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Effective Health Care

Bulletin on the effectiveness of health service interventions for decision makers

This bulletin summarises the research evidence for the diagnosis and evaluation of urinary tract infections in children under five years of age.

Diagnosing urinary tract infection (UTI) in the under fives

- Urinary tract infection (UTI) is common in children under five. Children who are misdiagnosed can either fail to receive appropriate treatment or receive unnecessary treatment and investigation.
- All of the tests commonly used for the diagnosis of UTI are carried out on urine samples.
- A dipstick test which is positive for both nitrite and leukocyte esterase (LE) indicates a very high likelihood of a UTI.
- Dipstick negative for LE and nitrite or microscopic analysis negative for pyuria and bacteriuria of a clean voided urine (CVU), bag or nappy/pad specimen can be used to rule out UTI, avoiding the need for further investigation for UTI.
- *Acute Tc-99m-DMSA* remains the reference standard test for the localisation of UTI.
- In the absence of evidence of any effect on patient outcome, universal imaging (e.g. micturating cystourethrography (MCUG) for reflux or dimercaptosuccinic acid scintigraphy (DMSA) for renal scarring) cannot be justified; referral should be on an individual patient basis.

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CENTRE FOR REVIEWS AND DISSEMINATION

A. Background

Urinary tract infection (UTI) is common in children under five. The normal urinary tract is sterile. A UTI is a microbial infection of the urethra, bladder, ureters or kidneys[1] (Fig 1). Infection is most commonly caused by Gram-negative aerobic bacteria.[2]

A.1. Incidence/prevalence Boys are more susceptible before the age of three months; thereafter the incidence is substantially higher in girls.[3] Data on the true incidence of UTI are limited. It has been estimated that around 6.3% of girls and 2.4% of boys will be referred with UTIs by the age of five years.[4]

The aim of management should be prompt diagnosis, rapid treatment and the detection of any underlying cause that might predispose to further infection or lead to long-term renal damage.[5] Evidence based guidelines propose that the management of UTI in children can be divided into four phases: recognising a child at risk, diagnosis, short-term treatment, and imaging evaluation.[6]

Current UK recommendations, published over a decade ago, state that all children should be investigated after their first confirmed infection.[7] Symptoms of UTI in children are generally non-specific, and are easily missed.[5,8] Common clinical symptoms in children aged less than two years include pyrexia of unknown origin, feeding disorders, slow weight gain, vomiting, diarrhoea,[5] sepsis, and failure to thrive.[6] Between one and five years of age, fever, general malaise, frequency, abdominal discomfort and delayed bladder control are common presenting features.[5] Dysuria (painful or difficult urination) in this age group may be a symptom of UTI or may be due to external irritation (e.g. balanitis, vulvovaginitis, threadworms).[5] Recurrent UTI is defined as adequately treated symptomatic proven UTI that then recurs.

Most UTIs are not associated with any risk factor, however UTI can cause troublesome and often recurrent symptoms that may point to unsuspected complications and/or an abnormality of the urinary tract. These include:

- Urinary stasis: a stoppage of the flow or discharge of urine, which can happen at any level in the urinary tract.[5] This can be caused by stones, bladder dysfunction, including habitually infrequent or incomplete voiding, outflow obstruction or constipation.[5]
- Renal scarring: in a small proportion of children this is associated with future complications including poor renal growth, recurrent adult pyelonephritis (infection leading to inflammation of the kidney),[1] impaired glomerular (renal) function, early hypertension and end stage renal disease.[9]
- Reflux: occurs when urine passes from the bladder back into the ureter or kidney.[1] The importance of reflux as a risk factor is strongly debated.

It is thought that developmental abnormalities, detectable on pre-natal ultrasound, which result in an abnormal kidney, may also be the cause of subsequent reflux. A child presenting with a UTI and an abnormal kidney, may either have been born with the abnormal kidney or it may have been caused by the UTI.[10,11]

Rapid diagnosis and treatment is essential as delays increase the chance of renal damage.[5] Children who do not respond rapidly to treatment, those with an unusual organism, those who are seriously ill with bacteraemia, septicaemia or those who require intravenous fluids/antibiotics are the ones who need to be investigated for their renal status.

Children may be misdiagnosed, fail to receive appropriate treatment, receive unnecessary treatment or investigation.[12] Immediate treatment without confirmation of a UTI may also complicate the picture if there is other serious infection, and delay appropriate treatment and investigation.[5]

A.2. Nature of the evidence This bulletin is based on a systematic review carried out by the Centre for Reviews and Dissemination (CRD) for the NHS R&D Health Technology Assessment Programme.[13] The review summarises the available evidence for the diagnosis and evaluation of UTI in children under five years of age. Full details of the review methods will be available in the HTA report.

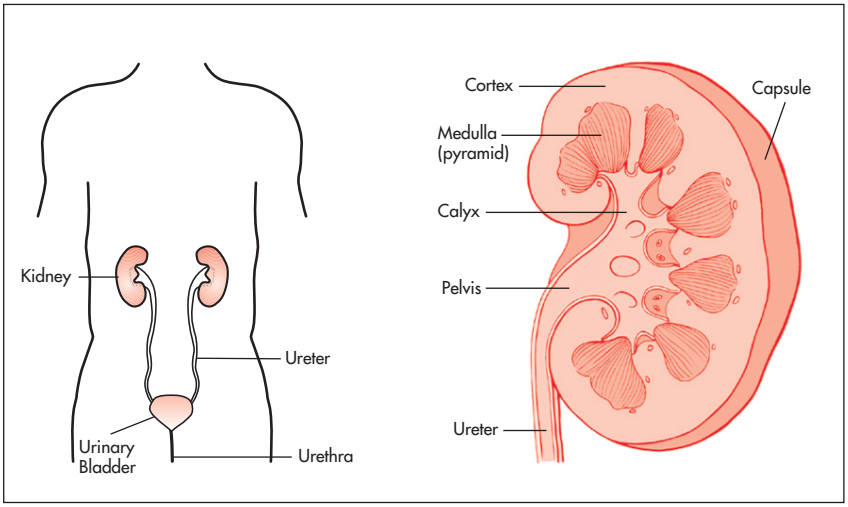

Fig. 1 The renal system and anatomy of the kidney.

B. Effectiveness of tests for diagnosing UTI

The first step in the diagnostic process is to identify children presenting to primary care who may have a UTI.

B1. Clinical examination It is difficult to specify the signs and

symptoms that a health care professional would use when deciding whether or not to test a child for UTI. Two studies looked at how good a clinical examination was at identifying children with possible UTI.[14,15] One study in the USA found that a combination of age, race, temperature, and absence of another source of fever, was a good indicator for ruling out disease in children aged less than two years.[14] The other study looked only at temperature and found that this was poor for ruling disease either in or out.[15]

Two studies looked at clinical features such as temperature, urine cloudiness, urine odour, and other clinical symptoms in the diagnosis of UTI.[16,17] Urine cloudiness was a reasonable test for the presence of UTI but all other clinical indicators were found to be poor.[17]

B2. Diagnostic tests All of the tests commonly used for the diagnosis of UTI are carried out on urine samples (see Table 1).

Table 1 Diagnostic tests for UTI

Test	Details
Urine sampling	All of the tests commonly used for the diagnosis of UTI are carried out on urine samples
Suprapubic aspiration (SPA)	Needle attached to syringe inserted through lower abdomen in to bladder
Transurethral catheterisation	Catheter inserted through the urethra into the bladder (can be attached externally to a bag)
Clean voided urine (CVU)	Requires cleansing, rinsing, and drying of perineum before collection of a midstream sample in a sterile container
Urine bags	Bag applied to perineum
Urine pads	Absorbent pad placed in nappy
Dipstick Tests	These generally involve dipping the reactive section of a dry phase chemistry reagent strip briefly into urine and then comparing the colour change with a reference chart[31]
Blood	Section to detect blood
Glucose	Section to detect glucose
Leukocyte esterase (LE)	Section to detect LE
Nitrite	Section to detect nitrite
Protein	Section to detect protein
Microscopy	Examination of urine sample through a microscope, usually in a laboratory
Pyuria	Examination for the presence of white blood cells Samples may be centrifuged before examination
Bacteriuria	Examination for the presence of bacteria. Urine sample may be unstained or Gram-stained
Culture	The reference standard test for UTI, performed in a laboratory, takes 48 hours to give a result, and is very accurate
Standard culture	Involves streaking urine on enrichment and selective media
Dipslide	A more recent development, the dipslide is a miniature culture plate, which is immersed in the urine immediately after voiding

Urine sampling

Thirteen studies compared the diagnostic accuracy of different methods for obtaining urine for testing.[18–30] All the different methods for collection of a urine sample are susceptible to contamination, which is associated with false-positive results (i.e. a test result that appears to be positive that is really negative).

Suprapubic aspiration (SPA) by trained staff using a local anaesthetic cream can be a rapid, reliable, safe technique and has been regarded as the reference standard for urine collection. However, it is invasive and ultrasound guidance may be needed. Five studies assessed the diagnostic accuracy of a clean voided urine (CVU) sample, using an SPA urine sample as the reference standard.[18–22] When both samples were cultured the agreement between the two sampling methods was good, suggesting that CVU may be an appropriate routine method of urine collection.

CVU samples are difficult to collect in young children who are not potty trained. A number of alternative collection methods have been developed, including bag, pad and nappy specimens. The limited data available suggests that both bag[22–25] and nappies/pads[26–29] may be acceptable substitutes for SPA. Further research is needed to confirm this.

Dipstick tests

Dipsticks have the advantage of providing an immediate result, and of being cheap and easy to perform and interpret.[31] A total of 39 studies reporting 107 data sets evaluated dipstick tests for the diagnosis of UTI. [15,17,32–68]

These studies assessed the usefulness of dipstick tests for nitrite, leukocyte esterase (LE), protein, glucose and blood, alone and in combination. Considerable differences (heterogeneity) exist between the studies (in terms of methods, samples, populations, analysis, etc), so the results should be interpreted with caution.

The research suggests that a strategy that combines the results of LE and nitrite testing appears to offer the best performance for ruling disease both in and out. For example, in an average primary care population, if a child has a dipstick positive for both nitrite and LE there is a high likelihood that they have a UTI (pooled LR+ = 28.2, 95% CI: 17.3, 46.0).[32–40] Likewise, if they test negative for both nitrite and LE then the likelihood of having a UTI is small (pooled LR- = 0.20, 95% CI: 0.16, 0.26).[17,32,36–48] Likelihood ratios (LR) describe how many more times a person with disease is likely to receive a particular test result than a person without disease. A LR of a positive test result is usually a number greater than 1, a LR of a negative test result usually lies between 0 and 1. Another test combination that showed promise, particularly for ruling out a UTI, was that of dipstick tests for nitrite, LE and protein.[34,39]

Four studies included in the review, all conducted over 30 years ago, assessed a test for glucose (Uriglox) that is no longer commercially available in the UK.[53,61,63,65]

There was insufficient information to make any judgement regarding the overall diagnostic accuracy of dipstick tests for protein, blood, or for combinations of three different tests.

Microscopy and culture

Microscopy and culture are generally requested in combination, but microscopy has

the advantage of producing a result more quickly, and may also provide additional, incidental information. Microscopy has some potential as a test that could be performed in the GP's surgery, but requires time, resources and training. It remains more expensive than a dipstick test and requires a degree of expertise to perform.

A total of 39 studies reporting 101 data sets evaluated microscopy for diagnosing UTI.[18–20,22,30,32,33,38,41–44,46–49,54–56,66,69–86] Microscopy was used to determine the presence of pyuria or bacteriuria, or combinations of the two.

The studies of microscopy showed considerable heterogeneity, in terms of results (estimates of sensitivity, specificity and likelihood ratios), cut-off points, types of urine samples and population. A urine sample that was positive for both pyuria and bacteriuria on microscopy was found to be very good for ruling in disease (pooled LR+ = 37.0, 95% CI: 11.0, 125.9).[38,43,49,54,56,72,73,86] Similarly, a urine sample that was negative for both pyuria and bacteriuria on microscopy was found to be very good for ruling out disease (pooled LR- = 0.11, 95% CI: 0.05, 0.23).[17,38,43,44,46,47,54,72] The evidence suggests that microscopy for pyuria and bacteriuria represents a more accurate test for UTI than the dipstick. This is balanced by trade-offs in time, skill and cost requirements.

Dipslide culture, a simplified method of culture, was investigated mainly in community screening settings, and for home monitoring of high risk patients.[59,62,87–92] The advantage of this method is that it can be performed outside the laboratory setting and is less labour intensive to perform and interpret. Given the increased cost of dipslide culture over microscopy or nitrite and LE dipstick, and the longer time taken to give a result, this test appears to be of limited value in the context of general diagnosis of UTI in the UK primary care setting.

Based on the results of this review, dipstick negative for LE and nitrite or microscopic analysis negative for pyuria and bacteriuria of a CVU, bag, or nappy/pad specimen can be used to rule out UTI. These patients can then be excluded from further investigation for UTI without the need for confirmatory culture.

Table 2 Summary of tests used for the different clinical applications

Aim	Main tests used or evaluated	Current reference standard
Localisation of UTI	Clinical features Laboratory-based Ultrasound (US) Dimercaptosuccinic acid scintigraphy (DMSA)	Acute DMSA
Detection of reflux	Ultrasound Cystosonography Radionuclide cystography Micturating cystourethrography (MCUG)	MCUG
Prediction of scarring	Clinical features Ultrasound MCUG Acute DMSA	Follow-up DMSA
Detection of scarring	Ultrasound Intravenous Urography (IVU) MAG3 renogram DMSA	Follow-up DMSA

C. Effectiveness of tests to further investigate UTI

Further investigation of a confirmed UTI is usually carried out with the aims of preventing progressive renal damage and its consequences, and identifying renal scarring and children who may be at risk of developing further scarring. The detection of an obstruction in the urinary tract or the presence of stones is also important. However, tests should only be carried out if (a) the results of the test will lead to a change in management of the child, and (b) this change is likely to lead to an improved outcome.

There are four main clinical applications of tests for the further investigation of UTI: localisation of UTI; prediction of scarring; detection of scarring and if present, detection of reflux; stones and the presence of dilatation suggesting obstruction. Table 2 summarises which tests are used for these different clinical applications.

IVU, DMSA, direct and indirect isotope cystography, MCUG, and cystosonography all require an intravenous injection or a bladder catheter so are considered to be invasive tests. All these tests, with the exception of cystosonography, also use radiation and give a varying radiation burden to the child. The judgement of when to undertake a test has to be made on an individual patient basis bearing in mind the cost-benefit.

None of the 72 diagnostic accuracy studies meeting the inclusion criteria for the systematic review fulfilled all the assessment criteria for quality of such studies.[93,94] Inadequate reporting was a problem in many studies: less than half of studies included an appropriate spectrum of patients, and reported selection criteria. Incorporation bias, verification bias, and disease progression bias were also inadequately addressed by around half of the studies.

C1. Localisation of UTI

Localisation of infection to either the lower (cystitis) or upper (acute pyelonephritis (APN)) urinary tract can be considered the first step. If APN can be ruled out then the child is not at immediate risk of scarring and further investigation is unlikely to be beneficial. Given that therapeutic delay is thought to be associated with renal damage[100] the possibility that children presenting with a first, lower UTI may benefit from monitoring for recurring infection remains open to question.

A total of 31 studies (61 evaluations) investigated the diagnostic accuracy of one or more tests to localise infection. Ultrasound was evaluated in 20 studies.[101–120] Performance was poor both in terms of ruling in and ruling out renal involvement.

Acute Tc-99m-DMSA remains the reference standard test for the localisation of UTI.[121–123]

Plasma C-reactive protein (CRP) showed some limited potential as a test for ruling out APN.[103,106,123–127] However, substantial further research would be required before routine use of this test could be recommended.

Little useful data were available on other clinical, laboratory and imaging based tests but in general those investigated showed poor accuracy for the localisation of UTI.[103,106,124–133] The median prevalence of APN in all the studies investigating localisation of UTI that included children with a confirmed UTI was 60%. Further research to identify an accurate non-invasive test for the localisation of UTI is therefore justified.

C2. Detection of reflux The idea that detection of reflux, thought to lead to an increased risk of scarring, is an important part of further investigation, is currently the subject of debate.

The only study of the effectiveness of imaging compared routine and selective imaging (combination of US and MCUG) for the detection of reflux.[134] This study found increased rates of reflux detection and antibiotic prophylaxis with routine imaging, but no reduction in scarring or recurrent UTIs. Other studies have shown that the presence of reflux, as determined by MCUG, correlates poorly with the presence of renal scarring.[135–138]

A recent systematic review found that renal damage was frequently present in the absence of reflux.[139]

The management of reflux and how this impacts on a patient's future risk of renal disease is also the subject of debate. A study comparing surgical to medical management of reflux found no difference in outcome between the two treatment groups.[140] Reflux has also been shown to disappear spontaneously or reduce to grade 1 in 73% of children diagnosed with reflux following a first UTI.[141]

MCUG (currently the reference standard test for reflux) is invasive and costly, involving considerable exposure to ionising radiation. The alternative tests for reflux, standard ultrasound, IVU, indirect voiding radionuclide cystography, N-acetyl-beta-D-glucosaminidase (NAG)/creatinine ratio, scintigraphy and a risk scoring system, were all found to be relatively poor.[116,142–165] Indirect radionuclide voiding cystography and IVU were found to have very good specificity but poor sensitivity for the detection of reflux. However there was considerable heterogeneity between all these studies.

Contrast enhanced ultrasound is currently a little-used technique, but it may have potential for the accurate diagnosis of reflux. It does not require exposure to ionising radiation, but remains an invasive procedure requiring catheterisation. The contrast used is not widely available.

Given the lack of evidence of a link between reflux and renal scarring, and the unproven benefit of treating reflux promptly, it is difficult to justify the routine use of MCUG in children with UTI.

Table 3 Tests to further investigate UTI

Test	Details
Ultrasonography	Ultrasound involves a skilled operator running a probe, with coupling gel, over the anatomical area of interest.
Standard ultrasound	Commonly used as the preliminary investigation for children with confirmed UTI because of its widespread availability, relatively low cost, and absence of side effects[95] Ultrasound may be used to rule out hydronephrosis, abscess or calculus.[96] It is also used to detect malformations such as complicated duplex kidneys.[96]
Contrast-enhanced cystosonography	Techniques used more recently to evaluate vesicoureteral reflux (VUR), they involve the introduction of an inert, micro-bubble contrast material into the bladder by catheter and the use of ultrasound to follow filling and voiding.[96] This technique is not universally accepted and has been tried and abandoned in many centres.
Radiological imaging	Radiological imaging of the renal system involves the introduction of a contrast medium to enable radiographic demonstration of the urinary tract.
Intravenous urography (IVU)	An IVU provides an anatomic image of the renal system, and can readily identify some urinary tract abnormalities.[97] It involves an intravenous (IV) injection of contrast media and a series of radiographs taken as the contrast media fills the kidneys, passes down the ureters and into the bladder. The use of IVU in children with UTI has dropped dramatically in the past 2 decades with the introduction of DMSA scanning.[98]
Micturating cystourethrography (MCUG)	The child is catheterised and the bladder filled via the catheter with contrast media. The filling and emptying of the bladder is viewed real time by a radiologist, images are taken as the bladder is filled and emptied to identify any reflux from the bladder into the ureters. It also provides an assessment of the size and shape of the bladder, and a means of detecting urethral anomalies in boys.[97]
Nuclear medicine	Nuclear medicine techniques involve the intravenous injection of a radioactive medium and detection of the emissions with a gamma camera.
Dimercaptosuccinic acid scintigraphy (DMSA)	A radioisotope is injected IV and is taken up by cells in the kidney. Imaging generally occurs 2 to 3 hours after injection. This technique provides information on renal structure and function, and on the presence or absence and extent of renal scarring following UTI.[99] Defects seen soon after the UTI i.e. within 6 weeks indicate renal involvement. As many defects disappear, a DMSA scan 3 – 6 months after the UTI is required to detect a scar.
Direct radionuclide cystography	The direct method requires catheterisation of the bladder and introduction of the radionuclide and fluid for maximum distension of the bladder, allowing imaging during filling, voiding and after voiding.
Indirect radionuclide cystography	Indirect radionuclide cystography does not require bladder catheterisation, but requires IV injection of a radio-pharmaceutical for the evaluation of renal function and urine drainage as well as the evaluation of the bladder during voiding, thus detection of vesicoureteral reflux.[8]

C3. Prediction of renal scarring Four studies (nine evaluations) investigated the ability of a variety of tests to predict renal scarring.[110,113,166,167] The diagnostic accuracies reported in these studies were poor and none of the tests (US, IVU, and presence of fever and elevated CRP levels) showed good accuracy. A recent systematic review also found that reflux is a weak predictor for renal damage in children hospitalised with UTI.[139]

A test that could predict whether a child was at risk of renal scarring would be useful if a treatment were available that could prevent that child from developing scarring. Anti-microbial therapy is often initiated in children with UTI prior to further investigation, and treatment delay is the only therapeutic factor thought to affect the development of

scarring.[9,100] The prediction of the development of renal scarring as a result of a current infection would, therefore, appear to be of academic interest alone.

C4. Presence of renal scarring

The presence of renal scarring as the result of a UTI is considered to be the most important predictor of renal disease, though not all children with renal scarring will have progressive scarring ending in renal failure.[100,168]

There is currently very little that can be done to treat children with renal scarring to prevent complications. If repeat infection is assumed to be the cause of progressive scarring then prophylactic antibiotics may be initiated. A systematic review of the effectiveness of long-term antibiotics in preventing UTI found no evidence to support their use; however very few trials met the inclusion criteria and those that did were small and of poor quality.[169]

Renal scintigraphy, generally using Tc-99m-DMSA, is the accepted reference standard for the detection of renal scarring. It may be used acutely to localise UTI and hence determine whether there is a risk of scarring from the current infection, and in sequential follow-up to monitor the development and progression of scarring. The diagnostic accuracy of a number of other tests for the detection of scarring has also been investigated. Alternative static and dynamic renal scintigraphic techniques, including Tc-99m-DTPA and Tc-99m-MAG3, were found to be good tests for the detection of scarring, correlating well with Tc-99m-DMSA. As dual information can be gathered from a single examination, this may be worth considering.

Seven studies evaluating ultrasound found it to be reasonable for ruling in scarring but poor for ruling out scarring.[150,170–175] Using colour and Doppler ultrasound, proved no better than routine ultrasound in the detection of renal scars.[109] It may be that ultrasound only detects more severe scarring, which may be of more clinical importance than scarring of any grade. While ultrasound carries benefits over Tc-99m-DMSA in that it is non-invasive, involves no ionising radiation and is easier and cheaper to perform, it is no substitute in the detection of renal scars.

Three studies assessing the diagnostic accuracy of indirect radionuclide cystography;[137,176,177] and four studies evaluating the diagnostic accuracy of IVU,[166,177–179] found both tests to be relatively poor.

D. Implications

D1. Implications for practice

Diagnosing UTI

The conclusions of the review in terms of practice are presented as an algorithm for the diagnosis of UTI in children under 5 (Fig 2). The algorithm is based on current available evidence. Where that evidence is ambiguous or absent, the following points need to be considered:

- It is not possible to further define which clinical signs and symptoms should inform the decision to test for UTI.
- In the absence of clear evidence, pad/nappy or bag may be used for collecting urine samples from non-toilet trained children.
- The evidence suggests that CVU samples had similar accuracy to SPA samples when cultured, and as CVU is a non-invasive collection method that can be employed in the GPs surgery, this was the method chosen for the algorithm.

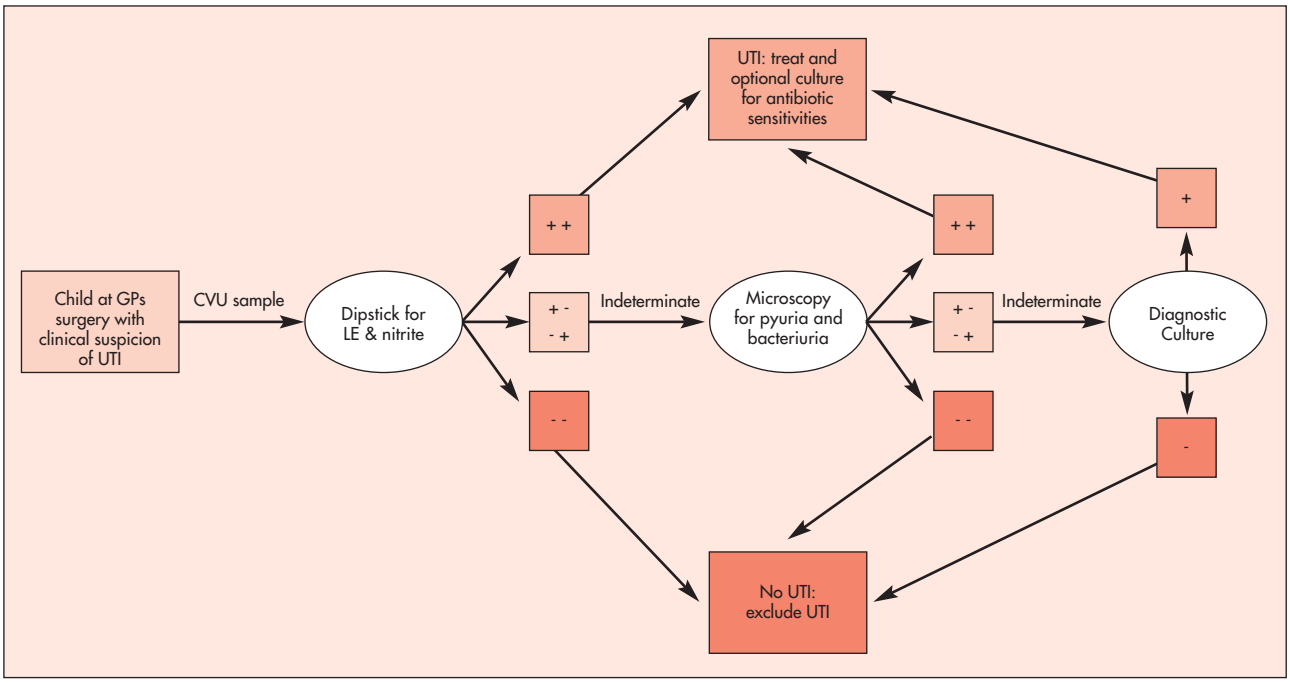

Fig. 2 Algorithm for diagnosis of UTI

There are four issues with regard to the diagnostic tests recommended in the algorithm which future research may inform:

- Should patients with an indeterminate dipstick test result be treated differently from those with a positive dipstick test result? One option would be to recommend culture in all children testing positive on either LE or nitrite dipstick.
- Should microscopy be included as a separate step, or should children with an indeterminate test result receive culture immediately?
- Does the accuracy of microscopy differ in children with an indeterminate dipstick test result? The studies of microscopy that contributed to the algorithm were carried out in children with a clinical suspicion of UTI, not in those who had already been tested with a dipstick.
- Should all children receive confirmatory culture regardless of previous test results?

Further investigation of UTI

While there was insufficient evidence to support an algorithm for the further investigation of UTI, the following recommendations are based on the available evidence:

- Routine imaging for children aged 2–10 years with an initial UTI is not recommended. For children under two there is no firm evidence base.
- All children aged 2–5 with an initial UTI should be monitored and investigated further if they experience a second UTI.
- A test for the localisation of UTI as an initial step in the investigation of these children allows the exclusion of all children with a lower UTI from further investigation.
- Based on current evidence the only accurate test for further investigation is a DMSA scan. These scans are costly, invasive and incur a radiation load. A non-invasive test would be desirable.
- Further research is required regarding the accuracy of ultrasound in diagnosing underlying abnormalities, and its impact on patient outcome.

There is insufficient evidence to recommend any routine further investigation.

In the absence of evidence of any effect on patient outcome, universal DMSA or MCUG cannot be justified. The decision on whether or not to perform these examinations should be made on an individual patient basis. Current thinking suggests that MCUG should be reserved for those children who have been deemed to require further investigation and the DMSA scan is abnormal or the ultrasound has shown an abnormal bladder. Further research regarding the effects of these imaging techniques on long-term patient outcome is urgently required.

D2. Implications for research A number of quality issues were highlighted in the existing body of evidence to assist with future research. A significant number of clinical questions requiring further research, around both the diagnosis and further investigation of UTI, were identified. Full details can be found in the HTA report.[13]

References

1. Dark G. *The on-line medical dictionary [database].* Academic Medical Publishing & CancerWEB; 1998. [cited 2004 23 June]. Available from: http://cancerweb.ncl.ac.uk/omd/index.html
2. *Urinary tract infections. Bacterial infections.* Merck; 2001. [cited 2002 11 January]. Available from: http://www.merck.com/pubs/mmanual/section17/chapter227/227a.htm
3. Jakobsson B, Esbjorner E, Hansson S. Minimum incidence and diagnostic rate of first urinary tract infection. *Pediatrics* 1999;104:222-6.
4. Coulthard MG, Lambert HJ, Keir MJ. Occurrence of renal scars in children after their first referral for urinary tract infection. *BMJ* 1997;315:918-9.
5. The management of urinary tract infection in children. *Drug Ther Bull* 1997;35:65-9.
6. Children's Hospital Medical Center Cincinnati. *Evidence based clinical practice guideline for patients 6 years of age or less with a first time acute urinary tract infection (UTI).* Cincinnati, OH: Children's Hospital Medical Center, 1999. Available from http://www.cincinnatichildrens.org
7. Working Group of the Research Unit of the Royal College of Physicians. Guidelines for the management of acute urinary tract infection in childhood. *J R Coll Physicians* 1991;25:36-43.
8. Society of Nuclear Medicine. *Procedure guideline for radionuclide cystography in children.* Reston, VA: Society of Nuclear Medicine, 2003. Available from http://www.interactive.snm.org
9. Larcombe J. Urinary tract infection in *Clinical Evidence*, London:BMJ Publishing, 2002.
10. Stock JA, Wilson D, Hanna MK. Congenital reflux nephropathy and severe unilateral fetal reflux. *J Urol* 1998;160:1017-8.
11. Sillen U. Vesicoureteral reflux in infants. *Pediatric Nephrology* 1999;13:355-61.
12. Downs SM. Technical report: urinary tract infections in febrile infants and young children. The Urinary Tract Subcommittee of the American Academy of Pediatrics Committee on Quality Improvement. *Pediatrics* 1999;103:e54.
13. Whiting P, Westwood M, Ginnelly L et al. A systematic review of tests for the diagnosis and evaluation of urinary tract infection (UTI) in children under five years: *Health Technol Assess* (forthcoming)
14. Gorelick MH, Shaw KN. Clinical decision rule to identify febrile young girls at risk for urinary tract infection. *Arch Pediatr Adolesc Med* 2000;154:386-90.
15. Rodriguez Cervilla J, Alonso Alonso C, Fraga Bermudez JM, et al. Urinary tract infection in children: Clinical and analytical prospective study for differential diagnosis in children with suspicion of an infectious disease. *Rev Esp Pediatr* 2001;57:144-52.
16. Struthers S, Scanlon J, Parker K, et al. Parental reporting of smelly urine and urinary tract infection. *Arch Dis Child* 2003;88:250-2.
17. Liptak GS, Campbell J, Stewart R, et al. Screening for urinary tract infection in children with neurogenic bladders. *Am J Phys Med Rehabil* 1993;72:122-6.
18. Aronson AS, Gustafson B, Svenningsen NW. Combined suprapubic aspiration and clean-voided urine examination in infants and children. *Acta Paediatr Scand* 1973;62:396-400.
19. Morton RE, Lawande R. The diagnosis of urinary tract infection: comparison of urine culture from suprapubic aspiration and midstream collection in a children's out-patient department in Nigeria. *Ann Trop Paediatr* 1982;2:109-12.
20. Pylkkanen J, Vilska J, Koskimies O. Diagnostic value of symptoms and

clean-voided urine specimen in childhood urinary tract infection. *Acta Paediatr Scand* 1979;68:341-4.

21. Ramage IJ, Chapman JP, Hollman AS, et al. Accuracy of clean-catch urine collection in infancy. *J Pediatr* 1999;135:765-7.
22. Hardy JD, Furnell PM, Brumfitt W. Comparison of sterile bag, clean catch and suprapubic aspiration in the diagnosis of urinary infection in early childhood. *Br J Urol* 1976;48:279-83.
23. Braude H, Forfar JO, Gould JC, et al. Diagnosis of urinary tract infection in childhood based on examination of paired non-catheter and catheter specimens of urine. *BMJ* 1967;4:702-5.
24. Benito Fernandez J, Sanchez Echaniz J, Mintegui Raso S, et al. Urinary tract infection in infants: use of urine specimens obtained by suprapubic bladder aspiration in order to determine the reliability of culture specimen of urine collected in perineal bag. *An Esp Pediatr* 1996;45:149-52.
25. Mendez EB. Are positive urine cultures obtained using recollector bags reliable? *Rev Chil Pediatr* 2003;74:487-91.
26. Farrell M, Devine K, Lancaster G, et al. A method comparison study to assess the reliability of urine collection pads as a means of obtaining urine specimens from non-toilet-trained children for microbiological examination. *J Adv Nurs* 2002;37:387-93.
27. Feasey S. Are Newcastle urine collection pads suitable as a means of collecting specimens from infants? *Pediatr Nurs* 1999;11:17-21.
28. Ahmad T, Vickers D, Campbell S, et al. Urine collection from disposable nappies. *Lancet* 1991;338:674-6.
29. Cohen HA, Woloch B, Linder N, et al. Urine samples from disposable diapers: an accurate method for urine cultures. *J Fam Pract* 1997;44:290-2.
30. Dayan PS, Chamberlain JM, Boenning D, et al. A comparison of the initial to the later stream urine in children catheterized to evaluate for a urinary tract infection. *Pediatr Emerg Care* 2000;16:88-90.
31. Hobbs FD, Delaney BC, Fitzmaurice DA, et al. A systematic review of near patient testing in primary care. *Health Technol Assess* 1997;1:1-231.
32. Dayan PS, Bennett J, Best R, et al. Test characteristics of the urine Gram stain in infants less than 60 or 60 days of age with fever. *Pediatr Emerg Care* 2002;18:12-4.
33. Giraldez M, Perozo M, González F, et al. Infección urinaria cinta reactiva y sedimento urinario vs. urocultivo para determinación de bacteriuria. *Salus militiae* 1998;23:27-31.
34. Lejeune B, Baron R, Guillois B, et al. Evaluation of a screening test for detecting urinary tract infection in newborns and infants. *J Clin Pathol* 1991;44:1029-30.
35. Marret M, Tay S, Yap HK, et al. Comparison of two rapid screening tests for urinary tract infection in children. *Ann Acad Med Singapore* 1995;24:299.
36. Marsik FJ, Owens D, Lewandowski J. Use of the leukocyte esterase and nitrite tests to determine the need for culturing urine specimens from a pediatric and adolescent population. *Diagn Microbiol Infect Dis* 1986;4:181-3.
37. Sharief N, Hameed M, Petts D. Use of rapid dipstick tests to exclude urinary tract infection in children. *Br J Biomed Sci* 1998;55:242-6.
38. Shaw KN, Hexter D, McGowan KL, et al. Clinical evaluation of a rapid screening test for urinary tract infections in children. *J Pediatr* 1991;118:733-6.
39. Wiggelinkhuizen J, Maytham D, Hanslo DH. Dipstick screening for urinary tract infection. *S Afr Med J* 1988;74:224-8.
40. Woodward MN, Griffiths DM. Use of dipsticks for routine analysis of urine from children with acute abdominal pain. *BMJ* 1993;306:1512.
41. Weinberg AG, Gan VN. Urine screen for bacteriuria in symptomatic pediatric outpatients. *Pediatr Infect Dis J* 1991;10:651-4.
42. Waisman Y, Zerem E, Amir L, et al. The validity of the uriscreen test for early detection of urinary tract infection in children. *Pediatrics* 1999;104:e41.
43. Shaw KN, McGowan KL, Gorelick MH, et al. Screening for urinary tract infection in infants in the emergency department: which test is best? *Pediatrics* 1998;101:E1-E5.
44. Lohr JA, Portilla MG, Geuder TG, et al. Making a presumptive diagnosis of urinary tract infection by using a urinalysis performed in an on-site laboratory. *J Pediatr* 1993;122:22-5.
45. Lagos Zuccone R, Carter S J, Herrera Labarca P. Utilidad de una tira reactiva y del aspecto macroscópico de la orina para descartar la sospecha clínica de infección del tracto urinario en niños ambulatorios. *Rev Chil Pediatr* 1994;65:88-94.
46. Bulloch B, Bausher JC, Pomerantz WJ, et al. Can urine clarity exclude the diagnosis of urinary tract infection? *Pediatrics* 2000;106:E60.
47. Armengol CE, Hendley JO, Schlager TA. Should we abandon standard microscopy when screening for urinary tract infections in young children? *Pediatr Infect Dis J* 2001;20:1176-7.
48. Anad FY. A simple method for selecting urine samples that need culturing. *Ann Saudi Med* 2001;21:104-5.
49. Matthai J, Ramaswamy M. Urinalysis in urinary tract infection. *Indian J Pediatr* 1995;62:713-6.
50. Demi M, Costa L, Zanardo V. Urinary tract infections in newborns: sensitivity, specificity, and predictive value of urinary screening with the reagent strip test. *Pediatr Med Chir* 1993;15:29-31.
51. Tahirovic H, Pasic M. A modified nitrite test as a screening test for significant bacteriuria. *Eur J Pediatr* 1988;147:632-3.
52. Boreland PC, Stoker M. Dipstick analysis for screening of paediatric urine. *J Clin Pathol* 1986;39:1360-2.
53. Kohler L, Fritz H, Schersten B. Screening for bacteriuria with Uriglox in children. *Acta Paediatr Scand Suppl* 1970;206:76-8.
54. Benito Fernandez J, Garcia Ribes A, Trebolazabala Quirante N, et al. Gram stain and dipstick as diagnostic methods for urinary tract infection in febrile infants. *An Esp Pediatr* 2000;53:561-6.
55. Wammanda RD, Aikhionbare HA, Ogala WN. Use of nitrite dipstick test in the screening for urinary tract infection in children. *West Afr J Med* 2000;19:206-8.
56. Craver RD, Abermanis JG. Dipstick only urinalysis screen for the pediatric emergency room. *Pediatr Nephrol* 1997;11:331-3.
57. Palmer LS, Richards I, Kaplan WE. Clinical evaluation of a rapid diagnostic screen (URISCREEN) for bacteriuria in children. *J Urol* 1997;157:654-7.
58. Labbe J. Usefulness of testing for nitrites in the diagnosis of urinary infections in children. *Union Med Can* 1982;111:261-5.
59. Fennell RS, Wilson SG, Garin EH, et al. The combination of two screening methods in a home culture program for children with recurrent bacteriuria. An evaluation of a culture method plus a nitrite reagent test strip. *Clin Pediatr* 1977;16:951-5.
60. Kunin CM, DeGroot JE. Sensitivity of a nitrite indicator strip method in detecting bacteriuria in preschool girls. *Pediatrics* 1977;60:244-5.
61. Todd J, McLain L, Duncan B, et al. A nonculture method for home follow-up of urinary tract infections in childhood. *J Pediatr* 1974;85:514-6.
62. Villanustre Ordonez C, Buznego Sanchez R, Rodicio Garcia M, et al. Comparative study of semiquantitative methods (leukocytes, nitrite test and uricult) with urine culture for the diagnosis of urinary tract infection during infancy. *An Esp Pediatr* 1994;41:325-8.
63. Dosa S, Houston IB, Allen LB, et al. Urinary glucose unreliable as test for urinary tract infection in infancy. *Arch Dis Child* 1973;48:733-7.
64. Holland PD, Doyle CT, English L. An evaluation of chemical tests for significant bacteriuria. *J Ir Med Assoc* 1968;61:128-30.

65. Schersten B, Dahlqvist A, Fritz H, et al. Screening for bacteriuria with a test paper for glucose. *JAMA* 1968;204:205-8.

66. Armengol CE, Hendley JO, Schlager TA. Urinary tract infection in young children cannot be excluded with urinalysis. *Pediatr Res* 2000;47:172A.

67. Parmington J, Kornberg A. Nitrite screening for urinary tract infection in a Pediatric Emergency Department. *Pediatr Emerg Care* 1989;5:285-6.

68. Doley A, Nelligan M. Is a negative dipstick urinalysis good enough to exclude urinary tract infection in Paediatric Emergency Department patients? *Emerg Med* 2003;15:77-80.

69. Arslan S, Caksen H, Rastgeldi L, et al. Use of urinary gram stain for detection of urinary tract infection in childhood. *Yale J Biol Med* 2002;75:73-8.

70. Rodriguez Caballero AM, Novoa Vazquez P, Perez Ruiz A, et al. Assessment of leukocyturia in the diagnosis of urinary tract infections. *Rev Esp Pediatr* 2001;57:305-8.

71. Hiraoka M, Hida Y, Hori C, et al. Urine microscopy on a counting chamber for diagnosis of urinary infection. *Acta Paediatr Jpn* 1995;37:27-30.

72. Hoberman A, Wald ER, Reynolds EA, et al. Is urine culture necessary to rule out urinary tract infection in young febrile children? *Pediatr Infect Dis J* 1996;15:304-9.

73. Hoberman A, Wald ER, Reynolds EA, et al. Pyuria and bacteriuria in urine specimens obtained by catheter from young children with fever. *J Pediatr* 1994;124:513-9.

74. Lin DS, Huang SH, Lin CC, et al. Urinary tract infection in febrile infants younger than eight weeks of age. *Pediatrics* 2000;105:E20.

75. Lin DS, Huang FY, Chiu NC, et al. Comparison of hemocytometer leukocyte counts and standard urinalyses for predicting urinary tract infections in febrile infants. *Pediatr Infect Dis J* 2000;19:223-7.

76. Pryles CV, Eliot CR. Pyuria and bacteriuria in infants and children. The value of pyuria as a diagnostic criterion of urinary tract infections. *Am J Dis Child* 1965;110:628-35.

77. Santos MA, Mos EN, Schmidt BJ, et al. Comparacion entre el estudio bacterioscopico cuantitativo y el urocultivo para el diagnostico de infeccion urinaria en pediatria. *Bol Méd Hosp Infant Méx* 1982;39:526-30.

78. Saxena H, Ajwani KD, Mehrotra D. Quantitative pyuria in the diagnosis of urinary infections in children. *Indian J Pediatr* 1975;42:35-8.

79. Schreiter G, Buhtz P. Diagnostic value of the cytologic and bacteriologic urine examinations in pediatrics. II. Comparison of leukocyturia and bacteriuria. *Dtsch Gesundheitsw* 1971;26:1318-23.

80. Littlewood JM, Jacobs SI, Ramsden CH. Comparison between microscopical examination of unstained deposits of urine and quantitative culture. *Arch Dis Child* 1977;52:894-6.

81. Lockhart GR, Lewander WJ, Cimini DM, et al. Use of urinary gram stain for detection of urinary tract infection in infants. *Ann Emerg Med* 1995;25:31-5.

82. Purwar VN, Agrawal SP, Dikshit SK. Gram stained urine slides in the diagnosis of urinary tract infections in children. *J Indian Med Assoc* 1972;59:387-8.

83. Vangone G, Russo G. Bacteria and leukocyte count in the urine in the diagnosis of urinary tract infections. *Pediatr Med Chir* 1985;7:125-9.

84. Vickers D, Ahmad T, Coulthard MG. Diagnosis of urinary tract infection in children: fresh urine microscopy or culture? *Lancet* 1991;338:767-70.

85. Manson R, Scholefield J, Johnston RJ, et al. The screening of more than 2,000 schoolgirls for bacteriuria using an automated fluorescence microscopy system. *Urol Res* 1985;13:143-8.

86. Hoberman A, Wald ER, Penchansky L, et al. Enhanced urinalysis as a screening test for urinary tract infection. *Pediatrics* 1993;91:1196-9.

87. Baum JD, Darrell JH, Lambert RA. Evaluation of dip inoculum urine culture. *Arch Dis Child* 1972;47:977-8.

88. Cid E, Fernandez Seara MJ, Buznego R, et al. Comparative study between Uricult and urine culture for the diagnosis of urinary infections in infants. *Rev Esp Pediatr* 1992;48:23-5.

89. Godard C, Frutiger P, Delarue C, et al. Testing for bacteriuria by home culturing in preschool girls. *Helv Pediatr Acta* 1979;34:209-12.

90. Mongeau JG, Robillard JE, Brousseau Y. Screening for bacteriuria in children: comparison of two dip-tests. *CMAJ* 1972;107:227-9.

91. Navarrete RV. Preventive aspects: vesical catheter and temporary supravesical catheterization. *Antibiot & Chemother* 1976;21:73-6.

92. Rich G, Glass NJ, Selkon JB. Cost-effectiveness of two methods of screening for asymptomatic bacteriuria. *Br J Prev Soc Med* 1976;30:54-9.

93. Whiting P, Rutjes AWS, Dinnes J, et al. The development and validation of methods for assessing the quality and reporting of diagnostic studies. *Health Technol Assess* 2004;8(25).

94. The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. *BMC Med Res Methodol* 2003;3:25. doi:10.1186/1471-2288-3-25.

95. Stokland E, Hellstrom M, Hansson S, et al. Reliability of ultrasonography in identification of reflux nephropathy in children. *BMJ* 1994;309:235-9.

96. Fotter R, editor. *Pediatric Uroradiology.* Berlin: Springer, 2001.

97. Ahmed SM, Swedlund SK. Evaluation and treatment of urinary tract infections in children. *Am Fam Physician* 1998;57:1573-80, 83-4.

98. Goldraich NP, Goldraich IH. Update on dimercaptosuccinic acid renal scanning in children with urinary-tract infection. *Pediatr Nephrol* 1995;9:221-6.

99. James JM, Testa HJ. Imaging techniques in the diagnosis of urinary tract infection. *Curr Opin Nephrol Hypertens* 1994;3:660-4.

100. Winberg J, Andersen HJ, Bergstrom T, et al. Epidemiology of symptomatic urinary tract infection in childhood. *Acta Paediatr Scand Suppl* 1974;252:1-20.

101. Andrich MP, Majd M. Evaluation of febrile urinary tract infections in children utilizing Technetium-99m DMSA scanning. *J Nucl Med* 1992;33:976.

102. Benador D, Benador N, Slosman DO, et al. Cortical scintigraphy in the evaluation of renal parenchymal changes in children with pyelonephritis. *J Pediatr* 1994;124:17-20.

103. Biggi A, Dardanelli L, Pomero G, et al. Acute renal cortical scintigraphy in children with a first urinary tract infection. *Pediatr Nephrol* 2001;16:733-8.

104. Bircan ZE, Buyan N, Hasanoglu E, et al. Radiologic evaluation of urinary tract infection. *Int Urol Nephrol* 1995;27:27-32.

105. Boudailliez B, Berro Y, Hosri JA, et al. A prospective study of imaging modalities in acute pyelonephritis (49 cases): DMSA renal scintigraphy versus power Doppler (PD) renal sonography. *Pediatr Nephrol* 1998;12:C132.

106. Castello Girona F, Vilaplana Canto E, Yeste Fernandez D, et al. 99mTc dimercaptosuccinic scan in the study of the first urinary tract infection in infants. *An Esp Pediatr* 1995;42:118-22.

107. Guermazi F, Lenoir P, Verboven M, et al. Technetium 99m labeled dimercaptosuccinic acid (99m Tc-DMSA) scintigraphy in the diagnosis and follow-up of urinary infections in children. *Arch Fr Pediatr* 1993;50:391-8.

108. el Hajjar M, Launay S, Hossein-Foucher C, et al. Power Doppler sonography and acute pyelonephritis in children: comparison with Tc-DMSA scintigraphy. *Arch Pediatr* 2002;9:21-5.

109. Hitzel A, Liard A, Vera P, et al. Color and power Doppler sonography versus DMSA scintigraphy in acute pyelonephritis and in prediction of renal scarring. *J Nucl Med* 2002;43:27-32.

110. Hitzel A, Liard A, Manrique A, et al. Comparative study of DMSA scintigraphy (DMSA) and Doppler sonography (DS) in the diagnosis of acute pyelonephritis and scarring in children. *J Nucl Med* 2000;41:209.

111. Ilyas M, Mastin ST, Richard GA. Age-related radiological imaging in children with acute pyelonephritis. *Pediatr Nephrol* 2002;17:30-4.

112. Jakobsson B, Nolstedt L, Svensson L, et al. 99mTechnetium-dimercaptosuccinic acid scan in the diagnosis of acute pyelonephritis in children: relation to clinical and radiological findings. *Pediatr Nephrol* 1992;6:328-34.

113. Jequier S, Jequier JC, Hanquinet S. Acute childhood pyelonephritis: predictive value of positive sonographic findings in regard to later parenchymal scarring. *Acad Radiol* 1998;5:344-53.

114. Krzemien G, Roszkowska-Blaim M, Brzewski M, et al. Comparison of power Doppler ultrasonography with 99mTc-DMSA renal scintigraphy in the diagnosis of acute pyelonephritis. *Pol Merkuriusz Lek* 2002;12:405-7.

115. Lavocat MP, Granjon D, Allard D, et al. Imaging of pyelonephritis. *Pediatr Radiol* 1997;27:159-65.

116. Morin D, Veyrac C, Kotzki PO, et al. Comparison of ultrasound and dimercaptosuccinic acid scintigraphy changes in acute pyelonephritis. *Pediatr Nephrol* 1999;13:219-22.

117. Sfakianakis GN, Mylonakis T, Zilleruelo G, et al. The importance of Technetium-99m Gh scintigraphy in infants with first UTI. *J Nucl Med* 1989;30:915-6.

118. Sreenarasimhaiah V, Alon US. Uroradiologic evaluation of children with urinary tract infection: are both ultrasonography and renal cortical scintigraphy necessary? *J Pediatr* 1995;127:373-7.

119. Bykov S, Chervinsky L, Smolkin V, et al. Power Doppler sonography versus Tc-99m DMSA scintigraphy for diagnosing acute pyelonephritis in children: Are these two methods comparable? *Clin Nucl Med* 2003;28:198-203.

120. Muro MD, Sanguesa C, Otero MC, et al. Acute pyelonephritis in pediatric age: comparative study between power Doppler ultrasound scan and DMSA. *Radiologia* 2002;44:237-42.

121. La Cava G, Sciagra R, Materassi M, et al. Accuracy of renal sequential scintigraphy for the recognition of renal involvement in pediatric patients affected by urinary tract infection. *Eur J Nucl Med* 1990;16:415.

122. Verboven M, Ingels M, Delree M, et al. 99mTc-DMSA scintigraphy in acute urinary tract infection in children. *Pediatr Radiol* 1990;20:540-2.

123. Buyan N, Bircan ZE, Hasanoglu E, et al. The importance of 99mTc DMSA scanning in the localization of childhood urinary tract infections. *Int Urol Nephrol* 1993;25:11-7.

124. Fretzayas A, Moustaki M, Gourgiotis D, et al. Polymorphonuclear elastase as a diagnostic marker of acute pyelonephritis in children. *Pediatrics* 2000;105:E28.

125. Gervaix A, Galetto-Lacour A, Gueron T, et al. Usefulness of procalcitonin and C-reactive protein rapid tests for the management of children with urinary tract infection. *Pediatr Infect Dis J* 2001;20:507-11.

126. Smolkin V, Koren A, Raz R, et al. Procalcitonin as a marker of acute pyelonephritis in infants and children. *Pediatr Nephrol* 2002;17:409-12.

127. Stokland E, Hellstrom M, Jacobsson B, et al. Early 99mTc dimercaptosuccinic acid (DMSA) scintigraphy in symptomatic first-time urinary tract infection. *Acta Paediatr* 1996;85:430-6.

128. Everaert K, Raes A, Hoebeke P, et al. Combined use of urinary alpha1-microglobulin and 99mTc DMSA scintigraphy in the diagnosis and follow-up of acute pyelonephritis and cystitis in children. *Eur Urol* 1998;34:486-91.

129. Landau D, Turner ME, Brennan J, et al. The value of urinalysis in differentiating acute pyelonephritis from lower urinary tract infection in febrile infants. *Pediatr Infect Dis J* 1994;13:777-81.

130. Landau D, Brennan J, Turner ME, et al. A negative urinalysis predicts the absence of acute pyelonephritis in febrile infants. *Pediatr Res* 1994;35:185.

131. Jantausch BA, Rifai N, Getson P, et al. Urinary N-acetyl-beta-glucosaminidase and beta-2-microglobulin in the diagnosis of urinary tract infection in febrile infants. *Pediatr Infect Dis J* 1994;13:294-9.

132. Capa Kaya G, Taskiran Y, Bak M, et al. Urinary N-acetyl-beta-glucosaminidase in children with upper urinary tract infection, in relation to Tc-99m DMSA scintigraphy. *Eur J Nucl Med* 2001;28:1156.

133. Prat C, Dominguez J, Rodrigo C, et al. Elevated serum procalcitonin values correlate with renal scarring in children with urinary tract infection. *Pediatr Infect Dis J* 2003;22:438-42.

134. Chateil JF, Diard F. Management of urinary tract infection in children. *Feuill Radiol* 1988;28:229-37.

135. Alon U, Pery M, Davidai G, et al. Ultrasonography in the radiologic evaluation of children with urinary tract infection. *Pediatrics* 1986;78:58-64.

136. Hellstrom M, Jacobsson B, Marild S, et al. Voiding cystourethrography as a predictor of reflux nephropathy in children with urinary-tract infection. *AJR Am J Roentgenol* 1989;152:801-4.

137. De Sadeleer C, De Boe V, Keuppens F, et al. How good is technetium-99m mercaptoacetyltriglycine indirect cystography? *Eur J Nucl Med* 1994;21:223-7.

138. Ditchfield MR, De Campo JF, Cook DJ, et al. Vesicoureteral reflux: an accurate predictor of acute pyelonephritis in childhood urinary tract infection? *Radiology* 1994;190:413-5.

139. Gordon I, Barkovics M, Pindoria S, et al. Primary vesicoureteric reflux as a predictor of renal damage in children hospitalized with urinary tract infection: A systematic review and meta-analysis. *J Am Soc Nephrol* 2003;14:739-44.

140. Piepsz A, Tamminen-Mobius T, Reiners C, et al. Five-year study of medical or surgical treatment in children with severe vesico-ureteral reflux dimercaptosuccinic acid findings. International Reflux Study Group in Europe. *Eur J Pediatr* 1998;157:753-8.

141. Wennerstrom M, Hansson S, Jodal U, et al. Disappearance of vesicoureteral reflux in children. *Arch Pediatr Adolesc Med* 1998;152:879-83.

142. Baronciani D, Bonora G, Andreoli A, et al. The value of ultrasound for diagnosing the uropathy in children with urinary-tract infections. *Riv Ital Pediatr* 1986;12:214-20.

143. Evans ED, Meyer JS, Harty MP, et al. Assessment of increase in renal pelvic size on post-void sonography as a predictor of vesicoureteral reflux. *Pediatr Radiol* 1999;29:291-4.

144. Mage K, Zoppardo P, Cohen R, et al. Imaging of the first urinary infection in children. Respective role of each examination technique in the initial assessment. A report on 122 observation. *J Radiol* 1989;70:279-83.

145. Mahant S, Friedman J, MacArthur C. Renal ultrasound findings and vesicoureteral reflux in children hospitalised with urinary tract infection. *Arch Dis Child* 2002;86:419-20.

146. Muensterer OJ. Comprehensive ultrasound versus voiding cysturethrography in the diagnosis of vesicoureteral reflux. *Eur J Pediatr* 2002;161:435-7.

147. Oostenbrink R, van der Heijden AJ, Moons KG, et al. Prediction of vesico-ureteric reflux in childhood urinary tract infection: a multivariate approach. *Acta Paediatr* 2000;89:806-10.

148. Tan SM, Chee T, Tan KP, et al. Role of renal ultrasonography (RUS) and micturating cystourethrogram (MCU) in the assessment of vesico-ureteric reflux (VUR) in children and infants with urinary tract infection (UTI). *Singapore Med J* 1988;29:150-2.

149. Verber IG, Strudley MR, Meller ST. 99mTc dimercaptosuccinic acid (DMSA) scan as first investigation of urinary tract infection. *Arch Dis Child* 1988;63:1320-5.

150. Dura Trave T, Gonzalez Montero R, Juste Ruiz M, et al. Usefulness of renal scintigraphy in the assessment of the first febrile urinary infection in children. *An Esp Pediatr* 1997;47:378-82.

151. Foresman WH, Hulbert WC, Rabinowitz R. Does urinary tract ultrasonography at hospitalization for acute pyelonephritis predict vesicoureteral reflux? *J Urol* 2001;165:2232-4.

152. Mage K, Zoppardo P, Cohen R, et al. Imagerie et premiere infection urinaire de l'enfant: place respective de chaque examen lors du bilan initial a propos de 122 observations. *J Radiol* 1989;70:279-83.

153. Salih M, Baltaci S, Kilic S, et al. Color flow Doppler sonography in the diagnosis of vesicoureteric reflux. *Eur Urol* 1994;26:93-7.

154. Bergius AR, Niskanen K, Kekomaki M. Detection of significant vesico-ureteric reflux by ultrasound in infants and children. *Z Kinderchir* 1990;45:144-5.

155. Berrocal T, Gaya F, Arjonilla A, et al. Vesicoureteral reflux: diagnosis and grading with echo-enhanced cystosonography versus voiding cystourethrography. *Radiology* 2001;221:359-65.

156. Berrocal Frutos T, Gaya Moreno F, Gomez Leon N, et al. Cystosonography with echoenhancer. A new imaging technique for the diagnosis of vesicoureteral reflux. *An Esp Pediatr* 2000;53:422-30.

157. Haberlik A. Detection of low-grade vesicoureteral reflux in children by color Doppler imaging mode. *Pediatr Surg Int* 1997;12:38-43.

158. Kessler RM, Altman DH. Real-time sonographic detection of vesicoureteral reflux in children. *AJR Am J Roentgenol* 1982;138:1033-6.

159. Mentzel HJ, Vogt S, John U, et al. Voiding urosonography with ultrasonography contrast medium in children. *Pediatr Nephrol* 2002;17:272-6.

160. Piaggio G, Degl' Innocenti ML, Toma P, et al. Cystosonography and voiding cystourethrography in the diagnosis of vesicoureteral reflux. *Pediatr Nephrol* 2003;18:18-22.

161. Radmayr C, Klauser A, Pallwein L, et al. Contrast enhanced reflux sonography in children: A comparison to standard radiological imaging. *J Urol* 2002;167:1428-30.

162. Von Rohden L, Bosse U, Wiemann D. Reflux sonography in children with an ultrasound contrast medium in comparison to radiologic voiding cystourethrography. *Paediat Prax* 1995;49:49-58.

163. Schneider K, Jablonski C, Weissner M, et al. Screening for vesicoureteral reflux in children using real-time sonography. *Pediatr Radiol* 1984;14:400-3.

164. Siamplis D, Vasiou K, Giarmenitis S, et al. Sonographic detection of vesicoureteral reflux with fluid and air cystography. Comparison with VCUG. *Rofo Fortschr Geb Rontgenstr Neuen Bildgeb Verfahr* 1996;165:166-9.

165. Valentini AL, Salvaggio E, Manzoni C, et al. Contrast-enhanced gray-scale and color Doppler voiding urosonography versus voiding cystourethrography in the diagnosis and grading of vesicoureteral reflux. *J Clin Ultrasound* 2001;29:65-71.

166. Stokland E, Hellstrom M, Jacobsson B, et al. Evaluation of DMSA scintigraphy and urography in assessing both acute and permanent renal damage in children. *Acta Radiol* 1998;39:447-52.

167. Stokland E, Hellstrom M, Jacobsson B, et al. Renal damage one year after first urinary tract infection: role of dimercaptosuccinic acid scintigraphy. *J Pediatr* 1996;129:815-20.

168. Merrick MV, Notghi A, Chalmers N, et al. Long-term follow up to determine the prognostic value of imaging after urinary tract infections. Part 1: Reflux. *Arch Dis Child* 1995;72:388-92.

169. Le Saux N, Pham B, Moher D. Evaluating the benefits of antimicrobial prophylaxis to prevent urinary tract infections in children: a systematic review. *CMAJ* 2000;163:523-9.

170. Barry BP, Hall N, Cornford E, et al. Improved ultrasound detection of renal scarring in children following urinary tract infection. *Clin Radiol* 1998;53:747-51.

171. LeQuesne GW, Davies R. Ultrasonic assessment of reflux nephropathy. *Pediatr Nephrol* 1986;16:335.

172. MacKenzie JR, Fowler K, Hollman AS, et al. The value of ultrasound in the child with an acute urinary tract infection. *Br J Urol* 1994;74:240-4.

173. Mucci B, Maguire B. Does routine ultrasound have a role in the investigation of children with urinary tract infection? *Clin Radiol* 1994;49:324-5.

174. Scherz HC, Downs TM, Caesar R. The selective use of dimercaptosuccinic acid renal scans in children with vesicoureteral reflux. *J Urol* 1994;152:628-31.

175. Antachopoulos C, Margeli A, Giannaki M, et al. Transient hypophosphataemia associated with acute infectious disease in paediatric patients. *Scand J Infect Dis* 2002;34:836-9.

176. Gordon I, Anderson PJ, Lythgoe MF, et al. Can technetium-99m-mercaptoacetyltriglycine replace technetium-99m-dimercaptosuccinic acid in the exclusion of a focal renal defect? *J Nucl Med* 1992;33:2090-3.

177. Pickworth FE, Vivian GC, Franklin K, et al. 99Tcm-mercapto acetyl triglycine in paediatric renal tract disease. *Br J Radiol* 1992;65:21-9.

178. McLorie GA, Aliabadi H, Churchill BM, et al. Technetium-99m-dimercapto-succinic acid renal scanning and excretory urography in diagnosis of renal scars in children. *J Urol* 1989;142:790-2.

179. Merrick MV, Uttley WS, Wild SR. The detection of pyelonephritic scarring in children by radioisotope imaging. *Br J Radiol* 1980;53:544-56.

Effective Health Care

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