced in those patients receiving antibiotics compared to those receiving NSAIDs (see Table 4). Culture of the primary pathogen was seen in 19% of subjects treated with ibuprofen and 4% of those treated with pivmecillinam.\textsuperscript{83}

**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 4). 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. 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.\textsuperscript{84}

**Predicting patients more likely to benefit from immediate antibiotic therapy rather than treatment with NSAIDs**

In a follow-up study clinical factors associated with an antibiotic prescription within 28 days of receiving ibuprofen were investigated.\textsuperscript{85} A number of factors were identified on univariate analysis: reporting of moderate to severe urgency/frequency (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 leucocytes (OR 4.8, 95% CI 1.65 to 14.22) or nitrates (OR 2.4, 95% CI 1.28 to 4.59) and urine culture positive (OR 7.7, 95% CI 2.93 to 20.21). Urine culture positivity could not be included within the final model as culture results are not available at point of empirical treatment. The final predictive model included five factors to which points were assigned based on the strength of the association. The sum of the scores ranged from 0 to 294 points: moderate to severe urgency/frequency (50 points); impairment of daily activities (19 points); erythrocytes positive (94 points); leucocytes positive (75 points); nitrates positive (56 points). A total of ≥210 points provided a good predictive model of which patients would improve with ibuprofen. Using this threshold, 58% of participants presenting with UTI within the study would be treated with antibiotics (rather than NSAID) and of the remaining females, only 6% would return to the practice because of symptomatic treatment failure. This approach has an estimated 84% sensitivity and 55% specificity. This implies an additional larger population of patients who could safely be managed with NSAIDs (and without antibiotics). A score of ≥219 successfully predicted all of those with pyelonephritis. This proposed scoring method therefore selects a lower risk population who could be targeted for NSAID treatment. However, this model underestimates those who might improve with a NSAID.

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 6 was similar in the two groups if urine culture at baseline was negative.\textsuperscript{85} This suggests that successfully predicting those with symptomatic bacteriuria might be useful to determine those most likely to benefit from antibiotic therapy.

NSAIDs are associated with worsening of asthma control, 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, however 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.\textsuperscript{88}

**R** Consider NSAIDs as first-line treatment in women aged <65 years with suspected uncomplicated lower UTI that describe their symptoms are mild.
Consider NSAIDs as an alternative to an antibiotic in women aged <65 years with suspected uncomplicated lower UTI when symptoms are moderate to severe with positive urinalysis following a discussion of risks and benefits.

Offer antibiotic treatment to women aged <65 years with suspected uncomplicated lower UTI that describe their symptoms are severe and rapid resolution of symptoms is required.

- Decision to use an NSAID or antibiotic should be shared between patient and prescriber and risks and benefits should be fully discussed and considered.
- 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 or worsen within three days.

3.2.4 Non-pharmacological treatment

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. 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.

Evidence for the effectiveness of cranberry products in preventing UTI is conflicting. Three systematic reviews and the body of RCTs which these include report inconsistent results on the incidence of new UTIs across a range of populations. A Cochrane review 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). The review included 24 studies with a total of 4,473 participants. 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.

Another systematic review and 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. 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.

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; I²=73%; n=3 studies).

A systematic analysis was carried out to investigate the status of evidence-based assessments on the use of cranberry and prevention of recurrent UTIs in healthy women.
particular, this review explored methodological differences that may be related to the conflicting findings. It suggested that differences 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 all influenced their overall results. Careful selection of the population of studies included in a meta-analysis is an important quality criterion which can lead to inaccuracies and inconsistency if not carried out appropriately. For example, there is evidence that cranberry may be more effective in prevention of uncomplicated UTI than UTIs caused by structural or functional complications, or catheterisation. 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.

Two systematic reviews noted that the inclusion of one RCT introduced substantial heterogeneity however one review 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. The third review 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, as noted above.

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.

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.

Probiotics are live micro-organisms which, when administered in adequate amounts, confer a health benefit on the host. They are thought to work by preventing other infectious bacteria from climbing up 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 authors report that despite the lack of efficacy, benefit cannot be firmly ruled out as the data were few, and derived from small studies with poor methodological reporting.

A further meta-analysis of RCTs involving use of Lactobacillus probiotics for prophylaxis of recurrent UTIs did not show a significant effect of the probiotic compared with placebo (RR 0.85, 95% CI 0.58 to 1.25). However, 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).

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). The study was sponsored by the product manufacturer. BNO 1045 was non-inferior to antibiotic therapy. 83.5% of 325 subjects randomised to BNO 1045 improved without antibiotics by day 38 compared with 89.8% randomised to fosfomycin (non-antibiotic rate difference: -6.26%; 95% CI -11.99 to -0.53%; 2-sided p=0.0014). An additional 10.2% of 334 subjects who received fosfomycin required a second course of antibiotics within 38 days. There were five (2%) cases of pyelonephritis in subjects 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 1,045 group (13 patients).

BN 1045 is not used routinely in Scotland and cannot be supplied on prescription. Patients can buy BN 1045 via online retailers.

**DATA ON OESTROGENS TO BE ADDED – WORK IN DEVELOPMENT**

**R** Advise women that Canephron® (BNO 1045) may be considered as a treatment option in women aged <65 years with suspected uncomplicated lower UTI.

☑ Decision making should be shared between patient and prescriber and risks and benefits should be fully discussed and considered.
### Table 4: RCTs of non-antibiotic pharmacological and non-pharmacological treatments v antibiotic treatment of uncomplicated LUTI in women

<table>
<thead>
<tr>
<th>Study</th>
<th>Study agent</th>
<th>Comparator antibiotic</th>
<th>No.</th>
<th>Bacteriuria at baseline (%)</th>
<th>Symptom duration following intervention (days)</th>
<th>Symptom resolution by day 3-4 (%)</th>
<th>Symptom resolution by day 7 (%)</th>
<th>Pyelonephritis (%)</th>
<th>Bacteriuria at follow up (%)</th>
<th>Follow antibiotic within one month (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleidorm (2010)</td>
<td>ibuprofen</td>
<td>ciprofloxacin</td>
<td>79</td>
<td>86 v 80</td>
<td>Not reported</td>
<td>58 v 52 (NS)</td>
<td>75 v 61 (NS)</td>
<td>Nil</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td></td>
<td>3 days</td>
<td>3 days</td>
<td></td>
<td></td>
<td></td>
<td>5.6 v 4.6 (mean) (p&lt;0.001)</td>
<td>39 v 56 (p&lt;0.001)</td>
<td>70 v 82 (p=0.004)</td>
<td>2.1 v 0.4 NS</td>
<td>35 v 14 (p&lt;0.001)</td>
</tr>
<tr>
<td></td>
<td>ibuprofen</td>
<td>fosfomycin</td>
<td>494</td>
<td>76 v 77</td>
<td></td>
<td></td>
<td></td>
<td>70 v 82 (p=0.004)</td>
<td>2.1 v 0.4 NS</td>
<td>35 v 14 (p&lt;0.001)</td>
</tr>
<tr>
<td></td>
<td>3 days</td>
<td>3 g once</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>70 v 82 (p=0.004)</td>
<td>2.1 v 0.4 NS</td>
<td>35 v 14 (p&lt;0.001)</td>
</tr>
<tr>
<td>Gagyor (2015)</td>
<td>diclofenac</td>
<td>norfloxacin</td>
<td>253</td>
<td>72 v 74</td>
<td>4 v 2 (median) (p&lt;0.001)</td>
<td>54 v 80 (p&lt;0.001)</td>
<td>83 v 96 (p=0.003)</td>
<td>5 v 0 (p=0.031)</td>
<td>28 v 7 (day 10) (p&lt;0.001)</td>
<td>55** v 15 (p&lt;0.001)</td>
</tr>
<tr>
<td></td>
<td>3 days</td>
<td>3 days</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>28 v 10 (day 14) (p&lt;0.01)</td>
<td>46 v 10 (p&lt;0.01)</td>
</tr>
<tr>
<td>Kronenberg (2017)</td>
<td>ibuprofen</td>
<td>pivmecillinam</td>
<td>383</td>
<td>67 v 64</td>
<td>6 v 3 (median) (p&lt;0.01)</td>
<td>39 v 74 (p&lt;0.01)</td>
<td>63 v 91 (p&lt;0.01)</td>
<td>4 v 0 (p&lt;0.01)</td>
<td>28 v 10 (day 14) (p&lt;0.01)</td>
<td>46 v 10 (p&lt;0.01)</td>
</tr>
<tr>
<td></td>
<td>3 days</td>
<td>3 days</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>28 v 10 (day 14) (p&lt;0.01)</td>
<td>46 v 10 (p&lt;0.01)</td>
</tr>
<tr>
<td>Vik (2018)</td>
<td>BNO 0145</td>
<td>fosfomycin</td>
<td>659</td>
<td>79 v 73</td>
<td>Not reported</td>
<td>70 v 74* (NS)</td>
<td>78 v 82* (NS)</td>
<td>2 v 0.2</td>
<td>16 v 10</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7 days</td>
<td>3 g once</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>16 v 10</td>
<td></td>
</tr>
</tbody>
</table>

All comparisons are study drug v antibiotic
NS = not significant
* values estimated from graphs
** 58/82 (71%) of subjects who took antibiotics did so within three days of enrolment and the majority with the rescue antibiotic fosfomycin
4 Lower urinary tract infection in women aged 65 years and above

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. 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. Asymptomatic bacteruria (ASB) also rises with age, especially those in long-term residential facilities, where it can be as high as 50%. Asymptomatic bacteriuria can lead to overdiagnosis of UTI and unnecessary antibiotic prescribing. Antibiotic prescribing is higher in older adults, especially those in residential settings, and older adults are more likely to harbour resistant bacteria. It is recognised that age of 65 years has been traditionally used as a cut off, but that this is not 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, and older women in care homes or requiring assisted living, to which the majority of the evidence identified below applies.

4.1.1 Clinical assessment

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. 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 identified a single study which suggested that inability to perform a number of acts 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, however, 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), however 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.

Two studies included in this meta-analysis reported presence of delirium to be a predictor of UTI, and absence of this symptom helped to rule out UTI. In addition, SIGN guideline 157: Risk reduction and management of delirium recommends that regulation of bladder and bowel function in people at risk of delirium should be considered to reduce the incidence.

4.1.2 Urinary symptoms

The meta-analysis cited in section 4.1.1 also 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.

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 or urgency and UTI.98

- Be aware that women aged 65 years and above, especially those in residential facilities, may not display the traditional symptoms and signs of UTI that are seen in a younger cohort.
- 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.

- Remember sepsis and other causes of delirium in an unwell older adult with abnormal vital signs.

4.1.3 Urinalysis and dipstick testing

A prospective observational study between two cohorts of 100 patients.101 Of the 33 positive cultures, 10 had negative reagent strips. Thirteen of the 14 positive nitrite tests were culture positive for a specificity of 92.8% and a sensitivity of 36.1%. Positive cultures did not infer a diagnosis of UTI. Of the 67 positive reagent strips, 41 (61.2%) were associated with negative cultures. Likelihood ratios in both groups affirmed the inability of the reagent strips to help significantly in decision making, with positive and negative LR in the indeterminate range (control group: 2.8 and 0.31, symptomatic group: 2.7 and 0.46, respectively). The authors concluded that reagent testing is an unreliable method of identifying patients with positive blood 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-urológic problems, which suggests that many positive cultures in elderly patients with non-focal systemic symptoms are false-positive tests reflecting asymptomatic bacteriuria and not UTIs.

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. Urinary 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).

- Use of dipsticks for diagnosis of UTI in women aged 65 years and above in residential care is not recommended.

- Do not send urine for culture to rule in urinary tract infection in women aged 65 years and above in residential care.

Urine cultures will lead to false positives if used to diagnose diffuse symptoms in elderly patients in residential homes and will lead to over-diagnosis.

- Send urine for culture to confirm the pathogen and antibiotic susceptibility in women aged 65 years and above started on antibiotics for a UTI.

4.2 Management

4.2.1 Self care

There is a lack of evidence for self-care interventions to reduce UTI risk in this population. 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.102 Another small cross-sectional study did not identify a significant association between daily fluid intake and
Evidence from premenopausal women, however, suggests increase fluid intake can be beneficial in reducing incidence, and represents a low-cost, no-harm intervention (see section 3.2.1).49 In this population factors such as poor mobility, cognitive impairment, and medication are likely to impact on 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.103

Materials to support public awareness of the importance of hydration are available from Health Protection Scotland.51

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.104

Materials to support promotion of continence are available from the Care Inspectorate.105,106

4.2.2 Pharmacological treatment: Antimicrobials

In older females, antimicrobials remain an effective way to achieve clinical cure of LUTI.55 No evidence was identified that describes specifically the risks inherent to antimicrobial treatment of acute UTI in women aged >65 years, but the risks described for women aged <65 are likely to be similar. In addition, elderly people are more likely to be affected by multimorbidity and therefore be subject to polypharmacy which can be associated with preventable harm.107

Choice of agent

No specific studies were available which examine choice of antimicrobial agents for treatment of LUTI in this age group. However, with increasing age, individuals are more likely to have significant comorbidities and be on long-term medications for these, and may therefore be at higher risk of drug interactions, and other side effects of antimicrobial treatment.108

Consider use of the same agents for treatment of LUTI in women aged 65 years and above as in younger females, but exert particular caution in the context of impaired renal function, drug interactions and ecological side effects, such as CDI.

Duration of treatment

One RCT was identified which provides data on effectiveness of different durations of treatment for LUTI in elderly females, suggesting that three day courses are as effective as seven day courses in controlling most symptoms of LUTI, apart from urgency, and are less likely to cause side effects.109

Rationale for prophylactic antimicrobials in recurrent UTI

A systematic review with meta-analysis, which included three RCTs comparing long-term antimicrobials with vaginal oestrogens, oral lactobacilli, and D-Mannose, respectively, reported that daily dose prophylactic antimicrobials are an effective measure to prevent recurrent UTI in this age group, reducing the risk of recurrent UTI by 24% while prophylaxis is ongoing (RR 0.76, 95% CI 0.61 to 0.95).110 However the NNT is almost fourfold higher than in females under 65 years (8.5 v 2.2) (see section 3.2.2).73

Adverse events

Adverse events caused by prophylactic antimicrobials for prevention of recurrent UTI are common, and a systematic review 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%).78
Resistance to trimethoprim-sulfamethoxazole increased to >90% after only one month of continuous prophylaxis, and, while resistance levels were seen to decrease after prophylaxis was stopped, levels remained above preprophylaxis baseline at 15 month follow up.\textsuperscript{110}

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

**✓** Materials to support public awareness of the importance of hydration are available from Health Protection Scotland.\textsuperscript{51}

**✓** Where prophylactic antibiotics are used to prevent recurrent UTI the duration of treatment should be limited to 3–6 months.

### 4.2.3 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 outperform daily prophylaxis with nitrofurantoin in preventing recurrent UTI without a statistically significant rise in adverse events.\textsuperscript{110}

No evidence was identified which provides data on the use of NSAIDs specifically in women aged 65 years and above.

*ADD DATA ON OESTROGENS AND OTHER NON-ANTIMICROBIALS – WORK IN DEVELOPMENT*

### 4.2.4 Non-pharmacological treatment

Proanthocyanidins present in cranberry products have been shown to inhibit adherence of *E. coli* to uroepithelial cells.\textsuperscript{86} The lack of adverse effects and avoidance of antimicrobial resistance make cranberry products a particularly appealing strategy for prevention of UTI in the older population, however evidence for their effectiveness is conflicting (see section 3.2.4). 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.

A Cochrane review suggested that cranberry products were not effective in preventing UTIs. The review included 24 studies with a total of 4,473 participants. 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. A subgroup analysis used data from two of the four studies which recruited older people (n=413). The remaining two studies had significant data flaws. Compared with placebo, water or no treatment, cranberry products did not significantly reduce the occurrence of symptomatic UTI in older people (RR 0.75, 95% CI 0.39 to 1.44).\textsuperscript{87}

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% proanthocyanidins, equivalent to 9 mg) with placebo in patients at high-risk (n=516) and low-risk (n=412) of UTI. There was a high dropout rate in this study. Results were stratified according to both a clinical and a scientific definition of UTI.\textsuperscript{111}

The clinical definition required a minimum of one of the following characteristics:

- pain before, during, or after micturition
- increased frequency of micturition
- pain in abdomen
- haematuria
- foul smell
- signs of common sickness (fever >37.9°C or 1.5°C above baseline temperature,
- chills, nausea, vomiting
Management of suspected bacterial lower UTI in adult women

- anorexia, fatigue and reduced mobility, or signs of delirium (e.g., confusion, deterioration in mental or functional status).
- a positive test (nitrite test, leukocyte esterase test, dipslide, or culture),
- antibiotic treatment for UTI, or UTI reported in the medical record.

The scientific definition required:
- The presence of micturition-related symptoms and signs confirmed with a positive dipslide or culture. A urine dipslide or culture was considered to be positive when there were $10^5$ CFU/mL or more bacteria, with no more than two species of organisms present.

Cranberry capsules did not reduce the incidence of UTI in high-risk patients if UTI was given a scientific definition (25.3 v 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 v 84.8 per 100 patient-years at risk, p=0.04; treatment effect 0.74, 95% CI 0.57 to 0.97). 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/day.

A further RCT investigated the effect of cranberry capsules (72 mg proanthocyanidins/day) on bacteriuria and pyuria in older women in nursing homes (mean age 86.4). The trial showed no significant decrease in pyuria or bacteriuria with cranberry compared with placebo (29.1% v 29.0%; OR 1.01, 95% CI 0.61 to 1.66; p=0.98).\(^{112}\)

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.\(^{92}\) However 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.
5 Catheter-associated lower urinary tract infection in women

5.1 Diagnosis

5.1.1 Clinical assessment

Most signs and symptoms in bacteriuric catheterised patients are non-specific and, therefore, 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. 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 the Scottish Antimicrobial Prescribing Group (https://www.sapg.scot/media/4570/decision-aid-for-management-of-cauti.pdf).

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.113

- CA-UTI in patients with indwelling urethral, indwelling suprapubic, or intermittent catheterization is defined by the presence of symptoms or signs compatible with UTI with no other identified source of infection along with ≥10³ colony-forming units (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 (Strength of recommendation A: Quality of evidence III).

- 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 (Strength of recommendation A: Quality of evidence III).

- In the catheterised patient, pyuria (presence of pus in the urine) is not diagnostic of CA-bacteriuria or CA-UTI (Strength of recommendation A: Quality of evidence II).
  - The presence, absence, or degree of pyuria should not be used to differentiate CA-ASB from CA-UTI (Strength of recommendation A: Quality of evidence II).
  - Pyuria accompanying CA-ASB should not be interpreted as an indication for antimicrobial treatment (Strength of recommendation A: Quality of evidence II).
  - The absence of pyuria in a symptomatic patient suggests a diagnosis other than CA-UTI (Strength of recommendation A: Quality of evidence III).

- 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 (Strength of recommendation A: Quality of evidence III).

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 helpful in assessing clinical signs and symptoms.
5.1.2 Dipstick testing

No evidence was identified for use of dipstick testing in patients with indwelling catheters and symptoms suggestive of CA-UTI. Most patients with an indwelling catheter will have bacteria in their urine and therefore test positive for nitrites and leucocytes even in the absence of CA-UTI, rendering dipstick testing less sensitive to the detection of clinically significant bacteriuria. 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.\textsuperscript{32}

5.2 Management

5.2.1 Non-pharmacological treatment

A cohort study undertaken in older hospitalised adults in Israel with an indwelling catheter in situ for longer than 7 days showed no association between catheter replacement and clinical failure of CA-UTI treatment.\textsuperscript{114}

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.\textsuperscript{115}

Both studies showed similar rates of resolution of the acute symptoms with antibiotic treatment, however 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 three days of treatment and were less likely to have symptomatic recurrence at the late post-treatment follow up. In the cohort study, there was no significant advantage of catheter replacement (propensity score-match 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 days of febrile illness for participants discharged alive in the matched population (median 2 days, interquartile range (IQR) 1–5 days v 1.5 days, IQR 0.75–4 days, p=0.50).

There is insufficient evidence available to support a recommendation either in favour of or against the replacement of catheters before antimicrobial treatment as a strategy to prevent CA-UTI.

5.2.2 Pharmacological treatment: Antimicrobials

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

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 (95% CI 1.1 to 1.5, calculated by SIGN) and 2.5 cases per person-year (95% CI 2.2 to 2.8, calculated by SIGN) for no prophylaxis. The incidence rate ratio (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.\textsuperscript{116}

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, but 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.

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. In the probabilistic analysis, 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.

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 national guidance from NICE and IDSA. Do not prescribe antibiotics to prevent UTI in patients using intermittent self catheterisation for bladder emptying.

5.2.3 Pharmacological treatment: Non-antimicrobials

No evidence was identified to provide data on pharmacological non-antimicrobial management of CA-UTI.
6 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 health professionals when discussing urinary tract infection with patients and carers and in guiding the development of locally produced information materials.

6.1 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.

<table>
<thead>
<tr>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Explain the symptoms of UTI, how to tell a UTI might be present and when to seek medical advice, eg from GP or pharmacist</td>
</tr>
<tr>
<td>• Inform women of the cause of UTIs and the effect UTIs have on the body</td>
</tr>
<tr>
<td>• Discuss with women how having other conditions can make them more susceptible to UTIs, eg diabetes. Offer time to answer questions women may have</td>
</tr>
<tr>
<td>• Discuss implications of recurring UTIs on health in general, including the bladder</td>
</tr>
<tr>
<td>• 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 three hours before taking the sample.</td>
</tr>
<tr>
<td>• Provide women with the SIGN patient version of this guideline to help people understand and manage UTIs</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Explain the difference between a 3-day and a 7-day course of antibiotics and the reasons for using one or the other</td>
</tr>
<tr>
<td>• Ensure women understand the need to finish the course of antibiotics</td>
</tr>
<tr>
<td>• Advise women how long it will be before they start to feel better after starting treatment</td>
</tr>
<tr>
<td>• Inform women of common side effects associated with treatment and advise them not to be concerned and not to stop treatment without instruction from a healthcare professional</td>
</tr>
<tr>
<td>• Discuss potential drug interactions with other prescribed medicines women are taking</td>
</tr>
<tr>
<td>• 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</td>
</tr>
<tr>
<td>• Explain the long-term effects that can happen when taking long-term prophylactic antibiotics</td>
</tr>
<tr>
<td>• Discuss steps women can take to reduce chances of having further UTIs, including adopting a healthy lifestyle, eg</td>
</tr>
<tr>
<td>- drinking plenty of fluid</td>
</tr>
<tr>
<td>- diet</td>
</tr>
<tr>
<td>- exercise</td>
</tr>
<tr>
<td>- plenty of sleep</td>
</tr>
<tr>
<td>- avoidance of spermicide containing contraceptives</td>
</tr>
</tbody>
</table>
6.2 Publications from SIGN
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.

6.3 Sources of further information

Bladder Health
bladderhealthuk.org/bladder-conditions/cystitis/bacterial-cystitis

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.

National Urinary Catheter Passport
https://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
https://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 you make the best choices about your health and wellbeing.

NHS Inform

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

Patient.info is a health information website which contains patient advice reviewed by doctors and other health professionals.
7 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.

7.1 Implementation strategy

Implementation of national clinical guidelines is the responsibility of each NHS Board 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.

7.2 Resource implications of key recommendations

NOT INCLUDED IN THIS VERSION

7.3 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.

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

7.3.1 Diagnosis

- The proportion of women who receive a diagnosis of UTI who have ≥2 urinary symptoms and a positive dipstick test result for nitrites.
- The proportion of women who receive a diagnosis of UTI who have ≥2 urinary symptoms and a negative dipstick test result for nitrites.
- The proportion of women aged 65 years and above 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.

7.3.2 Management

- The proportion of women consuming 2.5 L of fluids per day.
- The proportion of women using contraception which does not include spermacides.
- The proportion of women 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).

7.4 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.
8 The evidence base

8.1 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. 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 will be available on the SIGN website, www.sign.ac.uk at publication.

8.1.1 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.

8.1.2 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.

8.2 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 and including 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.

- 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 key 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 Development of the guideline

9.1 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.

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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

Euan Bremner Project Officer
Karen Graham Patient and Public Involvement Advisor
9.3 Consultation and peer review

A report of the consultation and peer review comments and responses is available in the supporting material section for this guideline on the SIGN website. All expert referees and other contributors made declarations of interest and further details of these are available on request from the SIGN Executive.

9.3.1 Specialist reviewers invited to comment on this draft

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General Practitioner, Glasgow

Mr Anthony McDavid
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9.3.2 Public consultation

The draft guideline was also available on the SIGN website for a period to allow all interested parties to comment.
Management of suspected bacterial lower UTI in adult women

Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>AMR</td>
<td>antimicrobial resistance</td>
</tr>
<tr>
<td>ASB</td>
<td>asymptomatic bacteriuria</td>
</tr>
<tr>
<td>CA-UTI</td>
<td>catheter-associated urinary tract infection</td>
</tr>
<tr>
<td>CDI</td>
<td>Clostridioides difficile infection</td>
</tr>
<tr>
<td>CFU</td>
<td>colony-forming unit</td>
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<tr>
<td>CI</td>
<td>confidence interval</td>
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<tr>
<td>E. coli</td>
<td>Escherichia coli</td>
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<tr>
<td>eGFR</td>
<td>estimated glomerular filtration rate</td>
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<tr>
<td>GMC</td>
<td>General Medical Council</td>
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<tr>
<td>GP</td>
<td>general practitioner</td>
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<tr>
<td>IDSA</td>
<td>Infectious Diseases Society of America</td>
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<tr>
<td>IRR</td>
<td>incidence rate ratio</td>
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<tr>
<td>IQR</td>
<td>interquartile range</td>
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<tr>
<td>LR-</td>
<td>negative likelihood ratio</td>
</tr>
<tr>
<td>LR+</td>
<td>positive likelihood ratio</td>
</tr>
<tr>
<td>LUTI</td>
<td>lower urinary tract infection</td>
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<tr>
<td>MA</td>
<td>marketing authorisation</td>
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<tr>
<td>MHRA</td>
<td>Medicines and Healthcare Products Regulatory Agency</td>
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<tr>
<td>MIC</td>
<td>minimum inhibitory concentration</td>
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<tr>
<td>MRSA</td>
<td>methicillin-resistant Staphylococcus aureus</td>
</tr>
<tr>
<td>NICE</td>
<td>National Institute for Health and Care Excellence</td>
</tr>
<tr>
<td>NNT</td>
<td>number needed to treat</td>
</tr>
<tr>
<td>NS</td>
<td>not significant</td>
</tr>
<tr>
<td>NSAID</td>
<td>non-steroidal anti-inflammatory drug</td>
</tr>
<tr>
<td>OR</td>
<td>odds ratio</td>
</tr>
<tr>
<td>PAC</td>
<td>proanthocyanidin</td>
</tr>
<tr>
<td>QALY</td>
<td>quality-adjusted life year</td>
</tr>
<tr>
<td>RCT</td>
<td>randomised controlled trial</td>
</tr>
<tr>
<td>RR</td>
<td>Relative risk</td>
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<tr>
<td>SAPG</td>
<td>Scottish Antimicrobial Prescribing Group</td>
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<tr>
<td>SIGN</td>
<td>Scottish Intercollegiate Guidelines Network</td>
</tr>
<tr>
<td>SMC</td>
<td>Scottish Medicines Consortium</td>
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<tr>
<td>UTI</td>
<td>urinary tract infection</td>
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</tbody>
</table>
Annex 1
Key questions addressed in this update

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.

<table>
<thead>
<tr>
<th>Guideline section</th>
<th>Key question</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.1</td>
<td>1. How should uncomplicated lower UTI be diagnosed in women aged under 65 years?</td>
</tr>
<tr>
<td></td>
<td>Population: Adult women aged 16–64 years</td>
</tr>
<tr>
<td></td>
<td>Interventions: a) Clinical assessment</td>
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<tr>
<td></td>
<td>b) Urinary symptoms (dysuria, urgency, frequency, cloudy urine)</td>
</tr>
<tr>
<td></td>
<td>c) Dipstick testing (nitrite, leucocyte esterase, haematuria)</td>
</tr>
<tr>
<td></td>
<td>Comparators: Laboratory culture of urine samples</td>
</tr>
<tr>
<td></td>
<td>Outcomes: Sensitivity, specificity, likelihood ratio, positive predictive value, negative predictive value, cost effectiveness</td>
</tr>
<tr>
<td>3.2</td>
<td>2. How should uncomplicated lower UTI be managed in women aged under 65 years?</td>
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<tr>
<td></td>
<td>Population: Adult women aged 16–64 years with:</td>
</tr>
<tr>
<td></td>
<td>• recurrent UTI</td>
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<tr>
<td></td>
<td>• non-recurrent UTI</td>
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<tr>
<td></td>
<td>Interventions: a) Self-care (personal hygiene, fluid intake, appropriate contraception)</td>
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<tr>
<td></td>
<td>b) Antibiotic treatment (amoxicillin, cephalexin, pivemecillinam, trimethoprim, fosfomycin, nitrofurantoin, ciprofloxacin, levofloxacin, moxifloxacin, nalidixic acid, norfloxacin, ofloxacin)</td>
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<tr>
<td></td>
<td>c) Non-antibiotic treatment (cranberry products, D-mannose, potassium citrate mixture, acidification, increased fluid intake, oestrogen, analgesia, diuretics, methenamine hippurate)</td>
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<td></td>
<td>d) Delayed treatment strategies</td>
</tr>
<tr>
<td></td>
<td>Comparators: Antibiotic v non-antibiotic treatment</td>
</tr>
<tr>
<td></td>
<td>Any intervention v no treatment</td>
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<tr>
<td></td>
<td>Outcomes: Bacteriological cure rate, time to symptomatic relief, symptom recurrence, development of antimicrobial resistance, adverse effects, cost effectiveness</td>
</tr>
<tr>
<td>4.1</td>
<td>3. How should uncomplicated lower UTI be diagnosed in women aged 65 years or above?</td>
</tr>
<tr>
<td></td>
<td>Population: Adult women aged ≥65 years</td>
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<tr>
<td></td>
<td>Interventions: a) Clinical assessment</td>
</tr>
<tr>
<td></td>
<td>b) Urinary symptoms (dysuria, urgency, frequency, cloudy urine)</td>
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<tr>
<td></td>
<td>c) Non-specific symptoms (eg new or worsening confusion or delirium, raised temperature, loss of diabetic control)</td>
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<tr>
<td></td>
<td>Comparators: Laboratory culture of urine samples</td>
</tr>
</tbody>
</table>
Outcomes: Sensitivity, specificity, likelihood ratio, positive predictive value, negative predictive value, cost effectiveness

4.2 How should uncomplicated lower UTI be managed in women aged 65 years or above?

Population: Adult women aged 16–64 years with:
- recurrent UTI
- non-recurrent UTI

Interventions: a) Self-care (personal hygiene, fluid intake, appropriate contraception)
   b) Antibiotic treatment (amoxicillin, cephalexin, pivemecillinam, trimethoprim, fosfomycin, nitrofurantoin, ciprofloxacin, levofloxacin, moxifloxacin, nalidixic acid, norfloxacin, ofloxacin)
   c) Non-antibiotic treatment (cranberry products, D-mannose, potassium citrate mixture, acidification, increased fluid intake, oestrogen, analgesia, diuretics, methenamine hippurate)
   d) Delayed treatment strategies

Comparators: 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

5.1 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: a) Clinical assessment
   b) Urinary symptoms (dysuria, urgency, frequency, cloudy urine)
   c) Non-specific symptoms (eg new or worsening confusion or delirium, raised temperature, loss of diabetic control)

Comparators: Laboratory culture of urine samples

Outcomes: Sensitivity, specificity, likelihood ratio, positive predictive value, negative predictive value, cost effectiveness

5.2 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: a) Self-care (personal hygiene, fluid intake, appropriate contraception)
   b) Antibiotic treatment (amoxicillin, cephalexin, pivemecillinam, trimethoprim, fosfomycin, nitrofurantoin, ciprofloxacin, levofloxacin, moxifloxacin, nalidixic acid, norfloxacin, ofloxacin)
   c) Non-antibiotic treatment (cranberry products, D-mannose, potassium citrate mixture, acidification, increased fluid intake, oestrogen, analgesia, diuretics, methenamine hippurate)
d) Delayed treatment strategies

Comparators:  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
Annex 2
Decision tree for urinary signs and symptoms

Diagnostic pathway using symptoms and dipstick testing

At presentation

1 symptom of possible UTI
Pretest probability: 12%

Urinary symptoms

Frequency (LR+1.12)
Pretest probability ↑ to 66%

Frequency (LR+1.34)
Pretest probability ↑ to 66%

Frequency (LR+0.39)
Pretest probability ↓ to 42%

Vaginal symptoms

Vaginal discharge (LR-1.10)
Pretest probability ↑ to 66%

Vaginal discharge (LR-0.65)
Pretest probability ↑ to 54%

Vaginal discharge (LR-1.10)
Pretest probability ↑ to 64%

Vaginal discharge (LR-0.65)
Pretest probability ↑ to 52%

Dipstick test results

+ Nitrites (LR+4.42)
Post-test probability 90%

- Nitrites (LR-0.33)
Post-test probability 53%

+ Nitrites (LR+4.42)
Post-test probability 84%

- Nitrites (LR-0.33)
Post-test probability 38%

+ Nitrites (LR+4.42)
Post-test probability 78%

- Nitrites (LR-0.33)
Post-test probability 29%

+ Nitrites (LR+4.42)
Post-test probability 68%

- Nitrites (LR-0.33)
Post-test probability 20%
Management of suspected bacterial lower UTI in adult women

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