Scope of Guidelines

Specialist assessment and management is required for children who are considered at high risk of serious illness (underlying structural urinary tract abnormalities or neurogenic bladder or kidney transplant recipients). These children are beyond the scope of these guidelines and it is important that they are excluded from the recommendations detailed below.

GUIDELINES

a. We do not recommend routine renal tract imaging following a first urinary tract infection (UTI) except in the circumstances described below. (1B)

Renal Ultrasound

b. We suggest that children who have had a first UTI and who haven’t had a second or third trimester antenatal ultrasound that includes the urinary tract, have a renal ultrasound performed to assess the kidney and urinary collecting system (2B).

c. We suggest that a renal ultrasound be considered in children who:
   - Have concurrent bacteraemia (2B)
   - Are less than 3 months of age (2C)
   - Have a urine culture with atypical organisms (e.g. Staphlococcus aureus or Pseudomonas) (2C)
   - Lack a clinical response to 48 hours of antibiotic if sensitive organism (2C)
   - Have renal impairment or significant electrolyte derangement (2D)
   - Have an abdominal mass (2D)
   - Have a poor urinary stream (2D)

Micturating Cystourethrogram (MCUG)

d. We suggest that MCUG to detect vesicoureteric reflux (VUR) may be clinically useful in children with recurrent pyelonephritis. (2D)

e. We suggest that MCUG may be clinically useful in male children with bilateral hydroureteronephrosis or bladder wall thickening on ultrasound, to exclude urethral pathology. (2D)

f. We suggest that prophylactic antibiotics should be given at the time of MCUG. (2B)

Dimercaptosuccinic acid scan (DMSA)

g. We do not recommend DMSA in the acute phase (0 - 4 weeks) of a UTI (1D)

h. We suggest that DMSA in the follow-up phase (at least 3 months after UTI) may be undertaken if there is clinical concern over reduced kidney function (2D)
UNGRADED SUGGESTIONS FOR CLINICAL CARE

Renal Ultrasound

a. Minimum requirements for renal ultrasound should include high resolution scanning, imaging kidneys in 3 planes and bladder in 2 planes. Report should include measurements of maximum renal length, maximum transverse pelvic dimension at the exit of the pelvis from the renal parenchyma, the presence of calyceal dilatation, bladder wall thickness and pre-and post-void bladder volumes if possible. (Ungraded)

Micturating Cystourethrogram

b. In older children sedation/anxiolysis with midazolam or nitrous oxide may reduce distress associated with the procedure (Ungraded).

IMPLEMENTATION AND AUDIT

Units should consider an audit of current practices of assessment and treatment of children with symptoms of UTI that includes a review of patient outcomes and alignment of current procedures with the guideline recommendations. Following audit and review, key areas for focus of an implementation strategy should be identified and a site specific plan developed.

BACKGROUND

Renal tract imaging after urinary tract infection aims to identify children with renal tract abnormalities that increase their risk of repeated infections. This is based firstly on the assumption that recurrent infections damage the kidneys which in the long term, may lead to high blood pressure and end stage kidney failure and secondly that preventative treatments are effective. Preventative treatment options include low dose antibiotics for long periods of time, surgical interventions to correct vesicoureteric reflux and complementary therapies such as cranberry products.

The first assumption on which renal tract imaging has been justified is the detrimental long term effect of repeated urinary tract infections. Evidence on which this assumption is made is not convincing because retaining a large and representative sample of children with a relatively minor illness for long term follow-up is difficult. Studies that have managed to follow children over long periods tend to retain those with more serious illness which leads to over estimation of rates of hypertension due to selection bias. A systematic review of the prevalence of hypertension following reflux nephropathy showed that 6-28% had hypertension [1]. The risk of hypertension after childhood UTI is likely to be small. Registry data demonstrates that the frequency of end stage kidney disease following pyelonephritic scarring or reflux nephropathy is around 0.5% in the USA, 4% in Australia and Sweden, 7.3% in England and Wales and around 15% in some European countries [2]. It is difficult to be precise about a risk of end stage kidney disease after UTI, but it would appear quite low given the available data.

The second assumption that preventative treatment is effective is also questionable. The benefit in low dose antibiotic treatment is small and accompanied by a substantial risk of a subsequent infection by bacteria resistant to the prophylactic drug. Surgical interventions to correct VUR are effective in correcting the reflux but do not appear to greatly reduce the risk of further UTI. Complementary therapies suggest a benefit but studies are not large or rigorous and include only small numbers of children. In summary, current literature suggests that the available preventative strategies are not convincingly effective. Refer to sub-topic KHA-CARI Diagnosis and Treatment of Urinary Tract Infection in Children: Long Term Management – Recurrent Urinary Tract Infection and Vesicoureteric Reflux for detail.

Available research findings for renal tract imaging assessment can determine which modality is optimal for identifying various aspects of the urinary tract. Renal ultrasound is useful for identifying structural abnormalities of the urinary tract. Structural abnormalities detected by ultrasound occur in between 10 and 75% (median around 30%) of children scanned after a UTI [2]. Abnormalities tend to be seen more
often in younger children. Renal ultrasound may suggest an obstructive uropathy which can be diagnosed with a MAG3 renal scan (pelvi-ureteric or uretero-vesical obstruction) or MCU (posterior urethral valves or other urethral pathology). Micturating cystourethrogram is the gold standard test to detect VUR and between 30 and 40% of children with a UTI will have VUR detected [2]. A DMSA scan is considered the most appropriate test for detection of renal parenchymal abnormalities. The NICE evidence compilation concludes that 5% of children who have had a UTI have renal parenchymal abnormalities [2]. A later systematic review of 33 studies [3] showed that 57% of children had changes when measurements were made in the acute phase (< 15 days after UTI) and 15% had renal parenchymal changes when measured during the follow-up phase (> 5 months post UTI). There is insufficient evidence to conclude whether performing a DMSA scan to detect these abnormalities is beneficial to the patient in the long term [2, 4].

**SEARCH STRATEGY**

**Databases searched** MeSH terms and text words for UTI, bacteriuria, bacterial infection, pyuria or pyelonephritis with MeSH terms and text words for ultrasonography, VUR, micturating cystourethrogram, DMSA/DPTA scans, or radiography combined with MeSH terms and text words for paediatric populations. The search was carried out in Medline. The Cochrane Renal Group Trials Register was also searched for trials not indexed in Medline.

**Date of search/ies:** 1950 to 15 August 2014.

**WHAT IS THE EVIDENCE?**

**Clinical efficacy**

A systematic review of 73 studies evaluating the various modes of renal tact imaging demonstrated that there is insufficient evidence of clinical effectiveness for routine imaging in children after a confirmed UTI [5]. This conclusion was similar to that detailed in the very comprehensive evidence summary compiled for the National Institute for Health and Clinical Excellence: Urinary tract infection in children [2]. Since these evidence compilations were published, there have been no rigorous, new primary studies published that address the question of clinical efficacy.

**End stage renal failure**

Registry data provides summarised frequencies of the apparent causal diagnosis for people with end stage renal disease [2]. While these registries have good quality data on rates of end stage disease and treatment modalities, the quality of the data around attributable diagnoses is less rigorous given the complexities of end stage disease, the delayed development of end stage disease and the lower clinical imperative to make an accurate etiological diagnosis. However, since long term, prospective studies of children with UTI are small and incorporate a biased sample, registry data is likely to provide more data than these small scale UTI cohorts. Renal obstruction can lead to end stage renal failure and posterior urethral valves are the most common congenital abnormality causing renal obstruction. Around 0.5 to 1% of children presenting with UTI will have obstruction [6, 7]

**Hypertension**

NICE guidelines [2] compiled the findings from studies that reported frequency and risk of hypertension in children with UTI and summarised with the statement that hypertension may be associated with childhood UTI but the risk is likely to be small and associated only with more severe or bilateral renal scarring. Since the NICE guideline was published one study of 664 children with VUR and blood pressure measured at 1 to 9 years post- UTI reported that 20 children (3%) developed hypertension overall. Using Kaplan Meier analysis, the frequency was estimated as 2% at 10 years of age, 6% at 15 years of age and 15% at age 21 years [8].

**Growth**

NICE guidelines report the studies that have measured kidney growth after UTI and conclude that there is little evidence for a long term effect on kidney growth [2]. A study published after the NICE
guidelines, measured overall body growth and glomerular filtration rate in children who had experienced a UTI [9]. Patients were grouped based on their VUR status and compared, with results showing little or no difference in growth indices between the groups.

**Frequency of Renal Tract Abnormalities**

**Ultrasound**

NICE guidelines [2] summarise published studies that report abnormalities identified from renal ultrasound and report large variability with the range of frequency being 10 to 75%. An Italian study of children with first febrile UTI reported that 13% (38/282) had abnormalities [10]. A second Italian study of children under 2 years of age with UTI stated that 44.6% had a dilated renal pelvis identified on ultrasound [11]. A study of 820 children in Hong Kong reported ultrasound abnormalities in 8.9% of children with first febrile UTI [7]. These studies are not the complete list of reports however the pattern of variability and the likely range of frequencies is likely covered by these. Renal ultrasound is usually abnormal in children with posterior urethral valves causing renal obstruction. Precise estimates of test performance of ultrasound for posterior urethral valves and renal tract obstruction are not available. In some cases these abnormalities may be detected during prenatal ultrasonography [12].

**Micturating cystourethrogram**

The NICE evidence summary reports that the rate of vescicoureteric reflux in children who have had a UTI is between 8 and 40% [2]. Studies published since the NICE review do not contradict the variability and probable range stated here. The same three studies described for ultrasound [10-12] report frequencies of 23.8%, 55% and 22% respectively.

**Technetium-99m-dimercaptosuccinic acid scan (DMSA)**

The NICE evidence summary includes information from 9 prevalence studies and 6 studies on new or progressive scars with a concluding statement that the prevalence of renal parenchymal defects in children who have had a UTI is about 5% and it occurs more in boys than girls [2]. A systematic review of 33 studies in children with an initial UTI [3] gave an estimated rate of 57% (95% CI 50-64%) who had changes consistent with acute pyelonephritis on the acute phase DMSA (<15 days) and 15% (95% CI 11-18) with renal scarring on the follow-up DMSA (>5 months). A systematic review of 13 diagnostic test studies in children with a first UTI reported the following:

- Pooled sensitivity of DMSA for dilating VUR: 79% (95% CI: 66, 88)
- Pooled specificity of DMSA for dilating VUR: 53% (95% CI: 41, 64)
- Pooled +ve likelihood ratio (LR) of DMSA for dilating VUR: 1.7 (95% CI: 1.3-2.2) and pooled –ve LR of DMSA for dilating VUR: 0.4 (95% CI: 0.23, 0.69) [13].

**MAG3 (Technetium-99m-mercaptoacetyltriglycine) or DTPA**

MAG3 or DTPA are the radiopharmaceuticals used for dynamic renal scanning to identify urinary tract obstruction at the pelvi-ureteric or uretero-vesical junction. Obstruction may be suggested by renal ultrasound or MUG and can be confirmed or excluded based on results of dynamic renal scans.

**Imaging findings and risk of UTI recurrence**

The NICE evidence compilation details 8 studies assessing risk factors for repeat UTI and report dilating VUR to be associated with future UTI in children [2]. A large record linkage analysis quantitated this risk and estimated the hazard ratio for grades 4 to 5 VUR as 4.38 (95% CI 1.26 to 15.29) [14]. An earlier cohort of children followed after UTI report grades 3-5 VUR to independently predict recurrence of UTI with an odds ratio of 3.6 (95% CI 1.5 to 8.3) [15] as did defects on early (3-10 days post UTI diagnosis) DMSA scan with an odds ratio of 1.5 (95% CI 0.7 to 3.5). A study of 148 children with voiding dysfunction report a significant association between ultrasound detected post void residual urine and number of UTIs [16].

Recurrence risk in children with VUR has been reported in several studies, a recent but very small study of 44 children with VUR reported that 19 of 25 children with grades 4-5 VUR experienced recurrent UTIs compared with 1 of 19 children with grades 1-3 VUR experiencing a repeat UTI (odds
Another recent primary study of 142 children provides data on DMSA abnormalities in children with grades 5 VUR, a sensitivity of 24.7% and specificity of 92.5%. Detection of grades 4 and 5 VUR by DMSA was an independent risk factor of recurrent UTI with an odds ratio of 8.01 (95% CI 2.01 to 30.51) [20].

**Imaging findings, risk of renal parenchymal abnormalities**

All grade VUR was significantly associated with renal scarring in a systematic review of 80 studies of children with a UTI and imaging results with an odds ratio of 4.8 (95% CI 4.3 to 5.5). The odds ratio for children with grades 3-5 VUR was 5.7 (95% CI 4.5 to 7.3) [21] which was similar to that found in an earlier review of 10 studies with a relative risk of 5.6 [22].

**Comparative test performances**

**Ultrasound compared to MCUG for detecting VUR.** NICE guidelines summarise relative test performance of 12 studies comparing renal ultrasound to MCUG for identification of VUR and report sensitivity to range from 10.9% to 90.9% [2]. An earlier systematic review [23] of 15 studies reported an average false positive rate of 35% and sensitivity of 34% with children as the unit of analysis and ranges for sensitivity and specificity of 11 to 89%, and 15 to 93% respectively. Using kidneys as the unit of analysis the average false positive rate was lower at 10% but with similarly low sensitivity 34% with the ranges for sensitivity and specificity of 7 to 97%, and 50 to 100% respectively. A recent primary study provides data on 820 children with UTI and imaging results [7]. From this data ultrasound had a sensitivity of 13.8% and specificity of 92.6% for detection of VUR. In children with grades 4 and 5 VUR the sensitivity was 24.6% and specificity 92.5% Several other recent primary studies have been published since the systematic reviews and report similar findings of low sensitivity for ultrasound identification of VUR [10, 24].

**Ultrasound compared to DMSA for detecting renal parenchymal abnormalities.** Nine studies are summarised in the NICE guideline and the range of sensitivities and specificities for ultrasound for identification of DMSA detected renal parenchymal defects are 3.4% to 100% and 61.0 to 100% [2] respectively. An earlier systematic review included 13 studies analysing ultrasound for DMSA detected renal parenchymal abnormalities [23]. Studies using children as the unit of analysis had an average false positive rate of 19% with sensitivity 89% (ranges sensitivity 24 to 100%, specificity 49 to 97%). When kidneys were the unit of analysis, the average false positive rate was 7% with sensitivity 67% (ranges sensitivity 23 to 87%, specificity 63 to 100%).

**MCUG compared to DMSA for detecting renal parenchymal abnormalities.** A comprehensive systematic review and economic analysis included four studies investigating the use of MCUG to detect renal parenchymal abnormality [25]. Sensitivities ranged from 68 to 86% and specificities from 37 to 82%. Thirteen studies that compared MCUG to DMSA for detection of renal parenchymal abnormalities were compiled in an earlier systematic review [23]. When children were the unit of analysis, the average false positive rate and sensitivity were 18% and 38% respectively (ranges sensitivity 28 to 46%, specificity 50 to 95%). Studies using kidneys as the unit of measurement gave an average false positive rate or 27% with sensitivity 56% (ranges sensitivity 30 to 82%, specificity 21 to 100%).

**DMSA compared to MCUG for detecting VUR.** A systematic review and meta-analysis [23] included 13 studies evaluating DMSA for detection of VUR. The average false positive rate when children were the unit of analysis was 58% and the average sensitivity was 84% (ranges sensitivity 46 to 91%, specificity 8 to 84%). Tests performance was lower when kidneys were the unit of analysis, average false positive rate 25% and sensitivity 51% (ranges sensitivity 20 to 96%, specificity 52 to 87%). A study in 2010 provides data from 612 children from which test performance can be calculated [7] and report a sensitivity of 24.7% and specificity of 92.5%. Detection of grades 4 and 5 VUR by DMSA had a low sensitivity of 26% and high specificity of 94.0%. A smaller study of 303 children with data allowing calculation of test performance of DMSA for detection of VUR had a sensitivity of 46.3% and specificity of 80.7% for detection of grade of VUR and 88.9% and 75.5% for detection of grades 4 and 5 [26]. Another recent primary study of 142 children provides data on DMSA abnormalities in children with...
VUR and reports a sensitivity for all VUR as 88.1% and specificity 36.0% and for grade 3 to 5 VUR a sensitivity of 100% and specificity of 33.9% [27]. These studies indicate that an abnormal DMSA result detects almost all cases of severe VUR.

SUMMARY OF THE EVIDENCE

There is insufficient evidence to demonstrate a clinical benefit for renal tract imaging after first UTI in children. Renal ultrasound can detect structural integrity of the renal tract system, while micturating cystourethrogram is the test of choice for detecting vesicoureteric reflux and a dimercaptosuccininc acid scan is the best test for identifying renal parenchymal abnormalities. Abnormalities of the renal tract are identified in 10 - 75% of children following a UTI. Few children with renal tract obstruction or grades 4 and 5 VUR will have normal ultrasound findings. Grades 4 and 5 VUR increase the risk of repeat UTI. Very few children (<5%) with UTI will develop hypertension and end stage renal failure.

WHAT DO THE OTHER GUIDELINES SAY?

European Association of Urology. Guidelines on urological infections [28]

- Investigation should be undertaken after two episodes of UTI in a girl and one in boys. The objective is to rule out the unusual occurrence of obstruction, vesicoureteric reflux (VUR) and dysfunctional voiding (eg as caused by a neuropathic disorder).

Ultrasound

- Renal and bladder ultrasonography is strongly recommended in infants with febrile UTI to exclude obstruction of the upper and lower urinary tract. Abnormal results are found in ~15% of cases, and 1-2% have abnormalities that require prompt action (e.g., additional evaluation, referral, or surgery) (subcommittee on Urinary Tract 1). In other studies, renal ultrasound revealed abnormalities in up to 37% of cases, whereas voiding cystourethography (VCUG) showed vesicoureteral reflux (VUR) in 27% of cases [24]. Dilating VUR is missed by ultrasound in around one third of cases [29]. Post-void residual urine should be measured in toilet-trained children to exclude voiding abnormalities as a cause of UTI.

Radionuclide scanning

- Changes in DMSA clearance during acute UTI indicate pyelonephritis or parenchymal damage, correlated well with the presence of dilating reflux and the risk of further pyelonephritis episodes, break-through-infections [30] and future renal scarring. DMSA scanning may be used as a first-line diagnostic procedure based on observations that dilating VUR occurs in almost all children with abnormal DMSA scan [29, 31]. These findings are different in neonates. After the first symptomatic, community-acquired UTI, the majority of renal units with VUR grade III or higher had normal early DMSA scanning[32].

Voiding Cystourethography

- VCUG is still the gold standard to exclude or confirm VUR. Due to the risk of renal scarring, VCUG is recommended after the first episode of febrile UTI in boys and girls. The timing of VCUG does not influence the presence or severity of VUR [33, 34]. Performance of early VCUG in patients with proven sterile urine does not cause any significant morbidity [35]. Another option is doing DMSA first, followed by VCUG if there is renal cortical uptake deficiency after urinary tract infection.


- The routine use of imaging in the localisation of UTI is not recommended.
- Infants and children with atypical UTI (seriously ill, poor urine flow, abdominal mass, raised creatinine, septicaemia, failure to respond to suitable antibiotics in 48 hours, non-E.coli organism isolated) should have ultrasound of the urinary tract during the acute infection to identify structural abnormalities of the urinary tract such as obstruction.
- For infants younger than 6 months with first time UTI that responds to treatment, ultrasound should be carried out within 6 weeks of the UTI.
- For infants and children aged 6 months and older with first time UTI that responds to treatment, routine ultrasound in not recommended unless the infant or child has atypical UTI.
• Infants and children who have had a lower urinary tract infection should undergo ultrasound (within 6 weeks) only if they are younger than 6 months have had recurrent infections
• A DMSA scan 4-6 months following the acute infection should be used to detect renal parenchymal defects
• If the infant or child has a subsequent UTI while awaiting DMSA, the timing of the DMSA should be reviewed and consideration given to doing it sooner
• Routine imaging to identify VUR is not recommended for infants and children who have had a UTI, except in specific circumstances
• When a micturating cystourethrogram is performed prophylactic antibiotics should be given orally for 3 days with MCU taking place on the second day


• Below the age of 2 years, an ultrasound and micturating cystourethrogram (MCU) are recommended. These investigations will detect most cases of reflux nephropathy or those ‘at-risk’ in this age group. Urinary tract ultrasonography will identify hydronephrosis, dilatation of ureter, bladder hypertrophy, ureterocele and post-void residual urine. Ultrasonography should be performed within 2-4 weeks following the UTI. Children requiring hospitalization for complicated UTI should preferably be screened with an ultrasound before their discharge
• The MCU is useful for the diagnosis and grading of VUR, and detection of posterior urethral valves, ureterocele and bladder or urethral diverticuli. MCU is usually performed 4-8 weeks after treatment of the UTI. Concerns that obtaining a MCU too soon after a UTI result in a false-positive study are ill founded. It is rare for reflux to be detected during UTI and then to disappear following treatment(3). In order to prevent infection following catheterization, the MCU should be done under cover of prophylactic antibiotics (6). Amoxicillin is administered orally in a dose of 50 mg/kg, 1 h before the procedure and 25 mg/kg 6 h later. Alternatively, gentamicin (2-3 mg/kg intramuscular) may be given 30 minutes before the MCU
• If available, renal scintigraphy using 99mTc-radiolabeled dimercaptosuccinic acid (DMSA) or glucoheptonate (GHA) should be performed in all children below two years of age. Renal scintigraphy (ideally performed 3 months after treatment of the UTI) is an excellent technique for detecting renal cortical scarring
• Between the ages of 2-5 years, an MCU is not immediately required, unless the symptoms suggest an underlying obstruction. An ultrasound and a DMSA (or GHA) renal scan are done, and MCU performed only if either of the former investigations is abnormal. By pursuing this policy, the number of cystograms performed in this age group is restricted to patients having renal anomalies. In case facilities for radionuclide scans are not available, MCU should be performed as for younger children
• Children over the age of 5 years can be reliably screened with ultrasonography per-formed by an expert. Imagine with MCU and renal scan are necessary only if abnormalities are found on ultrasound examination
• The presence of VUR can also be demonstrated on direct radionuclide cystography (DRCG). However, grading of reflux using this method is not reliable. DRCG does not evaluate the morphology of the urethra and bladder, and is thus not useful for establishing a diagnosis of posterior urethral valves or other anomalies. This technique is therefore not suitable as the initial procedure for evaluation of the lower urinary tract.
• Children with more than one episode of UTI, irrespective of age, are evaluated with ultrasound and MCU. A renal cortical scan (DMSA or GHA) to detect scars is recommended.
• Patients showing hydronephrosis in the absence of VUR should be evaluated by diuretic renography using 99mTc-labeled diethylenetriamine-pentaacetic acid (DTPA) or mercaptoacetyl-glycine (MAG-3). These techniques provide quantitative assessment of renal function and drainage of the dilated collecting system

**American Academy of Pediatrics. Urinary tract infection: Clinical Practice guideline for the Diagnosis and Management of the initial UTI in febrile infants and children 2 to 24 months,[37]**

• Febrile infants with UTIs should undergo renal and bladder ultrasonography (evidence quality C; Observational studies, vaso control and cohort design)
• VCUG should not be performed after the first febrile UTI; VCUG is indicated if renal bladder ultrasound reveals hydronephrosis, scarring or other findings that would suggest either high grade VUR or obstructive uropathy, as well as in other atypical or complex clinical
circumstances (evidence quality B, RCTs or diagnostic studies with minor limitations, overwhelmingly consistent evidence from observational studies)

Spanish Consensus Development Conference [38]
- The current strategy of routine use of diagnostic imaging tests should be substituted by another strategy in which the use of these tests is individualized, taking into account each patients level of risk.

Kidney Disease Outcomes Quality Initiative: No recommendation.

UK Renal Association: No recommendation.

Canadian Society of Nephrology: No recommendation.

European Best Practice Guidelines: No recommendation.

International Guidelines: No recommendation.

SUGGESTIONS FOR FUTURE RESEARCH

None made.

CONFLICT OF INTEREST

Michael Ditchfield, Sean Kennedy and Gabrielle Williams, have no relevant financial affiliations that would cause a conflict of interest according to the conflict of interest statement set down by KHA-CARI.

REFERENCES


### Table 1. Summary of included studies

<table>
<thead>
<tr>
<th>Study ID</th>
<th>N</th>
<th>Study design and setting</th>
<th>Participants and Interventions</th>
<th>Follow up</th>
<th>Comments and results</th>
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<tr>
<td><strong>Clinical Efficacy</strong></td>
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<td>Westwood (2005) [4]</td>
<td>72</td>
<td>Systematic review of diagnostic cohort studies and RCTs.</td>
<td>Studies comparing an index test with the relevant reference standard.</td>
<td>NA</td>
<td>- Only 1 abstract of an RCT relevant assessing clinical efficacy which concluded that routine imaging with ultrasound and MCUG in children with a first UTI did not result in significantly reduced renal scarring or recurrent UTI after 2 years follow-up.</td>
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<td>Diagnostic accuracy</td>
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<td>- Localisation of infection (31 studies)</td>
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<td>- Detection VUR Standard Ultrasound (12 studies)</td>
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<td>- Detection VUR Contrast enhanced Ultrasound (19 studies)</td>
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<td>o +LR 14.1 (95%CI: 9.5, 20.8)</td>
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<td>o −LR 0.30 (95%CI: 0.13, 0.29)</td>
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<td>- Prediction of renal scarring (5 studies)</td>
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<td>o +LR range 1.1 to 3.1 (12.9 in one study)</td>
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<td>- Detection renal scarring (13 studies)</td>
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<td>o +LR range 1.3 to 171.3</td>
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<td>Limitations: Methodological and reporting was of low quality across most studies.</td>
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<td>Less than half of the studies included an appropriate spectrum of patients and reported selection criteria. Incorporation bias, verifications bias and disease progression bias inadequately addressed by around half of the studies.</td>
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<tr>
<td>Dick (1996) [5]</td>
<td>63</td>
<td>Systematic review of trials and observational studies.</td>
<td>Studies of more than 30 children with symptomatic UTI who had undergone diagnostic imaging.</td>
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<td>- No controlled trials or analytic studies identified that evaluated different management strategies.</td>
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<td>- Most studies focus on the prevalence of urologic anomalies and test sensitivity and specificity not on clinical effectiveness.</td>
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<td>- No studies provided any direct evidence to support the effectiveness of routine diagnostic imaging on the development of renal scars and clinical outcomes with a first UTI.</td>
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September 2014  
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<table>
<thead>
<tr>
<th>Study ID</th>
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<td>Simoes e Silva (2007) [8]</td>
<td>664</td>
<td>Retrospective cohort (review of medical records). Single centre (Brazil)</td>
<td>Children diagnosed with primary VUR. VUR evaluated by DMSA (78%), MCTU (11.3%), and US (10.7%). Outcome: Time until development of hypertension (&gt;95th percentile for age, sex and height).</td>
<td>Median 72 months (IQ range 13 to 110 months)</td>
<td>3% developed hypertension. Development of hypertension significantly associated with reflux laterality, presence of renal damage and severity of renal damage. Limitations: Single centre study, small number of children with VUR. Retrospective analysis. Univariate assessment.</td>
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<tr>
<td>Wong (2005) [1]</td>
<td>9 studies.</td>
<td>Review of observational studies.</td>
<td>Studies reporting VUR and hypertension in children.</td>
<td>NA</td>
<td>Reported prevalence of hypertension in patients with renal scarring ranged from 5.6 to 28%. Limitations: Limited detail provided on search strategy and exclusion criteria. Limited to English language. Majority of the studies were retrospective. Only 5/9 studies included a comparator group (i.e. patients without renal scarring). Limited assessment of confounding variables in studies. Later studies greater proportion of mild UTI patients due to better detection and management.</td>
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<td>Malaki (2011) [9]</td>
<td>106</td>
<td>Cross sectional. Single centre (Iran)</td>
<td>Children under 5 years with UTI and VUR of varying severity. Outcomes: eGFR, weight, and height, Height Standard Deviation Score (HSDS), Weigh to Height Index.</td>
<td>NA</td>
<td>There was no correlation between reflux severity and laterality of reflux. There was no correlation between reflux (presence or severity) with HSDS or WHI. Limitations: Small single centre study. Cross sectional analysis.</td>
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<td>Shaikh (2010) [3]</td>
<td>33 studies.</td>
<td>Systematic review of prospective cohort studies. (Up to January 2009).</td>
<td>Cohort studies of children presenting with a first UTI and inclusion of data on abnormalities on the acute phase of follow up DMSA scans. Outcomes: Prevalence of abnormalities on DMSA scan within 15 days; incidence of recurrent UTI; and prevalence of abnormalities on DMSA scan 5 months to 2 years after UTI.</td>
<td>NA</td>
<td>Pooled prevalence of VUR: 24% (95%CI: 20, 28). Prevalence of children with VUR grades IV or V: 2.5% (95%CI: 1.4, 3.7). Prevalence of acute phase DMSA abnormalities (29 studies): 57% (95%CI: 50, 64) with significant heterogeneity between studies. Prevalence of renal scarring 5 months to 2 years after UTI (14 studies): 18% (95%CI: 14, 23) with significant heterogeneity between studies. Cumulative meta analysis suggests stable renal scarring prevalence of 15% (95%CI: 11, 18) since 2002. RR of renal scarring with presence or absence of VUR: 2.62 (95%CI: 1.74, 3.94). Limitations: Most studies only report data on VUR grades III to V. Significant heterogeneity between studies. Study quality assessment not reported.</td>
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<td>diagnostic test studies. (Up to September 2010)</td>
<td>DMSA confirmed by MCUG. Children with VUR grades I-II defined as having no reflux. Evaluated the performance of acute phase DMSA in identifying VUR.</td>
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</table>
| Montini (2009) [10] | 300 | Prospective cohort from multi-centre RCT (Italy). | Children aged 1 month to 7 years presenting with first febrile illness with normal renal function and normal prenatal ultrasound findings for the renal tract. Outcome: US and MCUG as predictors of parenchymal renal damage on DMSA. | 12 months | Rate of renal scarring by DMSA at 12 months – 15%. Ultrasonography:  
  - Sensitivity: 26.7% (95%CI: 14.6, 41.9).  
  - Specificity: 89.8% (95%CI: 85.4, 93.2).  
  - +LR 2.7, -LR 0.7.  
  MCUG  
  - Sensitivity: 51.1% (95%CI: 35.8, 66.3).  
  - Specificity: 83.1% (95%CI: 78.0, 87.5).  
  - +LR 3.0, -LR 0.38.  
Limitations: High loss to follow-up of children (63 from 363) with positive acute DMSA scan. Single centre. Urine collection using sterile bags could have resulted in higher false positive UTI. |
| Zaffanello (2009a) [11] | 65  | Prospective cohort. Single-centre (Italy) | Children <2 years presenting with first febrile UTI with normal prenatal renal function. US within 3-4 days of admission, VCUG after 1 month and DMSA at 6 months. | 6 months  | Prevalence of dilated pelvis identified by US – 44.6%. VUR detected by VCUG in 55.4% with VUR≥3 occurring in 38.5% of the children. Renal scarring by DMSA was observed in 18.5% of children. No significant correlation between pelvic dilatation and renal scarring (P=0.199). Significant correlation between VUR grading and OR: 6.66 (95%CI: 1.84, 24.1)  
Limitations: Small single centre observational study. Selectively included babies normally included in the high UTI group. Variable treatment with antimicrobials with 21 treated orally as outpatients hospital and the remaining intravenously as inpatients. Limited detail and diagnosis of UTI. |
| Wong (2010) [7] | 820 | Retrospective review of medical records. Multi-centre (Hong Kong) | Children <2 years admitted and diagnosed with first febrile UTI and no known renal abnormalities. UTI diagnosed by fever, positive urinalysis and positive culture of a single organism from suprapubic, catheter or clean-catch sample. | NA        | US normal in 91.1% and abnormal in 8.9%. Dilated pelvis identified in 7.9%. VCUG identified VUR in 23.8% with VUR≥3 in 10.5%. DMSA identified renal scarring in 8%. US for identifying VUR:  
  - Sensitivity: 13.8% (95%CI: 9.5, 19.7)  
  - Specificity: 92.6% (95%CI: 90.2, 94.5)  
US for identifying VUR grades IV and V:  
  - Sensitivity: 67.7% (95%CI:49.3, 82.0)  

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<td>US, VCUG and DMSA.</td>
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<td>DMSA for identifying VUR:</td>
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<td>• Sensitivity: 26% (95%CI: 20, 33)</td>
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<td></td>
<td>• Specificity: 94% (95%CI: 92, 96)</td>
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<td>Limitations: Retrospective review. DMSA scan not conducted on 25% due to normal US and VCUG. Excluded 89 patients due to missing US and VCUG data.</td>
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<td>• Recurrent UTI reason for referral in 26% of cases.</td>
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<td>Limitations: Retrospective review.</td>
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<td>Conway (2007)[14]</td>
<td>74,974 children attending clinics of which 611 had a first UTI.</td>
<td>Retrospective review of electronic medical records database. Multi-centre (US).</td>
<td>Children &lt;6 years with at least 2 visits to primary care paediatric clinics. Risk factor analysis for recurrent UTI (occurring at least 14 days after a typical 10 day treatment).</td>
<td>NA</td>
<td>• Recurrent UTI occurred in 13.5% (83) of the children with a confirmed first UTI or a recurrence rate of 12% per year.</td>
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<td>• Multivariable HR’s for recurrent UTI and VCUG:</td>
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<td>• Normal: 1 (reference).</td>
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<td>• VUR grade 1-3: 1.05 (95%CI: 0.43, 2.57)</td>
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<td>• VUR grade 4-5: 4.38 (95%CI:1.26, 15.29)</td>
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<td>Paneretto (1999) [15]</td>
<td>290</td>
<td>Prospective cohort. Single centre (Australia)</td>
<td>Children under 5 years presenting to ED with a first UTI. Renal tract imaging within 4 weeks – US, MCUG and DMSA. US and DMSA repeated at 12 months.</td>
<td>12 months</td>
<td>• VUR was detected in 83 (29%).</td>
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<td>• Recurrent UTI reported in 38 (13%) and confirmed in 36 (12%).</td>
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<td>• Association of VUR grade 3 – 5 with recurrent UTI:</td>
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<td>• OR 3.6 (95%CI: 1.5, 8.3)</td>
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<td>Shaikh (2005) [16]</td>
<td>148</td>
<td>Retrospective review of medical records. Single centre (US)</td>
<td>Children diagnosed with voiding dysfunction. US conducted routinely to provide post void urine volumes.</td>
<td>NA</td>
<td>• Recurrent UTI occurred in 24%.</td>
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<td>• Positive correlation between post void urine volume and the number of UTIs (r=0.3, P&lt;0.002).</td>
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<td>• Area under ROC for post void urine volume predicting recurrent UTI was 0.617.</td>
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<td>Dias (2010) [18]</td>
<td>740</td>
<td>Retrospective review of medical records. Single centre (Brazil)</td>
<td>Children diagnosed with primary VUR. VUR diagnosis by VCUG. Urine samples collected by clean catch or sterile bags.</td>
<td>Median 65.2 months (IQ range, 30.8, 115.3)</td>
<td>• UTI occurred in 38% of the children.</td>
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<td>• 10% had 2 episodes</td>
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<td>• 7% had 3 or more episodes</td>
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<td>• Risk ratios for recurrent UTI:</td>
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<td></td>
<td>• VUR III-V and I/II: 0.97 (95%CI: 0.79, 1.2)</td>
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<td>• VUR IV-V and I-III: 1.2 (95%CI: 1.01, 1.4)</td>
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<td>• Renal damage: 1.15 (95%CI: 0.97, 1.38)</td>
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| Nakamura (2009) [19] | 58     | Retrospective review of medical records. Single-centre (Japan) | Children under 1 year with VUR who received antibiotics and DMSA scan. | NA        | Adjusted odds ratios for recurrent UTI:  
  - VUR IV-V: 1.7 (95%CI: 1.1, 2.6)  
  Limitations: Single centre retrospective review. Reliability of occurrence UTI based on records. Use of bag sample for infants.                                                                                                                                                                                     |
  - VUR grade 1-3 in 31%  
  - VUR grade 4-5 in 69%  
  - Association of recurrent UTI with VUR grades  
    - Grades 1-3 and 4-5 OR: 6.45 (95%CI: 0.76, 50.42)  
  Limitations: Retrospective review. Small single centre study.                                                                                                                                                                                                                     |
| Espindola (2012) [21] (abstract) | 80 studies including 11,410 children | Systematic review. | Prospective and retrospective studies of children with UTI, DMSA scan and cystography. | NA        |  
  - All-grade VUR was significantly associated to both acute pyelonephritis (OR=2.0 ; 95%CI: 1.8-2.3) and renal scarring (OR=4.8 ; 95%CI: 4.3-5.5).  
  - High-grade (≥3) was also significantly related to acute pyelonephritis (2.4; 95%CI: 1.9-3.1) and renal scarring (OR=5.7; 95%CI: 4.5-7.3).  
  - Pooled estimates were found with heterogeneity, partly explained by the delay between UTI and late DMSA scan, and by the number of UTI.  
  Limitations: Mixed retrospective and prospective studies. Limited results and methodology available in abstract.                                                                                                                                                     |
| Zaffenello (2009b) [22] | 13 studies including | Systematic review. | Prospective and retrospective studies evaluating the prevalence and incidence of kidney damage in children with VUR. | NA        |  
  - 6 studies retrospective, 4 prospective, 2 clinical trials 1 RCT.  
  - Pooled RR for chronic renal damage determined by DMSA associated with VUR: 3.73 (95% CI: 2.95, 3.91). Significant heterogeneity.  
  Limitations: Mixed retrospective and prospective trials. Significant unaccounted heterogeneity.                                                                                                                                                                         |
| Howman-Giles (2002) [23] | 15 studies evaluated accuracy of US to detect VUR. | Systematic review | Studies of children with confirmed UTI including comparison of two or more renal tract imaging tests with a clinically important outcome. | NA        |  
  - Sensitivity and specificity:  
    - Child as unit: 11% to 89%; 15% to 93% (ns heterogeneity)  
    - Kidney as unit: 7% to 97%; 50% to 99% (sig heterogeneity)  
  Limitations: Mixed retrospective and prospective studies. Limited results and methodology available in abstract.                                                                                                                                                   |
### Study ID | N | Study design and setting | Participants and Interventions | Follow up | Comments and results
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 | | | | | | • Mean Diagnostic Odds Ratio:
  o Child as unit: 4.48 (95%CI: 2.29, 11.25)
  o Kidney as unit: 127.20 (95%CI: 26.48, 280.90)
• Area under the curve 0.349.

6 studies evaluated accuracy of US to detect renal parenchymal abnormalities with child as the reporting unit.
• Sensitivity: 28% to 96%, specificity: 39% to 99% (sig heterogeneity)
• Diagnostic odds ratio: 60.0 (95%CI: -43.2, 163.2)

13 studies evaluated accuracy of MCUG to detect renal parenchymal abnormalities:
• Sensitivity and specificity:
  o Child as unit: 28% to 46%; 50% to 95% (sig heterogeneity)
  o Kidney as unit: 30% to 82%; 21% to 100% (sig heterogeneity)
• Mean Diagnostic Odds Ratio:
  o Child as unit: 4.17 (95%CI: 0.82, 7.52)
  o Kidney as unit: 19.59 (95%CI: -19.57, 58.76)

13 studies evaluated accuracy of DMSA to detect VUR:
• Sensitivity and specificity:
  o Child as unit: 46% to 91%; 8.3% to 84% (ns heterogeneity)
  o Kidney as unit: 20% to 96%; 52% to 87% (sig heterogeneity)
• Mean Diagnostic Odds Ratio:
  o Child as unit: 3.76 (95%CI: -0.13, 7.66)
  o Kidney as unit: 19.59 (95%CI: 2.09, 3.81)

Limitations: Small number of small studies that provided direct method comparisons and heterogeneity.

Montini (2009) [10]
Sastre (2007) [24]

| Study ID | N | Study design and setting | Participants and Interventions | Follow up | Comments and results
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Sastre (2007) [24] | 301 | Prospective cohort. Multi-centre (Spain) | Children with community or hospital acquired UTI attending acute care hospitals. | | • Hospital acquired UTI in 51 (17%).
• Abnormal US scan in 108 of 291 (37.1%)
• No VUR in 191/262 (73%)
• VUR in 71 of 262 (27%)
• Sensitivity of US for VUR: 48% (95%CI: 37, 60)
• Specificity of US for VUR: 67% (95%CI: 60, 73)

Limitations: High exclusion rate (63% of eligible participants) due to urine obtained from bag, or collection method unknown.
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• Sensitivity ranged from 21.6% to 47.1%  
• Specificity ranged from 50% to 96.2%.  
• Pooled +LLR: 1.9 (95%CI: 1.2, 3.1). (sig heterogeneity)  
• Pooled – LLR: 0.8 (95%CI0.74, 0.87)  
Limitations: Studies assessed as being of poor quality with only 4 including an appropriate spectrum of patients. Interpretation limited due to heterogeneity. |
| Swerkersson (2007) [26] | 303 | Retrospective review. Single centre (Sweden) | Children less than 2 years with a first time non obstructive UTI. US, MCUG, DMSA conducted within 3 months of diagnosis. Follow up DMSA scan at 1 to 2 years. | | • DMSA for identifying any grade of VUR:  
  o Sensitivity: 46.3% (95%CI: 35.1, 57.7)  
  o Specificity: 80.7% (95%CI: 74.8, 85.6)  
• DMSA for identifying VUR grades IV and V:  
  o Sensitivity: 88.9% (95%CI:50.7,99.4)  
  o Specificity: 75.5% (95%CI: 70.1, 80.2)  
Limitations: Single centre retrospective review. Unknown proportion of first time UTI patients included in study population. |
| Tseng (2007) [27] | 142 | Retrospective review. Single centre (Taiwan) | Children less than 2 years with a first time UTI who underwent both MCUG and DMSA. DMSA undertaken within 2 days and MCUG within 1 month of diagnosis of UTI. | | • DMSA for identifying any grade of VUR:  
  o Sensitivity: 88.1% (95%CI: 73.5, 95.5)  
  o Specificity: 36.0% (95%CI: 26.8, 46.3)  
• DMSA for identifying VUR grades IV and V:  
  o Sensitivity: 100% (95%CI:80.8, 100)  
  o Specificity: 33.9% (95%CI: 25.7, 43.1)  
Limitations: Single centre retrospective review. Extended review period of 10 years. High exclusion rate (90/232) for children who did not undergo both MCUG and DMSA. |