Guidelines for the management of acute urinary tract infection in childhood

REPORT OF A WORKING GROUP OF THE RESEARCH UNIT, ROYAL COLLEGE OF PHYSICIANS

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Chronic pyelonephritis (reflux nephropathy) is found in about 20% of children and adults with end stage renal failure [1]. Prospective studies have shown that children who presented up to 30 years ago with urinary infection and chronic pyelonephritis now have a 20% risk of hypertension and a 10% risk of chronic renal failure [2–5]. The considerable variation in management of acute urinary tract infections in childhood [6] prompted the Research Unit of the Royal College of Physicians to convene a Working Group to consider guidelines for good practice, to identify areas where more research is needed and to develop procedures that could be used for audit.

In this report, a statement supported by research is followed by a reference number, statements recognising the need for further research by (R), and subjects suitable for audit are indicated by (A). A list of proposed audit measures is given in Appendix 1.

Diagnosis of urinary tract infection

As most scars are present at the first investigation [7–9], early diagnosis and prompt treatment are especially important during the first year of life. At home, any infant with a rectal temperature above 38.5°C with no definite cause should have a urine sample collected within 24 hours [10]. In all infants and children admitted to hospital with pyrexia, even with another diagnosis, a urine sample should be examined (A). Other indications for examining the urine are as follows:

- Unexplained vomiting or abdominal pain
- Frequency of micturition, dysuria or eneuresis
- Failure to thrive
- Prolonged jaundice in the newborn
- Non-specific illness
- Suspected sexual abuse
- Haematuria or hypertension

The yield of positive results when urine specimens are taken at home for the above indications, including fever, would be a suitable research project (R).

Taking a specimen

A clean-catch urine in an infant or a mid-stream urine specimen in an older child is the ideal. Only social cleanliness and dryness are required [10]. If these techniques are not effective, a bag urine should be obtained while the infant is held upright [8] and the specimen transferred from the bag as soon as it is passed [10]. A negative result (see below) from a bag urine specimen is reliable, but a positive result should be confirmed by a clean-catch specimen or, in infants, with suprapubic puncture or rarely by a catheter specimen (A). If suprapubic aspiration is needed, the infant should be referred to hospital for day-care or inpatient investigation.

Criteria for diagnosis of urinary tract infection

The diagnosis of urinary infection is confirmed if in one specimen there is a pure growth of more than 10^5 bacteria per microlitre. Lower counts of bacteria may be found persistently in urinary tract infection, particularly in boys [11]. This will be an indication for repeating the culture or obtaining a suprapubic aspiration. Pyuria (>10 white blood cells per microlitre of uncentrifuged urine) is usually found in the presence of acute symptoms but is not diagnostic [12]. Pus cells suggest inflammation and may be a helpful indicator in the absence of genital inflammation or when antibiotics have already been prescribed. The absence of pus cells [13] or the presence of a mixed growth of bacteria is evidence against, but does not exclude, an infection. A urinary infection can only be ruled out if a

urine culture before treatment is sterile. Any growth on culture of a catheter or suprapubic specimen is usually clinically significant. The number of colonies of pathogens isolated from suprapubic specimens needs to be compared with results from clean-catch specimens (R).

Urine microscopy can make a useful contribution to diagnosis, especially when urgent treatment must be initiated without awaiting culture results. It has an acceptably low false negative rate and the technique is easily learnt [13].

The nitrite test is a reliable sign of infection when positive but has up to a 48% false negative rate [14]; other studies have shown a substantially lower false negative rate [15]. A prerequisite of the test is that the urine must have been in the bladder for at least an hour so that there is time for bacterial conversion of nitrate into nitrite . If so, the false negative rate is considerably lower. In addition, routine bacteriological examination must always be performed (A). Other chemical tests, eg for hypoglycosuria, are less satisfactory [16]. Although proteinuria occurs in advanced reflux nephropathy [17], it is not diagnostic of acute urinary infection (R).

Specimen transport

The specimen of urine should ideally be collected in a sterile container, chilled immediately to 4°C and examined in the laboratory within 2 hours (A). The method and time of collection must be stated on the pathology request to enable the microbiologist to give an accurate opinion (A). An alternative is to refrigerate the specimen at 4°C in the main compartment of a domestic refrigerator for at most 48 hours before examination. The temperature of the general practice refrigerator should be checked regularly (A).

Another possibility is to transport the urine in 1.8% boric acid, but the correct amount of urine must be added to the bottle to ensure the correct concentration of boric acid (A). There are some data [18] which suggest that boric acid preserves pus cells and bacteria, and does not inhibit the growth of pathogens, but more research is needed in this area in children (R).

Dipslide

The dipslide is a miniature culture plate which is immersed in the urine immediately after voiding. This eliminates the delay so often incurred during transport of the specimen to the laboratory. It has been fully tested in 'field' conditions amongst primary schoolgirls who collected their own samples at home without vulval cleansing. This study showed a nil false negative rate, together with an acceptably low false positive rate [16].

Dipslides can also be inoculated by voiding urine directly on to the culture medium ('Dipstream'); this makes the method simpler and cheaper but yields a somewhat higher false positive rate; this can be minimised by disregarding micro-organisms such as coagulase negative staphylococci which are not recognised as common urinary pathogens in childhood [16]. However, this method has the disadvantage that it does not provide a urine specimen for microscopy.

Dipslides have failed to gain popularity in practice perhaps because their comparatively short shelf life (A) precludes bulk purchase by general practitioners. Nevertheless, they are an efficient and reliable means of documenting bacteriuria before treatment is initiated.

Management of the infant or child with acute symptomatic urinary tract infection

Management is greatly helped by detailed discussion with the parents and child, supplemented by written guidelines (Appendix 2).

After an appropriate specimen of urine has been obtained, treatment should immediately be started, especially in infants under 2 years old, with the 'best guess' antibacterial agent in full dosage (A). It can be changed if necessary after 48 hours when drug sensitivities of the organism are available or if there has been no clinical response (A). Drugs suitable for oral administration for short full-dose courses include co-trimoxazole, trimethoprim, nitrofurantoin and orally administered cephalosporins. The sulphonamide component of co-trimoxazole is more likely to result in adverse effects, but resistance to trimethoprim in the community may be higher [19]. However, the Working Group did not reach consensus on this point as some members held that co-trimoxazole and trimethoprim were no different in tolerance, compliance, side effects or emergence of resistance [20]. Resistance of urinary pathogens to amoxycillin, even in primary care, is currently too high for this drug to be used as a first choice (A). A course of 5–7 days is usually prescribed but the optimum length of treatment is not known (R). After the short course of treatment the urine should be examined to ensure that the infection has been eradicated (A). Prophylactic antibiotics should not be stopped while the urine is collected (A).

A low dose of a suitable antibacterial drug should be continued prophylactically at least until investigation of the urinary tract has been completed. The drug dose should be adjusted to the child's weight (A). Agents currently suitable for prophylaxis include trimethoprim (1–2 mg/kg/day), co-trimoxazole (trimethoprim 1–2 mg and sulphamethoxazole 5–10 mg/kg/day) and nitrofurantoin (1 mg/kg/day). Amoxycillin is not satisfactory (A). To reduce the risk of dental decay, liquid preparations of these drugs must be sugar-free and must not be diluted with sugar-containing diluents.

In children with minor symptoms it is acceptable to wait for the results of the urine culture (which may need to be repeated) before starting treatment.

In children under 5 years old and those with

demonstrated abnormalities on imaging, urine microscopy and culture should be carried out once every 3 months for at least 2 years or at times when they are feverish or unwell (A). Most members of the Working Group favoured examination of the urine every 3 months. A minority proposed that, if the infection has been eradicated and appropriate imaging investigations are negative, no further urine samples should be collected except from children who presented with obvious symptoms, for example those over 5 years old with dysuria, or fever and malaise. The reason for this suggestion is that there is evidence that asymptomatic urinary infection without scars does not affect prognosis [9], although there may be some slight decline in renal function in adult life [21]. However, following the use of antibiotics for other infections in the presence of asymptomatic bacteriuria, the child is more likely subsequently to be infected with a more virulent organism [22, 23].

The long-term management of children with recurrent infection, renal scars or vesicoureteric reflux was not discussed by the Working Group.

Imaging studies

As a significant number of important abnormalities will be detected in both sexes, all children diagnosed as having a urinary tract infection should have some form of imaging after the first proved infection [24]. Although guidance on the most suitable types of imaging in the various age groups was agreed by the majority of the Working Group (see below), these must be considered interim suggestions until the results of more definitive research are available. The reasons for this uncertainty are as follows:

- Few children in whom an abnormality has been detected have had an ultrasound examination of the kidneys and bladder, a ^{99m}Tc/ dimercaptosuccinic acid (DMSA) scan and an intravenous urogram (IVU). The sensitivity and specificity of each of these tests remain to be assessed on larger numbers (R) [25–29].
- Different units vary considerably in the quality of images and interpretation of DMSA scans (A).
- The results of ultrasound scanning depend on the experience and skill of the operator (A); small focal scars may not be detected even by the best operator [30]. Such small scars in older children may not be of therapeutic importance, since the risk of further scarring developing after 7 years of age is small (R) [9, 31].
- The IVU produces poor renal outlines in the first year of life, even when the staff are experienced (R). It can provide information on pelvicalyceal appearances and ureteric calibre, and sometimes a reduced nephrogram or enlargement of the affected kidney can be seen.
- In some cases an abnormality shown on DMSA scanning (due to hypoperfusion) shortly after the beginning of an infection has resolved 3 months later [29, 32]. These early reversible changes may

Table 1. Comparison of radiation dosage sustained in the course of various imaging procedures of the urinary tract in childhood.

	MCU Estimated doses assuming 2 min fluoroscopy and 10 films	DRC	IRC Mag 3 Tc-99^m, 200 MBq	IVU Average from 8 films and 77s fluoroscopy (20 hospitals)*	DMSA Tc-99^m, 80 MBq
Effective dose equivalent (EDE)	5.4 mSv [39]	0.3 mSv [33]	1 mSv [41,42]	4.4 mSv [43]	1 mSv [42]
Gonad dose	6.0 mSv (male)	<0.02 mSv (male)	0.4 mSv (male) (MIRD calculation)	4.34 mSv (male)	0.96 mSv (male)
	1.0 mSv (female)	0.02 mSv (female)	0.65 mSv (female) (bladder void 2 h)	3.58 mSv (female)	0.48 mSv (female)
	[39]	[40]	[41]	[43]	[44]
Kidney dose	2 mSv (average dose at this hospital)	Negligible	0.65 mSv [41]	5.6 mSv [43]	13.4 mSv [44]

*Some physicians believe that an adequate IVU can be obtained with 4 rather than 8 films.

indicate a vulnerable kidney or may be of no clinical importance (R).
- An IVU performed during an acute infection may fail to detect the inflammatory change preceding a scar (R).
- Units carrying out these investigations may not have enough patients to provide appropriate experience (A).

The contrast micturating cystourethrogram (MCU) is the only technique that shows the urethra or reflux into the lower third of the ureter, but it does require a urethral catheter. The radiation dosage is about twenty times the dose of a direct radionuclide cystogram (DRC) which uses a radioactive tracer instead of contrast medium [33] (Table 1). The indirect radionuclide cystogram (IRC) is particularly useful in the toilet-trained child because the tracer is given intravenously and does not involve inserting a catheter into the bladder. The DRC has higher sensitivity than the MCU for detection of vesicoureteric reflux [34, 35]. Many institutions have compared the IRC with both the MCU and the DRC. In six reported studies, the sensitivity of the IRC is as good as that of the DRC and the MCU [36, 37]. Only one study reported poor results for the IRC [38].

The Working Group agreed that all boys having their first cystourethrogram should have an MCU (A). If nuclear medicine facilities are available, the DRC has the advantage of a lower radiation dose. The IRC is particularly useful for studies in older children to determine whether reflux has resolved.

Further research on the relative value of different imaging procedures is still required (R).

Recommended imaging studies (R)

Under the age of 1 year

During the acute phase, every infant should have a good quality ultrasound examination of the kidneys and bladder, and a plain abdominal radiograph of the kidneys, to exclude renal stones and lumbosacral spinal defects (A). A cystourethrogram (see below) should be carried out when the urine is sterile (A). Prophylactic antibiotics should be given until the result of the cystourethrogram is known. An immediate DMSA scan is optional, but it is essential after 3 months when the ultrasound should be repeated. The Working Group believed that, although the DMSA scan is preferable in this age group, an IVU will provide useful information if nuclear imaging is not available.

Between the ages of 1 and 7 years

The appropriate investigations for this age group are controversial. The Working Group did not reach a consensus but agreed that renal ultrasound and plain abdominal radiography should be performed, followed by DMSA scan or IVU (A). Most members felt that in this age group a cystourethrogram should be confined to children with one of the following:

- Abnormalities shown in the above investigations
- Clinical history suggestive of acute pyelonephritis
- A family history of reflux or reflux nephropathy
- Recurrent infections

After the 7th birthday

If there is no history suggestive of a previous infection, renal ultrasound and a plain radiograph of the abdomen should be carried out (A). If these results are normal, the child should be kept under surveillance for 2 years by checking the urine for infection every 3 months (A). Some members of the Working Group suggested that in the absence of symptoms these repeat urine examinations were unnecessary (R).

A minority of members took the view that IVU with or without DMSA scan should be done at the initial stage (R). If the infection recurs, or if there is a previous history suggestive of a urinary tract infection, most members agreed that an IVU with or without DMSA scan should be performed.

A cystogram is rarely needed in this age group, except for children with a demonstrated abnormality in the upper renal tract or those with previously detected reflux.

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Appendix 1. List of items suitable for audit

- Has the urine been examined in children with pyrexia above 38.5°C for more than 24 hours if no other definite cause for fever has been found?
- Has the urine been examined in all children admitted to hospital with pyrexia even if there is some other apparent diagnosis?
- Are positive bag urines in infants being confirmed by referral to hospital for suprapubic puncture or, in older children, by clean-catch specimens within 72 hours of the initial urine sample?
- Are urine samples immediately chilled to 4°C after collection? Are there arrangements for checking the temperature of the practice refrigerator? Is the time of the urine collection recorded on the pathology request form? Is the interval between collection and examination in the laboratory less

than 2 hours or, if not, has 1.8% boric acid been added in the correct amount?
- Are dipslides within their 'shelf life'?
- Are nitrite tests for infection being supported by bacteriological examination?
- Has a urine specimen been examined before giving antibiotics?
- Has antibiotic treatment been started immediately after sending the specimens to the laboratory?
- Is the choice of initial antibiotic suitable — *not* amoxycillin? Is the dose appropriate for age and weight?
- Is the result of the microbiological examination communicated promptly to the referring doctor, by telephone if positive?
- Is the antibiotic changed if appropriate on receipt of the drug sensitivities of the organism?
- Is the urine re-examined after 5–7 days to ensure that infection has been eradicated?
- Is a suitable dose of an appropriate antibacterial drug continued at least until completion of the urinary tract investigation?
- Is investigation appropriate? (see above)
- Are there clinico-radiological review sessions in the imaging department to monitor the results of the investigations performed?

Appendix 2. Information for parents of children with urinary tract infections (not discussed at the workshop), prepared by Dr Katherine Verrier-Jones FRCP, Consultant Paediatric Nephrologist, Cardiff Royal Infirmary, Newport Road, Cardiff CF2 1SZ.

When to suspect urinary tract infection in a child or baby

Your child or baby may have infected urine without having the fishy smell and burning pain on passing urine that occurs in adults with cystitis. In a baby or toddler you should think of urinary infection if your child is unwell and has a high temperature, unless there is clear evidence for some other explanation. You should also think of it in a baby that has repeated bouts of fever, or vomiting, jaundice or poor weight gain, and, of course, in any child that does have symptoms related to passing urine.

What to do if you think your child might have a urine infection

It is important to treat urinary tract infection quickly, particularly in very young children because prolonged infection may make them quite ill, and delay in treatment may damage the kidneys. You should contact your doctor as soon as you suspect that your baby or child might have infected urine and ask for an urgent appointment and urine test.

How to diagnose urinary tract infection

Urinary infection can only be diagnosed with certainty if a clean urine sample is collected in a sterile container and sent without delay to the laboratory for examination. The full result will not be available for 48 hours. In babies and toddlers an adhesive plastic bag can be used to collect the sample.

Treatment

In babies and toddlers who are unwell and any child with distressing symptoms, your doctor will not wait for the laboratory results but will straight away start treatment with antibiotic, most commonly Trimethoprim. It may be necessary to change the antibiotic after 48 hours if the child is not obviously better. In this case the laboratory result will probably show that the germ causing the infection is not sensitive to the antibiotic first chosen, and will also indicate what other antibiotic to choose. Full treatment should be continued for 5–10 days; after that, all children under 5, and older children who have been quite unwell, should continue to take a small regular dose of antibiotic (Nitrofurantoin or Trimethoprim) until the kidneys and bladder have been checked.

What to expect after treatment

Doctors believe that all young children who have had a urinary tract infection should have simple tests to check the kidneys and bladder are normal. If any abnormality is found, suitable tests will be arranged. For children the tests should include an ulrasound scan of the kidneys (like the scans used to measure the baby during pregnancy) and an x-ray to show the kidneys. Further tests will be necessary in very young children and when the ultrasound scan is abnormal. Older children with recurrent distressing symptoms may also need further tests. When the tests have been completed make sure that you understand the results, and the reason why further tests and treatment may be necessary.

What may happen in the future

Boys rarely get further infections, and if they do, it usually happens quite soon after the first one. But girls often do get further infections. It does not necessarily mean that there is something seriously wrong, but it might be an indication for further investigation and a new treatment plan. In some children, long-term, low dose antibiotic treatment is used to reduce the risk of further infections, particularly in very young children who may have some abnormality of the urinary tract (such as vesicoureteric reflux). Ask enough questions so that you understand the reasons for your child's need for prolonged treatment and can help your child to get better.

General measures to reduce the risk of recurrent infection and genital soreness in girls

1. Encourage regular bladder emptying 4 hourly or before each meal and before going to bed.
2. To make sure that the bladder is completely empty ask your child to try again after 5–10 minutes.
3. Treat constipation adequately with diet and laxatives.
4. Avoid tight trousers.
5. Bath regularly, dry carefully afterwards.
6. Avoid highly scented soap, do not use bubble bath or wash hair in the bath.
8. Wipe bottom clean from front to back.
9. Use soft absorbant toilet paper.
10. Ensure easy access to satisfactory toilets at school.
11. Treat thrush and thread worms.
12. Discourage masturbation.

Background papers. The background papers prepared by some members of the Working Group (listed below) are available from the Publications Department, Royal College of Physicians, 11 St Andrews Place, London NW1 4LE, on payment of £6.00 to cover costs of photocopying and postage.

Modell, M.	Diagnosis of urinary tract infection in children in general practice
Haycock, G.B.	Choice of imaging studies in childhood urinary tract infection
White, R.H.R.	Initial imaging of urinary tract following infection, where radionuclides are not available
Gordon, I.	Urinary tract infection: follow-up studies
Whitaker, R.H.	Guidelines for parents of children with vesicoureteric reflux

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