Long term follow up to determine the prognostic value of imaging after urinary tract infections. Part 2: scarring

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Abstract

Long term follow up of children with urinary tract infections, in whom imaging investigations were performed at presentation, has been used to identify features that distinguish those at greatest risk of progressive renal damage. No single investigation at presentation was able to predict subsequent deterioration but, by employing a combination of imaging investigations, it was possible to separate groups with high or low probability of progressive damage. In the low risk group the incidence of progressive damage was 0·2% (95% confidence interval (CI) 0 to 1·3%). The combination of both scarring and reflux at presentation, or one only of these but accompanied by subsequent documented urinary tract infection, was associated with a 17-fold (95% CI 2·5 to 118) increase in the relative risk of progressive renal damage compared with children without these features.

The recommended combination of investigations at presentation for girls of any age and boys over 1 year is ultrasound and dimercaptosuccinic acid (DMSA) scintigraphy in all, to detect both scarring and significant structural abnormalities, renography in children with dilatation of any part of the urinary tract on ultrasound, to distinguish dilatation from obstruction, and an isotope voiding study in all who have acquired bladder control. This gives the best separation between those at high and those at low risk of progressive damage with least radiation dose and lowest rate of instrumentation. Micturating cystourethrography (MCU) should be restricted to girls who have not acquired bladder control, unless there is reason to suspect a significant structural abnormality such as urethral valves. A single non-febrile urinary tract infection that responds promptly to treatment is not a justification for performing MCU in boys under 1 year or in children of any age with bladder control. No case can be made for any abbreviated schedule of investigation. These risk factors should be taken into account when designing follow up protocols.

(*Arch Dis Child* 1995; 72: 393–396)

Keywords: vesicoureteric reflux, urinary tract infection, reflux nephropathy.

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Accepted 23 January 1995

Imaging investigations are generally considered essential in the work-up of children with a urinary tract infection.[1] Much attention has been paid to the importance of identifying vesicoureteric reflux before the development of overt reflux nephropathy, although the limitations of the tests that detect reflux have been largely overlooked.[2] The prognostic importance of focal scarring is widely recognised; that of diffuse scarring is less well documented.[3] However, most series with follow up have employed intravenous urography, even though scintigraphy (with technetium (^{99m}Tc) labelled dimercaptosuccinic acid (^{99m}Tc-DMSA) in particular) has been shown to detect cortical loss in substantially more kidneys than does excretion urography.[4–8] The value of ultrasound is more contentious.[9 10] There are surprisingly few data on the clinical consequences of the abnormalities found either by scintigraphy or ultrasound and their ability to predict long term deterioration while, in the absence of any control group, the effectiveness of treatment in preventing progressive damage is unproved.[11] A recent small retrospective study (which placed more reliance on intravenous urography than scintigraphy) did find an association between the severity of scarring and the duration of the delay before initiating appropriate treatment, although it is not clear whether this referred to scarring at presentation or on follow up.[12] It is thus not surprising that a survey of paediatricians in the UK showed 'an alarming conflict of practice' concluding 'the management of urinary tract infection is in disarray' and 'any investigative protocol should be realistic and suitable for implementation by all paediatricians'.[13] We report here follow up of children referred to a single centre (providing a regional service) for imaging after a urinary tract infection, in order to determine whether the identification of scarring at presentation either in isolation, when considered in association with reflux or with subsequent episodes of urinary infection, can

Table 1 Correlation between ultrasound and DMSA in individual kidneys; examinations performed within one month of each other

	Initial ultrasound normal	*Cortical loss on initial ultrasound*	*Total*
Initial DMSA normal	1570	48	1618
Cortical loss on initial DMSA	162	286	448
Total	1732	334	2066

Table 2 Associations between the presence or absence of scarring at presentation and the subsequent appearance or progression of scarring

	Girls		Boys	
	<1 year	*≥1 year*	*<1 year*	*≥1 year*
No of kidneys in which no scarring was observed at presentation	372	5492	510	1973
No (%) in which scars developed	13 (3·5)	56 (0·98)	6 (1·2)	19 (0·96)
No of kidneys with scarring at presentation	56	697	63	247
No (%) in which scarring progressed	8 (14·3)	59 (8·5)	10 (15·9)	16 (6·5)
Difference in % (95% CI)	10·8 (1·4 to 20·1)	7·5 (5·4 to 9·6)	14·7 (5·6 to 23·8)	5·5 (2·4 to 8·6)

Table 3 Associations between urinary tract infections (UTIs) after the index event and appearance or progression of scarring

	Girls		Boys	
	<1 year	*≥1 year*	*<1 year*	*≥1 year*
No having no further UTIs	93	1790	107	607
No (%) with progressive scarring	2 (2·2)	42 (2·4)	3 (2·8)	14 (2·3)
No having further UTIs	59	607	91	204
No (%) with progressive scarring	8 (13·6)	38 (6·3)	5 (5·5)	8 (3·9)
Difference in % (95% CI)	11·4 (2·2 to 20·6)	3·9 (1·9 to 6·0)	2·7 (−2·9 to 8·3)	1·6 (−1·3 to 4·5)

stratify the risk of progressive renal damage. The role of vesicoureteric reflux in the same population is analysed in more detail in the companion paper.[2]

Patients and methods

The population studied has been described previously.[2] The reports of imaging and other investigations were obtained from case notes, which were also the source of data on urine cultures, surgical procedures, other investigations, and follow up. The departmental records contained duplicate contemporaneous hard copies of all nuclear medicine reports and examinations, which were reviewed. Renal scintigraphy (^{99m}Tc-DMSA, 1 MBq/kg, four projections 1·5 to 3 hours after injection) was performed as described previously, not earlier than 24 hours after labelled diethylenetriaminepenta-acetic acid (^{99m}Tc-DTPA) renography or three hours after labelled mercaptoacetyl triglycine (^{99m}Tc-MAG3, 0·2 MBq/kg) renography and when children were in remission.[4 14] A scoring system was used to assess the extent of scarring and the magnitude of any changes.[15] Ultrasound was performed by one of three experienced paediatric radiologists or trainees under their supervision. Statistical analysis was performed using the confidence interval analysis (CIA) package.[16]

Results

There was concordance between ultrasound and scintigraphy for the presence or absence of scarring in 89·8% of the 2066 children in whom the results of both were available (table 1). Ultrasound failed to detect cortical loss in 162 of 448 kidneys in which a scintigraphic abnormality was reported (36·2%) while scintigraphy was considered normal in 48 (14·3%) of those with ultrasound reports of cortical thinning or loss. Abnormalities other than cortical loss, most commonly a dilated renal pelvis, were detected by ultrasound in 176 children (209 kidneys, 7·3% of the kidneys examined by ultrasound). Significant dilation of the renal pelvis was also identified in all by renography, which was in any case necessary to differentiate between physiological dilatation, obstruction, and reflux. Progressive renal damage occurred more commonly in children who had cortical loss at presentation (table 2), and in girls in whom further urinary tract infections were confirmed (table 3) but not boys. The number of older children in each year is small and it was not possible to identify a cut off beyond which there was no risk of damage to previously normal kidneys. Only one boy and four girls who presented over the age of 8 years with unscarred kidneys subsequently developed cortical loss, but these were scattered throughout the range. Multiple recurrences of infection were frequent in both sexes. There was a tendency for a greater number of subsequent infections to be associated with progression of scarring in girls under 1 year, but no such association was evident in older girls or in boys.

Any single abnormal feature occurred in only about a half of the children who suffered progressive renal damage (table 4). Considering each test separately, the probability of progressive damage was highest in girls under 1 year with vesicoureteric reflux (odds ratio 14·5) and in boys under 1 with scarring at presentation (odds ratio 13·5) (table 5). The documentation of either reflux or further urinary tract infection did not confer a significantly increased risk of progressive damage in boys under 1, nor did further urinary tract infection in boys over 1 year. Results of three imaging investigations (ultrasound, scintigraphy, and either MCU or the indirect isotope voiding study) were available both at presentation and on follow up in 623 children. All of this group also had both initial and follow up urine cultures. Although the sensitivity

Table 4 Associations with subsequent deterioration

	No in group	*No (%) deteriorating*	*Relative risk (95% CI)*
Kidneys without cortical loss at presentation	6069	67 (1·1)	
Kidneys with cortical loss at presentation	870	66 (7·6)	6·94 (4·98 to 9·68)
Kidneys without vesicoureteric reflux	4945	69 (1·4)	
Kidneys with vesicoureteric reflux	1197	82 (6·4)	4·66 (3·40 to 6·38)
Children without further urinary infections	2597	61 (2·3)	
Children with further urinary infections	961	59 (8·5)	2·61 (1·84 to 3·71)

Table 5 Odds ratio (95% CI) for subsequent deterioration compared with those in whom this feature was not present at presentation

	Girls		*Boys*	
	<1 year	*≥1 year*	*<1 year*	*≥1 year*
Vesicoureteric reflux (MCU or IVS)	14·5 (1·8 to 118)	4·4 (3·0 to 6·5)	1·5 (0·4 to 5·8)*	5·1 (2·4 to 10·5)
Cortical loss (DMSA or ultrasound)	4·1 (1·6 to 10·3)	8·3 (5·7 to 12·1)	13·5 (4·7 to 48·4)	6·7 (3·4 to 13·3)
Further urinary infections	6·3 (1·3 to 30·7)	2·7 (1·7 to 4·2)	1·7 (0·7 to 4·1)*	2·0 (0·5 to 8·4)*

*Note: a lower limit for the 95% CI of less than 1·0 indicates that the difference in risk is not statistically significant.
IVS=indirect isotope voiding study.

and specificity of each investigation was relatively poor when considered singly, there was a strong correlation between the number of abnormal investigations at presentation and the risk of subsequent deterioration ($r=-0·961$, 95% confidence interval (CI) $-0·518$ to $-0·998$). Considering follow up urine culture results in conjunction with the initial imaging, children with any two abnormal test results had a relative risk of progressive damage of 17·9 (95% CI 2·5 to 118) compared with those in whom no test or only a single test was abnormal (table 6).

Discussion

Previous long term follow up studies that considered the role of imaging have, for the most part, employed excretion urography,[17 18] even though there is ample evidence that scintigraphy gives a substantially lower radiation dose than excretion urography and is appreciably more sensitive than either excretion urography or ultrasound for detecting both reversible and irreversible renal damage.[4–8] Studies to determine the long term prognostic significance of abnormalities detected by scintigraphy and ultrasound have been restricted to small or selected groups.[19 20] The long term significance of the abnormalities found by these techniques has principally been inferred by extrapolation from earlier studies using less sensitive modalities and has not been directly observed, the assumption being made that both reveal similar pathology. It could, however, be argued that these investigations are too sensitive or the information provided is not strictly comparable and could lead to inappropriate treatment.[21] It is thus important to follow up these children to establish the true position.

The good agreement between scintigraphy and ultrasound in the present series, while at first sight at variance with experience elsewhere,[9 10 22] is associated with a number of synergistic factors, in particular the large number of true negatives, where no technique revealed an abnormality and who remained well on follow up. Moreover all ultrasound examinations were performed by or under the direct supervision of an experienced paediatric radiologist. Nevertheless the difficulty in differentiating by ultrasound between scarring and fetal lobulation, the delay before scars are detectable and the poor reproducibility are well documented.[9 10 22–24] Experimental and clinical studies with DMSA indicate that although false negatives occur, mainly associated with concentric cortical thinning or scars which have retracted, false positives are rare.[25 26] Our findings, that ultrasound underestimates the prevalence of scarring by 36%, while DMSA misses 14% and cannot detect calculi, hydronephrosis, or ureterocoele are thus in accord with previous reports.

The role of ultrasound in urinary tract infection has been questioned.[9 10 22] None of the children in the present series with an abnormality seen on ultrasound alone deteriorated, although the number in this category is small. It is, however, clear that when employing ultrasound as the sole imaging that the pick-up rate of clinically important abnormalities is low. The absence of ionising radiation is not in itself a justification for performing an unproductive examination. However, the false negative rate of DMSA, due to its inability to detect concentric cortical thinning, plus the few significant structural abnormalities identified on routine ultrasound, do provide justification for ultrasound as a component of an integrated and structured plan, but not in isolation. The data in the accompanying paper reaffirm the importance of reflux as a risk factor, principally when associated with further episodes of infection, but also highlight the limitations of tests for the presence of vesicoureteric reflux.[2] Either reflux or scarring on DMSA scintigraphy was found at presentation in 69% of those who deteriorated, but the specificity of DMSA is much higher (0·88 compared with 0·45). Ultrasound had a higher specificity still (0·93) but a sensitivity of only 0·41. Thus while any single imaging test or any pair of tests was a relatively weak predictor of subsequent deterioration if considered in isolation (table 4), the combination of three imaging investigations when considered in conjunction with follow up urine culture was much more powerful (table 6).

Table 6 Relationship between number of abnormal tests and subsequent progressive renal damage in those with all test results available both at presentation and on follow up

	No with progressive damage/total (%)	*95% CI (%)*
All negative	0/197	0 to 1·9
Any one abnormal	1/216 (0·5)	0 to 2·6
Any two abnormal	6/121 (5·0)	1·8 to 10·5
Any three abnormal	8/58 (13·8)	6·2 to 25·4
All four abnormal	10/31 (32·3)	16·7 to 51·4
Zero or one abnormal	1/413 (0·2)	0 to 1·3*
More than one abnormal	24/210 (11·4)	7·1 to 15·7*

*Relative risk 17·9 (95% CI 2·5 to 118).
Correlation coefficient between percentage deteriorating and number of tests abnormal $-0·961$ (95% CI $-0·998$ to $-0·518$.
The tests were abdominal ultrasound, DMSA scintigraphy, indirect isotope voiding study or MCU, and follow up urine culture.

In boys under 1 year, neither reflux nor recurrent urinary tract infection was associated with an increased risk of progressive renal damage, while cortical loss at presentation carried a 13·5-fold increased risk. In contrast reflux was the most important risk factor in girls of this age (table 6). In older children reflux and cortical loss were of similar predictive value, while subsequent infection was only marginally less significant. After the first year the extent of scarring did not correlate with the risk of further infections. A plot of the frequency of number of documented episodes of infection suffered by each child can be fitted by a single exponential function. The usual explanation for this mathematical function is that each individual episode is a random event uninfluenced by previous history. However, in girls, but not in boys, the risk of appearance or progression of scarring is substantially increased by further documented infections. In contrast reflux is not a risk factor in boys under 1 year (tables 3 and 4). It is difficult to account for this discrepancy unless there are differences in aetiological factors between the sexes. One possible explanation is that, in the neonate, infection is more commonly haematogenous than ascending.[27 28]

These findings indicate that the combination of imaging investigations, possibly in association with urine culture at a lower than the current level of suspicion, could be used to stratify risk and thus target follow up. Any single test, if used as a selection criterion for identifying children at risk of progressive damage, misses about half of those who deteriorate. Renography is the least productive, distinguishing whether dilatation found at ultrasound is associated with obstruction; the only additional information obtained in patients without dilatation is an independent estimate of split function. However, the same activity of MAG3 has to be administered for the indirect isotope voiding study whether or not it is preceded by renography. The radiation dose is unaffected but little would be lost in most patients if it were to be omitted. Using the three imaging modalities plus urine culture and accepting an abnormality in any one as the criterion of risk of progressive damage identified all of those who subsequently deteriorated, and would have reduced the number to be followed up by one third. Requiring two of the tests to be abnormal identified a group with a 17-fold increased risk and reduced the number to be followed up by two thirds. Had the latter policy been followed in the subgroup with full initial and follow up data, continued intensive follow up would have been obtained in 210 children and this would have detected 24 cases of progressive damage. Extending surveillance to the remaining 413 would have yielded only one additional case. No child in whom all the investigations were normal suffered progressive renal damage. There is almost certainly selection bias in this group weighting it with high risk patients. Thus if the policy were applied more generally the savings are likely to be greater.

We wish to thank the Radiological Research Trust for financial support and the staff of the medical records departments at all the hospitals involved for their patience and help.

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