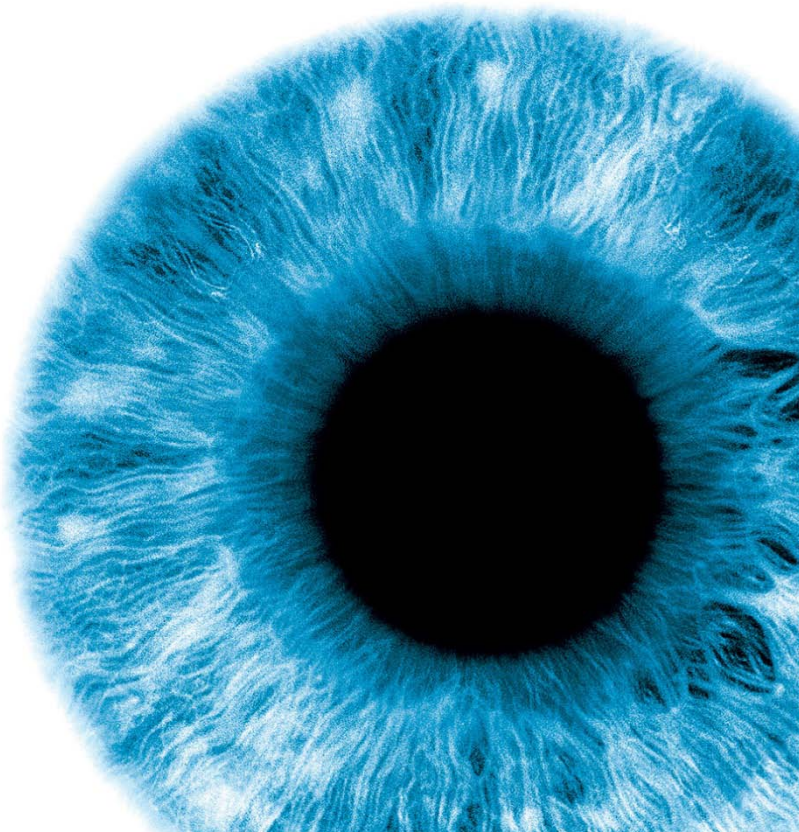
NICE National Institute for Health and Care Excellence

# Urinary tract infection in children

## Evidence Update October 2013

A summary of selected new evidence relevant to NICE clinical guideline 54 'Urinary tract infection in children: diagnosis, treatment and long-term management' (2007)

**Evidence Update 48**



Evidence Updates provide a summary of selected new evidence published since the literature search was last conducted for the accredited guidance they relate to. They reduce the need for individuals, managers and commissioners to search for new evidence. Evidence Updates highlight key points from the new evidence and provide a commentary describing its strengths and weaknesses. They also indicate whether the new evidence may have a potential impact on current guidance. For contextual information, this Evidence Update should be read in conjunction with the relevant clinical guideline, available from the NICE Evidence Services topic page for urinary tract infection.

**Evidence Updates do not replace current accredited guidance and do not provide formal practice recommendations.**

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# Introduction

This Evidence Update identifies new evidence that is relevant to, and may have a potential impact on, the following reference guidance:

[1] **Urinary tract infection in children. NICE clinical guideline 54 (2007)**

A search was conducted for new evidence from 4 August 2010 to 10 April 2013. A total of 3805 pieces of evidence were initially identified. Following removal of duplicates and a series of automated and manual sifts, 19 items were selected for the Evidence Update (see Appendix A for details of the evidence search and selection process). An Evidence Update Advisory Group, comprising topic experts, reviewed the prioritised evidence and provided a commentary.

Although the process of updating NICE guidance is distinct from the process of an Evidence Update, the relevant NICE guidance development centres have been made aware of the new evidence, which will be considered when guidance is reviewed.

## NICE Pathways

- Urinary tract infection in children. NICE Pathway

## Quality standards

- Urinary tract infection in infants, children and young people under 16. NICE quality standard 36

## Feedback

If you have any comments you would like to make on this Evidence Update, please email contactus@evidence.nhs.uk

[1] NICE-accredited guidance is denoted by the Accreditation Mark

# Key points

The following table summarises what the Evidence Update Advisory Group (EUAG) decided were the key points for this Evidence Update. It also indicates the EUAG's opinion on whether the new evidence may have a potential impact on the current guidance listed in the introduction. For further details of the evidence behind these key points, please see the full commentaries.

The section headings used in the table below are taken from the guidance.

**Evidence Updates do not replace current accredited guidance and do not provide formal practice recommendations.**

| | Potential impact on guidance | |
|---|---|---|
| **Key point** | **Yes** | **No** |
| **Diagnosis** | | |
| • Risk factors for urinary tract infection (UTI) among children with fever may differ slightly between boys and girls, and risk of UTI appears to increase with the number of risk factors present. | | ✓ |
| • Limited evidence suggests that circumcised boys appear to have a lower risk of UTI than uncircumcised boys; however, the role of circumcision in preventing UTI is not determined. | | ✓ |
| • Parental reporting of malodorous urine may increase the probability of UTI among young children being assessed for suspected UTI, but low sensitivity and specificity prevent firm diagnosis. | | ✓ |
| • Urine sampling via catheterisation may be associated with a higher success rate, and less pain, than suprapubic aspiration. Urine cultures from catheter samples appear to be highly sensitive and specific, whereas cultures from bag sampling may give high false-positive results (reduced specificity). | ✓* | |
| • C-reactive protein level in combination with ultrasound measurement of the anteroposterior diameter of the renal pelvis during a UTI may have some potential to predict renal damage at 1 year after the UTI. | | ✓ |
| **Management** | | |
| • Cranberry products do not appear to prevent recurrence of UTIs. Limited evidence found no significant difference between cranberry syrup and trimethoprim. | | ✓ |
| • Age less than 1 year and a high recurrence rate of UTI appear to be independent risk factors for UTI caused by antibiotic-resistant bacteria. | | ✓ |
| • Limited evidence suggests that antibiotic prophylaxis may prevent recurrent UTIs in children at risk of recurrence. | | ✓ |
| • Antibiotic prophylaxis does not appear to have an effect on recurrent UTIs or pyelonephritis in children with vesicoureteric reflux (VUR). Some evidence indicates that antibiotic prophylaxis could reduce risk of renal damage in these children, but this may be outweighed by potential issues of increased drug resistance. | | ✓ |

| Key point | Potential impact on guidance: Yes | Potential impact on guidance: No |
|---|---|---|
| • Antibiotic prophylaxis and endoscopic injection seem to reduce febrile UTI recurrence in girls, but may not be as effective in boys. | | ✓ |
| • Preliminary evidence suggests that oral methylprednisolone[2] in conjunction with antibiotics may reduce renal scarring after acute pyelonephritis in hospitalised children at high risk of renal scarring. | | ✓ |
| **Imaging tests** | | |
| • UTIs caused by *Enterococcus* spp. may be associated with more urinary abnormalities and may also have specific antibiotic resistance profiles, both of which need appropriate imaging and antibiotic therapy. | | ✓ |
| • Ultrasound imaging alone may be sufficient in children with a first UTI (particularly when weighed against greater radiation exposure in other techniques), with micturating cystourethrogram (MCUG) needed only in those at greater risk. | | ✓ |
| • Prevalence of VUR among all children could be as high as one-third, and prevalence does not appear to be different between children with and without UTI. Data may indicate a reduced benefit from imaging in UTI, particularly in the detection of VUR, and there may be scope to further reduce imaging to identify VUR. | ✓* | |
| • Acute-phase dimercaptosuccinic acid scintigraphy scan (DMSA) has limited ability to identify risk of VUR in children with a first febrile UTI. | | ✓ |
| • More aggressive imaging strategies (such as DMSA for all patients with febrile UTI, with a further option of MCUG if indicated) may have higher sensitivity and lower specificity for detecting VUR and renal scarring. However, they also appear to be associated with higher costs and radiation exposure. The NICE imaging protocol appears to be relatively low cost with a high specificity but low sensitivity for detecting VUR and scarring. Radiation exposure per patient with the NICE protocol (0.5 mSv) appears to be higher than some guidelines (0.14 mSv – American Academy of Pediatrics) but lower than others (2.05 mSv – top down approach). The clinical impact of differing radiation exposures was not assessed by the studies. | ✓* | |
| **Surgical intervention** | | |
| • The added benefit of surgical or endoscopic correction of VUR over antibiotic prophylaxis alone remains unclear. | | ✓ |
| **Follow-up** | | |
| • The risk of long-term complications after UTI in childhood appears to be low. | | ✓ |

[2] Oral methylprednisolone is not recommended by current guidance and at the time of publication of this Evidence Update did not have UK marketing authorisation for this indication.

* Evidence Updates are intended to increase awareness of new evidence and do not change the recommended practice as set out in current guidance. Decisions on how the new evidence may impact guidance will not be possible until the guidance is reviewed by NICE following its published processes and methods. For further details of this evidence in the context of current guidance, please see the full commentary.

# 1 Commentary on new evidence

These commentaries analyse the key references identified specifically for the Evidence Update. The commentaries focus on the 'key references' (those identified through the search process and prioritised by the EUAG for inclusion in the Evidence Update), which are identified in bold text. Supporting references provide context or additional information to the commentary. Section headings are taken from the guidance.

## Glossary of abbreviations

This glossary lists selected abbreviations that are repeated throughout this Evidence Update.

**DMSA** Dimercaptosuccinic acid scintigraphy scan – a radionuclide scan of the kidneys used to identify renal parenchymal defects, some of which are due to chronic pyelonephritic scarring

**MCUG** Micturating cystourethrogram – the most common test used in the UK for the detection of vesicoureteric reflux in children

**UTI** Urinary tract infection

**VUR** Vesicoureteric reflux – the passage of urine from the bladder back into a ureter and, in higher grades of VUR, to the kidneys

## 1.1 Diagnosis

**General risk factors**

NICE clinical guideline 54 (NICE CG54) recommends that infants and children presenting with unexplained fever of 38°C or higher should have a urine sample tested after 24 hours at the latest.

A technical report by **Finnell et al. (2011)** formed the basis of the revised American Academy of Pediatrics (AAP) guideline on the diagnosis and management of initial UTIs in children with fever aged 2–24 months (AAP Subcommittee on Urinary Tract Infection 2011). This report updated the technical report developed for the first AAP guideline on UTI published in 1999. It is of relevance to most sections of NICE CG54 and is referred to throughout this Evidence Update.

One of the areas discussed by Finnell et al. (2011) was risk factors for UTI. The report noted that the prevalence of UTI among young children with a fever but no obvious source was approximately 5%. However, the authors stated it was possible to identify groups at greater risk, and went on to report several risk factors. Among boys, UTI risk factors were: temperature above 39°C; fever for more than 24 hours; no apparent fever source; and being non-black. For girls, risk factors were: age less than 12 months; temperature above 39°C; fever for at least 2 days; absence of another source of infection; and being white. Among boys and girls, likelihood ratios increased with the number of risk factors present (in boys, ranging from 0.34 with no factors to 5.49 with all 4 factors, and in girls ranging from 1.02 with no factors to 2.13 with all 5 factors). In boys, being circumcised reduced the risk of UTI (see the section 'Circumcision' below for more details of circumcision and UTI risk).

The evidence suggests that risk factors for UTI among children with fever may differ slightly between boys and girls, and risk of UTI appears to increase with the number of risk factors present. The risk factors identified by Finnell et al. (2011) are broadly consistent with those

already noted by NICE CG54 and, therefore, this evidence is unlikely to have an impact on the guideline.

**Key reference**

Finnell SM, Carroll AE, Downs SM et al. (2011) Technical report–diagnosis and management of an initial UTI in febrile infants and young children. Pediatrics 128: e749–70

**Supporting reference**

Subcommittee on urinary tract infection, steering committee on quality improvement and management (2011) Urinary tract infection: clinical practice guideline for the diagnosis and management of the initial UTI in febrile infants and children 2 to 24 months. Pediatrics 128: 595–610

### Circumcision

The full version of NICE CG54 notes that the risk of UTI is higher in uncircumcised than circumcised boys. NICE CG54 does not, however, include any recommendations about circumcision for preventing UTI.

A Cochrane review by **Jagannath et al. (2012)** investigated whether routine neonatal circumcision is safe and effective for preventing UTIs in male infants. Inclusion criteria were randomised controlled trials (RCTs), quasi-RCTs and cluster RCTs of medical circumcision in male newborns (at birth or within 4 weeks) with or without urogenital abnormalities. No relevant studies were identified. The authors stated that the lack of RCTs prevented any conclusions about the safety and efficacy of the intervention.

The technical report by **Finnell et al. (2011)** (see 'General risk factors' in section 1.1 'Diagnosis' for details) also discussed circumcision. These authors identified a meta-analysis of observational studies that indicated an approximately threefold to fourfold decreased risk of UTI among circumcised boys.

Data from observational studies suggest that circumcised boys appear to have a lower risk of UTI than uncircumcised boys; however, the role of circumcision in preventing UTI is not determined. The absence of evidence, combined with potential ethical issues over the use of routine circumcision to prevent a condition such as UTI (which for most patients has no serious consequences), means that this evidence is unlikely to have an impact on NICE CG54.

**Key reference**

Jagannath VA, Fedorowicz Z, Sud V et al. (2012) Routine neonatal circumcision for the prevention of urinary tract infections in infancy. Cochrane Database of Systematic Reviews issue 11: CD009129

### Offensive urine

NICE CG54 recommends that infants and children with symptoms and signs suggestive of UTI should have a urine sample tested for infection. The guideline includes a table of presenting signs and symptoms, with offensive urine listed as one of the least common.

A prospective, consecutive cohort study (n=396) in Canada by **Gauthier et al. (2012)** examined the association between parental reporting of malodorous urine and UTI in children aged between 1 and 36 months (median age=12 months). Children presenting to the emergency department of a paediatric hospital for whom a urine culture was ordered for suspected UTI (that is, unexplained fever, irritability or vomiting) were assessed for eligibility. Exclusion criteria included antibiotics (other than for prophylaxis) given in the previous 48 hours, diabetes or other metabolic disease, and ureterostomy or urinary catheter in place. Patients whose urine for culture was collected by bag were also excluded. A standardised questionnaire was answered by parents, which included questions about vomiting, gastrointestinal symptoms, pain on urination and strength and offensiveness of urine smell.

The primary outcome was a UTI diagnosed by urine culture. The cut-off values for the number of microorganisms needed for diagnosis depended on urine sampling method:

- Bladder catheterisation: ≥$50\times10^6$ bacteria/litre (or ≥$10\times10^6$ *Pseudomonas* spp./litre), excluding lactobacilli, corynebacteria and coagulase-negative staphylococci.
- Clean-catch or midstream void: ≥$100\times10^6$ bacteria/litre, excluding lactobacilli, corynebacteria and coagulase-negative staphylococci.
- Suprapubic aspiration: any amount of gram-negative bacteria (or ≥$10\times10^6$ gram-positive bacteria/litre).

Among the 331 children in the final analysis, 51 (15%) had a UTI. Malodorous urine was reported in 57% of the children with a UTI and 32% of those without a UTI. Logistic regression analysis indicated an association of malodorous urine with UTI (odds ratio=2.83, 95% confidence interval [CI] 1.54 to 5.20, p value not stated) with sensitivity of 0.57 (95% CI 0.42 to 0.70) and specificity of 0.68 (95% CI 0.62 to 0.74). The positive likelihood ratio was 1.79 (95% CI 1.33 to 2.40), and the negative likelihood ratio was 0.63 (95% CI 0.23 to 0.45).

Limitations of the evidence included that:

- There is no standard definition of malodorous urine, and the study relied on subjective parental opinion of urine smell.
- Malodorous urine may have been reported spontaneously by some parents, which may have led to a urine culture.
- Only 51 children had a UTI, limiting the possibility of subgroup analyses.

Evidence suggests that parental reporting of malodorous urine may increase the probability of UTI among young children being assessed for suspected UTI, but low sensitivity and specificity prevent firm diagnosis. These data are consistent with NICE CG54, which recognises offensive urine as one of the least common signs and symptoms of UTI.

**Key reference**

Gauthier M, Gouin S, Phan V et al. (2012) Association of malodorous urine with urinary tract infection in children aged 1 to 36 months. Pediatrics 129: 885–90

### Urine collection

NICE CG54 states that a clean catch urine sample is the recommended method for urine collection. If a clean catch urine sample is unobtainable:

- Other non-invasive methods, such as urine collection pads, should be used.
- When it is not possible or practical to collect urine by non-invasive methods, catheter samples or suprapubic aspiration should be used.

The technical report by **Finnell et al. (2011)** (see 'General risk factors' in section 1.1 'Diagnosis' for details) discussed methods of urine collection. Data from 2 RCTs indicated that pain scores were significantly higher with suprapubic aspiration than with catheterisation (data not reported), and that success rates for suprapubic aspiration (66% and 60%) were lower than with catheterisation (83% and 78%). It was further noted in the technical report that in comparison with suprapubic aspiration, urine cultures from samples obtained by catheter were 95% sensitive and 99% specific.

For urine cultures from samples collected by bag, the original 1999 technical report noted that specificity ranged from 14% to 84%, and the updated report stated that these figures had not improved. The authors reported that cultures of bag specimens are difficult to interpret, and potentially 85% of positive cultures could be false positives. Bag specimens were not, however, ruled out from the AAP guideline for urinalysis.

The evidence suggests that urine sampling via catheterisation may be associated with a higher success rate, and less pain, than suprapubic aspiration. Urine cultures from catheter

samples appear to be highly sensitive and specific, whereas cultures from bag sampling may give more false-positive results (reduced specificity). These findings led the AAP to recommend that urine specimens for culture should be obtained only via catheterisation or suprapubic aspiration. The AAP guideline is specifically aimed at children with fever aged 2 to 24 months, in whom obtaining a clean catch sample is likely to be more difficult because of potential contamination from the prepuce or vagina. Children of this age group are within the scope of NICE CG54, which covers all children under 16 years. Therefore, this evidence may have a potential impact on current recommendations; however, details of any impact are outside the scope of the Evidence Update. Decisions on how the new evidence may impact guidance will not be possible until the guidance is reviewed by NICE following its published processes and methods.

**Laboratory tests in UTI**

***C-reactive protein***

NICE CG54 recommends that C-reactive protein alone should not be used to differentiate acute pyelonephritis/upper UTI from cystitis/lower UTI in infants and children. It does not include any recommendations about the use of C-reactive protein in any other diagnostic capacity, such as predicting longer term renal damage.

A population-based, prospective study (n=270) in Sweden by **Preda et al. (2011)** analysed the ability of ultrasound in combination with clinical and laboratory data (including measurement of C-reactive protein) to predict permanent renal damage detected on 1-year DMSA. An additional aim was to construct an imaging algorithm. All children under 1 year, diagnosed with a first symptomatic community-acquired UTI at the emergency department of a single hospital were eligible. Those with known urogenital or anorectal malformation, or neurological disease, were excluded.

Data recorded included:

- bacteriuria (any bacterial growth in a suprapubic aspiration sample, or $>10^5$ colony-forming units [CFU] in 2 midstream void or bag samples)
- febrile UTI (rectal temperature ≥38.5°C)
- C-reactive protein (highest measurement)
- serum creatinine
- leukocyturia (graded 0 to 4 by dipstick)
- acute ultrasound and DMSA
- MCUG
- late DMSA (1 year after inclusion for those with abnormal acute DMSA or with recurrent febrile UTI).

A stepwise multiple logistic regression model was used to identify independent predictors for renal damage, and the most promising factors were analysed in a logistic model. The most appropriate cut-off points for predictive factors were determined using area under the receiver operating characteristic curve (AUC), and a final algorithm was then developed.

Renal damage was observed on 1-year DMSA in 70 of 270 patients. Five independent predictors of renal damage were found, as indicated by their AUC values (from univariate analysis) and adjusted odds ratio (AOR; from multivariate analysis):

- C-reactive protein: AUC=0.77, AOR=1.92 (95% CI 1.52 to 2.43, p<0.0001).
- Anteroposterior diameter of the renal pelvis (measured by ultrasound): AUC=0.61, AOR=8.90 (95% CI 1.95 to 40.50, p=0.0047).
- Serum creatinine: AUC=0.67, AOR=1.06 (95% CI 1.02 to 1.10, p=0.0066).
- Leukocyturia: AUC=0.63, AOR=1.51 (95% CI 1.11 to 2.05, p=0.0082).
- Non-*Escherichia coli* bacteria: AUC=0.58, AOR=3.51 (95% CI 1.01 to 12.21, p=0.0486).

After analysing combinations of these 5 factors across a range of cut-offs, an algorithm was created. C-reactive protein (70 mg/litre or greater), combined with anteroposterior diameter (10 mm or greater), had a sensitivity of 87% and specificity of 59% for renal damage. No predictive values or likelihood ratios were reported.

Limitations of the evidence included that:

- The authors did not analyse whether the outcome of renal damage at 1 year was associated with other outcomes that may be of greater relevance for patients, such as hypertension or renal failure.
- C-reactive protein may be low if children with fever present early and so re-testing may be needed.

The evidence suggests that C-reactive protein level in combination with ultrasound measurement of the anteroposterior diameter of the renal pelvis during a UTI may have some potential to predict renal damage at 1 year after the UTI. Although this finding is not consistent with recommendations in NICE CG54, further research is needed to confirm findings. This evidence is unlikely to have an impact on the current guideline.

**Key reference**

Preda I, Jodal U, Sixt R et al. (2011) Imaging strategy for infants with urinary tract infection: a new algorithm. The Journal of Urology 185: 1046–52

## 1.2 Management

### Cranberries for preventing UTIs

NICE CG54 recommends that children who have had a UTI should be encouraged to drink an adequate amount, but no recommendations are made about specific foods or drinks for preventing UTIs.

A Cochrane review by **Jepson et al. (2012)** analysed RCTs and quasi-RCTs of cranberry juice or other cranberry products for preventing UTIs. Only studies of susceptible populations were included, namely pregnant women, older people, children, people needing intermittent catheterisation, and people with recurrent UTIs, in-dwelling catheters or abnormalities of the urinary tract. Studies involving treatment of UTIs or of conditions not caused by bacteria were excluded. A total of 24 studies (n=4473) were identified, of which 5 were specifically in children (n=563). Several cranberry products were tested (juice, concentrate, tablets and capsules) against a variety of comparators (placebo, no treatment, water, methenamine hippurate, antibiotics or lactobacillus). Only 13 of the 24 studies were suitable for meta-analysis. The primary outcome was incidence of UTIs (confirmed by a catheter, midstream or clean-catch urine sample).

Compared with control (placebo, water or no treatment), cranberry products did not reduce symptomatic UTI across all susceptible populations with 1 or more UTI at follow-up (RR=0.86, 95% CI 0.71 to 1.04, p=0.13; 13 studies, n=2462), nor in a subgroup of children with recurrent UTI (RR=0.48, 95% CI 0.19 to 1.22, p=0.12; 2 studies, n=309). One RCT compared cranberry syrup with trimethoprim 1.6 mg/kg daily for prophylaxis of repeat symptomatic UTI in 192 children aged 1 month to 13 years who had recurrent UTI, VUR of any degree, or renal pelvic dilatation associated with a UTI. Follow-up was up to 1 year. The study found no statistically significant difference between the treatments (RR=0.69, 95% CI 0.32 to 1.51, p=0.36). The review found no difference in gastrointestinal adverse effects between cranberry products and placebo or no treatment (RR=0.83, 95% CI 0.31 to 2.27, p=0.72; 4 studies, n=597), although none of the studies that used this outcome were specifically among children.

Limitations of the evidence included that:

- Many studies reported compliance issues and high drop-out rates, potentially because of palatability or acceptability of the products, particularly juice.
- The appropriate dose of proanthocyanidin-A (the suspected active ingredient in cranberries) has not been formally quantified, and levels of this ingredient varied (or were not reported) in the products used across the trials, particularly tablets and capsules.
- Most studies were small and lacked power to detect differences between treatments.

The evidence suggests that cranberry products do not appear to prevent recurrence of UTIs. Limited evidence found no significant difference between cranberry syrup and trimethoprim (at a dose lower than the 2 mg/kg recommended in the British National Formulary for Children), but this needs further investigation in larger studies. The problems of inter-product variability (especially in proanthocyanidin-A concentration), the lack of a clear effect of cranberry on UTI recurrence, and limitations of the current data mean that this evidence is unlikely to have an impact on NICE CG54.

**Key reference**

Jepson RG, Williams G, Craig JC (2012) Cranberries for preventing urinary tract infections. Cochrane Database of Systematic Reviews issue 10: CD001321

### Antibiotic treatment and prophylaxis

NICE CG54 states that for infants and children 3 months or older with acute pyelonephritis/upper UTI, the use of an oral antibiotic with low resistance patterns is recommended. In older children, the choice of antibiotics should be directed by locally developed multidisciplinary guidance. The guideline also recommends that laboratories should monitor resistance patterns of urinary pathogens and make this information routinely available to prescribers. The guideline further states that antibiotic prophylaxis should not be routinely recommended in infants and children after first UTI, but may be considered following recurrent UTI.

#### *Antibiotic resistance in UTI*

A retrospective observational cohort study (n=344) in Turkey by **Kizilca et al. (2012)** investigated risk factors for antibiotic resistance in children with UTI caused by bacteria that produce extended-spectrum beta-lactamase (ESBL). Production of ESBL is a mechanism involved in antibiotic resistance among gram-negative bacteria. Patients diagnosed with a UTI in an outpatient clinic of a paediatric nephrology department were included. Diagnosis was based on a positive urine culture (≥50,000 CFU/ml) from catheter samples. Cultures were also tested for antibiotic susceptibility and production of ESBL. All patients received ultrasound, MCUG and DMSA, and medical files were retrospectively reviewed for information related to previous management of UTIs.

Test results indicated that:

- 148 patients had ESBL-producing bacteria and 196 patients had non-ESBL-producing bacteria.
- 86% of UTIs were caused by *E coli* and 14% by *Klebsiella* spp. (of which 41.4% and 53.2% respectively were ESBL-producing).
- Antibiotic resistance rates among ESBL and non-ESBL-producing bacteria to the antibiotics tested were:
  - trimethoprim/sulfamethoxazole: ESBL=83.1%, non-ESBL=62.2%
  - quinolones: ESBL=47.3%, non-ESBL=9.7%
  - aminoglycosides: ESBL=39.9%, non-ESBL=9.7%
  - nitrofurantoin: ESBL=18.2%, non-ESBL=4.6%.

Although there was evidence that patients who tested positive for ESBL-producing bacteria had a history of longer total duration of antibiotic prophylaxis (24.7 months versus 19.6 months, p=0.021) and higher rates of cephalosporin use (29.7% versus 17.4%, p=0.009), logistic regression did not identify these as independent risk factors. The only 2 independent factors for likelihood of infection with ESBL-producing bacteria were age less than 1 year (OR=1.74, 95% CI 1.08 to 2.78, p=0.022) and a high recurrence rate of UTI (OR=2.25, 95% CI 1.70 to 2.98, p=0.0001).

Limitations of the evidence included that the study was from Turkey, therefore local bacteria and antibiotic resistance patterns may be different from the UK, which may limit transferability of results. Additionally, the study was retrospective, and whether patients were secondary or tertiary referrals was not reported.

Evidence suggests that age less than 1 year and a high recurrence rate of UTI appear to be independent risk factors for UTI caused by antibiotic-resistant bacteria. This evidence is broadly consistent with the need for a cautious approach to antibiotic prophylaxis in UTI, as recommended by NICE CG54. The findings also reinforce the need to consider and monitor antibiotic resistance in UTI (which may be more common in some patient groups) and to develop local prescribing guidance for managing such issues.

**Key reference**

Kizilca O, Siraneci R, Yilmaz A et al. (2012) Risk factors for community-acquired urinary tract infection caused by ESBL-producing bacteria in children. Pediatrics International 54: 858–62

***Antibiotic prophylaxis in children at risk of recurrence of UTI***

A Cochrane review by **Williams and Craig (2011)** assessed long-term antibiotics (daily for at least 2 months) in preventing recurrent UTI. RCTs and quasi-RCTs that compared antibiotics with placebo or no treatment, or that compared 2 or more antibiotics, were included. Studies of children under 18 years at risk of recurrence of UTI were included, but studies were excluded if more than 50% of participants were predisposed to UTI (for example, because of a renal tract abnormality, or neurological, urological or muscular disease). A total of 12 studies (n=1557) were identified: 5 were of antibiotics compared with placebo or no treatment; 4 studies compared 2 or more different antibiotics; 1 compared different doses of the same antibiotic; and the remaining 2 crossover studies did not provide suitable data for meta-analysis. Length of antibiotic treatment ranged from 10 weeks to 12 months. The primary outcome was recurrent symptomatic UTI.

When all relevant studies were analysed, antibiotics did not appear to reduce the risk of symptomatic UTI recurrence compared with placebo or no treatment (RR=0.75, 95% CI 0.36 to 1.53, p=0.43; 4 studies, n=1024), but heterogeneity was high ($I^2$=62%). However, when the two later and largest studies were pooled, the effect of antibiotics in reducing the risk of UTI recurrence was significant (RR=0.68, 95% CI 0.48 to 0.95, p=0.024; 2 studies, n=914), and there was no heterogeneity ($I^2$=0%). Antibiotic prophylaxis did not have a significant effect on UTIs in children either with VUR (RR=0.65, 95% CI 0.39 to 1.07, p=0.088; 2 studies, n=371) or without VUR (RR=0.56, 95% CI 0.15 to 2.12, p=0.4; 3 studies, n=491), although this was not the main focus of the review (prophylaxis in VUR is covered in greater detail by Nagler et al. 2011 in the next section). Risk of antibiotic resistance did not appear to be significantly greater in antibiotic treatment groups than in placebo or no-treatment groups (RR=2.4, 95% CI 0.62 to 9.26, p=0.21; 2 studies, n=118).

Limitations of the evidence included that:

- Only 1 study clearly reported patient screening and reasons for exclusion or non-enrolment, therefore assessment of selection bias was limited.
- Definitions and criteria for diagnosis of UTI differed between studies and were often poorly reported.

- Misclassification was not considered in most studies.

Limited evidence suggests that antibiotic prophylaxis may prevent recurrent UTIs in children at risk of recurrence. The limitations of the review mean that this evidence is unlikely to have an impact on the statement in NICE CG54 that antibiotic prophylaxis should not be routinely recommended after first UTI, but may be considered for recurrent UTI. Further research is needed.

**Key reference**

Williams G, Craig JC (2011) Long-term antibiotics for preventing recurrent urinary tract infection in children. Cochrane Database of Systematic Reviews issue 3: CD001534

***Antibiotic prophylaxis in children with VUR***

A Cochrane review by **Nagler et al. (2011)** evaluated the effects of the currently available treatment options, including antibiotic prophylaxis, in patients with VUR. RCTs and quasi-RCTs of VUR treatments (including antibiotics, surgery, non-invasive techniques or a combination) in patients of any age with VUR diagnosed by MCUG, with or without UTI, were included. Patients with VUR associated with posterior urethral valves, spina bifida, other urological abnormalities or kidney transplants were excluded. A total of 20 studies (n=2324) were included, all of which were in children under 18 years. The primary outcomes were repeat symptomatic UTI or febrile UTI.

At 1–2 years (compared with no treatment or placebo), long-term, low-dose antibiotic prophylaxis did not significantly reduce repeat symptomatic UTI (RR=0.68, 95% CI 0.39 to 1.17, p=0.16; 5 studies, n=846) or febrile UTI (RR=0.77, 95% CI 0.47 to 1.24, p=0.28; 6 studies, n=946). At 1–3 years, risk of the combined outcome of new or progression of renal damage on DMSA testing was reduced with antibiotic prophylaxis (RR=0.35, 95% CI 0.15 to 0.80, p=0.014; 3 studies, n=446), but no significant difference was seen when these outcomes were analysed separately. Although side effects appeared infrequent when reported, antibiotics increased the likelihood of bacterial drug resistance (RR=2.94, 95% CI 1.39 to 6.25, p=0.005; 4 studies, n=132 UTIs).

Limitations of the evidence included that:

- In many studies, the authors noted that it was difficult to discern who the children were and how many were reviewed for inclusion; therefore, evaluating selection bias was difficult.
- There was considerable heterogeneity among the studies analysed (for example, the authors noted that definitions and criteria for diagnosis of UTI and renal abnormalities differed greatly), and only 3 studies were adequately blinded.
- The evidence available on outcomes that may be of greater relevance to patients, such as hypertension and renal failure, was limited by small numbers of events.
- For the primary outcome of UTI, most patients had lower grades of VUR, so the results may not necessarily apply to those with the highest grades.

The technical report by **Finnell et al. (2011)** (see 'General risk factors' in section 1.1 'Diagnosis' for details) also examined antibiotic prophylaxis in children with VUR. A systematic review and meta-analysis was performed of RCTs (minimum 6-month follow-up) comparing antibiotic treatment with no treatment or placebo for preventing recurrent UTI in children who had undergone MCUG to diagnose VUR. A total of 8 studies were identified, of which 6 compared antibiotics with no treatment and 2 were placebo controlled. The primary outcome was pyelonephritis or febrile UTI diagnosed by fever and urine culture. A secondary outcome was any type of UTI including cystitis, non-febrile UTI and asymptomatic bacteriuria.

No significant effect of antibiotics was seen for prevention of pyelonephritis or febrile UTI in children of any age with any grade of VUR, or in children aged 2 to 24 months with any grade of VUR (nor when grades were analysed individually). A significant effect was observed with

antibiotic prophylaxis on prevention of any UTI in children of any age with any grade of VUR (risk ratio=0.70, 95% CI 0.51 to 0.96, p=0.03; 8 studies, n=1020). However, this effect was for a secondary outcome in which all forms of UTI were included, and the effect size was driven mainly by reductions in cystitis or asymptomatic bacteriuria that are unlikely to cause renal damage. Additionally, this meta-analysis included 2 abstracts that had not resulted in published articles; exclusion of data from the 2 abstracts resulted in a non-significant effect.

Taken together, the 2 reviews suggest that antibiotic prophylaxis does not appear to have an effect on recurrent UTIs or pyelonephritis in children with VUR. Some evidence indicates that antibiotic prophylaxis could reduce risk of renal damage in these children, but this may be outweighed by potential issues of increased drug resistance. The limitations of the evidence mean that these results are unlikely to have an impact on the statement in NICE CG54 that antibiotic prophylaxis should not be routinely recommended after first UTI, but may be considered for recurrent UTI. Further research is needed.

**Key reference**

Nagler EV, Williams G, Hodson EM et al. (2011) Interventions for primary vesicoureteric reflux. Cochrane Database of Systematic Reviews issue 6: CD001532

***Antibiotic prophylaxis compared with endoscopic injection in VUR***

A review of a multicentre RCT in Sweden and Norway by **Brandström et al. (2011)** evaluated treatment of VUR with antibiotic prophylaxis, endoscopic injection or surveillance. The full results of the RCT have been previously published and were considered during the latest review of the need to update NICE CG54.

Children from 23 paediatric centres (128 girls, 75 boys) aged 1 to less than 2 years with VUR grade 3 or 4 diagnosed by MCUG were included. Exclusion criteria were previous urogenital surgery, malformation, neurological disease, kidney stones, glomerular filtration rate less than 70 ml/minute/1.73 $m^2$, and split renal function below 15%. MCUG, DMSA and an optional lower urinary tract function test were performed before randomisation and after 2 years. Children were randomised to antibiotic prophylaxis with trimethoprim, endoscopic injection with Deflux, or surveillance. Follow-up was 2 years.

Recurrent febrile UTI was seen more frequently in girls (42/128; 67 UTIs) than boys (7/77; 8 UTIs; p=0.0001 for difference). In girls, recurrence rates were significantly lower than surveillance (57%) with both prophylaxis (19%; hazard ratio=0.22, 95% CI 0.10 to 0.49, p=0.0002) and endoscopic treatment (23%; hazard ratio=0.28, 95% CI 0.13 to 0.58, p=0.0007). However, in boys, there was no difference between the groups. New renal damage occurred in 2 boys (1 in each of the endoscopic and surveillance groups) and 13 girls (8 in the surveillance group, 5 in the endoscopic group and none in the prophylaxis group; p=0.0054 for difference between the surveillance and prophylaxis group). A previous article by Sillén et al. (2010), reporting data from the same RCT, noted more renal damage at 2 years in children with lower urinary tract dysfunction (85%) than in those without dysfunction (51%, p<0.001).

The main limitation of the evidence was that children under 1 year, or aged 2 years or over, were not included; therefore, no information can be gained about management of VUR in these age groups. This limitation may reduce the relevance of this study to the UK, where an MCUG to look for VUR is more likely to be performed in very young children (MCUG is only specifically recommended by NICE in children under 6 months with atypical or recurrent UTI). However, the narrow age range may help to eliminate confounders and heterogeneity. Additionally, the study did not fully achieve its recruitment target. The reduced size meant that once children were allocated to the 3 treatment arms, subgroups (particularly when further divided by sex) were small.

The evidence suggests that recurrent febrile UTI appears to be more common in girls than boys. Antibiotic prophylaxis and endoscopic injection seem to reduce UTI recurrence in girls,

but may not be as effective in boys. These data are unlikely to have an impact on the statement in NICE CG54 that antibiotic prophylaxis should not be routinely recommended after first UTI, but may be considered for recurrent UTI. The greater effect of antibiotic prophylaxis and endoscopic treatment in girls may warrant further research.

**Key reference**

Brandström P, Jodal U, Sillén U et al. (2011) The Swedish reflux trial: review of a randomized, controlled trial in children with dilating vesicoureteral reflux. Journal of Pediatric Urology 7: 594–600

**Supporting reference**

Sillén U, Brandström P, Jodal U et al. (2010) The Swedish reflux trial in children: V. Bladder dysfunction. The Journal of Urology 184: 298–304

### Methylprednisolone for renal scarring in acute pyelonephritis

NICE CG54 does not include any recommendations about the use of methylprednisolone[3] in the management of acute pyelonephritis.

A double-blind RCT (n=84) in Taiwan by **Huang et al. (2011)** determined whether methylprednisolone can prevent renal scarring after acute pyelonephritis. Children aged 1 week to 16 years, admitted to a single tertiary referral centre and diagnosed with a first febrile UTI, were screened for eligibility. Patients were included if they:

- Had evidence of UTI, defined as core temperature 38°C and positive urine culture (namely: $\geq 10^5$ CFU/ml from a clean, midstream urine sample in older children; $\geq 10^3$ CFU/ml from catheter sample; or any growth from suprapubic aspiration sample in younger children; and 5 leukocyte cells per high-power field).
- Were at high risk of renal scar formation (namely, if a defect was noted on DMSA performed within 48 hours of admission, or there was an abnormal finding on renal ultrasonography if DMSA was performed to diagnose acute pyelonephritis between 48 and 72 hours after admission). Patients were removed from the study if an abnormal result on ultrasonography was followed by a normal result on DMSA.

Exclusion criteria were: history of UTI; previous treatment with antibiotics; urogenital uropathy (except VUR); DMSA not performed within 72 hours of admission; and no photopenic (low radiation uptake) finding or diffuse photopenic kidney on DMSA, or space-occupying lesions on ultrasonography, except those progressing to abscess formation.

All patients received antibiotic therapy: initially intravenous cephalothin and gentamicin until they were afebrile for 48 hours, followed by oral antibiotics for 14 days and then low dose trimethoprim or cephalothin until MCUG 2–4 weeks later. In addition, patients were randomised to either oral methylprednisolone (1.6 mg/kg/day in 4 divided doses; n=19) or placebo (n=65), every 6 hours for 3 days.

On follow-up DMSA (6 months after treatment), the primary outcome of renal scarring was seen in 33% (6/18) of children receiving methylprednisolone and in 60% (39/65) of those on placebo ($p<0.05$). The median volume of cortical defect in each kidney was 0.0 ml with methylprednisolone and 1.5 ml with placebo ($p<0.01$).

Limitations of the evidence included that:

- The study was conducted in a single centre among a small number of children, with no reported power calculation.
- Only 19 children received methylprednisolone (patients were allocated to intervention and control in a ratio of approximately 1:3, which the authors justified on ethical grounds) and 1 was lost to follow-up; therefore, any conclusions are limited.

[3] Oral methylprednisolone is not recommended by current guidance and at the time of publication of this Evidence Update did not have UK marketing authorisation for this indication.

- Ultrasonography has a lower sensitivity and specificity than DMSA for acute pyelonephritis; therefore, the method for identifying patients at high risk of renal scarring may have been inconsistent.

Preliminary evidence suggests that oral methylprednisolone in conjunction with antibiotics may reduce renal scarring after acute pyelonephritis in hospitalised children at high risk of renal scarring. However, limitations of the evidence mean it is unlikely to have an impact on NICE CG54 and further research is needed.

**Key reference**

Huang YY, Chen MJ, Chiu NT et al. (2011) Adjunctive oral methylprednisolone in pediatric acute pyelonephritis alleviates renal scarring. Pediatrics 128: e496–504

## 1.3 Imaging tests

### Imaging and management of atypical UTIs

NICE CG54 includes a list of criteria used to define atypical UTI, one of which is infection with non-*E coli* organisms. The guideline recommends that infants and children with atypical UTI should have ultrasound of the urinary tract during the acute infection to identify structural abnormalities of the urinary tract, such as obstruction. This is to ensure prompt management.

A prospective cohort study (n=326 patients with 355 UTI episodes) in Israel by **Marcus et al. (2012)** analysed community-acquired enterococcal UTIs in a tertiary paediatric centre. The study objectives were to characterise the UTIs and to examine risk factors, association with renal abnormalities, antibiotic susceptibility and suitability of treatment, in comparison with gram-negative UTIs. Children under 18 years with a UTI diagnosed by positive urine culture during a 5-year period were included. Those who developed a UTI more than 48 hours after admission to hospital, or within 48 hours of discharge, were excluded (in order that only community-acquired infections were considered).

Urine for culture was collected in various ways, with cut-offs for positive diagnosis dependant on collection method: suprapubic aspiration (any bacterial growth); bladder catheterisation ($>10^4$ CFU/ml); or midstream catch ($>10^5$ CFU/ml). Bag collection and mixed cultures were excluded. Cultures were also tested for antibiotic susceptibility. Other clinical, laboratory and radiological data, such as any underlying disorders and previous antibiotic use, were collected from medical records and by healthcare professionals. The centre's UTI management policy was ultrasonography and MCUG in children hospitalised with UTI who were male, younger than 6 years or had recurrent UTI. Patients were analysed as 2 comparison groups: those with enterococcal UTI and those with gram-negative UTI.

Among all UTIs, 22 (6.2%) were caused by *Enterococcus* spp. and 333 (93.8%) by gram-negative bacteria (mostly *E coli*, *Klebsiella* spp. and *Pseudomonas aeruginosa*). Enterococcal UTI was associated with significantly more underlying urinary abnormality than gram-negative UTI (70.0% versus 43.7%, p=0.03) and more inappropriate antibiotic therapy (22.0% versus 5.6%, p=0.02). The unsuitable antibiotics used for enterococcal UTI were cefuroxime and ceftriaxone. The resistance profiles of both UTI groups were significantly different for 9 of the 12 antibiotics tested, with enterococcal UTIs often displaying resistance to antibiotics commonly used in treating UTIs.

Limitations of the evidence included that:

- The study involved only hospitalised patients and was based at a centre that also receives tertiary referrals, so more complex cases may have been included. This may have led to higher observed rates of enterococcal UTIs than those seen in other studies, and results may not, therefore, be applicable to other settings.

- The study was set in in Israel where rates of circumcision are likely to be higher than the UK (although data were not reported), which may limit transferability of results.

The evidence suggests that UTIs caused by *Enterococcus* spp. may be associated with more urinary abnormalities and may also have specific antibiotic resistance profiles, both of which need appropriate imaging and antibiotic therapy. This is consistent with the acknowledgment in NICE CG54 that infection with non-*E coli* organisms constitutes an atypical UTI and ultrasound imaging should be performed to identify structural abnormalities.

**Key reference**

Marcus N, Ashkenazi S, Samra Z et al. (2012) Community-acquired enterococcal urinary tract infections in hospitalized children. Pediatric Nephrology 27: 109–14

### Ultrasound imaging alone

NICE CG54 recommends ultrasound as the initial imaging technique when indicated (in children under 6 months, atypical UTI or recurrent UTI), with further techniques such as DMSA and MCUG to be used in more specific circumstances.

A retrospective cohort study (n=1185) in Finland by **Hannula et al. (2011)** evaluated whether ultrasound alone is sufficient for imaging of the urinary tract, or if important pathological findings would be missed in the absence of MCUG. Case histories were reviewed of children under 15 years who had undergone both renal ultrasound and MCUG at a hospital paediatric department between 1993 and 2003 for community-acquired UTI (82% first UTI, the rest recurrent UTIs).

Initial ultrasound was normal in 72.7% (861/1185) of patients. The 324 abnormal ultrasound findings were classified as either clinically significant or insignificant. The most common clinically significant abnormalities were hydronephrosis or dilated ureter (n=120), ureteral duplication (n=60), and scarred kidney (n=16). Among those with normal ultrasound, abnormal findings on MCUG were seen in 33.1% (285/861) of patients, including 97 cases of grade 3 to 5 VUR. During follow-up of these 97 cases (mean length=6.9 years), 57 patients received no active treatment (with 87.7% resolution of VUR) and 40 were treated surgically (with 95% resolution of VUR; difference in rates of VUR resolution not statistically analysed). New renal scarring was detected on ultrasound in 11 of the 97 cases, but no associated renal impairment was observed.

As well as the 97 cases of grade 3 to 5 VUR, the authors also reported 2 cases of clinically significant non-VUR related abnormalities, which they diagnosed as 'non-obstructive posterior urethral valve'. Therefore, the authors claimed that 42 patients (40 with VUR who had surgery, plus 2 with non-VUR disorders) may have benefited from MCUG. This meant 4.9% (42/861) of children may have been negatively affected if MCUG had not been performed.

Limitations of the evidence included that:

- The observational nature of the study meant antibiotic and surgical treatments were left to clinical decision, and these approaches may have had an impact on the natural history of VUR.
- DMSA was not used in the study, but this technique may allow more sensitive assessment of renal damage (although the authors suggested that ultrasound was likely to be sensitive enough to pick up clinically important renal scars).

The technical report by **Finnell et al. (2011)** (see 'General risk factors' in section 1.1 'Diagnosis' for details) also evaluated ultrasonography in a model based on results from 14 studies and using a strategy where ultrasound alone was performed on all children with UTI. The model indicated that following ultrasound after a first UTI, 15% of findings were positive and the false-negative rate was 70%. Of the abnormal findings, 88% were true positives and between 1% and 24% were false positives. Of the true positives, 40%

represented problematic findings (namely some dilation of the collecting system, as would be found with MCUG). The authors noted that this represented only a small proportion of children (15%×88%×40%=5%). However, they concluded that although the sensitivity of ultrasound may be low, it is less invasive, uncomfortable and risky than MCUG.

The evidence suggests that ultrasound imaging alone may be sufficient in children with a first UTI (particularly when weighed against greater radiation exposure from other techniques), with MCUG needed only in those at greater risk. This is consistent with recommendations in NICE CG54 that, where imaging is indicated, ultrasound should be first line and MCUG used only in specific circumstances, such as atypical or recurrent UTI.

**Key reference**

Hannula A, Venhola M, Perhomaa M et al. (2011) Imaging the urinary tract in children with urinary tract infection. Acta Paediatrica 100: e253–9

### Prevalence of VUR in UTI

NICE CG54 states that routine imaging to identify VUR is not recommended for infants and children who have had a UTI, except in specific circumstances (such as atypical or recurrent UTI; further details are in tables of the recommended imaging schedule within the guideline).

Two studies recently examined the prevalence of VUR in UTI.

A retrospective cohort study (n=2036) in Finland by **Hannula et al. (2010)** analysed the prevalence of VUR in children with proven, likely, unlikely and false diagnoses of UTI. Reports were reviewed of renal ultrasound and MCUG performed at a hospital paediatric department between 1993 and 2003 for community-acquired UTI in children under 15 years. Patients with known urinary abnormalities or conditions that may predispose to UTI were excluded. UTI diagnoses were classified by reliability using the following criteria:

- Proven: 2 samples from clean void or bag collection (≥$10^5$ CFU/ml and species known, same bacteria in both samples), or 1 sample from suprapubic aspiration (any growth).
- Likely: 1–2 samples from clean void or bag collection (≥$10^5$ CFU/ml in 1 sample, or ≥$10^5$ in 1 sample and ≥$10^4$–$10^5$ in the other).
- Unlikely: 1–2 samples from clean void or bag collection ($10^4$–$10^5$ CFU/ml but species known).
- False: 1–2 samples from clean void or bag collection (<$10^3$–$10^4$ CFU/ml or mixed bacterial flora), or 1 sample from suprapubic aspiration (no growth).
- No microbial data.

The mean age was 2.0 years (standard deviation [SD] 2.4) in the ‘proven’ group, 3.4 years (SD 2.9) in the ‘likely’ group, 3.2 years (SD 2.8) in the ‘unlikely’ group, 3.0 years (SD 2.8) in the ‘false’ group and 4.7 years (SD 2.9) in the ‘no data’ group (statistical analysis of differences in age between groups not provided).

Diagnosis of UTI was proven in 28.6%, likely in 30.5%, unlikely in 17.4% and false in 7.1% of children (data were unavailable in 16.4%). Among the 1185 children who had MCUG, 34.2% were diagnosed with VUR of any grade. Rates of VUR were similar in those with proven (37.4%) and false (34.8%) UTI diagnoses (relative risk=1.08, 95% CI 0.7 to 1.7, p=0.75).

A retrospective study (n=406) in Finland by **Venhola et al. (2010)** also examined the association between VUR and UTI. Reports were reviewed of renal ultrasound and MCUG in consecutive children aged 0–5 years admitted or referred with UTI to either of 2 hospitals. UTI diagnoses were classified by reliability using the following criteria:

- Certain: clean void or bag collection sample (monoculture >$10^5$ CFU/ml); catheter sample (monoculture ≥$10^3$ CFU/ml); or suprapubic aspiration sample (pyuria plus any growth).
- Possible: criteria for ‘certain’ UTI detailed above not fulfilled.

- Improbable: no pyuria and no bacterial growth in urine.

Diagnosis of UTI was certain in 76.6%, possible in 13.8% and improbable in 9.6% of children. Among the 347 children who had MCUG, 34.6% were diagnosed with VUR of any grade. Rates of VUR were similar for all reliabilities of UTI diagnosis: certain (35.5%), possible (28.2%) and improbable (36.0%), although no formal statistical analysis was performed.

The main limitation of both the Hannula et al. 2010 and Venhola et al. 2010 studies were their retrospective nature. The authors of both studies also noted that the true prevalence of VUR in a healthy population cannot easily be established because of ethical issues with performing invasive techniques such as MCUG on healthy people. However, they concluded that traditional estimates of the prevalence of VUR in healthy populations (about 1%) would not have led to such high rates of VUR in the groups of children with unreliable UTI diagnoses.

In addition to the 2 studies discussed above, the technical report by **Finnell et al. (2011)** (see 'General risk factors' in section 1.1 'Diagnosis' for details) also examined VUR prevalence. The authors identified 12 cohort studies published between 1995 and 2004, which provided estimates of the prevalence of VUR among children with UTI of between 18% and 35%. The weighted average prevalence was 34% (but this value was influenced by a single large retrospective study).

Taken together, the evidence suggests that prevalence of VUR among all children could be as high as one-third, and prevalence does not appear to be different between children with and without UTI. These data may indicate a reduced benefit from imaging in UTI, particularly in the detection of VUR, and there may be scope for further reduction in imaging to identify VUR. This evidence may, therefore, have a potential impact on NICE CG54. However, details of any impact are outside the scope of the Evidence Update. Decisions on how the new evidence may impact guidance will not be possible until the guidance is reviewed by NICE following its published processes and methods.

**Key references**

Hannula A, Venhola M, Renko M et al. (2010) Vesicoureteral reflux in children with suspected and proven urinary tract infection. Pediatric Nephrology 25: 1463–9

Venhola M, Hannula A, Huttunen NP et al. (2010) Occurrence of vesicoureteral reflux in children. Acta Paediatrica 99: 1875–8

### DMSA in identifying children at risk of VUR

NICE CG54 recommends that DMSA, 4–6 months following the acute infection, should be used to detect renal parenchymal defects (but only for atypical or recurrent UTIs in children under 3 years, and for recurrent UTIs in children 3 years or older). The guideline does not include any recommendations to use early DMSA to detect children at risk of VUR.

A systematic review and meta-analysis by **Mantadakis et al. (2011)** evaluated the accuracy of acute DMSA to identify children at risk of VUR. Observational cohort studies were included of children with a first febrile, culture-diagnosed UTI and an acute-phase DMSA assessment (namely within 3 months of infection diagnosis) of grade 3 to 5 VUR that was subsequently confirmed by MCUG. Exclusion criteria were single-sex studies and those published in languages other than English, Spanish, French, German, Italian or Greek, unless data could be extracted from the abstract, tables or figures. A total of 13 studies (n=2702) were identified: 9 in patients under 2 years; 3 in children 16 years or under; and 1 in neonates. Patients with less severe VUR (grades 1 or 2) were grouped with those without reflux. Patient-based and renal-unit-based analyses were performed, using bivariate random-effects models. Hierarchical summary receiver operating characteristic (HSROC) curves were also constructed.

For the patient-based analysis (8 studies, n=2108), DMSA had a sensitivity of 79%, specificity of 53% and area under the HSROC curve of 0.71. For the renal-unit-based analysis (5 studies, n=594), DMSA had a sensitivity of 60%, specificity of 65% and area under the HSROC curve of 0.67. The authors concluded that the sensitivity and specificity values represented 'poor performance', and that the area under the HSROC curve values did not fall within the range 0.80 to 0.90 generally considered indicative of good diagnostic tests.

Limitations of the evidence included that:

- Results may not apply equally across ages and sexes because of differing natural history of UTI in boys and girls and across different age groups.
- Diagnostic accuracy of DMSA may be affected by age (for example, younger children may be more likely to have abnormal scans).
- Substantial heterogeneity was observed in both the patient and the renal-unit analyses ($I^2$ values of 91% and 87% respectively), possibly resulting from differences in patient characteristics and timing or methodology of imaging.

The evidence suggests that acute-phase DMSA has limited ability to identify risk of VUR in children with a first febrile UTI. This evidence is, therefore, unlikely to have an impact on NICE CG54, which does not currently include any recommendations to use DMSA in the acute phase to identify VUR.

**Key references**

Mantadakis E, Vouloumanou EK, Georgantzi GG et al. (2011) Acute Tc-99m DMSA scan for identifying dilating vesicoureteral reflux in children: a meta-analysis. Pediatrics 128: e169–79

### Diagnostic ability, financial cost and radiation exposure of imaging algorithms

Although the imaging schedule recommended by NICE CG54 for infants and children who have had a UTI is relatively conservative (for example, it does not promote the routine use of either DMSA or MCUG and recommends these tests only in specific circumstances – mainly atypical or recurrent UTI), more recent guidelines from The Royal Children's Hospital of Melbourne and The American Academy of Pediatrics have introduced imaging strategies that appear to be associated with even less radiation exposure.

A study by **La Scola et al. (2013)** evaluated the ability of several diagnostic imaging algorithms to detect VUR and permanent renal scarring after a first febrile UTI. Financial costs and radiation exposure for each algorithm were also calculated. The analysis used data from a cohort of 304 children (all aged 2–36 months, with an uncomplicated first UTI and normal antenatal ultrasonography) taken from the 'Italian Renal Infection Study 1' (IRIS1). All children had ultrasonography and DMSA within 10 days of the UTI and MCUG within 2 months. Those with acute pyelonephritis identified by DMSA had a further DMSA after 12 months to detect scarring.

Diagnostic algorithms from guidelines published after 2006 were eligible. The following guidelines were analysed:

- The Royal Children's Hospital of Melbourne (2006)
- NICE (2007)
- The top down approach (2007)
- The American Academy of Pediatrics (AAP) (2011)
- The Italian Society of Pediatric Nephrology (2011).

Each algorithm was modelled using patient data from the IRIS1 study to determine diagnostic ability and the theoretical financial costs and radiation exposure incurred. Algorithms were compared to a reference protocol in which ultrasonography, MCUG and late DMSA would be performed on all children. An estimated value for radiation exposure of 1 mSv was used for both MCUG and DMSA (which the full version of NICE CG54 notes is equivalent to 4 months

of natural background radiation or about 40–50 chest radiographs). Estimated costs for individual tests were not reported. Primary outcomes were diagnosis of VUR and UTI-related renal scarring for each algorithm, compared with the reference protocol. Secondary outcomes were the total financial cost and radiation dose incurred.

In the original IRIS1 study, VUR was identified in 66 (22%) and parenchymal scarring in 45 (15%) of the 304 children. Results obtained from the algorithm modelling were as follows.

For detection of VUR:

- The top down approach had highest sensitivity (76%) but the lowest specificity (54%).
- NICE and the AAP had the highest specificities (91% and 90%) but the lowest sensitivities (29% and 27%).

For detection of scarring:

- The top down approach again had the highest sensitivity (100%) but the lowest specificity (56%).
- The Italian Society of Pediatric Nephrology and NICE had the highest specificities (86% and 84%) but the lowest sensitivities (44% and 38%).

Full data for the diagnostic ability of each algorithm, including confidence intervals and positive and negative likelihood ratios, were reported by the authors but are not reproduced here.

For financial costs and radiation exposure:

- The top down approach was most expensive (total=€52,268; per patient=€172) and resulted in the highest radiation exposure (total=624 mSv; per patient=2.05 mSv).
- The AAP had the least radiation exposure (total=42 mSv; per patient=0.14 mSv) at a total cost of €28,457 (per patient=€94).
- NICE was the least costly (total=€26,838; per patient=€88), with a total radiation exposure of 156 mSv. Its per-patient radiation value of 0.5 mSv was third lowest, within the range 0.14 to 2.05 mSv, across the 5 guidelines assessed.

The fact that the AAP had the lowest radiation dose but a higher cost than NICE may be explained by its more frequently recommended use of ultrasound (for all infants with fever under 24 months), whereas NICE recommend it only for children under 6 months and atypical UTIs.

Limitations of the evidence included that:

- The exclusion criteria for the IRIS1 study (abnormal antenatal renal ultrasound; abnormal postnatal renal function; and severe clinical sepsis, dehydration, and vomiting) may bias the results, but these presentations are uncommon and unlikely to substantially affect the data.
- Exact details of how the algorithms were applied to each of the 304 children were not reported, and the way the algorithms were interpreted may likely have a bearing on outcomes from the model.

A study by **Routh et al. (2012)** also assessed the financial costs and radiation exposure of different imaging strategies after a first febrile UTI. A decision model was constructed to compare 2 initial imaging approaches for VUR:

- 'Top-down' imaging: all patients receive DMSA and ultrasound, followed by MCUG if a renal defect is detected by the DMSA.
- 'Bottom-up' imaging: all patients receive ultrasound and MCUG.

The analysis was limited to immediate outcomes of the imaging strategy. The probability estimates used in the model for incidence of VUR (38.7%) and detection of renal lesions

(ultrasound=11.2%, DMSA [without VUR]=32.7%, DMSA [with VUR]=52.4%) were based on pooled results from a systematic literature review. The estimated radiation exposure per test (based on 'effective dose', which took into account exposure and radiosensitivity of different organs) was 0.06 mSv for MCUG (specifically, pulsed fluoroscopy MCUG) and 0.7 mSv for DMSA. Cost estimates per test, based on Medicare reimbursements, were $226 for ultrasound, $366 for MCUG and $681 for DMSA. Model outcomes were: number of patients undergoing each test; population-level direct medical costs; average per-patient radiation dose; and number of accurate diagnoses of VUR. The index case was a child aged 1 year diagnosed with a first febrile UTI. An identical cohort of 100,000 hypothetical index cases was put through each imaging strategy.

The model gave the following results:

- Total costs for top-down imaging were $82.9 million (per patient=$829) and $59.2 million (per patient=$592) for bottom-up imaging.
- Radiation dose per patient with top-down imaging was 0.72 mSv and 0.06 mSv for bottom-up imaging.
- The bottom-up approach identified all 38,700 patients with VUR, whereas the top-down approach only identified 20,300 (52%), although it is not clear whether patients would receive benefit or harm from a missed diagnosis (see the Cochrane review by Nagler et al. 2011 in 'Antibiotic prophylaxis in children with VUR' in section 1.2 'Management' and 'Surgical management of VUR' in section 1.4 'Surgical intervention' for details of the limitations and uncertainties around interventions for VUR).

Limitations common to both La Scola et al. (2013) and Routh et al. (2012) included that:

- Outcomes such as VUR and renal scarring may not necessarily have many negative long-term clinical consequences, and the studies did not assess outcomes that may be of greater relevance for patients, such as hypertension and renal failure. Interpreting results without these data make conclusions about the relative merits of the algorithms difficult.
- The modelling of the algorithms was based on short-term management of a first febrile UTI and did not consider children with recurrent UTI. Further radiological exams in these children may have increased diagnostic findings but would also increase costs and radiation.
- Both models relied on estimated values and involved data from outside the UK, which may reduce the validity of the findings for an NHS setting.
- The estimates of renal scarring detected by DMSA appear to be higher than the rates of around 5–15% reported in other literature discussed by the full version of NICE CG54.

Taken together, the evidence suggests that more aggressive imaging strategies (such as DMSA for all patients with febrile UTI, with a further option of MCUG if indicated) may have higher sensitivity and lower specificity for detecting VUR and renal scarring. However, they also appear to be associated with higher costs and radiation exposure. The imaging protocol recommended by NICE CG54 appears to be relatively low cost with a high specificity but low sensitivity for detecting VUR and scarring. Radiation exposure per patient with the NICE protocol (0.5 mSv) appears to be higher than some guidelines (0.14 mSv – AAP) but lower than others (2.05 mSv – top down approach). The clinical impact of differing radiation exposures was not assessed by the studies.

Unless they are severe, most renal defects detected on DMSA appear to have limited long-term clinical impact, and there is uncertainty over the effectiveness of established interventions (see Williams and Craig 2011 in section 1.2, Nagler et al. 2011 in section 1.4 and Toffolo et al. 2012 in section 1.5 for more details of interventions for, and long-term impacts of, UTI). Therefore, the clinical benefit of increased imaging must be weighed against potential complications of imaging and the greater costs, radiation exposure and stress for the patient. There may be potential to reduce radiation exposure below the levels associated with

the current NICE imaging protocol. Therefore, these data could have a potential impact on NICE CG54. For example, the AAP guideline does not include DMSA in its imaging pathway.

Details of any impact are outside the scope of the Evidence Update. Decisions on how the new evidence may impact guidance will not be possible until the guidance is reviewed by NICE following its published processes and methods.

**Key references**

La Scola C, De Mutiis C, Hewitt IK et al. (2013) Different guidelines for imaging after first UTI in febrile infants: yield, cost, and radiation. Pediatrics 131: e665–71

Routh JC, Grant FD, Kokorowski PJ et al. (2012) Economic and radiation costs of initial imaging approaches after a child's first febrile urinary tract infection. Clinical Pediatrics 51: 23–30

## 1.4 Surgical intervention

**Surgical management of VUR**

NICE CG54 states that surgical management of VUR is not routinely recommended.

The Cochrane review by **Nagler et al. 2011** (see 'Antibiotic prophylaxis in children with VUR' in Section 1.2 'Management' for details) evaluated several treatments for VUR, which included surgical management.

Although combined surgical and antibiotic treatment caused a 57% reduction in febrile UTI by 5 years compared with antibiotics alone (RR=0.43, 95% CI 0.27 to 0.70, p=0.00073; 2 studies, n=449), it did not decrease the risk of either new or progressive renal damage, or symptomatic UTI.

Limitations of the evidence included that most patients analysed for this aspect of the review had higher grades of VUR, so results may not necessarily apply to those with the lowest grades. However, surgical intervention would not often be considered in less serious cases of VUR that may be more likely to resolve spontaneously.

The authors concluded that the added benefit of surgical or endoscopic correction of VUR over antibiotic prophylaxis alone remains unclear; therefore, this evidence is unlikely to have an impact on NICE CG54.

## 1.5 Follow-up

NICE CG54 recommends that routine or long-term follow-up is not needed for infants and children:

- who do not undergo imaging investigations
- whose imaging results are normal
- with a minor, unilateral renal parenchymal defect (unless they have recurrent UTI or family history or lifestyle risk factors for hypertension)
- who are asymptomatic after an episode of UTI
- with asymptomatic bacteriuria.

Two studies recently examined long-term outcomes of childhood UTIs.

An observational follow-up study in Finland by **Hannula et al. (2012)** reported long-term clinical outcomes among a population-based cohort with a history of UTI in childhood. The original cohort comprised 1161 children aged 0–14 years who underwent renal ultrasound and MCUG at a hospital paediatric department between 1993 and 2003. A random sample of 193 patients (stratified by ultrasound results and VUR grade) were followed up, either through attendance at a clinic, or via telephone interview or assessment of medical records. Mean follow-up time was 11.1 years (range 6–17 years) after the original childhood UTI, and mean

age at follow-up was 13.0 years. The follow-up included a questionnaire about UTI recurrence; use and duration of antimicrobial prophylaxis; general health; medication; details of pregnancy; and family history of hypertension. Additionally and where possible, blood pressure was measured, blood samples were taken, and urinalysis and ultrasonography were performed.

Among the 193 sampled patients:

- 87% had radiological imaging following their first UTI
- 53% had received antibiotic prophylaxis
- 22% had urinary tract surgery (all of whom had VUR grade 3 to 5)
- 39% had a recurrence of UTI.

In the 150 patients with available ultrasound data, 22 (15%) had a unilateral parenchymal defect, which was considered to be new damage in 18 cases (all of whom had VUR grade 3 to 5). If extrapolated to the whole cohort, and taking into account the stratified sampling, this would equate to 36 of 1161 (3%) patients who may potentially develop new renal damage. No cases of impaired renal function (measured by serum cystatin C concentration, estimated glomerular filtration rate, haematuria and proteinuria) or hypertension were seen among the 120 patients who attended the clinic in person. Height was normally distributed and within normal limits in all patients.

Limitations of the evidence included that:

- The observational nature of the study meant that the potential effects of antibiotic prophylaxis and surgery on the natural history of VUR could not be excluded.
- Most data for UTI recurrence were obtained from medical records but some were obtained solely from patients, which may have introduced bias.

A systematic review by **Toffolo et al. (2012)** also evaluated long-term consequences of childhood UTIs, VUR and scarring. Retrospective and prospective cohort studies, RCTs, and population-based studies (mean follow-up >2 years) of children aged 0–18 years with first or recurrent UTIs (5 studies) and/or VUR (14 studies) and scarring (1 study) were included. Among the 20 cohorts of children (n=3573) identified, only 11 cohorts excluded obstructive uropathies, neurogenic bladder or other complex urological conditions. VUR was diagnosed in 84% of all children, and renal scarring at baseline was present in 47% of the 2214 children evaluated for it.

Results for the main outcomes of interest were:

- Renal function: among 8 prospective studies, chronic kidney disease (CKD) was present in 55 of 1029 children at the end of follow-up, but only 4 of these children had previously normal renal function (data were not available for 8 children, and CKD was already present at baseline in the remainder). Therefore, only 0.4% of children with baseline normal renal function experienced a decrease during follow-up.
- Hypertension: among 17 studies (2938 children), most reported a low prevalence of hypertension (2–6%) at the end of follow-up. Hypertension appeared to be more frequent when CKD was more prevalent.
- Growth: among 5 cohorts (659 children), growth did not seem to be affected by UTIs.
- Pregnancy-related complications: a study including 65 pregnancies among 41 women found no significant difference between patients and controls for pre-eclampsia, operative delivery, prematurity, birth weight, or malformations.

Limitations of the evidence include that:

- The authors reported substantial heterogeneity between studies in terms of population, criteria for diagnosing UTI, assessment of outcomes, and length and completeness of

follow-up. This issue, along with the lack of studies in children with uncomplicated UTIs, made it difficult to draw firm conclusions from the evidence base.

- In 14 of the cohorts, enrolment began before the 1980s, when prenatal ultrasound was not routine. As a result, UTI was the first sign of urinary tract malformations, which would be less likely in modern practice.
- In 12 cohorts, selection was retrospective based on VUR or scarring, with some scarring identified on intravenous urography, which would only identify major scars.

Taken together, the evidence suggests that the risk of long-term complications after UTI in childhood appears to be low. These data are consistent with NICE CG54.

**Key references**

Hannula A, Perhomaa M, Venhola M et al. (2012) Long-term follow-up of patients after childhood urinary tract infection. Archives of Pediatrics & Adolescent Medicine 166: 1117–22

Toffolo A, Ammenti A, Montini G (2012) Long-term clinical consequences of urinary tract infections during childhood: a review. Acta Paediatrica 101: 1018–31

## 1.6 Information and advice for children, young people and parents or carers

No new key evidence was found for this section.

# 2 Evidence uncertainties

The following uncertainties, which are listed in the UK Database of Uncertainties about the Effects of Treatments (UK DUETs), are associated with evidence discussed in this Evidence Update:

- Are cranberry juice and other alternative or complimentary therapies effective in reducing urinary tract infections?
- Long-term antibiotics for preventing recurrent urinary tract infection in children
- Effective interventions for primary vesicoureteric reflux
- Routine neonatal circumcision for the prevention of urinary tract infections in infancy
- The natural history of vesicoureteral reflux in scintigraphically confirmed renal scarring in both genders
- Urinary tract infections in children as a risk factor for development of CKD and hypertension

Further evidence uncertainties for urinary tract infection in children can be found in the UK DUETs database and in the NICE research recommendations database.

UK DUETs was established to publish uncertainties about the effects of treatments that cannot currently be answered by referring to reliable up-to-date systematic reviews of existing research evidence.

# Appendix A: Methodology

## Scope

The scope of this Evidence Update is taken from the scope of the reference guidance:

- Urinary tract infection in children. NICE clinical guideline 54 (2007)

## Searches

The literature was searched to identify studies and reviews relevant to the scope. Searches were conducted of the following databases, covering the dates 4 August 2010 (the end of the search period for the latest review of the need to update NICE clinical guideline 54) to 10 April 2013:

- AMED (Allied and Complementary Medicine Database)
- CDSR (Cochrane Database of Systematic Reviews)
- CENTRAL (Cochrane Central Register of Controlled Trials)
- CINAHL (Cumulative Index to Nursing and Allied Health Literature)
- DARE (Database of Abstracts of Reviews of Effects)
- EMBASE (Excerpta Medica database)
- HTA (Health Technology Assessment) database
- MEDLINE (Medical Literature Analysis and Retrieval System Online)
- MEDLINE In-Process
- NHS EED (Economic Evaluation Database)

Table 1 provides details of the MEDLINE search strategy used (based on the search strategy for the reference guidance), which was adapted to search the other databases listed above. The search strategy was used in conjunction with validated Scottish Intercollegiate Guidelines Network search filters for RCTs, systematic reviews and observational studies.

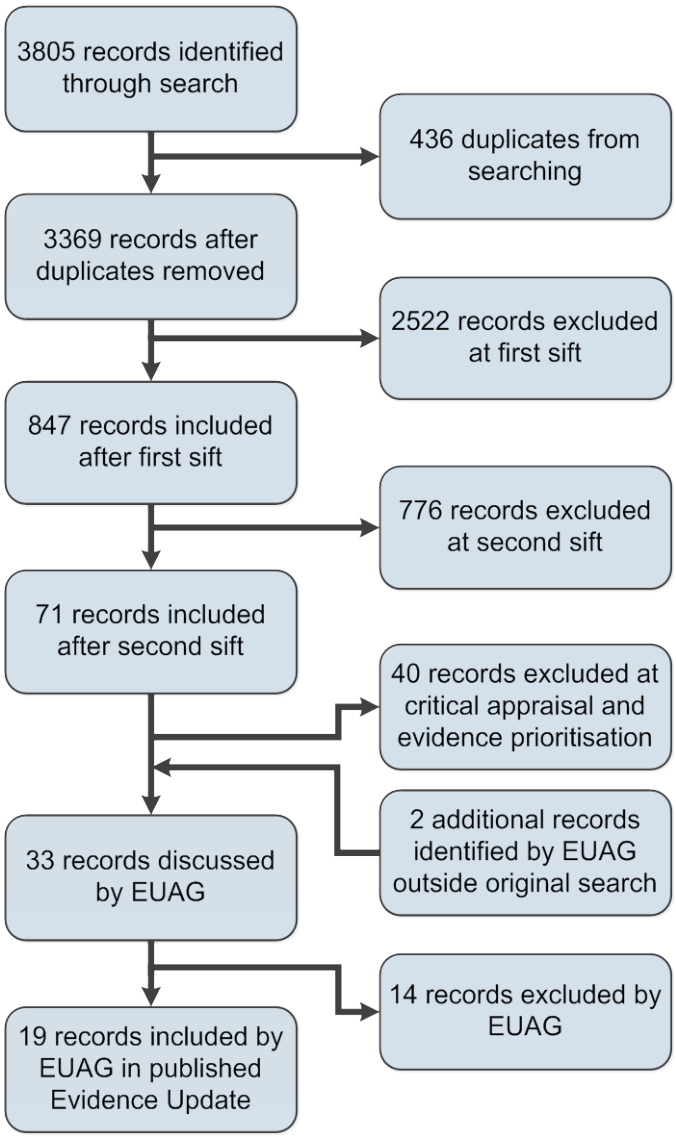
Additionally, 1 study (Hannula et al. 2010) was identified outside of the literature search. Figure 1 provides details of the evidence selection process. The long list of evidence excluded after review by the Chair of the EUAG, and the full search strategies, are available on request from contactus@evidence.nhs.uk.

There is more information about how NICE Evidence Updates are developed on the NICE Evidence Services website.

**Table 1 MEDLINE search strategy (adapted for individual databases)**

| | |
|---|---|
| **1** | exp Urinary Tract/ |
| **2** | ((urin$ or renal$) adj (system$ or tract$)).tw. |
| **3** | exp Urinary Tract Infections/ |
| **4** | ((bladder$ or genitourin$ or kidney$ or pyelo$ or renal$ or ureter$ or ureth$ or urin$ or urolog$ or urogen$) adj5 infect$).tw. |
| **5** | UTI.tw. |
| **6** | ((upper or lower) adj5 urin$).tw. |
| **7** | Cystitis/ |
| **8** | Cystitis, Interstitial/ |
| **9** | cystitis$.tw. |
| **10** | (bladder$ adj5 (ulcer$ or ulcus)).tw. |
| **11** | or/1-10 |
| **12** | Proteinuria/ |
| **13** | proteinuri$.tw. |
| **14** | Albuminuria/ |
| **15** | albuminuri$.tw. |
| **16** | ((protein$ or albumin$) adj5 urin$).tw. |
| **17** | Bacteriuria/ |
| **18** | bacteriuria$.tw. |
| **19** | ((bacteria$ or microbial$) adj5 (bladder$ or genitourin$ or kidney$ or renal$ or ureter$ or ureth$ or urin$ or urolog$ or urogen$)).tw. |
| **20** | Pyuria/ |
| **21** | pyuri$.tw. |
| **22** | Schistosomiasis haematobia/ |
| **23** | (schistosomiasis adj2 (haematobia or urin$)).tw. |
| **24** | or/12-23 |
| **25** | Vesico-Ureteral Reflux/ |
| **26** | ((vesicorenal$ or vesico?ureteral$ or vesicour$) adj reflux).tw. |
| **27** | VUR.tw. |
| **28** | ((backflow$ or bladder$ or cystoureteral$ or ureter$ or urether$) adj5 reflux$).tw. |
| **29** | or/25-28 |
| **30** | Pyelonephritis/ |
| **31** | pyelonephriti$.tw. |
| **32** | pyonephrosi$.tw. |
| **33** | pyelocystiti$.tw. |
| **34** | or/30-34 |
| **35** | 11 or 24 or 29 or 34 |

**Figure 1 Flow chart of the evidence selection process**




EUAG – Evidence Update Advisory Group

# Appendix B: The Evidence Update Advisory Group and Evidence Update project team

## Evidence Update Advisory Group

The Evidence Update Advisory Group is a group of topic experts who review the prioritised evidence obtained from the literature search and provide the commentary for the Evidence Update.

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