National Institute for Health and Care Excellence

Catheter-associated urinary tract infection: antimicrobial prescribing guideline

Evidence review

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Draft for Consultation

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1 Context

1.1 Background

A urinary catheter is a flexible tube used to empty the bladder and collect urine in a drainage bag. They can either be inserted through the urethra (an indwelling or urethral catheter) or through a small opening made in the lower abdomen (suprapubic catheter). Catheters are usually inserted by a doctor or nurse and remain in the bladder, allowing urine to flow through them and into a drainage bag. Catheters may be used short term (usually up to around 14 days) or long term (weeks). A urethral catheter may also by inserted and removed intermittently by a person themselves, or a carer, to drain urine and be removed when the bladder is empty (NHS Choices).

The main problems caused by urinary catheters are urinary tract infections in the urethra, bladder or, less commonly, the kidneys (NHS Choices). Catheter-associated urinary tract infection occurs because bacteria are able to bypass the bodies defence mechanisms (such as the urethra and the passing of urine) and gain entry to the bladder (Health Protection Surveillance Centre [2011]). The dominant risk for a catheter-associated infection is the duration of catheterisation, with nearly all people with a catheter developing bacteria in their urine (bacteriuria) within 1 month of catheterisation (Loveday et al. 2014). However not all of these bacteria result in infection (asymptomatic bacteriuria) and antibiotics are generally not indicated. Only those who are unwell should be treated, as treatment of asymptomatic bacteriuria increases side effects and antibiotic resistance but does not reduce mortality or prevent symptomatic episodes (Public Health England [2017]).

Urinary tract infection is the most common healthcare acquired infection accounting for 19% of all such infection, with between 43% and 56% of urinary tract infections associated with an indwelling urethral catheter (HPA [2012]; Smyth et al. 2008). Urinary tract infection extends hospital length of stay and can be expensive to treat (Ploughman et al. 1997; Tambyah et al. 2002). In some settings, for example critical care, it can be a major cause of urinary tract infection-related sepsis, or urosepsis, accounting for between 5% and 16% of cases, with an associated mortality rate of between 20% and 60% (European Association of Urology [2017]; Rosser et al.1999).

Symptoms of catheter-associated urinary tract infection (European Association of Urology [2017]) include:

- new onset or worsening fever and rigors
- altered mental status
- malaise or lethargy with no other identified cause
- flank pain
- costovertebral angle tenderness
- acute haematuria
- pelvic discomfort

In people who have had their catheter removed, symptoms include (European Association of Urology [2017]):

- dysuria, urgency or frequent urination
- suprapubic pain or tenderness.

Laboratory diagnosis is defined as microbial growth ≥10^3 colony forming units/mL of one or more bacterial species in a single sample, a catheter sample or mid-stream sample for those people whose catheter has been removed within 48 hours. The presence of white blood cells in the urine (pyuria) is not diagnostic for catheter-associated urinary tract infection and when seen in people with asymptomatic bacteriuria and a catheter should not be an indication for antibiotic treatment. However, the absence of pyuria in a symptomatic person may suggest a diagnosis other than catheter-associated urinary tract infection (European Association of Urology [2017]).

The most common uropathogen causing urinary tract infection in adults is *Escherichia coli*. In men, *Escherichia coli* accounted for approximately 70% to 95% of cases and in women for about 80% of cases. *Staphylococcus saprophyticus* accounts for 5% to 10% of cases. *Candida albicans* rarely causes urinary tract infection. When it does, it is usually in hospitalised people with risk factors such as an indwelling catheter, immunosuppression, diabetes mellitus, or antibiotic treatment. Other causative organisms are *Staphylococcus species, Proteus mirabilis, and enterococci.* Common organisms causing urinary tract infection in children include *Escherichia coli* (about 75% or more of cases), *Klebsiella species*, and *Staphylococcus saprophyticus.* However, catheter-associated urinary tract infection is usually associated with more than just bacterial species and are often caused by organisms that are antibiotic resistant (European Association of Urology [2017]).

1.2 Managing infections that require antibiotics

In most cases catheter-associated urinary tract infection will require antibiotic therapy. However, antibiotics should only be started where there is clear evidence of infection. In some instances the condition of the individual may necessitate prompt effective antibiotic treatment within 1 hour of diagnosis (or as soon as possible) in patients who have sepsis or life threatening infection. In these patients therapy should not be delayed but urine and/or blood samples for culture should, if possible, be obtained prior to treatment.

In line with the Department of Health guidance (Start Smart Then Focus) and the NICE guideline on antimicrobial stewardship consider reviewing intravenous antibiotic prescriptions at 48 to 72 hours, documenting response to treatment and any available microbiology results to determine if the antibiotic should be continued or switched to a narrower spectrum or an oral antibiotic.

1.2.1 Self-care

The NICE guideline on antimicrobial stewardship: changing risk-related behaviours in the general population (2017) recommends that people should be given verbal advice and written information that they can take away about how to manage their infection themselves at home with self-care if it is safe to do so.

1.2.2 Antibiotic prescribing strategies

The NICE guideline on antimicrobial stewardship: systems and processes for effective antimicrobial medicine use (2015) recommends that when antimicrobials are prescribed, prescribers should:

- Consider supplying antimicrobials in pack sizes that correspond to local (where available) and national guidelines on course lengths.

- Follow local (where available) or national guidelines on prescribing the shortest effective course, the most appropriate dose, and route of administration.
- Undertake a clinical assessment and document the clinical diagnosis (including symptoms) in the patient's record and clinical management plan.
- Document in the patient's records (electronically wherever possible):
  - the reason for prescribing an antimicrobial
  - the plan of care as discussed with the patient, their family member or carer (as appropriate), including the planned duration of any treatment.
- Take into account the benefits and harms for an individual patient associated with the particular antimicrobial, including:
  - possible interactions with other medicines or any food and drink
  - the patient's other illnesses, for example, the need for dose adjustment in a patient with renal impairment
  - any drug allergies (these should be documented in the patient's record)
  - the risk of selection for organisms causing healthcare associated infections, for example, *C. difficile*.
- Document in the patient's records the reasons for any decision to prescribe outside local (where available) or national guidelines.

The NICE guideline on antimicrobial stewardship: changing risk-related behaviours in the general population (2017) recommends that resources and advice should be available for people who are prescribed antimicrobials to ensure they are taken as instructed at the correct dose, via the correct route, for the time specified. Verbal advice and written information that people can take away about how to use antimicrobials correctly should be given, including:

- not sharing prescription-only antimicrobials with anyone other than the person they were prescribed or supplied for
- not keeping them for use another time
- returning unused antimicrobials to the pharmacy for safe disposal and not flushing them down toilets or sinks.

1.3 Safety netting advice

The NICE guideline on antimicrobial stewardship: changing risk-related behaviours in the general population recommends that safety netting advice should be shared with everyone who has an infection (regardless of whether or not they are prescribed or supplied with antimicrobials). This should include:

- how long symptoms are likely to last with and without antimicrobials
- what to do if symptoms get worse
- what to do if they experience adverse effects from the treatment
- when they should ask again for medical advice.

1.4 Symptoms and signs of a more serious illness or condition (red flags)

The NICE clinical knowledge summary (CKS) on UTI (lower) - men (with an indwelling catheter) suggests arranging emergency admission to hospital if a man is severely unwell with symptoms or signs suggestive of urosepsis (for example nausea and vomiting, confusion, tachypnoea, tachycardia, or hypotension).

The NICE CKS guidance on UTI (lower) - women (with an indwelling catheter – no haematuria) suggests advising all women to seek medical attention if they develop fever, loin pain, or do not respond to treatment. If loin pain or fever develops in association with a urinary tract infection then suspect pyelonephritis, and manage accordingly.

2 Evidence selection

A range of evidence sources are used to develop antimicrobial prescribing guidelines. These fall into 2 broad categories:

- Evidence identified from the literature search (see section 2.1 below)
- Evidence identified from other information sources. Examples of other information sources used are shown in the interim process guide (2017).

See appendix A: evidence sources for full details of evidence sources used.

2.1 Literature search

A literature search was developed to identify evidence for the effectiveness and safety of interventions for managing all urinary tract infections (UTIs) (see appendix C: literature search strategy for full details). The literature search identified 6,695 references. These references were screened using their titles and abstracts and 17 references were obtained and assessed for relevance. Eleven references of systematic reviews and randomised controlled trials (RCTs) were assessed as relevant to the guideline review question (see appendix B: review protocol). Ten percent of studies were screened to establish inter-rater reliability, and this was within the required threshold of 90%.

The methods for identifying, selecting and prioritising the best available evidence are described in the interim process guide. Eight references were prioritised by the committee as the best available evidence and were included in this evidence review (see appendix F: included studies). One additional study (Raz et al. 2000) was identified from citation tracking and was included.

The 3 references that were not prioritised for inclusion are listed in appendix I: studies not prioritised. Also see appendix E: evidence prioritisation for more information on study selection.

The remaining 6 references were excluded. These are listed in appendix J: excluded studies with reasons for their exclusion.

See also appendix D: study flow diagram.

2.2 Summary of included studies

A summary of the included studies is shown in tables 1 and 2. Details of the study citation can be found in appendix F: included studies. An overview of the quality assessment of each included study is shown in appendix G: quality assessment of included studies.

Table 1: Summary of included studies: non-pharmacological interventions

Study	Number of participants	Population	Intervention	Comparison	Primary outcome
Cranberry juice concentrate					
Gunnarsson et al. 2017 DB. RCT. Sweden. Follow-up at 5 to 14 days	n=92 (per-protocol)	Hospitalised adult women (aged >60 years) with hip fracture and a peri-operative indwelling urinary catheter[1]	2 cranberry powder capsules three times daily for 5 days post-operatively	Placebo	Positive urine culture[3] at day 5 or 14 post-operatively
Catheter change before antibiotics					
Raz et al. 2000 Open label RCT. Israel. Follow-up was at 3, 7 and 28 days.	n=54	Older adults resident in long-term care facilities with an indwelling urinary catheter for either urinary retention or incontinence.	Catheter change before intravenous then oral antibiotics[4]	No catheter change before intravenous then oral antibiotics[4]	Clinical and microbiological cure at follow-up

Abbreviations: RCT, Randomised controlled trial; DB, Double blind

[1] Planned catheter removal at 2 days post-operatively

[2] 550 mg capsule containing 4.19 mg of the putative active ingredient (proanthocyanidins), first dose given at least 30 minutes before catheterisation

[3] Amongst those participants with a sterile urine culture at admission (positive was $>10^4$ colony forming units/mL)

[4] Initial antibiotics was either ciprofloxacin 400 mg or ofloxacin 300 mg (intravenously) twice daily. Once afebrile for ≥24 hour's participants were switched to oral therapy with ciprofloxacin 500 mg or ofloxacin 200 mg twice daily. Antibiotic therapy was for 14 days

Table 2: Summary of included studies: antimicrobials for managing catheter-associated urinary tract infection

Study	Number of participants	Population	Intervention	Comparison	Primary outcome
Antibiotics versus no treatment for bacteriuria					
Leone et al. 2007 RCT. France. Follow-up was at days 7 and 15	n=60	Hospitalised adults (aged 18 years or over) in intensive care with an indwelling urethral catheter for at least 48 hours and a positive urine culture[1]	Antibiotics (according to culture[2]) for 3 days and catheter change (4 hours after first dose of antibiotics)	No antibiotics or catheter change	Occurrence of urosepsis
Duration of antibiotics					
Darouiche et al. 2014 NI. RCT. USA. Follow-up at end-of-therapy	n=55 (per-protocol)	Hospitalised adults (age not defined[3]) with spinal cord injury and either a transurethral or suprapubic[4] catheter and a lower urinary tract infection[5]	Antibiotics (according to culture[6]) for 5 days plus catheter change	Antibiotics (according to culture[6]) for 10 days with original catheter retained	Clinical cure at end-of-therapy

Abbreviations: RCT, Randomised controlled trial; p, P value; NI, Non-inferiority; PC, Placebo controlled

[1] Positive urine culture defined as ≥10^5 colony forming units /mL

[2] Antibiotics were amoxicillin, ciprofloxacin, co-amoxiclav, ceftriaxone, colimycin, piperacillin plus clavulanic acid, cefepime, amikacin, fosfomycin and fluconazole

[3] Mean age in the 5 day group 61.5 years (standard deviation [SD] ±13 years) and in the 10 day group 58.3 years (SD ±14.8 years), p=0.24

[4] n=10 (6 in the 5 day group and 4 in the 10 day group, p=0.73) with suprapubic catheter

[5] Significant bacteriuria (≥10^5 colony forming units/mL) and pyuria (>10 white blood cells per high power field) plus ≥1 of the following fever (temperature >100°F), suprapubic or flank discomfort, bladder spasm, increased spasticity, worsening dysreflexia and cloudy urine

[6] Empirical antibiotics (oral fluoroquinolone and amoxicillin), In allergy or where oral route not applicable IV aztreonam and vancomycin were used, in people with previous resistant infection antibiotics were according to previous cultures

Table 3: Summary of included studies: antimicrobial prophylaxis for preventing catheter associated urinary tract infection

Study	Number of participants	Population	Intervention	Comparison	Primary outcome
Antibiotics prophylaxis at catheter removal					
Marschall et al. 2013 Systematic review. Multiple countries. Follow-up up to 6 weeks	n=1,520 (7 studies[1])	Hospitalised adults (age not defined) with short-term catheterisation[2] (≤14 days)	Antibiotic prophylaxis[3] at the time of catheter removal	Placebo or other control	Symptomatic urinary tract infection at follow-up
Antibiotics prophylaxis in short-term catheterisation					
Lusardi et al. 2013. Systematic review. Multiple countries. Follow-up at variable time points	n=844 (6 RCTs)	Hospitalised adults (age not reported) with short-term transurethral or supra-pubic catheterisation (≤14 days)	Antibiotic prophylaxis	No prophylaxis, other antibiotic prophylaxis and timing of prophylaxis	Asymptomatic bacteriuria and symptomatic bacteriuria or urinary tract infection
Dieter et al. 2014. DB. PC. RCT. USA. Follow-up at 3 weeks	n=159	Hospitalised adults (age >21 years) with transurethral catheter after pelvic reconstructive surgery[4]	Nitrofurantoin 100 mg once daily (oral) for up to 7 days	Placebo	Suspected or culture-proven urinary tract infection at follow-up
Antibiotic prophylaxis in urodynamic studies					
Foon et al. 2012. Systematic review. Multiple countries. Follow-up at multiple time points.	n=973 (9 RCTs)	Adults (aged 18 to 82 years) undergoing urodynamic studies involving catheterisation	Antibiotic prophylaxis[5]	Placebo	Urinary tract infection or asymptomatic bacteriuria
Antibiotic prophylaxis in long-term catheterisation (indwelling or intermittent)					
Niël-Weise et al. 2012. Systematic review. Multiple countries.	n=504 (8 RCTs)	Hospitalised and non-hospitalised adults and children with long-term catheterisation	Antibiotic prophylaxis[6]	Placebo or no intervention (and continuation or	Patient reported outcome measures and clinical outcomes (including

Study	Number of participants	Population	Intervention	Comparison	Primary outcome
Follow-up at multiple time points.		(intermittent, intra-urethral, indwelling or suprapubic)		discontinuation of prophylaxis in 1 RCT)	complications and adverse events)

Abbreviations: RCT, Randomised controlled trial; p, P value; NI, Non-inferiority; PC, Placebo controlled

[1] Five published RCTs, 1 unpublished RCT and 1 non-randomised controlled trial

[2] Five studies were in post-surgical populations (general surgery, prostatectomy, abdominal surgery) and 2 RCTs included patients from medical and surgical wards (1 excluded genitourinary surgery)

[3] Antibiotics were ciprofloxacin (3 studies), co-trimoxazole (2 studies), nitrofurantoin (1 study) and cefotaxime (1 study)

[4] Pelvic organ prolapse, urinary incontinence, or both

[5] Antibiotics co-amoxiclav, ciprofloxacin, co-trimoxazole, norfloxacin, nitrofurantoin and trimethoprim administered from 24 hours before to 72 hours after urodynamics (any dose, duration or route of administration)

[6] Continuous use or only when clinically indicated, broad or narrow spectrum and route of administration considered

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3 Clinical effectiveness

Full details of clinical effectiveness are shown in appendix H: GRADE profiles. The main results are summarised below.

3.1 Non-pharmacological interventions

3.1.1 Catheter change before antibiotics

The evidence review for changing a catheter for managing catheter-associated urinary tract infection (UTI) is based on 1 prospective open-label randomised controlled trial (RCT; Raz et al. 2000). The RCT was in older adults (mean age 72.6 years) with permanent indwelling urinary catheter for retention or incontinence who were resident in a long term care facility. The intervention was catheter change before antibiotics compared with no catheter change before antibiotics. Antibiotic therapy was either ciprofloxacin 400 mg or ofloxacin 300 mg (intravenously) twice daily. Once afebrile for ≥24 hour's participants could be switched to oral antibiotics (ciprofloxacin 500 mg or ofloxacin 200 mg twice daily). Antibiotics were given for 14 days. The study is limited by a lack of blinding, small sample size and ≈16% loss to follow-up.

At 72 hours there was a significant difference in cure or improvement favouring catheter change (n=54, 92.6% versus 40.7%, relative risk [RR] 2.27, 95% confidence interval [CI] 1.42 to 3.63, number needed to treat [NNT] 2, 95% CI 2 to 4; moderate quality evidence) and also at 28 days (n=54, 88.9% versus 59.3%, RR 1.5, 95% CI 1.07 to 2.11, NNT 4, 95% CI 2 to 14; low quality evidence) but not at 7 days. There was no significant difference in recurrence or treatment failure at either 7 or 28 days. Catheter change intervention was significantly associated with fewer mean days of fever (n=54, MD -1.7, 95% CI -2.71 to -0.69; low quality evidence). Mortality was also significantly lower in the intervention group with 2 deaths in the control group (both due to urosepsis at days 2 and 3 respectively) and none in the intervention group (n=54, 0% versus 7.4%, RR 0.2, 95% CI 0.01 to 3.98; very low quality evidence). The study also found a significant benefit in microbiological growth versus no growth with catheter change intervention at 72 hours ($p<0.001$), 7 days ($p=0.01$) and 28 days ($p=0.02$).

3.1.2 Cranberry juice concentrate

The evidence review for cranberry juice concentrate for preventing catheter-associated UTI is based on 1 RCT (Gunnarsson et al. 2017) in adult females (aged >60 years) with hip fracture and a perioperative urinary catheter with planned removal at 48 hours post-operatively. The evidence is limited to the hospital surgical setting and did not include other people in hospital or those with a longer term urinary catheter. Additionally, all patients in the study received antibiotic prophylaxis to prevent wound infection. The primary endpoint of the study was a positive urinary culture (single pathogen >10^4 cfu/mL) at day 5 or 14 postoperatively in those people with a sterile urine culture at admission. Clinical symptoms of UTI and health-related quality-of-life were secondary outcomes of the study but results for these were not reported.

In the intention to treat population (ITT) there was no significant difference between cranberry juice concentrate (2 capsules of 550 mg of cranberry powder, three times daily [each capsule contained 4.19 mg of proanthocyanidin]) and placebo for positive urine culture at either 5 or 14 days post-operatively (111 participants, 37.7% versus

38%, RR 0.99, 95% CI 0.45 to 2.13; low quality evidence). There was also no significant difference between cranberry juice concentrate and placebo for positive urine culture in the per-protocol analysis at either 5 or 14 days (RR 0.82; 95% CI 0.34 to 1.93; low quality evidence).

3.2 Non-antimicrobial pharmacological interventions

No systematic reviews or RCTs were identified that assessed non-antimicrobial pharmacological interventions for managing or preventing catheter-associated UTI in adults or children.

3.3 Antimicrobials for managing catheter-associated urinary tract infection in adults

The evidence review for antibiotics for managing catheter-associated UTI in adults is based on 2 RCTs (Darouiche et al. 2014 and Leone et al. 2007). These studies are limited in their generalisability due to the study populations (people in intensive care and people with spinal cord injury).

3.3.1 Antibiotics for asymptomatic bacteriuria in people with a short-term catheter

Leone et al. (2007) assessed the evidence for the use of antibiotics for asymptomatic bacteriuria in patients with short-term catheterisation in adults (aged >18 years, n=60) admitted to a medico-surgical intensive care unit (ICU). It included people with an initially sterile urine culture who then had a positive urine culture occurring at least 48 hours after catheterisation (>10^5 cfu/mL of no more than 2 different pathogens). The RCT compared a short-course (3-days) of antibiotics, according to microbiological sensitivities and a catheter change (4 hours after first antibiotic dose) with no antibiotics and no catheter change. Antibiotics included amoxicillin, ciprofloxacin, co-amoxiclav, ceftriaxone, colimycin, piperacillin plus clavulanate, cefipime, amikacin, fosfomycin and fluconazole. In those people who developed urosepsis, tazocillin with clavulanate was also used. No doses or frequency of administration information was reported and concomitant medicine use is not described.

No significant differences were found in the number of patients with urosepsis at follow-up, although it is unclear what the follow-up period for this outcome was (n=60, 10% versus 10%, RR 1.0, 95% CI 0.22 to 4.56, p=1.00, low quality evidence). There was no significant difference at follow-up (again it is unclear what the follow-up point was for this outcome) in the proportion of patients with bacteraemia or severe sepsis (n=60, 23.3% with catheter change and short course of antibiotics versus 16.7% with no catheter change and no antibiotics, RR 1.4, 95% CI 0.50 to 3.92, p>0.05, low quality evidence). There was a significant difference in the proportion of patients with a positive urine culture at day-7 (bacterial growth in the urine sample of >10^5 cfu/mL) favouring antibiotic treatment and catheter change (n=60, 30% versus 70%, RR 0.43, 95% CI 0.24 to 0.78, p=0.009, NNT=3, 95% CI 2 to 6; moderate quality evidence) but this difference was not significant at day-15 (n=60, 26.7% versus 36.7%, RR 0.73, 0.34 to 1.55, p>0.05, low quality evidence).

3.3.2 Antibiotic course length in people with a long-term catheter

The evidence for duration of antibiotic treatment for catheter-associated UTI in adults with long-term catheterisation (either transurethral or suprapubic) is based on 1 non-

inferiority study (Darouiche et al. 2014) of hospitalised adults with a spinal cord injury. The RCT compared a catheter change and a 5-day course of antibiotics with 10 days of antibiotics and no catheter change. Antibiotics were an oral quinolone and amoxicillin (or for those with an allergy to quinolones and penicillin, or could not take antibiotics orally, intravenous aztreonam and vancomycin) or in patients with previous history of antibiotic-resistant infection, antibiotics were chosen according to microbiological sensitivities (urine sample obtained after the new catheter was inserted). UTI was the presence of significant bacteriuria (defined as $>10^5$ cfu/mL) and pyuria (>10 white blood cells per high power field) plus 1 or more sign or symptom of UTI. The study was limited to mostly men (55 of 58 participants) and was not blinded for investigators or patients.

No significant differences were found between the groups for clinical cure at the end of therapy (100% versus 100%, RR 1.0, 95% CI 0.93 to 1.07, (p<0.001 significant for non-inferiority), moderate quality evidence). For the outcomes of resolution of pyuria at end of therapy (89.3% versus 88.9%, upper bounds of the 95% CI for difference was 16%, p=0.19, moderate quality evidence) and microbiological response at end of therapy (82.1% versus 88.9%, upper bound of 95% CI for difference was 26%, p=0.5, low quality evidence) the non-inferiority criteria were not met (not more than 10% difference). Significantly more people in the 5 day group than the 10 day group had a recurrent UTI (32.1% in the 5 day group versus 11.1% in the 10 day group; hazard ratio (HR) 0.76, 95% CI 0.59 to 0.99, p=0.043; low quality evidence).

3.4 Antimicrobials for preventing catheter-associated urinary tract infection in adults

The evidence review for antibiotic prophylaxis for preventing catheter-associated UTI in adults is based on 4 systematic reviews (Foon et al. 2012; Lusardi et al. 2013; Marschall et al. 2013 and Niël-Weise et al. 2012) and 1 RCT (Dieter et al. 2014).

3.4.1 Antibiotic prophylaxis for adults with a long-term (indwelling or intermittent) catheter

One systematic review (Niël-Weise et al. 2012) of 5 RCTs compared antibiotic prophylaxis with antibiotics only when clinically or microbiologically indicated (and matched placebo), although the authors do not define what these terms mean. The evidence is limited to very specific populations of people; older people in nursing homes with an indwelling catheter (1 RCT) and adults (mostly males) using intermittent catheterisation either in hospital (3 RCTs) or at home (1 RCT) for managing neurogenic bladder.

Four RCTs included in the systematic review assessed the rate of bacteriuria (either symptomatic or asymptomatic; not defined) in mostly male participants using intermittent catheterisation for neurogenic bladder. In meta-analysis of 2 RCTs, people in the antibiotics prophylaxis group (nitrofurantoin 100 mg once daily or co-trimoxazole 160/800 mg once daily) had fewer episodes of bacteriuria than those who received them when microbiologically indicated (2 RCTs, n=77; Incidence Density Rate [IDR] 0.61, 95% CI 0.44 to 0.87, with significant heterogeneity [I^2=82%], using a fixed effect model, low quality evidence). One RCT of (mostly male) adults using intermittent catheterisation at home for neurogenic bladder (not included in the meta-analysis) also favoured prophylaxis with nitrofurantoin (100 mg twice daily) (n=62; 9 events in 90 catheter weeks with prophylaxis versus 25 events in 85 catheter weeks with control, RR 0.34, 95% CI 0.156 to 0.74 [NICE analysis]; moderate quality evidence). Evidence from 1 other included RCT involving (mostly

male) hospitalised adults using intermittent catheterisation for neurogenic bladder found no significant benefit of antibiotic prophylaxis with low dose co-trimoxazole (40/200 mg once daily) compared with antibiotics when microbiologically indicated for the number of episodes of bacteriuria (low to moderate quality of evidence).

Two RCTs showed inconsistent results for the outcome of symptomatic bacteriuria in (mostly male) adults using intermittent catheterisation for neurogenic bladder. In 1 RCT, fewer participants had at least 1 episode of symptomatic bacteriuria with antibiotic prophylaxis (low dose co-trimoxazole 40/200 mg once daily) compared with antibiotics when microbiologically indicated (n=126; 6.1% versus 31.7%, RR 0.19, 95% CI 0.07 to 0.53; NNT=4, 95% CI 3 to 8, moderate quality evidence). In the other RCT, which compared co-trimoxazole (160/800 mg once daily) with antibiotics only when clinically indicated, there was no significant difference in the rate of symptomatic bacteriuria.

One cross-over trial in the systematic review (Niël-Weise et al. 2012) compared antibiotic prophylaxis (norfloxacin 200 mg daily) with antibiotics when clinically indicated in 34 older adults with indwelling urinary catheters who were in nursing homes. There were no statistically significant differences for episodes of symptomatic UTI (1 UTI in 276 weeks with prophylaxis versus 12 UTIs in 259 catheter weeks in the control group, incidence rate ratio (IRR) 0.08, 95% CI 0.62 to 9.75; very low quality evidence), or rates of visual encrustation (4 events in 276 catheter weeks with prophylaxis versus 19 events in 259 catheter weeks with control, IRR 0.2, 95% CI 0.02 to 1.52; low quality evidence) and catheter obstructions (2 events in 276 catheter weeks with prophylaxis versus 8 events in 259 catheter weeks with control, IRR 0.23, 95% CI 0.04 to 1.4; low quality evidence). The prophylaxis group had a higher number of participants with improved general condition (1 RCT, n=46, 52.2% versus 4.3%, RR 12.0, 95% CI 1.7 to 84.9, p=0.01; NNT=3 (95% CI 2 to 4) very low quality evidence).

3.4.2 Antibiotic prophylaxis before or during short-term catheterisation in hospital

The evidence for antibiotic prophylaxis in hospitalised adults before or during short-term catheter use for preventing catheter-associated UTI comes from 1 systematic review (Lusardi et al. 2013) and 1 RCT (Dieter et al. 2014).

Antibiotic prophylaxis compared with placebo or no treatment

The systematic review (Lusardi et al. 2013) included 6 RCTs comparing antibiotic prophylaxis (cefazolin 200 mg 8 hourly for 3 days; levofloxacin 250 mg or ciprofloxacin 500 mg once daily until removal of catheter; co-trimoxazole 200/240 mg once before surgery; ampicillin 3 g, 3 doses administered before, during and after catheterisation; aztreonam 2 g single dose, and ciprofloxacin 250 or 500 mg from day 2 post-operatively until removal of catheter) with placebo or no prophylaxis in hospitalised adults with a urinary catheter (1 study included people with suprapubic catheter) for at least 24 hours and undergoing non-urological surgery in 4 studies. Two further studies included hospitalised adults with indwelling catheter for at least 7 days for bladder dysfunction associated with neurological disorders. The evidence is limited to hospital settings and in most cases studies included more women than men. Five of the included studies used bacteriuria (asymptomatic or symptomatic) as the primary outcome although definition of significant varied (≥10^3 cfu/mL in 2 trials and ≥10^5 cfu/mL in 3 trials). In the remaining study UTI was defined as ≥10^5 cfu/mL accompanied by urinary symptoms. There were also differences in time of follow-up (days 1, 3, 6 and 7 or at removal of catheter).

Five RCTs in the systematic review provided data on the outcome of asymptomatic bacteriuria, but only 3 RCTs of surgical patients were sufficiently homogeneous to allow meta-analysis. This showed a significant benefit with antibiotic prophylaxis compared with placebo or no prophylaxis (437 participants, 8.2% versus 31.3%, RR 0.20, 95% CI 0.13 to 0.31; I^2=0.0%; NNT=5, 95% CI 4 to 7, moderate quality evidence). One further study of surgical patients found significantly fewer cases of symptomatic bacteriuria with co-trimoxazole (200/240 mg single dose before surgery) antibiotic prophylaxis compared with placebo or no prophylaxis (n=90; 6.3% versus 31%, RR 0.20, 95% CI 0.06 to 0.66; NNT=4, 95% CI 3 to 11, moderate quality evidence).

Two RCTs of non-surgical patients could not be pooled for the outcome of asymptomatic bacteriuria due to heterogeneity. One study showed no benefit with antibiotic prophylaxis (n=78; RR 0.63, 95% CI 0.34 to 1.13; low quality evidence) and the other showed significant benefit with antibiotic prophylaxis compared to placebo or no prophylaxis (n=162; 10% versus 53.7%, RR 0.19, 95% CI 0.09 to 0.37; NNT=3, 95% CI 2 to 4, moderate quality evidence).

Evidence from a systematic review (Lusardi et al. 2013) found that antibiotic prophylaxis compared with placebo was associated with a significantly lower risk of pyuria (the presence of white cells in the urine) in surgical patients (2 RCTs, 241 participants; 7.5% versus 32.9%, RR 0.23, 95% CI 0.13 to 0.42; I^2=0.0%; NNT=4, 95% CI 3 to 7, moderate quality evidence). Antibiotic prophylaxis in surgical patients was also associated with significantly reduced febrile (high temperature) morbidity (2 RCTs, 286 participants; 12.5% versus 23.2%, RR 0.53, 95% CI 0.31 to 0.89; I^2=53%, NNT=10, 95% CI 6 to 52, very low quality evidence).

An RCT (Dieter et al. 2014) compared antibiotic prophylaxis with placebo in hospitalised adult women (aged 57 years [SD] ±13) undergoing pelvis surgery to prevent culture proven (>100,000 cfu/mL of a single organism) or clinically suspected UTI within the first 3 weeks after surgery. The study is limited by recall bias as many participants were discharged home shortly after surgery and relied on patient diaries. The study also largely excluded older participants (ages 75 to 80 years) due to the use of a creatinine clearance <60mL/min as a reason for exclusion. Additionally the study may have been underpowered (sample size too small) to detect a true difference in primary outcome. The RCT found that the risk of requiring treatment for a UTI within 3 weeks of catheterisation for pelvic organ prolapse surgery or urinary incontinence surgery was not significantly associated with prophylactic use of nitrofurantoin compared with placebo (n=159; 22.2% with placebo versus 12.8% with intervention, RR 1.73, 95% CI 0.85 to 3.52, moderate quality evidence).

Choice of antibiotic prophylaxis

One RCT included in Lusardi et al. (2013) compared levofloxacin with ciprofloxacin (no doses stated) and found no significant difference in asymptomatic bacteriuria at follow-up (n=46; RR 4.23, 95% CI 0.21 to 83.53; very low quality evidence). Another included RCT compared ciprofloxacin 250 mg with ciprofloxacin 1000 mg daily until removal of catheter and found no significant difference in asymptomatic bacteriuria (n=113; RR 1.37, 95% CI 0.58 to 3.21; very low quality evidence).

Dosing and course length of antibiotic prophylaxis

One RCT included in Lusardi et al. (2013) compared antibiotics given at catheterisation (ampicillin 3 g intramuscularly in 3 divided doses: 1 hour before, at the time of, and 6 hours after insertion of the catheter) with antibiotics given throughout the period of catheterisation (ampicillin 1 g intramuscularly three times daily).

Antibiotics at catheterisation only significantly reduced cases of bacteriuria at follow-up compared to giving antibiotics throughout the period of catheterisation (n=52; 12.5% versus 42.9%, RR 0.29, 95% CI 0.09 to 0.91; NNT=4, 95% CI 2 to 13, low quality evidence).

3.4.3 Antibiotic prophylaxis at the time of short-term catheter removal in hospital

The evidence for the use of prophylactic antibiotics in hospitalised adults at the time of the removal of a short-term catheter to prevent subsequent UTI comes from 1 systematic review (Marschall et al. 2013). The study defined short-term catheterisation as a maximum of 14 days duration and symptomatic UTI as detection of measurable bacteriuria (not defined) and the presence of at least 1 sign or symptom compatible with UTI. The systematic review included trials of antibiotics (ciprofloxacin or co-trimoxazole, a single dose given before removal of catheter in 2 RCTs; ciprofloxacin 3 day course starting before catheter removal; nitrofurantoin 2 doses, first dose before removal of catheter; ciprofloxacin 4 doses for 2 days, first dose before removal of catheter; co-trimoxazole single dose; cefotaxime 3 doses twice daily, first before removal of catheter) at the time of removal of short-term catheter compared with placebo or other control intervention, no dosage amount (mg) was reported. The follow-up period for included studies varied from 2 days to 6 weeks. The study is limited by its heterogeneous population (people undergoing prostate surgery, general surgery and mixed, surgical and non-surgical, study participants). The largest study (accounting for 24% weight in the random effects model) was not a randomised trial but a comparison of 2 surgeons whose surgical experience and techniques may have varied from each other. Additionally, only 4 included studies had a placebo control arm. The median duration of catheterisation varied between studies and ranged from less than 2 days to longer than 30 days.

In a meta-analysis of 7 controlled studies (6 randomised trials and 1 non-randomised trial) antibiotic prophylaxis was associated with a significantly lower risk of symptomatic UTI at 2 to 42 days follow-up (1520 participants, 4.7% versus 10.5%, RR 0.45, 95% CI 0.28 to 0.72; I^2=16%, NNT=18, 95% CI 12 to 31, moderate quality evidence). The authors analysis was repeated without the non-randomised study being included and similar results were obtained (6 RCTs, n=807, 5.7% versus 14.1%, RR 0.45, 95% CI 0.23 to 0.86; high quality evidence). In sub-group analysis the significant effect of antibiotic prophylaxis on risk of symptomatic UTI was maintained for surgical patients (5 RCTs, n=1393, 4.8% versus 10.3%, RR 0.45, 95% CI 0.29 to 0.59; moderate quality evidence) but not for mixed hospital populations (2 RCTs). Additional subgroup analysis of the surgical studies shows significant benefit for patients predominantly undergoing prostate surgery (2 RCTs, n=809, 3.57% versus 8.18%, RR 0.41, 95% CI 0.22 to 0.79; low quality evidence) but not for those undergoing other surgery (3 RCTs, n=584, 6.1% versus 14.1%, RR 0.45, 95% CI 0.18 to 1.14; I^2=51%, random effects model used, low quality evidence). There was significant benefit of antibiotic prophylaxis in 3 RCTs in which patients had a catheter for longer than (median) 5 days (n=1009, 3.34% versus 9.5%, RR 0.34, 95% CI 0.19 to 0.59; moderate quality evidence) and in 3 RCTs which had a median duration of catheterisation less than 5 days (n=223, 4.6% versus 14%, RR 0.35, 95% CI 0.13 to 0.90; moderate quality evidence). However, this may be due to the presence of a prostate study in both analyses. When the analyses were repeated without the prostate studies there was significant benefit in studies with longer median duration (>5 days) of catheterisation (2 RCTs of general and abdominal surgery population, n=296, 3.8% versus 16.7%, RR 0.25, 95% CI 0.10 to 0.59; high quality evidence) but not for studies with shorter duration (<5 days) of catheterisation (2 RCTs of mixed

medical and surgical population, n=127, 3.22% versus 12.3%,RR 0.41, 95% CI 0.02 to 10.96, I^2=69%, random effects model used; very low quality evidence).

3.4.4 Antibiotic prophylaxis during short-term catheterisation for urodynamic procedures

The evidence on the use of prophylactic antibiotics during urodynamic studies (which usually involve short-term urinary catheterisation) to prevent UTIs comes from 1 systematic review (Foon et al. 2012). The study included 9 RCTs and quasi-RCTs comparing the use of prophylactic antibiotics (nitrofurantoin 50 mg, four doses for 1 day, dose and duration not reported in 1 RCT; trimethoprim 200 mg single dose 2 hours before catheterisation; ciprofloxacin 500 mg one hour before catheterisation, given for 3 days in 1 RCT but no dose reported; co-trimoxazole no dose or duration reported; norfloxacin 400 mg single dose; cinoxacin 500 mg twice daily for 5 days; co-amoxiclav 375 mg single dose 30 minutes before catheterisation) versus a placebo or no treatment in patients undergoing urodynamic studies. The primary outcome in all the included studies was the presence of symptoms (frequency or dysuria) with or without dipstick urine positive for nitrites and leucocyte esterase, with or without culture (>10^5 cfu/mL). Significant bacteriuria was defined as the presence of >100,000 bacteria per mL of mid-stream urine sample. Outcomes were assessed at varying times from day 1 to 7 following studies. The trials were conducted in hospital or outpatient settings. The study is limited to adult participants (aged 18 to 82 years) and only 230 of the 973 participants were male.

In a meta-analysis of 4 trials (Foon et al. 2012) prophylactic antibiotics did not significantly reduce the number of episodes of symptomatic UTI following urodynamic studies (415 participants, 19.9% with antibiotics versus 27.6% with placebo or no treatment, RR 0.73, 95% CI 0.52 to 1.03; I^2=0.0%, low quality evidence) but did significantly reduce the number of people with significant bacteriuria following urodynamic studies (9 trials, 970 participants, 4.1% with antibiotic prophylaxis versus 12.5% with placebo or no treatment, RR 0.35, 95% CI 0.22 to 0.56; I^2=0.0%, NNT=12, 95% CI 9 to 21, moderate quality evidence). This effect was significant in both males (3 trials, 176 participants, 2.3% versus 13.3%, RR 0.21, 95% CI 0.06 to 0.78; I^2=4.0%, NNT=10, 95% CI 6 to 31, low quality evidence) and females (7 trials, 757 participants, 4.7% versus 12.1%, RR 0.40, 95% CI 0.24 to 0.67; I^2=0.0%, NNT=14, 95% CI 9 to 29, moderate quality evidence). In a single study of those with spinal cord injury undergoing urodynamic study, antibiotic prophylaxis was not significantly different to placebo or no treatment for the outcome of bacteriuria but the number of participants was low (n=37; RR 0.15, 95% CI 0.01 to 2.72; very low quality evidence). There was a significant reduction in the number of participants with haematuria with antibiotic prophylaxis (2 trials, 344 participants; 6.3% versus 13.7%, RR 0.46, 95% CI 0.23 to 0.91; I^2=0.0%, NNT=14, 95% CI 8 to 89, low quality evidence) but not for the outcomes of fever or dysuria.

3.4.5 Identifying people more likely to have a catheter-associated urinary tract infection

The evidence for identifying people more likely to be at risk of catheter-associated UTI comes from 1 RCT (Dieter et al. 2014) of catheterised post-surgical women (see also section 3.3.2).

Evidence from 1 RCT (Dieter et al. 2014, n=159) found that treatment for UTI was higher in menopausal women (29%) than in premenopausal women (12%; p=0.01). Treatment was lower in people with diabetes (0%) than without diabetes (20%, p=0.04). UTI was significantly associated with duration of catheterisation (median 1

day, Intra quartile range [IQR] 1 to 3 for no UTI and median 2 days, IQR 1 to 4 for UTI, p=0.03). Factors not significantly associated with UTI (p>0.5) were hormone therapy, smoking, history of UTI, severity of prolapse, preoperative post void residual volume, creatinine clearance, operative time, estimated blood loss, procedure, type of catheterisation and overnight stay.

3.5 Antimicrobials for managing catheter-associated urinary tract infection in children

No systematic reviews or RCTs were identified.

3.6 Antimicrobials for preventing catheter-associated urinary tract infection in children

The evidence review for antibiotic prophylaxis for preventing catheter-associated UTI in children is based on very limited evidence from 1 systematic review of RCTs (Niël-Weise et al. 2012). All children were using intermittent self-catheterisation for either neurogenic bladder or spina bifida.

3.6.1 Antibiotic prophylaxis for children with a long-term (indwelling or intermittent) catheter

Antibiotic prophylaxis compared with placebo or no treatment

Evidence for antibiotic prophylaxis compared with placebo comes from 2 RCTs included in a systematic review (Niël-Weise et al. 2012). Both RCTs included children using intermittent catheterisation for neurogenic bladder. The intervention used in both RCTs was antibiotic prophylaxis (nitrofurantoin 25 mg or 50 mg daily depending on the child's weight) compared with placebo (and antibiotics when clinically indicated).

The RCTs showed inconsistent results for the outcome of symptomatic UTI. One RCT (n=15) found the incidence rate of symptomatic UTI was not significantly different between the antibiotic prophylaxis group and the antibiotics when clinically indicated group (IDR 0.50, 95% CI 0.17 to 1.44; very low quality evidence). The second RCT had 4 cases of symptomatic UTI in 430 catheter-weeks in the antibiotic prophylaxis group compared with 2 cases in 389 catheter-weeks in the antibiotics when clinically indicated group (incidence rate ratio [IRR] 1.8, 95% CI 0.32 to 10.16; very low quality evidence).

Antibiotic dosing and course length

One RCT included in the systematic review (Niël-Weise et al. 2012) compared different regimens of antibiotic prophylaxis (trimethoprim, nitrofurantoin, cefuroxime, co-trimoxazole or combination of these) in children using intermittent catheterisation for spina bifida. The study assessed the effect of continuous antibiotic prophylaxis compared with stopping antibiotic prophylaxis after 6 months.

There was no significant difference in the risk of febrile symptomatic UTI during follow-up over 18 months between children who continued to take antibiotic prophylaxis compared with those discontinuing antibiotic prophylaxis at 6 months (n=176; RR 0.50, 95% CI 0.09 to 2.66; very low quality evidence). However, children

who continued antibiotic prophylaxis did have significantly fewer afebrile symptomatic UTIs (n=176; IDR 0.69, 95% CI 0.55 to 0.87; low quality evidence).

4 Safety and tolerability

Details of safety and tolerability outcomes from studies included in the evidence review are shown in appendix H: GRADE profiles. The main results are summarised below.

See the summaries of product characteristics, British National Formulary (BNF) and BNF for children (BNF-C) for information on contraindications, cautions and adverse effects of individual medicines, and for appropriate use and dosing in specific populations, for example, hepatic impairment, renal impairment, pregnancy and breastfeeding.

4.1 Non-pharmacological interventions

4.1.1 Catheter change before antibiotics

No safety and tolerability data were presented in the randomised controlled trial (RCT) by Raz et al. (2000) for catheter change before antibiotics compared with no catheter change before antibiotics.

4.1.2 Cranberry juice concentrate

No safety and tolerability data were presented in the RCT by Gunnarsson et al. (2017) for cranberry juice concentrate compared with placebo.

4.2 Non-antimicrobial pharmacological interventions

No systematic reviews or RCTs were identified in adults or children.

4.3 Antimicrobials

Antibiotic-associated diarrhoea is estimated to occur in 2 to 25% of people taking antibiotics, depending on the antibiotic used (NICE clinical knowledge summary [CKS]: diarrhoea – antibiotic associated).

Allergic reactions to penicillins (such as phenoxymethylpenicillin) occur in 1 to 10% of treated people and anaphylactic reactions occur in less than 0.05% (BNF April 2018). People with a history of atopic allergy (for example, asthma, eczema, and hay fever) are at a higher risk of anaphylactic reactions to penicillins. People with a history of immediate hypersensitivity to penicillins may also react to cephalosporins and other beta-lactam antibiotics. See the NICE guideline on drug allergy: diagnosis and management for more information.

Quinolones, including ciprofloxacin, cause arthropathy in the weight-bearing joints of immature animals and are generally not recommended in children or young people who are growing (BNF April 2018).

Nitrofurantoin should be used with caution in those with renal impairment. Adults (especially the elderly) and children on long-term treatment should be monitored for liver function and pulmonary symptoms, with nitrofurantoin discontinued if there is a deterioration in lung function (BNF April 2018).

Trimethoprim has a teratogenic risk in the first trimester of pregnancy (folate antagonist), and manufacturers advise avoidance during pregnancy (BNF April 2018).

Co-trimoxazole is currently under restriction for use in the UK. It is advised that it only be used in urinary tract infections (UTI) where there is bacteriological evidence of sensitivity to co-trimoxazole. Co-trimoxazole should be used with caution in those with asthma, or people with blood disorders, GP6D deficiency or infants under 6 weeks (except for treatment or prophylaxis of pneumocystis pneumonia) (BNF April 2018).

Aminoglycosides are not absorbed from the gut and must be given by injection for systemic infections. Gentamicin is the aminoglycoside of choice in the UK. Loading and maintenance doses are calculated on the basis of the patient's weight and renal function, with adjustments made according to serum-gentamicin concentrations. Whenever possible treatment should not exceed 7 days. Amikacin is used in the treatment of serious infections caused by gentamicin-resistant Gram-negative bacilli (BNF April 2018).

4.3.1 Antibiotics in adults

Antibiotics for managing catheter-associated urinary tract infection

One RCT (Darouiche et al. 2014) in hospitalised adults with a spinal cord injury and long-term catheterisation (either transurethral or suprapubic) compared a catheter change and a short (5-day) course of antibiotics with a long (10-day) course of antibiotics and no catheter change. There was no significant difference in total adverse events in the long-course antibiotics group compared with short-course antibiotics (40.7% versus 64.3% respectively, relative risk [RR] 1.58, 95% confidence interval [CI] 0.93 to 2.69; low quality evidence). However, significantly more people had recurrent UTI in the short-course group compared with the 10 day group (hazard ratio [HR] 0.76, 95% CI 0.59 to 0.99, p=0.043; low quality evidence). No significant differences were found between groups for new UTI, *Clostridium difficile* colitis or death.

No safety or tolerability data were presented in the RCT by Leone et al. (2007) on the use of antibiotics for asymptomatic bacteriuria in patients with short-term catheterisation in adults.

Antibiotic prophylaxis for preventing catheter-associated urinary tract infection

A systematic review (Niël-Weise et al. 2012) found no significant difference in adverse events between antibiotic prophylaxis and antibiotics used only when microbiologically indicated in adults using intermittent catheterisation. There was no significant difference between antibiotic prophylaxis and antibiotics used only when clinically indicated in the rates of adverse events in older people in nursing homes (596 events in 276 catheter-weeks versus 744 events in 259 catheter-weeks, respectively, incidence rate ratio (IRR) 0.75, 95% CI 0.25 to 2.25; low quality evidence).

Evidence from a systematic review (Lusardi et al. 2013) on antibiotic prophylaxis before or during catheterisation included 3 RCTs that reported adverse effects with antibiotics. One RCT reported 23 adverse effects, none were judged to be treatment related and there were no serious adverse events. A second RCT reported no serious adverse reactions to co-trimoxazole. The third RCT reported that 3 patients taking ciprofloxacin had moderate gastrointestinal symptoms on the second day of

antibiotic prophylaxis, and the treatment was discontinued (very low quality evidence).

A systematic review (Foon et al. 2012) of antibiotic prophylaxis during short-term catheterisation for urodynamic procedures found no significant difference in adverse events between antibiotics and placebo (2 RCTs, 262; 1.5% versus 0.0%, RR 4.47, 95% CI 0.22 to 89.94; very low quality evidence).

No safety or tolerability data were presented in the RCT by Dieter et al. (2014) on short-term post-operative antibiotic prophylaxis and the systematic review by Marschall et al. (2013) on antibiotic prophylaxis at the time of catheter removal.

4.3.2 Antibiotics in children

No safety or tolerability data were presented in the single systematic review (Niël-Weise et al. 2012) that reported outcomes in children.

5 Antimicrobial resistance

The consumption of antimicrobials is a major driver for the development of antibiotic resistance in bacteria, and the 3 major goals of antimicrobial stewardship are to:

- optimise therapy for individual patients
- prevent overuse, misuse and abuse, and
- minimise development of resistance at patient and community levels.

The NICE guideline on antimicrobial stewardship: systems and processes for effective antimicrobial medicine use recommends that the risk of antimicrobial resistance for individual patients and the population as a whole should be taken into account when deciding whether or not to prescribe an antimicrobial.

When antimicrobials are necessary to treat an infection that is not life-threatening, a narrow-spectrum antibiotic should generally be first choice. Indiscriminate use of broad-spectrum antibiotics creates a selective advantage for bacteria resistant even to these 'last-line' broad-spectrum agents, and also kills normal commensal flora leaving people susceptible to antibiotic-resistant harmful bacteria such as *C. difficile*. For infections that are not life-threatening, broad-spectrum antibiotics (for example, co-amoxiclav, quinolones and cephalosporins) need to be reserved for second-choice treatment when narrow-spectrum antibiotics are ineffective (CMO report 2011).

The English surveillance programme for antimicrobial utilisation and resistance (ESPAUR) report reported that antimicrobial consumption declined significantly between 2014 and 2015, with community prescribing from general and dental practice decreasing by more than 6%. Antibiotic prescribing in primary care in 2015 is at the lowest level since 2011, with broad-spectrum antibiotic use (antibiotics that are effective against a wide range of bacteria) continuing to decrease in primary care.

Urinary tract infections (UTIs) are most commonly caused by *E. coli* (recorded in more than half of all the mandatory surveillance reports for *E. coli* bacteraemia when foci of infection are reported). Better management of UTIs is seen as a potential intervention to reduce the incidence of *E. coli* bacteraemia. The ESPAUR report 2016 states that between 2010 and 2014 the rate of bloodstream infections caused by *E. coli* and *Klebsiella pneumoniae* increased by 15.6% and 20.8% respectively. Between 2014 and 2015 the number of cases continued to increase; *E. coli* bloodstream infections increased by a further 4.6% and *K. pneumoniae* increased by 9%.

Overall, there is wide variation in the rates of resistance to antibiotics across England. For example by CCG trimethoprim resistance in Gram-negative UTI ranges from 16.3% to 66.7%; this may be related to variation in sending urine samples for laboratory testing. However, 86% of CCGs have resistance rates greater than 25%, highlighting that trimethoprim can no longer be advised as the first-line empiric antibiotic treatment for UTIs in England.

5.1 Antimicrobial resistance in the included studies

Two systematic reviews included data on antimicrobial resistance. One systematic review (Lusardi et al. 2013) compared antibiotic prophylaxis with placebo before or during catheterisation for the preventing catheter-associated UTI in adults undergoing surgery and found a significant difference in the number of gram negative strains isolated assessed before catheter removal with prophylaxis (1 RCT, n=93; 0%

with antibiotic prophylaxis versus 41.4% for control, RR 0.05, 95% CI 0.00 to 0.79; low quality evidence) and after 6 weeks (1 RCT, n=177; 19% with antibiotic prophylaxis versus 52.9% with control, RR 0.36, 95% CI 0.23 to 0.56; moderate quality evidence).

A second systematic review (Niël-Weise et al. 2012) found significantly higher rates of resistance in the antibiotic prophylaxis group compared with antibiotics used when clinically indicated in older adults in nursing homes (1 RCT, n=63; 90.9% versus 19.5% of isolated strains compared to the number of strains, RR 4.66, 95% CI 2.47 to 8.80; very low quality evidence). However, significantly lower rates of gram negative isolates compared to the total number of isolates were found in the antibiotic prophylaxis group compared with the antibiotics when clinically indicated group (1 RCT, n=63; 22.7% versus 75.6%, RR 0.30, 95% CI 0.14 to 0.66; low quality evidence). In one RCT included in the systematic review by Niël-Weise et al. 2012, there was no significant difference in resistant bacteriuria due to co-trimoxazole resistant organisms between antibiotic prophylaxis and antibiotics used when microbiologically indicated in adults using intermittent catheterisation (1 RCT, n=126 participants; RR 0.95, 95% CI 0.77 to 1.17; very low quality evidence).

6 Other considerations

6.1 Resource impact

6.1.1 Antibiotics

One systematic review (Lusardi et al. 2013) assessed resource impact of antibiotic prophylaxis for preventing UTI before or during short-term catheterisation in hospitalised adults.

One included randomised controlled trial [RCT] comparing antibiotic prophylaxis (levofloxacin or ciprofloxacin) with placebo calculated hospital stay in pre-surgery and post-surgery phases. There was no significant difference between the mean pre-surgical stay [standard deviation, SD] in the placebo group (5.9 [±7.5] days) and the levofloxacin (3.9 [±3.6] days, mean difference [MD] -2.00, 95% confidence interval [CI] -5.08 to 1.08, p=0.20; low quality evidence) and ciprofloxacin (3.3 [±3.7] days, MD -2.60, 95% CI -5.72 to 0.52, p=0.10; low quality evidence) groups. There was no significant difference between the mean post-surgical stay in the placebo group (7.6 [±6.6] days) and the ciprofloxacin (7.4 [±5.4] days, MD -0.20, 95% CI -3.41 to 3.01, p=0.90; low quality evidence) and levofloxacin (6.0 [±4.2] days, MD -1.6, 95% CI -4.50 to 1.30, p=0.28; low quality evidence) groups.

In a second included RCT comparing antibiotic prophylaxis with placebo, the mean hospital stay was significantly higher in the placebo group than in the intervention group (8 days [±1.4 days] compared with 7 days [±1.2 days] (MD -1.0, 95% CI -1.52 to -0.48, p=0.0002; low quality evidence). Febrile morbidity with urinary tract infection (UTI) prolonged hospitalisation significantly to a mean stay of 9.2 days ([±1.6] days, p< 0.05).

In a third included RCT comparing antibiotic prophylaxis with placebo, the average hospital stay was 6 days and 5.6 days for abdominal hysterectomy, and 6.1 days and 7.6 days for vaginal hysterectomy patients, in the prophylaxis group and placebo groups respectively.

Recommended antibiotics include nitrofurantoin, trimethoprim, penicillins, cephalosporins, quinolones and aminoglycosides. All are available as generic formulations, see Drug Tariff for costs.

Nitrofurantoin 25mg/5ml oral suspension is more expensive than other oral suspensions, such as trimethoprim 50mg/5ml. The cost of a 300 ml bottle of nitrofurantoin is £446.95 compared with £2.22 for a 100 ml bottle of trimethoprim (Drug Tariff, February 2018).

6.2 Medicines adherence

Medicines adherence may be a problem for some people with medicines that require frequent dosing (for example, some antibiotics) (NICE guideline on medicines adherence). Longer treatment durations (for example, for antibiotic prophylaxis) may also cause problems with medicines adherence for some people.

7 Terms used in the guideline

Asymptomatic bacteriuria

The presence of bacteria in the urine at levels often regarded as being clinically significant but in patients without any clinical symptoms or signs of infection (for example dysuria, pain, frequency or urgency).

Bacteriuria

The presence of bacteria in the urine.

Incidence density rate

Incidence rate is the number of new cases per population at risk in a specific time period (for example 3 cases per 1000 per year), when each individual's time in a study (person-time) is used to calculate the rate it is called the incidence density rate or person-time incidence rate.

Incidence rate ratio

A ratio of 2 incidence rates, an incidence rate is the number of new cases per population at risk in a specific time period (for example 3 cases per 1000 per year).

Non-inferiority study

A clinical study which attempts to show that an experimental treatment is not substantially worse than a control treatment by more than a specified margin.

Urosepsis

Sepsis caused by an infection of the urinary tract.

Appendices

Appendix A: Evidence Sources

Key area	Key question(s)	Evidence sources
Background	• What is the natural history of the infection? • What is the expected duration and severity of symptoms with or without antimicrobial treatment? • What are the most likely causative organisms? • What are the usual symptoms and signs of the infection? • What are the known complication rates of the infection, with and without antimicrobial treatment? • Are there any diagnostic or prognostic factors to identify people who may or may not benefit from an antimicrobial?	• NICE guideline NG15: Antimicrobial stewardship: systems and processes for effective antimicrobial medicine use (2015) • NICE guideline NG63: Antimicrobial stewardship: changing risk-related behaviours in the general population (2017) • NICE Quality standard QS90: Urinary tract infections in adults (2015) • NICE Clinical knowledge summary on UTI (lower) – women • NICE Clinical knowledge summary on UTI (lower) – men • European Association of Urology guidelines on urological infections (2017) • NHS Choices – Urinary catheter (2018) • Health Protection Surveillance Centre guidelines for the prevention of catheter associated urinary tract infection (2011) • Public Health England - Diagnosis of urinary tract infections (UTIs) (2017) • Health Protection Agency (HPA) - English National Point Prevalence Survey on Healthcare-associated Infections and Antimicrobial Use (2012) • Loveday et al. (2014) • Smyth et al. (2008) • Ploughman et al. (1997)

Key area	Key question(s)	Evidence sources
		• Tambyah et al. (2002) • Rosser et al. (1999)
Safety netting	• What safety netting advice is needed for managing the infection?	• NICE clinical knowledge summary on UTI (lower) - women • NICE clinical knowledge summary on UTI (lower) - men
Red flags	• What symptoms and signs suggest a more serious illness or condition (red flags)?	• NICE clinical knowledge summary on UTI (lower) - women • NICE clinical knowledge summary on UTI (lower) - men
Non-pharmacological interventions	• What is the clinical effectiveness and safety of non-pharmacological interventions for managing the infection or symptoms?	• Evidence review - see appendix F for included studies
Non-antimicrobial pharmacological interventions	• What is the clinical effectiveness and safety of non-antimicrobial pharmacological interventions for managing the infection or symptoms?	• Evidence review - see appendix F for included studies • British National Formulary (BNF) (December 2017)
Antimicrobial prescribing strategies	What is the clinical effectiveness and safety of antimicrobial prescribing strategies (including back-up prescribing) for managing the infection or symptoms?	• Evidence review - see appendix F for included studies
Antimicrobials	• What is the clinical effectiveness and safety of antimicrobials for managing the infection or symptoms?	• Evidence review - see appendix F for included studies • NICE guideline NG15: Antimicrobial stewardship: systems and processes for effective antimicrobial medicine use (2015) • NICE clinical knowledge summary on diarrhoea – antibiotic associated • British National Formulary (BNF) (December 2017)

Key area	Key question(s)	Evidence sources
	• Which people are most likely to benefit from an antimicrobial?	• Evidence review - see appendix F for included studies
	• Which antimicrobial should be prescribed if one is indicated (first, second and third line treatment, including people with drug allergy)?	• Evidence review - see appendix F for included studies
	• What is the optimal dose, duration and route of administration of antimicrobials?	• Evidence review - see appendix F for included studies • British National Formulary (BNF) (December 2017) • BNF for children (BNF-C) (December 2017) • Summary of product characteristics
Antimicrobial resistance	• What resistance patterns, trends and levels of resistance exist both locally and nationally for the causative organisms of the infection • What is the need for broad or narrow spectrum antimicrobials? • What is the impact of specific antimicrobials on the development of future resistance to that and other antimicrobials?	• Evidence review - see appendix F for included studies • NICE guideline NG15: Antimicrobial stewardship: systems and processes for effective antimicrobial medicine use (2015) • European surveillance programme for antimicrobial utilisation and resistance (ESPAUR) report (2016) • Chief medical officer (CMO) report (2011)
Resource impact	• What is the resource impact of interventions (such as escalation or de-escalation of treatment)?	• Evidence review - see appendix F for included studies • Drug Tariff (February 2018)
Medicines adherence	• What are the problems with medicines adherence (such as when longer courses of treatment are used)?	• Evidence review - see appendix F for included studies • NICE guideline NG76: Medicines adherence: involving patients in decisions about prescribed medicines and supporting adherence (2009)

Key area	Key question(s)	Evidence sources
Regulatory status	What is the regulatory status of interventions for managing the infection or symptoms?	• Summary of product characteristics

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2

Appendix B: Review protocol

Review protocol for catheter associated urinary tract infections			Notes
I	Review question	What pharmacological (antimicrobial and non-antimicrobial) and non-pharmacological interventions are effective in managing catheter-associated urinary tract infections (UTIs)?	• antimicrobial includes antibiotics • non-antimicrobial includes analgesia and bladder instillation • search will include terms for catheter-associated urinary tract infection.
II	Types of review question	Intervention questions will primarily be addressed through the search.	These will, for example, also identify natural history in placebo groups and causative organisms in studies that use laboratory diagnosis, and relative risks of differing management options.
III	Objective of the review	To determine the effectiveness of prescribing interventions in managing catheter associated urinary tract infection to address antimicrobial resistance in line with the major goals of antimicrobial stewardship. This includes interventions that lead prescribers to: • optimise therapy for individuals • reduce overuse, misuse or abuse of antimicrobials	The secondary objectives of the review of studies will include: • indications for prescribing an antimicrobial (for example 'red flags' and illness severity), thresholds for treatment and individual patient factors affecting choice of antimicrobial

		All of the above will be considered in the context of national antimicrobial resistance patterns where available, if not available committee expertise will be used to guide decision-making.	• indications for no or delayed antimicrobial • indications for non-antimicrobial interventions • antimicrobial choice, optimal dose, duration (specifically length of treatment) and route for specified antimicrobial(s) • the natural history of the infection
IV	Eligibility criteria – population/ disease/ condition/ issue/domain	Population: Adults and children (aged 72 hours and older) with catheter-associated urinary tract infections of any severity. People with an indwelling short or long-term urinary catheter, an intermittent urinary catheter, or a suprapubic catheter. This review protocol includes catheter associated UTI in non-pregnant and pregnant women, men and children. Consideration will be given to differing management in subgroups based on age, gender, pregnancy, complicating factors and risk of resistance. Studies that use for example symptoms or signs (prognosis), clinical diagnosis or microbiological methods for diagnosing the condition.	Subgroups of interest, those: • with protected characteristics under the Equality Act 2010. • with true allergy • pregnant women • men • children (possible age groups) • older people (frailty, care home resident, dementia) • asymptomatic bacteriuria

			• people with risk factors for increased resistance[1]
V	Eligibility criteria – intervention(s)/ exposure(s)/ prognostic factor(s)	The review will include studies which include: • Non-pharmacological interventions[2]. • Non-antimicrobial pharmacological interventions[3]. • Antimicrobial pharmacological interventions[4]. For the treatment or prophylaxis of catheter-associated urinary tract infection in primary, secondary or other care settings (for example walk-in-centres, urgent care, and minor ailment schemes) either by prescription or by any other legal means of supply of medicine (for example patient group direction).	Limited to those interventions commonly in use (as agreed by the committee)
VI	Eligibility criteria – comparator(s)/ control or reference (gold) standard	Any other plausible strategy or comparator, including: • Placebo or no treatment. • Non-pharmacological interventions. • Non-antimicrobial pharmacological interventions. • Other antimicrobial pharmacological interventions.	

[1] Risk factors for increased resistance include: care home resident, recurrent UTI, previous hospitalisation, unresolving urinary symptoms, recent travel to country with increased resistance, previous UTI resistant to antibiotics (previous antibiotic use [trimethoprim]) (Source PHE management of infection guidance)
[2] Non-pharmacological interventions include: no intervention, watchful waiting, delayed prescribing, removal of catheter
[3] Non-antimicrobial pharmacological interventions include: analgesics and bladder instillation
[4] Antimicrobial pharmacological interventions include: delayed (back-up) prescribing, standby or rescue therapy, narrow or broad spectrum, single, dual or triple therapy, escalation or de-escalation of treatment. Antibiotics included in the search include those named in current guidance (plus the class to which they belong) plus other antibiotics agreed by the committee

VII	Outcomes and prioritisation	• Clinical outcomes such as: • mortality • infection cure rates (number or proportion of people with resolution of symptoms at a given time point, incidence of escalation of treatment) • time to clinical cure (mean or median time to resolution of illness) • reduction in symptoms (duration or severity) • rate of complications with or without treatment • safety, tolerability, and adverse effects (which people are most, or least likely to benefit from antimicrobials) • Thresholds or indications for antimicrobial treatment • Changes in antimicrobial resistance patterns, trends and levels as a result of treatment. • Patient-reported outcomes, such as medicines adherence, patient experience and patient satisfaction. • Ability to carry out activities of daily living. • Service user experience. • Health and social care related quality of life, including long-term harm or disability. • Health and social care utilisation (including length of stay, planned and unplanned contacts).	The committee have agreed that the following outcomes are critical: • reduction in symptoms (duration or severity) for example difference in time to substantial improvement • time to clinical cure (mean or median time to resolution of illness) • rate of complications[5] (including mortality) with or without treatment, including escalation of treatment • health and social care utilisation (including length of stay, ITU stays, planned and unplanned contacts) • thresholds or indications for antimicrobial treatment (which people are most, or least likely to benefit from antimicrobials) • an individual's risk factors for resistance and choice of antibiotic

[5] Ascending infection leading to pyelonephritis, renal failure, sepsis, recurrent infection, prostate involvement in men, urinary stones

		The Committee considered which outcomes should be prioritised when multiple outcomes are reported (critical and important outcomes). Additionally, the Committee were asked to consider what clinically important features of study design may be important for this condition (for example length of study follow-up, treatment failure/recurrence, important outcomes of interest such as sequela or progression to more severe illness).	The committee have agreed that the following outcomes are important: • patient-reported outcomes, such as medicines adherence, patient experience • changes in antimicrobial resistance patterns, trends and levels as a result of treatment
VIII	Eligibility criteria – study design	The search will look for: • Systematic review of randomised controlled trials (RCTs) • RCTs If insufficient evidence is available progress to: • Controlled trials • Systematic reviews of non-randomised controlled trials • Non-randomised controlled trials • Observational and cohort studies • Pre and post intervention studies (before and after) Time series studies	Committee to advise the NICE project team on the inclusion of information from other condition specific guidance and on whether to progress due to insufficient evidence.
IX	Other inclusion exclusion criteria	The scope sets out what the guidelines will and will not include (exclusions). Further exclusions specific to this guideline include: • non-English language papers, studies that are only available as abstracts	

		• in relation to antimicrobial resistance, non-UK papers.	
X	Proposed sensitivity/ sub-group analysis, or meta-regression	The search may identify studies in population subgroups (for example adults, older adults, children (those aged under 18 years of age), and people with co-morbidities or characteristics that are protected under the Equality Act 2010 or in the NICE equality impact assessment). These will be analysed within these categories to enable the production of management recommendations.	
XI	Selection process – duplicate screening/ selection/ analysis	All references from the database searches will be downloaded, de-duplicated and screened on title and abstract against the criteria above. A randomly selected initial sample of 10% of records will be screened by two reviewers independently. The rate of agreement for this sample will be recorded, and if it is over 90% then remaining references will screened by one reviewer only. Disagreement will be resolved through discussion. Where abstracts meet all the criteria, or if it is unclear from the study abstract whether it does, the full text will be retrieved. If large numbers of papers are identified and included at full text, the Committee may consider prioritising the evidence for example, evidence of higher quality in terms of study type or evidence with critical or highly important outcomes.	
XII	Data management (software)	Data management will be undertaken using EPPI-reviewer software. Any pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). 'GRADEpro' will be used to assess the quality of evidence for each outcome.	
XIII	Information sources – databases and dates	Medline; Medline in Process; Embase; Cochrane database of systematic reviews (CDSR); Database of abstracts of effectiveness (DARE) (legacy); Cochrane Central Register of Controlled Trials (CENTRAL); Health Technology Assessment (HTA) database; Clinicaltrials.gov • All the above to be searched from 2006 to present day. • Filters for systematic reviews, RCTS, and comparative studies to be applied, unless numbers without filters are low	

		• Searches to be limited to studies reported in English. • Animal studies and conference abstracts to be excluded Medicines and Healthcare products Regulatory Agency (MHRA) website; European Medicines Agency (EMA) website; U.S. Food and Drug Administration (FDA) website; Drug Tariff; MIMs • The above to be searched for advice on precautions, warnings, undesirable effects of named antimicrobials.	
XIV	Identify if an update	Not applicable at this time.	
XV	Author contacts	Web: https://www.nice.org.uk/guidance/indevelopment/gid-apg10002 Email: infections@nice.org.uk	
XVI	Highlight if amendment to previous protocol	For details please see the interim process guide (2017).	
XVII	Search strategy – for one database	For details please see appendix C of the full guideline.	
XVIII	Data collection process – forms/duplicate	GRADE profiles will be used, for details see appendix H of the full guideline.	
XIX	Data items – define all variables to be collected	GRADE profiles will be used, for details see appendix H of the full guideline.	

XX	Methods for assessing bias at outcome/ study level	Standard study checklists will be used to critically appraise individual studies. For details please see the interim process guide (2017). The risk of bias across all available evidence will be evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/	
XXI	Criteria for quantitative synthesis (where suitable)	For details please see the interim process guide (2017).	
XXII	Methods for analysis – combining studies and exploring (in)consistency	For details please see the interim process guide (2017).	
XXIII	Meta-bias assessment – publication bias, selective reporting bias	For details please see the interim process guide (2017).	
XXIV	Assessment of confidence in cumulative evidence	For details please see the interim process guide (2017).	
XXV	Rationale/ context – Current management	For details please see the introduction to the evidence review in the guideline.	
XXVI	Describe contributions of authors and guarantor	A multidisciplinary committee developed the guideline. The committee was convened by NICE and chaired by Dr Tessa Lewis in line with section 3 of Developing NICE guidelines: the manual.	

		Staff from NICE undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the guideline in collaboration with the committee. For details please see the methods chapter of the full guideline.	
XXVII	Sources of funding/support	Developed and funded by NICE.	
XXVIII	Name of sponsor	Developed and funded by NICE.	
XXIX	Roles of sponsor	NICE funds and develops guidelines for those working in the NHS, public health, and social care in England.	

1

Appendix C: Literature search strategy

1 Search format

The search strategy has been designed to cover four UTI protocols and it takes the following format:

Urinary Tract Infections

AND (Named Antibiotics OR Classes of Antibiotics OR Pain Relief OR NSAIDs OR Cranberry Products OR Alkalinising agents OR Bladder instillations OR Drinking Fluids OR Prescribing Strategies OR Self Care OR Catheter Removal)

AND (Systematic Reviews OR Randomised Controlled Trials OR Observational Studies)

AND Limits

Note there is an additional search in this format:

Named Antibiotics AND Drug Resistance AND Limits

2 Overview of search results

	No. of hits in MEDLINE	Position in the strategy
Search without any limits	65,619	Line 178
Search with limits	14,263	Line 184
Search with limits and Systematic Reviews	2,428	Line 200
Search with limits and RCTs (not SRs)	2,230	Line 217
Search with limits and Observational Studies (not SRs or RCTs)	3,795	Line 240
Search with limits (without SRs, RCTs, Observational)	5,810	Line 241
Named Antibiotics AND Drug Resistance	48,201	Line 257
Named Antibiotics AND Drug Resistance with Limits	20,072	Line 262

3 Contents of the search strategy

Main concepts	Coverage	Position in strategy
Urinary Tract Infections	Urinary tract infections Cystitis Vesico-ureteral reflux Pyelonephritis Catheter-Related Infections Bacteriuria Urosepsis Urethritis	Lines 1-20
Named Antibiotics	Trimethoprim Nitrofurantoin Fosfomycin Methenamine hippurate Gentamicin Amikacin Tobramycin Amoxicillin Ampicillin Co-amoxiclav	Lines 21-84

	Pivmecillinam Cefalexin Cefotaxime Cefixime Ceftriaxone Ciprofloxacin Ofloxacin Colistin Ertapenem Doxycycline Septrin Chloramphenicol Tazocin Aztreonam Temocillin Tigecycline Vancomycin Teicoplanin Linezolid Cefuroxime Cefradine Ceftazidime Levofloxacin	
Classes of Antibiotics	Aminoglycosides Penicillins Cephalosporins Quinolones Carbapenems Tetracyclines	Lines 86-93
Pain Relief	Paracetamol Ibuprofen Naproxen Codeine Diclofenac Analgesics Non-steroidal anti-inflammatory drugs	Lines 96-111
Non-pharmaceutical products	Cranberry products Barley products D-Mannose	Lines 113-119
Alkalinising agents	Potassium citrate Sodium citrate Sodium bicarbonate	Lines 121-127
Bladder instillations	Chlorhexidine solution Sodium chloride solution	Lines 129-133
Drinking Fluids	Fluid therapy Drinking water, beverages, fluids or liquids	Lines 135-139
Prescribing Strategies	Watchful waiting No intervention Active surveillance Delayed treatment Prescribing times Antibiotic prophylaxis	Lines 141-160
Self Care	Self management Self care secondary prevention Catheter removal	Lines 162-176
Systematic Reviews	Meta analysis Systematic Reviews Reviews	Lines 185-199

Randomised Controlled Trials	RCTs Controlled Clinical Trials Cross over studies	Lines 201-215
Observational Studies	Observational Study Epidemiologic Studies Case-Control Studies Cohort Studies Cross-Sectional Studies Controlled Before-After Studies	Lines 218-238
Limits	2006-Current Exclude Animal studies Exclude letters, editorials and letters	Lines 179-184
Additional search	Drug resistance	Lines 242-262

4 Key to search operators

/	Medical Subject Heading (MeSH) term
Exp	Explodes the MeSH terms to retrieve narrower terms in the hierarchy
.ti	Searches the title field
.ab	Searches the abstract field
*	Truncation symbol (searches all word endings after the stem)
adj*n*	Adjacency operator to retrieve records containing the terms within a specified number (*n*) of words of each other

5 Search strategy for MEDLINE

Database(s): **Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)** 1946 to Present

Search Strategy:

#	Searches	Results
1	exp urinary tract/	406398
2	exp urinary tract infections/	42175
3	exp cystitis/	8814
4	vesico-ureteral reflux/	7753
5	exp pyelonephritis/	14154
6	exp Urinary Calculi/	32650
7	Urethritis/	4483
8	Catheters, Indwelling/	17219
9	Urinary Catheters/	530
10	Urinary Catheterization/	13329
11	Catheter-Related Infections/	3344
12	Catheter Obstruction/	139
13	(UTI or CAUTI or RUTI or cystitis* or bacteriuria* or pyelonephriti* or pyonephrosi* or pyelocystiti* or pyuri* or VUR or urosepsis* or uroseptic* or urosepses* or urethritis*).ti,ab.	38919

14	((urin* or renal* or kidney*) adj1 (system* or tract* or calculus or calculi* or stone* or sepsis*)).ti,ab.	82884
15	((bladder* or genitourin* or genito urin* or kidney* or pyelo* or renal* or ureter* or ureth* or urin* or urolog* or urogen*) adj3 (infect* or bacteria* or microbial* or block* or obstruct* or catheter* or inflamm*)).ti,ab.	87091
16	((upper or lower) adj3 urin*).ti,ab.	21980
17	(bladder* adj3 (ulcer* or ulcus)).ti,ab.	151
18	(schistosomiasis adj3 (haematobia or hematobia or urin*)).ti,ab.	966
19	((vesicorenal* or vesicoureteral* or vesicoureteric* or vesico renal* or vesico ureteral* or vesico ureteric* or bladder* or cystoureteral* or ureter* or urether* or nephropathy*) adj3 (backflow* or reflux*)).ti,ab.	7989
20	or/1-19	576113
21	Trimethoprim/	6280
22	(Trimethoprim* or Monotrim*).ti,ab.	14565
23	Nitrofurantoin/	2517
24	(Nitrofurantoin* or Genfura* or Macrobid*).ti,ab.	2980
25	Fosfomycin/	1685
26	(Fosfomycin* or Phosphomycin* or Fosfocina* or Monuril* or Monurol* or Fomicyt*).ti,ab.	2378
27	Methenamine/	1045
28	(Methenamine* or hexamine* or hippurate* or Hiprex*).ti,ab.	2411
29	Gentamicins/	17268
30	(Gentamicin* or Cidomycin*).ti,ab.	21976
31	Amikacin/	3751
32	(amikacin* or Amikin*).ti,ab.	8118
33	Tobramycin/	3973
34	(tobramycin* or Nebcin*).ti,ab.	6203
35	Amoxicillin/	8654
36	(Amoxicillin* or Amoxil*).ti,ab.	12541
37	Ampicillin/	12932
38	ampicillin*.ti,ab.	20478
39	Amoxicillin-Potassium Clavulanate Combination/	2301
40	(co-amoxiclav* or Coamoxiclav* or Amox-clav* or Amoxicillin-Clavulanic Acid* or Amoxicillin-Potassium Clavulanate Combination* or Amoxi-Clavulanate* or Clavulanate Potentiated Amoxycillin Potassium* or Clavulanate-Amoxicillin Combination* or Augmentin*).ti,ab.	13396

41	Amdinocillin Pivoxil/	205
42	(pivmecillinam* or Pivamdinocillin* or Selexid*).ti,ab.	268
43	Cefalexin/	1974
44	(Cefalexin* or Cephalexin* or Keflex*).ti,ab.	2605
45	Cefotaxime/	5101
46	cefotaxime*.ti,ab.	7488
47	Cefixime/	711
48	(cefixime* or Suprax*).ti,ab.	1438
49	Ceftriaxone/	5210
50	(ceftriaxone* or Rocephin*).ti,ab.	8834
51	Ciprofloxacin/	11578
52	(Ciprofloxacin* or Ciproxin*).ti,ab.	21632
53	Ofloxacin/	5795
54	(ofloxacin* or Tarivid*).ti,ab.	6236
55	Colistin/	3071
56	(Colistin* or Colistimethate* or Colimycin* or Coly-Mycin* or Colymycin* or Colomycin* or Promixin*).ti,ab.	4291
57	(Ertapenem* or Invanz*).ti,ab.	1135
58	Doxycycline/	8515
59	(Doxycycline* or Efracea* or Periostat* or Vibramycin*).ti,ab.	11268
60	Trimethoprim, Sulfamethoxazole Drug Combination/	6306
61	(Septrin* or Co-trimoxazole* or Cotrimoxazole* or Sulfamethoxazole Trimethoprim Comb* or Trimethoprim Sulfamethoxazole Comb*).ti,ab.	5497
62	Chloramphenicol/	18958
63	(Chloramphenicol* or Cloranfenicol* or Kemicetine* or Kloramfenikol*).ti,ab.	24993
64	Piperacillin/	2423
65	(Tazocin* or Piperacillin* or Tazobactam*).ti,ab.	6222
66	Aztreonam/	1336
67	(Aztreonam* or Azactam*).ti,ab.	2743
68	(Temocillin* or Negaban*).ti,ab.	237
69	(Tigecycline* or Tygacil*).ti,ab.	2337
70	Vancomycin/	11836
71	(Vancomycin* or Vancocin*).ti,ab.	22446

72	Teicoplanin/	2067
73	(Teicoplanin* or Targocid*).ti,ab.	3233
74	Linezolid/	2421
75	(Linezolid* or Zyvox*).ti,ab.	4568
76	Cefuroxime/	2037
77	(Cefuroxime* or Cephuroxime* or Zinacef* or Zinnat* or Aprokam*).ti,ab.	3919
78	Cefradine/	540
79	(Cefradine* or Cephradine* or Nicef*).ti,ab.	699
80	Ceftazidime/	3461
81	(Ceftazidime* or Fortum* or Tazidime*).ti,ab.	7727
82	Levofloxacin/	2708
83	(Levofloxacin* or Evoxil* or Tavanic*).ti,ab.	6119
84	or/21-83	214218
85	20 and 84	18255
86	exp aminoglycosides/	142346
87	exp penicillins/	76761
88	exp cephalosporins/	39233
89	exp quinolones/	41144
90	exp Carbapenems/	8711
91	exp Tetracyclines/	44511
92	(Aminoglycoside* or Penicillin* or Cephalosporin* or Quinolone* or Carbapenem* or Tetracycline*).ti,ab.	120900
93	or/86-92	359234
94	20 and 93	22544
95	Anti-Infective Agents, Urinary/	2557
96	Acetaminophen/	15854
97	(paracetamol* or acetaminophen* or Panadol* or perfalgan* or calpol*).ti,ab.	20775
98	Ibuprofen/	7581
99	(ibuprofen* or arthrofen* or ebufac* or rimafen* or brufen* or calprofen* or feverfen* or nurofen* or orbifen*).ti,ab.	11191
100	Naproxen/	3730
101	(Naproxen* or Naprosyn* or Stirlescent*).ti,ab.	5450
102	Codeine/	4237

103	(codeine* or Galcodine*).ti,ab.	4407
104	Diclofenac/	6823
105	(Diclofenac* or Voltarol* or Dicloflex* or Econac* or Fenactol* or Volsaid* or Enstar* or Diclomax* or Motifene* or Rhumalgan* or Pennsaid*).ti,ab.	9698
106	(nsaid* or analgesic*).ti,ab.	87160
107	((nonsteroid* or non steroid*) adj3 (anti inflammator* or antiinflammator*)).ti,ab.	34162
108	analgesics/	43460
109	exp analgesics, non-narcotic/	299959
110	analgesics, short-acting/	8
111	or/96-110	400073
112	20 and 111	10492
113	Vaccinium macrocarpon/	645
114	(cranberry* or cranberries* or vaccinium macrocarpon*).ti,ab.	1247
115	Hordeum/	8153
116	(barley* or hordeum*).ti,ab.	15407
117	Mannose/	8489
118	(mannose* or d-mannose* or dmannose*).ti,ab.	24493
119	or/113-118	45484
120	20 and 119	1500
121	potassium citrate/	245
122	(potassium citrate* or Effercitrate*).ti,ab.	546
123	(sodium citrate* or Cymalon* or Cystocalm* or Micolette* or Micralax*).ti,ab.	2644
124	sodium bicarbonate/	4205
125	(sodium bicarbonate* or S-Bicarb* or SodiBic* or Thamicarb* or Polyfusor*).ti,ab.	5477
126	((alkalizer* or alkalinisation* or alkalinization* or alkalinising or alkalinizing) adj3 (drug* or agent* or therap*)).ti,ab.	191
127	or/121-126	10890
128	20 and 127	1049
129	Chlorhexidine/	7123
130	((chlorhexidine or sodium chloride*) adj3 (solution* or diluent* or instillation* or intravesical*)).ti,ab.	3327
131	Administration, Intravesical/	3418
132	(bladder* adj3 (instillat* or drug admin*)).ti,ab.	540
133	or/129-132	13618

134	20 and 133	1976
135	Drinking/ or Drinking Behavior/	19308
136	Fluid therapy/	17515
137	exp Beverages/	114331
138	((water* or fluid* or liquid* or beverage* or drinks) adj3 (consumption* or consume* or consuming* or intake* or drink* or hydrat* or rehydrat*)).ti,ab.	80871
139	or/135-138	210996
140	20 and 139	6845
141	watchful waiting/	2278
142	Antibiotic Prophylaxis/	11779
143	"no intervention*".ti,ab.	6125
144	(watchful* adj2 wait*).ti,ab.	2077
145	(wait adj2 see).ti,ab.	1225
146	(active* adj2 surveillance*).ti,ab.	5705
147	(expectant* adj2 manage*).ti,ab.	2738
148	((prescription* or prescrib*) adj4 ("red flag" or strateg* or appropriat* or inappropriat* or unnecessary or defer* or delay* or no or non or behaviour* or behavior* or optimal or optimi* or reduc* or decreas* or declin* or rate* or improv* or postcoital* or postcoitus* or postsex* or postintercourse* or post coital* or post coitus* or post sex* or post intercourse* or night* or nocturnal* or prophylaxis* or prophylactic* or prevent* or preoperative* or pre operative* or perioperative* or peri operative* or postoperative* or post operative*)).ti,ab.	25168
149	((misuse* or "mis-use*" or overuse* or "over-use*" or "over-prescri*" or abuse*) adj4 (bacter* or antibacter* or anti-bacter* or "anti bacter*" or antimicrobial or anti-microbial or "anti microbial" or antibiot* or anti-biot* or "anti biot*")).ti,ab.	1761
150	((delay* or defer*) adj3 (treat* or therap* or interven*)).ti,ab.	26341
151	or/141-150	82704
152	anti-infective agents/ or exp anti-bacterial agents/ or exp anti-infective agents, local/	844581
153	(antibacter* or anti-bacter* or antibiot* or anti-biot* or antimicrobial* or anti-microbial*).ti,ab.	401551
154	152 or 153	1017858
155	(postcoital* or postcoitus* or postsex* or postintercourse* or post coital* or post coitus* or post sex* or post intercourse* or night* or nocturnal* or delay* or defer* or back-up* or backup* or immediate* or rapid* or short* or long* or standby or "stand by" or rescue or escalat* or "de-escalat*" or (prescribing adj strateg*) or "red flag*" or prevent* or prophylaxis* or prophylactic*).ti,ab.	4758691

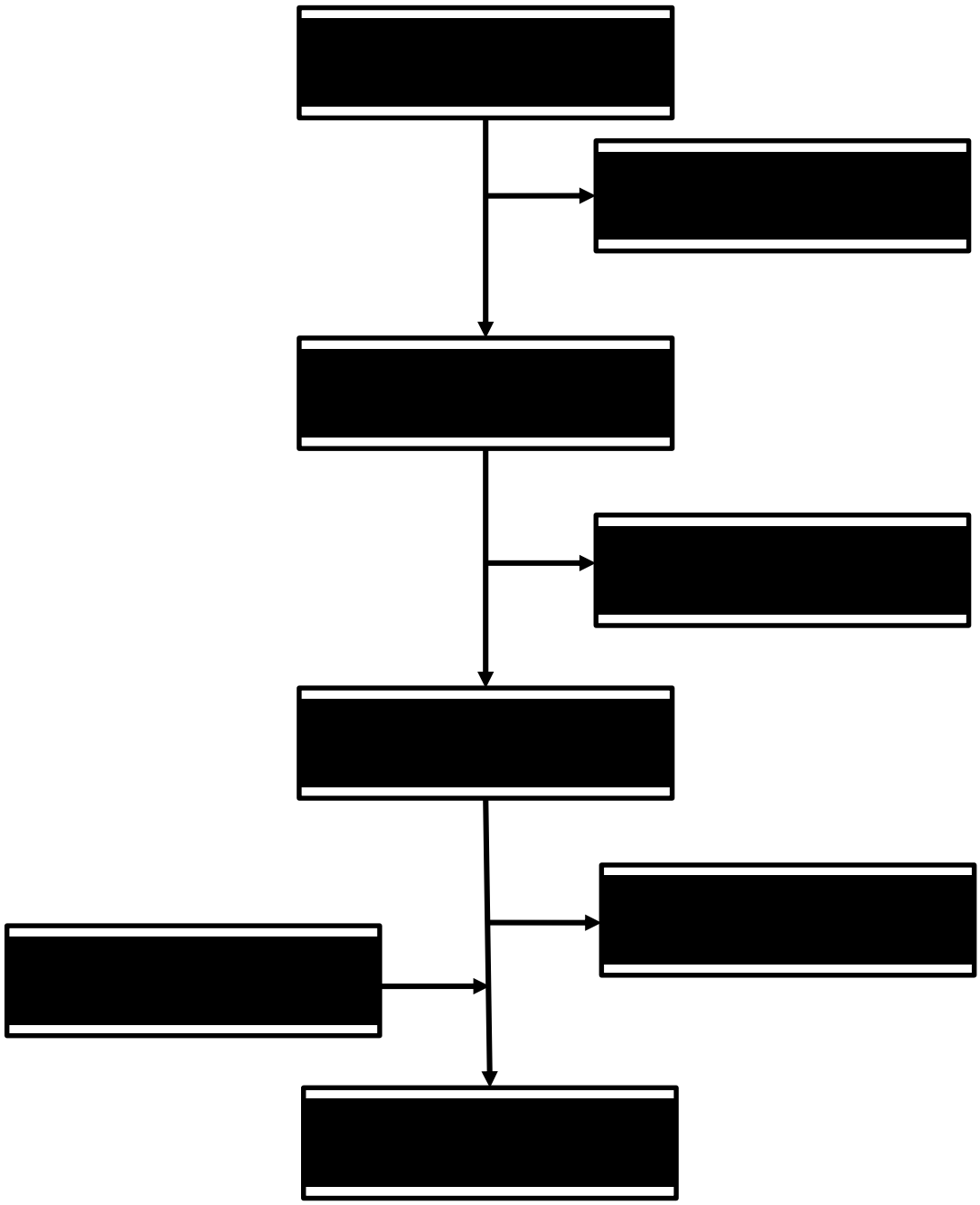
156	Coitus/	6880
157	Inappropriate prescribing/	1695
158	or/155-157	4764914
159	154 and 158	221871
160	151 or 159	292655
161	20 and 160	15345
162	Self Care/ or self medication/	32883
163	((self or selves or themsel*) adj4 (care or manag*)).ti,ab.	33223
164	Secondary Prevention/	17180
165	Hygiene/	14900
166	Baths/	4966
167	Soaps/	2343
168	((postcoital* or postcoitus* or postsex* or postintercourse* or post coital* or post coitus* or post sex* or post intercourse* or postmicturit* or micturit* or postmicturat* or micturat* or urinat* or defecat* or toilet* or lavatory or lavatories or perineal* or perineum*) adj3 (prophylaxis* or prophylactic* or treatment* or wipe* or wiping or hygiene* or hygienic* or clean* or douche* or douching* or bath* or soap* or wash* or shower*)).ti,ab.	1611
169	(second* adj3 prevent*).ti,ab.	21506
170	or/162-169	112930
171	20 and 170	1919
172	or/8-10	29047
173	Device Removal/	10427
174	172 and 173	753
175	(Catheter* adj3 (care* or removal* or removing* or remove* or "take* out" or "taking out" or change* or changing* or clean* or wash* or bath* or hygiene* or hygienic*)).ti,ab.	10138
176	174 or 175	10561
177	20 and 176	5423
178	85 or 94 or 95 or 112 or 120 or 128 or 134 or 140 or 161 or 171 or 177	65619
179	limit 178 to yr="2006 -Current"	21429
180	limit 179 to english language	19392
181	Animals/ not (Animals/ and Humans/)	4291504
182	180 not 181	15047
183	limit 182 to (letter or historical article or comment or editorial or news)	784

184 182 not 183	14263
185 Meta-Analysis.pt.	74747
186 Meta-Analysis as Topic/	15461
187 Network Meta-Analysis/	34
188 Review.pt.	2230816
189 exp Review Literature as Topic/	9193
190 (metaanaly* or metanaly* or (meta adj3 analy*)).ti,ab.	109466
191 (review* or overview*).ti.	389897
192 (systematic* adj5 (review* or overview*)).ti,ab.	109630
193 ((quantitative* or qualitative*) adj5 (review* or overview*)).ti,ab.	7343
194 ((studies or trial*) adj2 (review* or overview*)).ti,ab.	36022
195 (integrat* adj3 (research or review* or literature)).ti,ab.	8769
196 (pool* adj2 (analy* or data)).ti,ab.	22123
197 (handsearch* or (hand adj3 search*)).ti,ab.	7550
198 (manual* adj3 search*).ti,ab.	4715
199 or/185-198	2487695
200 184 and 199	2428
201 Randomized Controlled Trial.pt.	448607
202 Controlled Clinical Trial.pt.	91938
203 Clinical Trial.pt.	508233
204 exp Clinical Trials as Topic/	304614
205 Placebos/	34193
206 Random Allocation/	89847
207 Double-Blind Method/	143336
208 Single-Blind Method/	23779
209 Cross-Over Studies/	40867
210 ((random* or control* or clinical*) adj3 (trial* or stud*)).ti,ab.	1003782
211 (random* adj3 allocat*).ti,ab.	28603
212 placebo*.ti,ab.	189958
213 ((singl* or doubl* or trebl* or tripl*) adj (blind* or mask*)).ti,ab.	153095
214 (crossover* or (cross adj over*)).ti,ab.	74298
215 or/201-214	1721840
216 184 and 215	2933

217 216 not 200	2230
218 Observational Studies as Topic/	1959
219 Observational Study/	31517
220 Epidemiologic Studies/	7369
221 exp Case-Control Studies/	834068
222 exp Cohort Studies/	1623327
223 Cross-Sectional Studies/	234990
224 Controlled Before-After Studies/	218
225 Historically Controlled Study/	97
226 Interrupted Time Series Analysis/	243
227 Comparative Study.pt.	1770190
228 case control*.ti,ab.	102767
229 case series.ti,ab.	52479
230 (cohort adj (study or studies)).ti,ab.	133481
231 cohort analy*.ti,ab.	5462
232 (follow up adj (study or studies)).ti,ab.	43245
233 (observational adj (study or studies)).ti,ab.	70390
234 longitudinal.ti,ab.	186074
235 prospective.ti,ab.	454707
236 retrospective.ti,ab.	381342
237 cross sectional.ti,ab.	245513
238 or/218-237	3929955
239 184 and 238	5469
240 239 not (200 or 216)	3795
241 184 not (200 or 216 or 240)	5810
242 exp Drug Resistance, Bacterial/	72249
243 exp Drug Resistance, Multiple/	28752
244 ((bacter* or antibacter* or anti-bacter* or "anti bacter*") adj4 (resist* or tolera*)).ti,ab.	34156
245 ((antibiot* or anti-biot* or "anti biot*") adj4 (resist* or tolera*)).ti,ab.	42316
246 (multi* adj4 drug* adj4 (resist* or tolera*)).ti,ab.	12134
247 (multidrug* adj4 (resist* or tolera*)).ti,ab.	38335
248 (multiresist* or multi-resist* or "multi resist*").ti,ab.	6214
249 ((microb* or antimicrob* or anti-microb* or "anti microb*") adj4 (resist* or tolera*)).ti,ab.	22368

250	(superbug* or super-bug* or "super bug*").ti,ab.	448
251	Superinfection/	1644
252	(superinvasion* or super-invasion* or "super invasion*" or superinfection* or super-infection* or "super infection*").ti,ab.	5185
253	R Factors/	4157
254	"r factor*".ti,ab.	3648
255	(resist* factor* or "r plasmid*" or resist* plasmid*).ti,ab.	5218
256	or/242-255	180317
257	84 and 256	48201
258	limit 257 to yr="2006 -Current"	25203
259	limit 258 to english language	23256
260	259 not 181	20939
261	limit 260 to (letter or historical article or comment or editorial or news)	867
262	260 not 261	20072

Appendix D: Study flow diagram



Appendix E: Evidence prioritisation

Key questions	Included studies[1]		Studies not prioritised[2]	
	Systematic reviews	RCTs	Systematic reviews	RCTs
Which non-pharmacological interventions are effective?				
Cranberry juice concentrate	–	Gunnarsson et al. 2017	–	–
Catheter change	–	Raz et al. 2000	–	–
Which non-antimicrobial pharmacological interventions are effective?				
No evidence identified				
Is an antibiotic effective for managing catheter-associated UTI?				
Antibiotics versus placebo or no treatment	–	Leone et al. 2007	–	Pfefferkorn et al. 2009
Antibiotics versus different antibiotics	–	–	–	–
Dosage, course length and route of administration	–	Darouiche et al. 2014	–	–
Is antibiotic prophylaxis effective for preventing catheter-associated UTI?				
Antibiotics prophylaxis versus placebo or no treatment	Foon et al. 2012 Niël-Weise et al. 2012 Marschall et al. 2013 Lusardi et al. 2013	Dieter et al. 2014	–	Esposito et al. 2006 Petronella et al. 2012
Antibiotic prophylaxis versus different antibiotic prophylaxis	Lusardi et al. 2013	–	–	–
Dosage, course length and route of administration	Niël-Weise et al. 2012 Lusardi et al. 2013	–	–	–

[1] See appendix F for full references of included studies
[2] See appendix I for full references of not-prioritised studies, with reasons for not prioritising these studies

Appendix F: Included studies

Darouiche, RO, Al Mohajer, M; Siddiq, DM et al. (2014) Short versus long course of antibiotics for catheter-associated urinary tract infections in patients with spinal cord injury: a randomized controlled noninferiority trial. Archives of physical medicine and rehabilitation 95(2), 290-6

Dieter, AA; Amundsen, C; Edenfield AL et al. (2014) Oral Antibiotics to Prevent Postoperative Urinary Tract Infection: A Randomized Controlled Trial. Obstetrics & Gynaecology. Vol 123, No.1. January 2014, 96-103.

Foon, R; Toozs-Hobson, P; Latthe, P (2012) Prophylactic antibiotics to reduce the risk of urinary tract infections after urodynamic studies. Cochrane Database of Systematic Reviews 2012, Issue 10. Art. No.: CD008224

Gunnarsson, A-K; Gunningberg, L; Larsson S et al. (2017) Cranberry juice concentrate does not significantly decrease the incidence of acquired bacteriuria in female hip fracture patients receiving urine catheter: a double-blind randomized trial. Clinical interventions in aging 12, 137-143

Leone, M; Perrin, AS; Granier, I et al. (2007) A randomised trial of catheter change and short course antibiotics for asymptomatic bacteriuria in catheterized ICU patients. Intensive Care Medicine 33(4), 726-729

Lusardi, G; Lipp, A; Shaw C (2013) Antibiotic prophylaxis for short-term catheter bladder drainage in adults. The Cochrane database of systematic reviews (7), CD005428

Marschall, J; Carpenter, CR; Fowler, S et al. (2013) Antibiotic prophylaxis for urinary tract infections after removal of urinary catheter: meta-analysis. BMJ (Clinical research ed.) 346, f3147

Niël-Weise, BS; van den Broek, PJ; da Silva, EMK et al. (2012) Urinary catheter policies for long-term bladder drainage. Cochrane Database of Systematic Reviews 2012, Issue 8. Art. No.: CD004201

Raz, R; Schiller, D Nicolle, LE (2000) Chronic indwelling catheter replacement before antimicrobial therapy for symptomatic urinary tract infection. The Journal of Urology Vol. 164, October, 1254-1258.

Appendix G: Quality assessment of included studies

G.1 Antimicrobials

Table 4: Overall risk of bias/quality assessment – systematic reviews (SR checklist)

Study reference	Lusardi et al. 2013	Marschall et al. 2013	Foon et al. 2012	Niël-Weise et al. 2012
Did the review address a clearly focused question?	Yes	Yes	Yes	Yes
Did the authors look for the right type of papers?	Yes	Yes	Yes	Yes
Do you think all the important, relevant studies were included?	Yes	Yes	Yes	Yes
Did the review's authors do enough to assess the quality of the included studies?	Yes	Yes	Yes	Yes
If the results of the review have been combined, was it reasonable to do so?	Yes	Yes	Yes	Unclear[b]
What are the overall results of the review?	See GRADE profiles			
How precise are the results?	See GRADE profiles			
Can the results be applied to the local population?	Yes	Yes	Yes	Yes
Were all important outcomes considered?	Yes	No[a]	Yes	Yes
Are the benefits worth the harms and costs?	See GRADE profiles			

[a] The only outcome was prevention of urinary tract infection
[b] Their rationale for the pooling of data was unclear

Table 5: Overall risk of bias/quality assessment – randomised controlled trials (RCT checklist)

Study reference	Gunnarsson et al. 2017	Dieter et al. 2014	Raz et al. 2000	Darouiche et al. 2017	Leone et al. 2007
Did the trial address a clearly focused issue?	Yes	Yes	Yes	Yes	Yes
Was the assignment of patients to treatments randomised?	Yes	Yes	Yes	Yes	Yes
Were patients, health workers and study personnel blinded?	Yes	Yes	No[b]	No[b]	No[e]
Were the groups similar at the start of the trial?	Yes	Yes	Yes	Yes	Yes
Aside from the experimental intervention, were the groups treated equally?	Yes	Yes	Yes	No[c]	Yes
Were all of the patients who entered the trial properly accounted for at its conclusion?	Yes	Yes	Yes	Yes	Yes
How large was the treatment effect?	See GRADE profiles	See GRADE profiles	See GRADE profiles	See GRADE profiles	See GRADE profiles
How precise was the estimate of the treatment effect?	See GRADE profiles	See GRADE profiles	See GRADE profiles	See GRADE profiles	See GRADE profiles
Can the results be applied in your context? (or to the local population)	Yes	Yes	Yes	Yes	Yes
Were all clinically important outcomes considered?	No[a]	No[d]	No[d]	No[d]	Yes
Are the benefits worth the harms and costs?	See GRADE profiles	See GRADE profiles	See GRADE profiles	See GRADE profiles	See GRADE profiles

[a] Only 3 outcomes included (positive urine culture, clinical symptoms of urinary tract infection and Health Related Quality of Life), only positive urine culture results were reported
[b] Blinding of patients and health workers was not possible as the intervention included catheter change, however no report that investigators were blinded or uninvolved in patient care
[c] More patients in the intervention group received multiple antibiotics than in the control group
[d] Only clinical, microbiological and adverse events outcomes were reported
[e] Patients, health workers were not blinded to intervention, although data were analysed by a blinded investigator not involved with patient management or care

Appendix H: GRADE profiles

H.1 Non-pharmacological interventions in adults and children

Table 6: GRADE profile – catheter change before antibiotics for managing catheter-associated UTI

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Catheter change plus antibiotics[1]	No catheter change and antibiotics	Relative (95% CI)	Absolute		
Cure or improvement at 72 hours in older adults in long term care facilities (assessed with: clinical signs of UTI had disappeared or improved)												
1[2]	randomised trials	serious[3]	not applicable	no serious indirectness	no serious imprecision	none	25/27 (92.6%)	11/27 (40.7%)	p<0.001 NICE analysis: RR 2.27 (95% CI 1.42 to 3.63)	517 more per 1000 (from 171 more to 1000 more)	⊕⊕⊕O MODERATE	CRITICAL
Cure or improvement at 7 days in older adults in long term care facilities (after therapy) (assessed with: clinical signs of UTI had disappeared or improved)												
1[2]	randomised trials	serious[3]	not applicable	no serious indirectness	serious[4]	none	25/27 (92.6%)	21/27 (77.8%)	p=0.145 NICE analysis: RR 1.19 (95% CI 0.95 to 1.50)	148 more per 1000 (from 39 fewer to 389 more)	⊕⊕OO LOW	CRITICAL
Cure or improvement at 28 days in older adults in long term care facilities (after therapy) (assessed with: clinical signs of UTI had disappeared or improved)												
1[2]	randomised trials	serious[3]	not applicable	no serious indirectness	serious[4]	none	24/27 (88.9%)	16/27 (59.3%)[5]	p=0.015 NICE analysis: RR 1.5 (95% CI 1.07 to 2.11)	296 more per 1000 (from 41 more to 658 more)	⊕⊕OO LOW	CRITICAL
Microbiological growth (catheter specimen of urine) versus no growth at 72 hours												
1[2]	randomised trials	serious[3]	not applicable	no serious indirectness	no serious imprecision	none	24	8	p<0.001	-	⊕⊕⊕O MODERATE	CRITICAL
Microbiological growth (catheter specimen of urine) versus no growth at 7 days after therapy												
1[2]	randomised trials	serious[3]	not applicable	no serious indirectness	serious[4]	none	18	9	p=0.01	-	⊕⊕OO LOW	CRITICAL
Microbiological growth (catheter specimen of urine) versus no growth at 28 days after therapy												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Catheter change plus antibiotics[1]	No catheter change and antibiotics	Relative (95% CI)	Absolute		
1[2]	randomised trials	serious[3]	not applicable	no serious indirectness	serious[4]	none	13	5	p=0.02	-	⊕⊕OO LOW	CRITICAL
Recurrence of infection at 7 days in older adults in long term care facilities (after therapy)												
1[2]	randomised trials	serious[3]	not applicable	no serious indirectness	very serious[6]	none	2/27 (7.4%)	3/27 (11.1%)	NICE analysis: RR 0.67 (95% CI 0.12 to 3.68)	37 fewer per 1000 (from 98 fewer to 298 more)	⊕OOO VERY LOW	CRITICAL
Recurrence of infection at 28 days in older adults in long term care facilities (after therapy)												
1[2]	randomised trials	serious[3]	not applicable	no serious indirectness	very serious[6]	none	3/27 (11.1%)	7/27 (25.9%)	NICE analysis: RR 0.43 (95% CI 0.12 to 1.49)	148 fewer per 1000 (from 228 fewer to 127 more)	⊕OOO VERY LOW	CRITICAL
Treatment failure at day 7 in older adults in long term care facilities (after therapy)												
1[2]	randomised trials	serious[3]	not applicable	no serious indirectness	very serious[6]	none	0/27 (0%)	3/27 (11.1%)	NICE analysis: RR 0.14 (95% CI 0.01 to 2.64)	96 fewer per 1000 (from 110 fewer to 182 more)	⊕OOO VERY LOW	CRITICAL
Treatment failure at 28 days in older adults in long term care facilities (after therapy)												
1[2]	randomised trials	serious[3]	not applicable	no serious indirectness	very serious[6]	none	0/27 (0%)	4/27 (14.8%)	NICE analysis: RR 0.11 (95% CI 0.01 to 1.97)	132 fewer per 1000 (from 147 fewer to 144 more)	⊕OOO VERY LOW	CRITICAL
Mortality in older adults in long term care facilities (assessed with: Death from urosepsis)												
1[2]	randomised trials	serious[3]	not applicable	no serious indirectness	very serious[6]	none	0/27 (0%)	2/27 (7.4%)[7]	NICE analysis: RR 0.2 (95% CI 0.01 to 3.98)	59 fewer per 1000 (from 73 fewer to 221 more)	⊕OOO VERY LOW	CRITICAL
Mean days of fever in older adults in long term care facilities (measured with: Temperature 37.5°C or over; Better indicated by lower values)												
1[2]	randomised trials	serious[3]	not applicable	no serious indirectness	serious[8]	none	27	27	Intervention: 2.9 days (SD ±1.9) Control: 4.6 days (SD ±1.9)	MD 1.7 lower (2.71 to 0.69 lower)	⊕⊕OO LOW	CRITICAL

Abbreviations: UTI, Urinary tract infection; RR, Relative risk; p, P value; SD, Standard deviation; MD, Mean difference.

[1] Initial antibiotics was either ciprofloxacin 400 mg or ofloxacin 300 mg (intravenously) twice daily. Once afebrile for ≥24 hour's participants were switched to oral therapy with ciprofloxacin 500 mg or ofloxacin 200 mg twice daily. Antibiotic therapy was for 14 days. Catheter change was performed before initiation of catheter change

[2] Raz et al. 2000

[3] Downgraded 1 level - open label RCT

[4] Downgraded 1 level - at a default minimal important difference of 25% data suggest no meaningful difference or appreciable benefit with catheter change plus antibiotics

[5] Note authors state 16/27 (54%) but this would require a group n=30
[6] Downgraded 2 levels - at a 95% confidence interval, data are consistent with no meaningful difference, appreciable benefit or appreciable harm
[7] 2 patients died of urosepsis on days 2 and 3 of therapy in the no catheter change group
[8] Downgraded 1 level - at a default minimal important difference of 0.5 of the standard deviation of the control group (0.95) data suggest no meaningful difference or appreciable benefit with catheter change plus antibiotics

Table 7: GRADE profile – cranberry juice concentrate for preventing catheter-associated UTI

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cranberry juice concentrate[1]	Placebo	Relative (95% CI)	Absolute		
Positive urine culture at post-operative day 5 (ITT population) (assessed with: >10^4 cfu/mL urine specimen)												
1[2]	randomised trials	no serious risk of bias	not applicable	no serious indirectness	very serious[3]	none	14/53 (26.4%)	15/44 (34.1%)	NICE analysis: RR 0.77 (95% CI 0.42 to 1.42)	78 fewer per 1000 (from 198 fewer to 143 more)	⊕⊕OO LOW	CRITICAL
Positive urine culture at post-operative day 14 (ITT population) (assessed with: >10^4 cfu/mL)												
1[2]	randomised trials	no serious risk of bias	not applicable	no serious indirectness	very serious[3]	none	12/49 (24.5%)	10/43 (23.3%)	NICE analysis: RR 1.05 (95% CI 0.51 to 2.19)	12 more per 1000 (from 114 fewer to 277 more)	⊕⊕OO LOW	CRITICAL
Positive urine culture at post-operative days 5 or 14 (ITT population) (assessed with: >10^4 cfu/mL)												
1[2]	randomised trials	no serious risk of bias	not applicable	no serious indirectness	very serious[3]	none	23/61 (37.7%)	19/50 (38%)	RR 0.988 (95% CI 0.457 to 2.135)	5 fewer per 1000 (from 206 fewer to 431 more)	⊕⊕OO LOW	CRITICAL
Positive urine culture at post-operative day 5 (PP population) (assessed with: >10^4 cfu/mL)												
1[2]	randomised trials	no serious risk of bias	not applicable	no serious indirectness	very serious[3]	none	13/47 (27.7%)	13/33 (39.4%)	RR 0.588 (95% CI 0.288 to 1.516)	162 fewer per 1000 (from 280 fewer to 203 more)	⊕⊕OO LOW	IMPORTANT
Positive urine culture at post-operative day 14 (PP population) (assessed with: >10^4 cfu/mL)												
1[2]	randomised trials	no serious risk of bias	not applicable	no serious indirectness	very serious[3]	none	10/40 (25%)	9/33 (27.3%)	RR 0.889 (95% CI 0.312 to 2.536)	30 fewer per 1000 (from 188 fewer to 419 more)	⊕⊕OO LOW	IMPORTANT
Positive urine culture at post-operative days 5 or 14 (PP population) (assessed with: >10^4 cfu/mL)												
1[2]	randomised trials	no serious risk of bias	not applicable	no serious indirectness	very serious[3]	none	20/52 (38.5%)	16/37 (43.2%)	RR 0.820 (95% CI 0.348 to 1.933)	78 fewer per 1000 (from 282 fewer to 403 more)	⊕⊕OO LOW	IMPORTANT

Abbreviations: ITT, Intention-to-treat analysis; PP, Per protocol analysis; Cfu/mL, Colony forming units per millilitre; RR, Relative risk.

[1] Two capsules of the study drug 3 times a day. Each capsule contained 550 mg of cranberry powder with 4.19 mg of PAC (putative active ingredient).
[2] Gunnarsson et al. 2017
[3] Downgraded 2 levels - at a 95% confidence interval, data are consistent with no meaningful difference, appreciable benefit or appreciable harm

H.2 Antibiotics for managing catheter-associated UTI in adults

Table 8: GRADE profile - Antibiotics for asymptomatic bacteriuria in people with a short-term catheter

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Catheter change and short course of antibiotics[1]	No catheter change and no antibiotics	Relative (95% CI)	Absolute		
Urosepsis at follow-up in ICU patients with asymptomatic bacteriuria (Urosepsis defined as, see footnote[2])												
1[3]	randomised trials	no serious risk of bias	not applicable	no serious indirectness	very serious[4]	none	3/30 (10%)[5]	3/30 (10%)[6]	p=1 NICE analysis: RR 1.0 (95% CI 0.22 to 4.56)	0 fewer per 1000 (from 78 fewer to 356 more	⊕⊕OO LOW	CRITICAL
Bacteraemia or severe sepsis in ICU patients with asymptomatic bacteriuria												
1[3]	randomised trials	no serious risk of bias	not applicable	no serious indirectness	very serious[4]	none	7/30 (23.3%)[7]	5/30 (16.7%)[8]	p>0.05 NICE analysis: RR 1.40 (95% CI 0.50 to 3.92)	67 more per 1000 (from 83 fewer to 487 more)	⊕⊕OO LOW	CRITICAL
Positive urine culture at day 7 in ICU patients with asymptomatic bacteriuria (assessed with: >10^5 cfu/mL and no more than 2 different spp.)												
1[3]	randomised trials	no serious risk of bias	not applicable	no serious indirectness	serious[9]	none	9/30 (30%)	21/30 (70%)	p=0.009 NICE analysis: RR 0.43 (95% CI 0.24 to 0.78)	399 fewer per 1000 (from 532 fewer to 154 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Positive urine culture at day 15 in ICU patients with asymptomatic bacteriuria (assessed with: >10^5 cfu/mL and no more than 2 different spp.)												
1[3]	randomised trials	no serious risk of bias	not applicable	no serious indirectness	very serious[4]	none	8/30 (26.7%)	11/30 (36.7%)	p>0.05 NICE analysis: RR 0.73 (95% CI 0.34 to 1.55)	99 fewer per 1000 (from 242 fewer to 202 more)	⊕⊕OO LOW	CRITICAL

Abbreviations: ICU, Intensive care unit; RR, Relative risk; p, P value; Cfu/mL, Colony forming units per millilitre.

[1] Antibiotics used included amoxicillin, ciprofloxacin, amoxicillin plus clavulanic acid, ceftriaxone, colimycin, piperacillin plus clavulanic acid, cefepime, amikacin, fosfomycin and fluconazole
[2] presence of at least two of four signs: body temperature >38°C or <36°C; heart rate >90 beats/min; breathing rate >20 cycles/min or $PaCO_2$ <32 mmHg or mechanical ventilation; and white blood cell count >12 G/l or <4 G/l
[3] Leone et al. 2007
[4] Downgraded 2 levels - at a 95% confidence interval, data are consistent with no meaningful difference, appreciable benefit or appreciable harm
[5] No overall significant differences between groups noted for renal function, body temperature, white cells, duration of catheterisation after study inclusion, ICU length of stay or mortality
[6] Those with urosepsis were treated with ceftriaxone, ciprofloxacin and tazocillin plus clavulanic acid
[7] 2 with bacteraemia and 5 with severe sepsis
[8] 1 with bacteraemia and 4 with severe sepsis
[9] Downgraded 1 level – at a default minimal important difference of 25% data suggest no meaningful difference or appreciable benefit with catheter change and short course of antibiotics

Table 9: GRADE profile – 5 days versus 10 days in people with a long-term catheter

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Catheter change and 5 days of antibiotics[1]	10 days of antibiotics[1] with original catheter	Relative (95% CI)	Absolute		
Clinical cure[2] at end of therapy in adults with spinal cord injury (PP population)												
1[3]	randomised trials	serious[4]	not applicable	no serious indirectness	no serious imprecision	none	28/28 (100%)	27/27 (100%)	p<0.001[5] NICE analysis: RR 1.0 (95% CI 0.93 to 1.07)	0 fewer per 1000 (from 67 fewer to 68 more)	⊕⊕⊕O MODERATE	CRITICAL
Microbiological response[6] at end of therapy in adults with spinal cord injury (PP population)												
1[3]	randomised trials	serious[4]	not applicable	no serious indirectness	serious[7]	none	23/28 (82.1%)	24/27 (88.9%)	p=0.5[5] NICE analysis: RR 0.92 (95% CI 0.74 to 1.15)	71 fewer per 1000 (from 231 fewer to 133 more)	⊕⊕OO LOW	CRITICAL
Resolution of pyuria (white blood cells in the urine) at end of therapy in adults with spinal cord injury (assessed in the PP population)												
1[3]	randomised trials	serious[4]	not applicable	no serious indirectness	no serious imprecision	none	25/28 (89.3%)	24/27 (88.9%)	p=0.19[9] NICE analysis: RR 1.0 (95% CI 0.83 to 1.21)	0 per 1000 (from 151 fewer to 187 more)	⊕⊕⊕O MODERATE	CRITICAL
All adverse events												
1[3]	randomised trials	serious[4]	not applicable	no serious indirectness	serious[7]	none	18/28 (64.3%)	11/27 (40.7%)	P=0.09[10] NICE analysis: RR 1.58 (95% CI 0.93 to 2.69)	263 more per 1000 (from 29 fewer to 689 more)	⊕⊕OO LOW	CRITICAL
Recurrent urinary tract infection												
1[3]	randomised trials	serious[4]	not applicable	no serious indirectness	serious[7]	none	9/28 (32.1%)	3/27 (11.1%)	RR 0.35 (95% CI 0.10 to 1.14)	25 fewer per 1000 (from 44 fewer to 1 fewer)	⊕⊕OO LOW	CRITICAL

Abbreviations: PP, Per protocol analysis; RR, Relative risk; p, P value , HR, Hazard ratio.

[1] Antibiotics were empirical therapy then changed when sensitivities were available (beta-lactam and fluoroquinolones) both orally and intravenous, full list of antibiotics not reported.
[2] Clinical cure defined as an absence of urinary symptoms at the end of therapy
[3] Darouiche et al. 2014. This study also reported results of a multiple logistic regression analysis which found no association between gender, catheter type, history of hydronephrosis, pre-treatment organism or adjustment of antibiotics and microbiologic response (p>0.06)
[4] Downgraded 1 level - Blinding of assessor not reported, unequal treatment given to intervention and controls
[5] Please note that the trial design was non-inferiority, hence a significant p value (i.e. non-inferior) but no difference in relative risk
[6] Microbiological response defined as clearance of the causative organism at the end of therapy

[7] Downgraded 1 level - at a default minimal important difference of 25% data suggest no meaningful difference or appreciable harm with catheter change and 5 days of antibiotics
[8] p=0.5, suggests intervention is not non-inferior (upper bound of 95% CI 26% and the margin set for the study for non-inferiority was 10%)
[9] p=0.19 suggests intervention is not non-inferior (upper bound of 95% CI 16% and the margin set for the study for non-inferiority was 10%)
[10] Significant more people had recurrent urinary tract infection in the 5 day group than the 10 day group. No significant difference was found for new CAUTI, *C. diff* colitis or death

H.3 Antibiotic prophylaxis for preventing catheter-associated UTI in adults

Table 10: GRADE profile – antibiotic prophylaxis for adults with a long-term catheter[1]

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antibiotic prophylaxis	Antibiotics used when clinically indicated	Relative (95% CI)	Absolute		
Symptomatic urinary tract infection (older adults in nursing home with indwelling catheter)[2]												
1[3]	randomised trials[4]	very serious[5]	not applicable	no serious indirectness	serious[6]	none	1/276	12/259	NICE analysis: IRR 0.08 (95% CI 0.62 to 9.75)	-	⊕OOO VERY LOW	CRITICAL
Rate of visual encrustation (older adults in nursing home with indwelling catheter)[7]												
1[3]	randomised trials[4]	very serious[5]	not applicable	no serious indirectness	no serious imprecision	none	4/276	19/259	NICE analysis: IRR 0.2 (95% CI 0.02 to 1.52)	-	⊕⊕OO LOW	CRITICAL
Rate of catheter obstructions (older adults in nursing home with indwelling catheter) [7]												
1[3]	randomised trials[4]	very serious[5]	not applicable	no serious indirectness	no serious imprecision	none	2/276	8/259	NICE analysis: IRR 0.23 (95% CI 0.04 to 1.14)	-	⊕⊕OO LOW	CRITICAL
Rate of adverse events (older adults in nursing home with indwelling catheter) [7]												
1[3]	randomised trials[4]	very serious[5]	not applicable	no serious indirectness	no serious imprecision	none	596/276	744/259	NICE analysis: IRR 0.75 (95% CI 0.25 to 2.25)	-	⊕⊕OO LOW	CRITICAL
Patients general condition (older adults in nursing home with indwelling catheter[2])												
1[3]	randomised trials[4]	very serious[5]	not applicable	no serious indirectness	very serious[8]	none	12/23 (52.2%)	1/23 (4.3%)	NICE analysis: RR 12.0 (95% CI 1.70 to 84.89)	-	⊕OOO VERY LOW	CRITICAL
Microbial resistance pattern (number of isolated resistant strains/number of strains[1])												
1[3]	randomised trials[4]	very serious[5]	not applicable	no serious indirectness	serious[6]	none	20/22 (90.9%)	8/41 (19.5%)	NICE analysis: RR 4.66 (95% CI 2.47 to 8.80)	-	⊕OOO VERY LOW	CRITICAL
Number of gram-negative isolates (Gram-negative isolates/total number of isolates[1])												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antibiotic prophylaxis	Antibiotics used when clinically indicated	Relative (95% CI)	Absolute		
1[3]	randomised trials[4]	very serious[5]	not applicable	no serious indirectness	no serious imprecision	none	5/22 (22.7%)	31/41 (75.6%)	NICE analysis: RR 0.30 (95% CI 0.14 to 0.66)	-	⊕⊕OO LOW	CRITICAL
Rate of bacteriuria, asymptomatic or symptomatic (measured in adults using intermittent catheterisation)												
2[3]	randomised trials[9]	serious[10]	serious[11]	no serious indirectness	no serious imprecision	none	36	41	IDD -0.14 (95% CI -0.23 to -0.05)[12]	-	⊕⊕OO LOW	CRITICAL
Rate of bacteriuria, asymptomatic or symptomatic (measured in adults using intermittent catheterisation)[7]												
1[3]	randomised trials[4]	serious[10]	not applicable	no serious indirectness	no serious imprecision	none	9/90	25/85	NICE analysis: RR 0.34 (95% CI 0.156 to 0.74)	-	⊕⊕⊕O MODERATE	CRITICAL
Rate of bacteriuria, asymptomatic or symptomatic (measured in adults using intermittent catheterisation every 4 hours)												
1[3]	randomised trials[9]	serious[10]	not applicable	no serious indirectness	no serious imprecision	none	1	1	IDR 0.15 (95% CI 0.05 to 0.42)	-	⊕⊕⊕O MODERATE	CRITICAL
Rate of bacteriuria, asymptomatic or symptomatic (measured in adults using intermittent catheterisation every 8 hours)												
1[3]	randomised trials[9]	serious[10]	not applicable	no serious indirectness	serious[13]	none	1	1	IDR 0.49 (95% CI 0.21 to 1.12)	-	⊕⊕OO LOW	CRITICAL
At least 1 episode of bacteriuria, asymptomatic or symptomatic (measured in adults using intermittent catheterisation)												
1[3]	randomised trials[9]	serious[10]	not applicable	no serious indirectness	serious[14]	none	49/66 (74.2%)	52/60 (86.7%)	RR 0.86 (95% CI 0.72 to 1.02)[15]	121 fewer per 1000 (from 243 fewer to 17 more)	⊕⊕OO LOW	CRITICAL
Rate of symptomatic bacteriuria (measured in adults using intermittent catheterisation)												
1[3]	randomised trials[9]	serious[10]	not applicable	no serious indirectness	serious[13]	none	0	0	IDR 0.56 (95% CI 0.27 to 1.15)	-	⊕⊕OO LOW	CRITICAL
At least 1 episode of definite symptomatic bacteriuria (assessed in adults with intermittent catheterisation)												
1[3]	randomised trials[9]	serious[10]	not applicable	no serious indirectness	no serious imprecision	none	4/66 (6.1%)	19/60 (31.7%)	RR 0.19 (95% CI 0.07 to 0.53)[16]	257 fewer per 1000 (from 149 fewer to 295 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Rate of adverse events (events per catheterisation week in adults using intermittent catheterisation)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antibiotic prophylaxis	Antibiotics used when clinically indicated	Relative (95% CI)	Absolute		
1[3]	randomised trials[9]	serious[10]	not applicable	no serious indirectness	serious[13]	none	0	0	IDR 0.74 higher (95% CI 0.53 to 1.02 higher)	-	⊕⊕OO LOW	CRITICAL
At least 1 episode of adverse events (assessed in adults using intermittent catheterisation)												
1[3]	randomised trials[9]	serious[10]	not applicable	no serious indirectness	serious[14]	none	37/67 (55.2%)	40/62 (64.5%)	RR 0.86 (95% CI 0.64 to 1.14)	90 fewer per 1000 (from 232 fewer to 90 more)	⊕⊕OO LOW	CRITICAL
At least 1 episode of antibiotics for urinary tract infection (assessed in adults using intermittent catheterisation)												
1[3]	randomised trials[9]	serious[10]	not applicable	no serious indirectness	serious[14]	none	41/66 (62.1%)	48/60 (80%)	RR 0.78 (95% CI 0.62 to 0.97)	176 fewer per 1000 (from 24 fewer to 304 fewer)	⊕⊕OO LOW	CRITICAL
At least 1 episode of bacteriuria due to co-trimoxazole resistant organisms (assessed in adults using intermittent catheterisation)												
1[3]	randomised trials[9]	serious[10]	not applicable	no serious indirectness	no serious imprecision	none	47/66 (71.2%)	45/60 (75%)	RR 0.95 (95% CI 0.77 to 1.17)[17]	38 fewer per 1000 (from 173 fewer to 127 more)	⊕OOO VERY LOW	CRITICAL

Abbreviations: IDR, Incidence density rate; IRR, Incidence rate ratio; RR, Relative risk

[1] intermittent or indwelling urethral catheter
[2] Unclear how this was assessed
[3] Niel-Weise et al. 2012
[4] Cross-over design
[5] Downgraded 2 levels - Unclear risk of bias (random sequence generation and allocation concealment) and high risk of bias for incomplete outcome data
[6] Downgraded 1 level - wide 95% confidence intervals
[7] Events per catheterisation weeks not individuals
[8] Downgraded 2 levels – very wide 95% confidence interval
[9] Parallel group design used
[10] Downgraded 1 level - No study was rated as at low risk of bias by the Cochrane reviewers
[11] Downgraded 1 level – I^2>50%
[12] IDR, Incidence Density Differences (Incidence Density Rate for this analysis was 0.61 (95% CI 0.44 to 0.87; I^2=82%, Fixed effect model used by the authors)
[13] Downgraded 1 level - wide 95% confidence intervals with a low number of events
[14] Downgraded 1 level – at a minimal important difference of 25% data are consistent with no meaningful difference or appreciable harm with antibiotic use when clinically indicated
[15] Similar effects in sub-group analysis for both men (RR 0.85; 95% CI 0.71 to 1.03) and women (RR 0.89; 95% CI 0.57 to 1.38)
[16] The authors also calculated a risk difference (-0.26; 95% CI -0.39 to -0.13), in the studies all but 1 participant with the outcome was male (RR 0.20, 95% CI 0.07 to 0.56) the females risk ratio was non-significant (RR 0.30; 95% CI 0.01 to 6.47)
[17] Also from the same study 'At least 1 time recovery of co-trimoxazole resistant gram negative bacilli from weekly surveillance culture' (RR 1.17; 95% CI 0.80 to 1.72)

Table 11: GRADE profile – antibiotic prophylaxis versus placebo (or no treatment) before or during short-term catheterisation in hospital[1]

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antibiotic prophylaxis[2]	Placebo or no treatment[3]	Relative (95% CI)	Absolute		
Asymptomatic bacteriuria in surgical patients (assessed[4] with either >10[3] cfu/mL [2 RCTs] or >10[5] cfu/mL [1 RCT])												
3[5]	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	no serious imprecision	none	21/255 (8.2%)	57/182 (31.3%)	RR 0.20 (95% CI 0.13 to 0.31)	251 fewer per 1000 (from 216 fewer to 272 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Asymptomatic bacteriuria in surgical patients (assessed[7] with >10[5] cfu/mL)												
1[5]	randomised trials	serious[6]	not applicable	no serious indirectness	no serious imprecision	none	3/48 (6.3%)	13/42 (31%)	RR 0.20 (95% CI 0.06 to 0.66)	248 fewer per 1000 (from 105 fewer to 291 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Asymptomatic bacteriuria in non-surgical patients (assessed[8] with >10[5] cfu/mL)												
1[5]	randomised trials	serious[6]	not applicable	no serious indirectness	serious[9]	none	15/52 (28.8%)	12/26 (46.2%)	RR 0.63 (95% CI 0.34 to 1.13)	171 fewer per 1000 (from 305 fewer to 60 more)	⊕⊕OO LOW	CRITICAL
1[5]	randomised trials	serious[6]	not applicable	no serious indirectness	no serious imprecision	none	8/80 (10%)	44/82 (53.7%)	RR 0.19 (95% CI 0.09 to 0.37)	435 fewer per 1000 (from 338 fewer to 488 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Urinary tract infection treatment within 3 weeks of pelvic organ prolapse surgery or urinary incontinence surgery[10]												
1[11]	randomised trials	no serious risk of bias	not applicable	no serious indirectness	serious[9]	none	10/78 (12.8%)[12]	18/81 (22.2%)	RR 1.73 (95% CI 0.85 to 3.52)[13]	162 more per 1000 (from 33 fewer to 560 more)	⊕⊕⊕O MODERATE	CRITICAL
Pyuria (white blood cells in urine) in surgical patients												
2[5]	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	no serious imprecision	none	12/159 (7.5%)	27/82 (32.9%)	RR 0.23 (95% CI 0.13 to 0.42)	254 fewer per 1000 (from 191 fewer to 286 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Number of gram negative strains / total number of strains in surgical patients (assessed before catheter removal)[14]												
1[5]	randomised trials	serious[6]	not applicable	no serious indirectness	serious[9]	none	0/23 (0%)	29/70 (41.4%)	RR 0.05 (95% CI 0 to 0.79)	394 fewer per 1000 (from 87 fewer to 414 fewer)	⊕⊕OO LOW	CRITICAL
Number of gram negative strains / total number of strains in surgical patients (assessed six weeks after discharge)[14]												
1[5]	randomised trials	serious[6]	not applicable	no serious indirectness	no serious imprecision	none	24/126 (19%)	27/51 (52.9%)	RR 0.36 (95% CI 0.23 to 0.56)	339 fewer per 1000 (from 233 fewer to 408 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Febrile morbidity in surgical patients (assessed with: temperature above 38°C[15])												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antibiotic prophylaxis[2]	Placebo or no treatment[3]	Relative (95% CI)	Absolute		
2[5]	randomised trials	serious[6]	serious[16]	no serious indirectness	serious[9]	none	18/144 (12.5%)[17]	33/142 (23.2%)	RR 0.53 (95% CI 0.31 to 0.89) NICE analysis: RR 0.51 (95% CI 0.23 to 1.12 REM)	109 fewer per 1000 (from 26 fewer to 160 fewer)	⊕OOO VERY LOW	CRITICAL
Adverse reaction to antibiotics												
3[5]	randomised trials	serious[6]	very serious[18]	no serious indirectness	no serious imprecision	none	1 RCT reported 23 adverse reactions, none were judged to be treatment related and there were no serious adverse events. 1 RCT reported no serious adverse reactions to co-trimoxazole. 1 RCT reported 3 patients taking ciprofloxacin had moderate gastrointestinal symptoms on the second day of prophylaxis and so the drug was discontinued.				⊕OOO VERY LOW	CRITICAL
Length of stay (measured with mean length of pre-surgical stay (days) in hospital; Better indicated by lower values; data not pooled)												
1[5]	randomised trials	serious[6]	not applicable	no serious indirectness	serious[9]	none	3.9 days (±3.6 SD)[18]	5.9 days (±7.5 SD)	NICE analysis: MD -2.00 (95% CI -5.08 to 1.08, p=0.20)	-	⊕⊕OO LOW	IMPORTANT
1[5]	randomised trials	serious[6]	not applicable	no serious indirectness	serious[9]	none	3.3 days (±3.7 SD)[14]	5.9 days (±7.5 SD)	NICE analysis: MD -2.60 (95% CI -5.72 to 0.52, p=0.10)	-	⊕⊕OO LOW	IMPORTANT
Length of stay (measured with mean length of post-surgical stay (days) in hospital; Better indicated by lower values; 2 RCTs, data not pooled)												
1[5]	randomised trials	serious[6]	not applicable	no serious indirectness	serious[9]	none	6.0 days (±4.2 SD)[18]	7.6 days (±6.6 SD)	NICE analysis: MD -1.6 (95% CI -4.50 to 1.30, p=0.28)	-	⊕⊕OO LOW	IMPORTANT
1[5]	randomised trials	serious[6]	not applicable	no serious indirectness	serious[9]	none	7.4 days (±5.4 SD)[14]	7.6 days (±6.6 SD)	NICE analysis: MD –0.20 (95% CI -3.41 to 3.01, p=0.9)	-	⊕⊕OO LOW	IMPORTANT
Length of stay (measured with mean length of stay in hospital; Better indicated by lower values; 2 RCTs, data not pooled)												
1[5]	randomised trials	serious[6]	not applicable	no serious indirectness	serious[19]	none	7 days (±1.2 SD)[20]	8 days (±1.4 SD)	NICE analysis: MD -1.0 (95% CI -1.52 to -0.48, p=0.0002)	-	⊕⊕OO LOW	IMPORTANT
1[5]	randomised trials	serious[6]	very serious[18]	no serious indirectness	no serious imprecision	none	In 1 additional RCT the average hospital stay was 6 days and 5.6 days for abdominal hysterectomy and 6.1 days and 7.6 days for vaginal hysterectomy patients in the prophylaxis group and placebo groups respectively.				⊕OOO VERY LOW	IMPORTANT

Abbreviations: Cfu/mL, Colony forming units per millilitre; RR, Relative risk; I^2, a measure of heterogeneity; REM, Random effects model; MD, Mean Difference; SD, Standard deviation.

[1] Suprapubic or urethral catheter for up to 14 days

[2] Antibiotics in studies were cefazolin sodium, levofloxacin, ciprofloxacin, ampicillin, aztreonam and co-trimoxazole
[3] Placebo control in 5 studies, no prophylaxis in 1 study
[4] 1 RCT assessed bacteriuria on the 3rd post-op day and 2 RCTs before catheter removal
[5] Lusardi et al. 2013
[6] Downgraded 1 level - no study was assessed by the Cochrane reviewers as at low risk of bias
[7] Assessed at time of catheter removal, 3rd and 6 days post-operatively
[8] Assessed just before catheter removal or after a maximum of 7 days follow-up
[9] Downgraded 1 level – at a default minimal important difference of 25% data are consistent with no meaningful difference or appreciable benefit with antibiotic prophylaxis
[10] Clinically suspected or culture proven catheter associated - urinary tract infection (defined as >100,000 cfu of a single organism) within 3 weeks of surgery
[11] Dieter et al. 2014
[12] Nitrofurantoin 100 mg once daily during catheterisation
[13] p=0.12, in logistic regression (controlling for confounders including menopausal status, diabetes, pre-operative post void residual volume, creatinine clearance, hysterectomy and duration of catheterisation there was still no difference between nitrofurantoin and placebo (adjusted odds ratio 1.27, 95% CI 0.38 to 4.27, p=0.70)
[14] Ciprofloxacin versus placebo
[15] Definition of febrile morbidity varied between studies (1 study temperature >38°C orally for 2 consecutive days, with blood cultures; 2nd study temperature >38°C on at least 2 occasions four hours apart)
[16] Downgraded 1 level – I^2>50%
[17] 1st study cefazolin sodium 500 mg given peri-operatively then 8 hourly for 3 days (intravenously or intramuscularly); 2nd study co-trimoxazole 480 mg before surgery
[18] Levofloxacin versus placebo
[19] Downgraded 1 level - at a default minimal important difference of 0.5 SD of control arm (placebo 0.7) data are consistent with no meaningful difference or appreciable benefit with antibiotic prophylaxis
[20] Co-trimoxazole versus placebo, febrile morbidity and urinary tract infection prolonged hospitalisation significantly to a mean stay of 9.2 days (± 1.6 days) (p < 0.05).

Table 12: GRADE profile – choice of antibiotic prophylaxis before or during short term catheterisation in hospital[1]

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Antibiotic prophylaxis**	**Antibiotic prophylaxis**	**Relative (95% CI)**	**Absolute**		
Asymptomatic bacteriuria in surgical patients (assessed just before catheter removal with >10^3 cfu/mL)[2]												
1[3]	randomised trials	serious[4]	not applicable	no serious indirectness	very serious[5]	none	2/25 (8%)	0/21 (0%)	RR 4.23 (95% CI 0.21 to 85.53)	-	⊕OOO VERY LOW	CRITICAL
Asymptomatic bacteriuria in surgical patients (assessed just before catheter removal with >10^3 cfu/mL)[6]												
1[3]	randomised trials	serious[4]	not applicable	no serious indirectness	very serious[5]	none	10/54 (18.5%)	8/59 (13.6%)	RR 1.37 (95% CI 0.58 to 3.21)	50 more per 1000 (from 57 fewer to 300 more)	⊕OOO VERY LOW	CRITICAL
Abbreviations: Cfu/mL, Colony forming units per millilitre; RR, Relative risk												

[1] Suprapubic or urethral catheter for up to 14 days

[2] Levofloxacin 250 mg once daily versus ciprofloxacin 500 mg twice daily
[3] Lusardi et al. 2013
[4] Downgraded 1 level - no study was assessed by the Cochrane reviewers as at low risk of bias
[5] Downgraded 2 levels - at a 95% confidence interval, data are consistent with no meaningful difference, appreciable benefit or appreciable harm
[6] Ciprofloxacin 250 mg from 2nd post-operative day until catheter removal versus ciprofloxacin 1000 mg from 2nd post-operative day until catheter removal

Table 13: GRADE profile – dosing and course length of antibiotic prophylaxis before or during short term catheterisation in hospital

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antibiotic prophylaxis[1]	Antibiotic prophylaxis[2]	Relative (95% CI)	Absolute		
Asymptomatic bacteriuria in non-surgical patients (assessed[3] with >10[5] cfu/mL)												
1[4]	randomised trials	serious[5]	not applicable	no serious indirectness	serious[6]	none	3/24 (12.5%)	12/28 (42.9%)	RR 0.29 (95% CI 0.09 to 0.91)	304 fewer per 1000 (from 39 fewer to 390 fewer)	⊕⊕OO LOW	CRITICAL
Abbreviations: Cfu/mL, Colony forming units per millilitre; IM, Intramuscular; RR, Relative risk												

[1] Ampicillin 3 g IM, divided in three equal doses: 1 hour before, at the time of, and 6 hours after insertion of indwelling urinary catheter
[2] Ampicillin 3 x 1 g IM daily throughout the period of indwelling urinary catheterisation
[3] Assessed just before catheter removal or after a maximum of 7 days follow-up
[4] Lusardi et al. 2013
[5] Downgraded 1 level - no study was assessed by the Cochrane reviewers as at low risk of bias
[6] Downgraded 1 level – at a default minimal important difference of 25% data are consistent with no meaningful difference or appreciable benefit with antibiotic prophylaxis at catheterisation

Table 14: GRADE profile – Antibiotic prophylaxis at the time of short term catheter removal in hospital

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antibiotic prophylaxis at removal of short term[1] urethral catheter	Placebo or other control	Relative (95% CI)	Absolute		
Symptomatic urinary tract infection (assessed at 4 to 42 days): subgroup analyses												
7[2]	randomised trials[3]	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	31/665 (4.7%)	90/855 (10.5%)	RR 0.45 (95% CI 0.28 to 0.72)[5]	58 fewer per 1000 (from 29 fewer to 76 fewer)	⊕⊕⊕O MODERATE	CRITICAL
6[2, 6]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	23/404 (5.69%)	57/403 (14.1%)	RR 0.45 (95% CI 0.23 to 0.86)	-	⊕⊕⊕⊕ HIGH	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antibiotic prophylaxis at removal of short term[1] urethral catheter	Placebo or other control	Relative (95% CI)	Absolute		
6[2, 7]	randomised trials	serious[8]	no serious inconsistency	no serious indirectness	no serious imprecision	none	19/528 (3.59%)	72/704 (10.2%)	RR 0.36 (95% CI 0.22 to 0.59)	-	⊕⊕⊕O MODERATE	CRITICAL
5[2, 9]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	29/603 (4.8%)	82/790 (10.3%)	RR 0.45 (95% CI 0.29 to 0.59)	-	⊕⊕⊕O MODERATE	CRITICAL
2[2, 10]	randomised trials	no serious risk of bias	serious[11]	no serious indirectness	very serious[12]	none	2/62 (3.22%)	8/65 (12.3%)	RR 0.44 (95% CI 0.02 to 9.40)	-	⊕OOO VERY LOW	CRITICAL
3[2, 13]	randomised trials	no serious risk of bias	serious[11]	no serious indirectness	serious[14]	none	18/295 (6.1%)	41/289 (14.1%)	NICE analysis: RR 0.45 (95% CI 0.18 to 1.14)	-	⊕⊕OO LOW	CRITICAL
2[2, 15]	randomised trials	serious[8]	no serious inconsistency	no serious indirectness	serious[14]	none	11/308 (3.57%)	41/501 (8.18%)	NICE analysis: RR 0.41 (95% CI 0.22 to 0.79)	-	⊕⊕OO LOW	CRITICAL
3[2, 16]	randomised trials	serious[8]	no serious inconsistency	no serious indirectness	no serious imprecision	none	14/419 (3.34%)	56/590 (9.5%)	NICE analysis: RR 0.34 (95% CI 0.19 to 0.59)	-	⊕⊕⊕O MODERATE	CRITICAL
3[2, 17]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[14]	none	5/109 (4.6%)	16/114 (14%)	NICE analysis: RR 0.35 (95% CI 0.13 to 0.90)	-	⊕⊕⊕O MODERATE	CRITICAL
2[2, 18]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	6/158 (3.8%)	23/138 (16.7%)	NICE analysis: RR 0.25 (95% CI 0.10 to 0.59)	-	⊕⊕⊕⊕ HIGH	CRITICAL
2[2, 19]	trials	no serious risk of bias	serious[11]	no serious indirectness	very serious[12]	none	2/62 (3.22%)	8/65 (12.3%)	NICE analysis: RR 0.41 (95% CI 0.02 to 10.96)	-	⊕OOO VERY LOW	CRITICAL

Abbreviations: RR, Relative risk; I^2, a measure of heterogeneity.

[1] Duration of catheterisation less than 14 days
[2] Marschall et al. 2013
[3] Study included 5 RCTs, 1 unpublished study and 1 non-randomised controlled trial
[4] Downgraded 1 level – includes data from 1 unpublished study and 1 non-randomised trial
[5] Analysis repeated by NICE with Review Manager (5.3) software (authors used "Meta-Analyst" online tool) RR 0.42 (95% CI 0.28 to 0.63, I^2=18% fixed effect model)
[6] Analysis repeated without non-randomised study (NICE analysis: RR 0.42, 95% CI 0.27 to 0.67, I^2=31%, fixed effect model)
[7] Analysis repeated without unpublished study but with non-randomised study (NICE analysis RR 0.34, 95% CI 0.21 to 0.55)
[8] Downgraded 1 level – includes 1 non-randomised trial
[9] Subgroup analysis of only surgical patients includes unpublished study and non-randomised study (NICE analysis RR 0.44, 95% CI 0.29 to 0.66, I^2=6%, fixed effect model)

[10] Subgroup analysis in 2 studies of mixed hospital populations (NICE analysis RR 0.41, 95% CI 0.02 to 10.96, I^2=69%, random effects model)
[11] Downgraded 1 level – I^2 >50%
[12] Downgraded 2 levels - at a 95% confidence interval, data are consistent with no meaningful difference, appreciable benefit or appreciable harm
[13] Additional NICE subgroup analysis of 3 studies (including data from 1 unpublished study) of patients not predominantly undergoing urological surgery (the I^2=51% and with a fixed effect model the NICE analysis showed RR 0.45, 95% CI 0.27 to 0.77)
[14] Downgraded 1 level – at a default minimal important difference of 25% data are consistent with no meaningful difference or appreciable benefit with antibiotic prophylaxis
[15] Additional NICE subgroup analysis of 2 studies (including data from 1 non-randomised study) of patient undergoing prostate surgery
[16] Additional NICE subgroup analysis of 3 studies (including data from 1 non-randomised study, but excluding data from 1 unpublished study) of patients with a median duration of catheterisation >5 days
[17] Additional NICE subgroup analysis of 3 studies (excluding data from 1 unpublished study) of patients with a median duration of catheterisation <5 days
[18] Additional NICE subgroup analysis of 3 studies (excluding data from 1 non-randomised study (prostate) and from 1 unpublished study) of patients with a median duration of catheterisation >5 days
[19] Additional NICE subgroup analysis of 3 studies (excluding data from 1 study (prostate) and 1 unpublished study) of patients with a median duration of catheterisation <5 days.

Table 15: GRADE profile – antibiotic prophylaxis during short-term catheterisation for urodynamic procedures

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antibiotic prophylaxis	Placebo or no treatment	Relative (95% CI)	Absolute		
Symptomatic urinary tract infection in adults (antibiotic versus placebo or no antibiotic)												
4[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	40/201 (19.9%)	59/214 (27.6%)	RR 0.73 (0.52 to 1.03)[4]	74 fewer per 1000 (from 132 fewer to 8 more)	⊕⊕OO LOW	CRITICAL
Bacteriuria (>100,000 bacteria per millilitre/ >10^5 Cfu/mL) following urodynamic study in adults (antibiotics versus placebo)												
9[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	20/489 (4.1%)	60/481 (12.5%)	RR 0.35 (0.22 to 0.56)	81 fewer per 1000 (from 55 fewer to 97 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Bacteriuria (>100,000 bacteria per millilitre/ >10^5 Cfu/mL) following urodynamic studies in adult males (antibiotics versus placebo)												
3[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	2/86 (2.3%)	12/90 (13.3%)	RR 0.21 (0.06 to 0.78)	105 fewer per 1000 (from 29 fewer to 125 fewer)	⊕⊕OO LOW	CRITICAL
Bacteriuria (>100,000 bacteria per millilitre/ >10^5 Cfu/mL) following urodynamic studies in adult women (antibiotics versus placebo)												
7[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	18/385 (4.7%)	45/372 (12.1%)	RR 0.40 (0.24 to 0.67)	73 fewer per 1000 (from 40 fewer to 92 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Bacteriuria (>100,000 bacteria per millilitre/ >10^5 Cfu/mL) following urodynamic studies in patients with spinal injury (antibiotics versus placebo)												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	very serious[5]	none	0/18 (0%)	3/19 (15.8%)	RR 0.15 (0.01 to 2.72)	134 fewer per 1000 (from 156 fewer to 272 more)	⊕OOO VERY LOW	CRITICAL
Haematuria following urodynamic studies in adults (antibiotics versus placebo)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antibiotic prophylaxis	Placebo or no treatment	Relative (95% CI)	Absolute		
2[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	11/176 (6.3%)	23/168 (13.7%)	RR 0.46 (0.23 to 0.91)	74 fewer per 1000 (from 12 fewer to 105 fewer)	⊕⊕OO LOW	CRITICAL
Fever (not defined) following urodynamic studies in adults (antibiotics versus placebo)												
2[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	7/150 (4.7%)	1/149 (0.67%)	RR 5.16 (0.94 to 28.16)	28 more per 1000 (from 0 fewer to 182 more)	⊕⊕OO LOW	CRITICAL
Dysuria following urodynamic studies (antibiotics versus placebo)												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	very serious[5]	none	15/38 (39.5%)	21/44 (47.7%)	RR 0.83 (0.5 to 1.36)	81 fewer per 1000 (from 239 fewer to 172 more)	⊕OOO VERY LOW	CRITICAL
Adverse effects from antibiotics (antibiotics versus placebo)												
2[1]	randomised trials	serious[2]	no serious inconsistency[6]	no serious indirectness	very serious[5]	none	2/135 (1.5%)	0/127 (0%)	RR 4.47 (0.22 to 89.94)	-	⊕OOO VERY LOW	CRITICAL
Abbreviations: CI, Confidence interval; RR, Relative risk												

[1] Foon et al. 2012
[2] Downgraded 1 level - no study assessed by the Cochrane reviewers were assessed as at low risk of bias
[3] Downgraded 1 level - at a default minimal important difference of 25% data are consistent with no meaningful difference or appreciable benefit with antibiotic prophylaxis
[4] Also non-significant differences in sub-group populations (antibiotics vs. placebo in males; antibiotics vs. placebo in females; antibiotics vs. placebo in patients with spinal injury)
[5] Downgraded 2 levels - at a 95% confidence interval, data are consistent with no meaningful difference, appreciable benefit or appreciable harm
[6] 2 studies (1 study not estimable, no adverse events reported)

H.4 Antibiotic prophylaxis for preventing catheter-associated UTI in children

Table 16: GRADE profile – antibiotic prophylaxis for children with a long-term (indwelling or intermittent) catheter

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antibiotic prophylaxis	Antibiotics when microbiologically indicated	Relative (95% CI)	Absolute		
Symptomatic urinary tract infection (intermittent catheterisation in children with neurogenic bladder)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antibiotic prophylaxis	Antibiotics when microbiologically indicated	Relative (95% CI)	Absolute		
1[1]	randomised trials[2]	serious[3]	not applicable	no serious indirectness	very serious[4]	none	7	8[5]	-	IDR 0.50 higher (95% CI 0.17 to 1.44 higher)	⊕OOO VERY LOW	CRITICAL
Symptomatic urinary tract infection (intermittent catheterisation in children with neurogenic bladder)[6]												
1[1]	randomised trials[2]	serious[3]	not applicable	no serious indirectness	very serious[4]	none	4/430	2/389	-	NICE analysis: IRR 1.8 (95% CI 0.32 to 10.16)	⊕OOO VERY LOW	CRITICAL
Symptomatic urinary tract infection at least 1 episode (intermittent catheterisation in children with spina bifida)[7]												
1[1]	randomised trials[8]	serious[9]	not applicable	no serious indirectness	very serious[4]	none	2/88 (2.3%)	4/88 (4.5%)	RR 0.50 (95% CI 0.09 to 2.66)	23 fewer per 1000 (from 41 fewer to 75 more)	⊕OOO VERY LOW	CRITICAL
Afebrile symptomatic urinary tract infection (intermittent catheterisation in children with spina bifida)[7]												
1[1]	randomised trials[8]	serious[9]	not applicable	no serious indirectness	serious[10]	none	88	88	-	IDR 0.69 higher (95% CI 0.55 to 0.87 higher)[11]	⊕⊕OO LOW	CRITICAL
Abbreviations: IDR, Incidence density ratio; IRR, Incidence rate ratio; RR, Relative risk												

[1] Niel-Weise et al. 2012
[2] Cross-over design
[3] Downgraded 1 level - Unclear risk of bias related to random sequence generation and allocation concealment
[4] Downgraded 2 levels - at a 95% confidence interval, data are consistent with no meaningful difference, appreciable benefit or appreciable harm
[5] Of the 15 participants 8 had at least 1 urinary tract infection while taking antibiotics compared with 11 when taking placebo (cross-over design)
[6] Events per catheterisation weeks not individuals
[7] Children in this study were allocated to continue or discontinue antibiotic prophylaxis
[8] RCT parallel group design
[9] Downgraded 1 level - high risk of bias due to un-blinded study
[10] Downgraded 1 level - at a default minimal important difference of 25% data are consistent with no meaningful difference or appreciable benefit with antibiotic prophylaxis, additionally, in the forest plot for the Cochrane analysis (4.11.1) the IDR is reported as -0.37 (95% CI -0.61 to -0.13), it is uncertain whether the analysis reported in the text is in agreement with the forest plot

Appendix I: Studies not-prioritised

Study reference	Reason for exclusion
Esposito, S; Noviello, S; Leone, S et al. (2006) A pilot study on prevention of catheter-related urinary tract infections with fluoroquinolones. Journal of chemotherapy (Florence, and Italy). Vol 18 Pt 5. p494-501	Included in systematic review
Petronella, P; Scorzelli, M; Fiore, A et al. (2012) Antibiotic prophylaxis in catheter-associated urinary infections. The new microbiologica. Vol 35, Pt 2. p191-8	Included in systematic review
Pfefferkorn, U; Lea, S; Moldenhauer, Jorg et al. (2009) Antibiotic prophylaxis at urinary catheter removal prevents urinary tract infections: a prospective randomized trial. Annals of surgery Vol 249, Pt 4. p573-5	Included in systematic review

Appendix J: Excluded studies

Study reference	Reason for exclusion
Barnoiu, O; Sequeira-García Del Moral, J; Sanchez-Martínez, N et al. (2017) American cranberry (proanthocyanidin 120 mg): its value for the prevention of urinary tracts infections after ureteral catheter placement. Actas urologicas espanolas. Vol 39 Pt 2.p112-117	Non English language paper
Gulati, M; Ambike, D; Thatte, W (2014) A comparative study to assess the effect of amikacin sulfate and povidone iodine for bladder wash on catheter associated urinary tract infection in intensive care unit. Indian journal of critical care medicine. Vol 18. S55	Intervention out-of-scope
Mackway-Jones, K (2006) Prophylactic antibiotics in urinary catheterisation to prevent infection. Emergency Medicine Journal. Vol 23, Pt 8. p649. Erratum author is Garnham, F et al.	Not a systematic review or RCT
Schaeffer, EM (2012) Single-dose antibiotic prophylaxis for urinary catheter removal does not reduce the risk of urinary tract infection in surgical patients: A randomized double-blind placebo-controlled trial Journal of Urology. Vol 187, Pt 6 p2119	Not a systematic review or RCT
Scovell, J; Fletcher, S; Stewart J et al. (2015) A prospective randomized double-blinded placebo control trial on the effects of cranberry supplementation on bacterial colonization and symptomatic urinary tract infections in females with neurogenic bladder dysfunction dependent on self catheterization. Journal of urology. Vol 193 Pt 4 suppl. 1 e192-e193	Conference abstract only
Zacharias, S; Dwarakanath, S; Agarwal, M et al. (2009) A comparative study to assess the effect of amikacin sulfate bladder wash on catheter-associated urinary tract infection in neurosurgical patients. Indian Journal of Critical Care Medicine. Vol 13, Pt 1 PP 17-20	Intervention out-of-scope