Original Articles

Long term follow up to determine the prognostic value of imaging after urinary tract infections. Part 1: reflux


Abstract

In 3646 children with at least one confirmed urinary tract infection the prevalence of vesicoureteric reflux at presentation was correlated with progressive renal damage during follow up of not less than two and up to 16 years. Reflux was not demonstrated either at presentation or at any subsequent time in almost one half of the children who suffered progressive renal damage and was not a risk factor for progressive renal damage in boys under 1 year. It was an important risk factor in boys over 1 year and in girls of any age. The risk of progressive renal damage in children in whom micturating cystourethrogram (MCU) did not reveal vesicoureteric reflux was substantially greater than in those whose indirect isotope voiding study (IVS) did not show reflux. The risk of deterioration for those in whom reflux was demonstrated was similar for both techniques. This discrepancy indicates an appreciably higher false negative rate for the MCU than the IVS. Dilatation of the renal pelvis detected by ultrasound was associated with a significantly increased risk of progressive damage only when associated with reflux, but most children with progressive damage did not have a dilated collecting system at presentation.

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

Urinary tract infections are common, especially in women and girls; reflux nephropathy is considered to be a major preventable cause of end stage renal failure. There is a considerable body of evidence that most of the renal damage is initiated in childhood. It is widely taught that imaging investigations are an essential component of the work-up of children who have had a urinary tract infection.1 Many protocols of investigation have been proposed, most recently by a working party of the Royal College of Physicians of London which suggested a three tier approach depending on age at presentation,2 but there is no consensus on which investigations should be performed, nor indeed why imaging is necessary.3 A test for vesicoureteric reflux is usually recommended, especially in children under 2 years, as reflux may be considered an indication for surgery or otherwise affect management, although tests for reflux are often used inappropriately.4-7 If reliable criteria could be established for early identification of the children at greatest risk of subsequent progressive renal damage, it should be possible to concentrate on them, rather than spread resources thinly over a larger population, many of whom may be at low risk of progressive impairment.

Scintigraphic techniques for the detection of reflux have been shown to be substantially more sensitive than micturating cystourethrogram (MCU)8 and over recent years paediatricians have come increasingly to rely on ultrasound as a preliminary screening test as it eliminates ionising radiation. There are, however, few data on the power of any of the newer techniques to predict long term deterioration. Many centres still rely on MCU, while the place of ultrasound is increasingly being questioned. Knowledge of the prognostic significance of abnormal test results, and agreement on what use is to be made of this information, must precede establishing any protocol. Evaluation of any algorithm is complicated by the frequent spontaneous disappearance of vesicoureteric reflux before puberty and the low prevalence of long term sequelae, hence the need for a large series with long follow up.9 We have attempted to follow up the children referred to a single imaging centre (providing a regional service) for investigation after a urinary tract infection, to determine whether the findings of the investigations performed at presentation, either when considered singly or in combination, would have been able to distinguish those children at greatest (or least) risk of progressive renal damage. This paper analyses our findings in reflux; scarring is discussed separately in the accompanying paper.10
Patients and methods

All 3646 children without significant extrarenal pathology, referred between 1975 and 1990 to a single regional nuclear medicine centre for investigation of the renal tract after at least one bacteriologically confirmed urinary infection, were reviewed. During this period all paediatricians in the area referred patients to the same nuclear medicine department, which thus had the most complete record of children investigated by hospital based paediatricians in a defined geographical region (Edinburgh and the Lothians). The patients were not randomised or selected, each receiving whatever was considered "best practice" at the time. There was, however, broad agreement between the paediatricians that children with urinary tract infection should be managed similarly. The children were identified prospectively and reviewed retrospectively. Urinary tract infection was defined as bacteriuria of greater than $10^5$ organisms/ml. The minimum work-up comprised a full history and clinical examination, urine culture, blood chemistry, renography, renal scintigraphy, and a test for reflux. Almost all also had abdominal ultrasound, although in the early part of the period a few children did not have an ultrasound investigation. Those with major congenital anomalies, neurogenic bladder, significant extrarenal abnormalities or who had undergone renal tract surgery before their first scintigraphic examination, as well as those in whom all urine cultures had been sterile, were excluded from the present analysis. Progressive renal damage was defined as the development of new scars identified either on scintigraphy or on ultrasound, enlargement of existing ones, a decrease in relative function (technetium $^{99m}$Tc) labelled dimercaptosuccinic acid ($^{99m}$Tc-DMSA) uptake) greater than 6% compared with the previous value, failure of renal growth, increasing blood urea or rising serum creatinine.

The results of imaging and other investigations were obtained from the departmental records. Ultrasound and radiography reports were taken from the notes. The latter also provided the number and frequency of both normal and abnormal urine cultures, information concerning surgical procedures, any other investigations, and follow up. The nuclear medicine records enabled us to link to the records of subsequent hospital referrals in the area, whether paediatric or adult. Until 1988, gamma camera renography (labelled diethylaminoethyl-2-MC)

Results

The distribution of age at presentation is bimodal in both sexes (figure), with one peak of incidence in the first year, over 50% of whom were boys and a second in the fourth, more than 80% of whom were girls. Almost half of the children remained asymptomatic and were returned to the care of their general practitioners in under one year. All were subsequently followed up by their general practitioners, giving a mean follow up of 7-4 (range 1-15) years. It was longer than two years in 89.7% and than three years in 83.6%. Follow up imaging was performed at the discretion of the paediatrician, the principal indications being if further urinary tract infections were confirmed or suspected and in some cases before discharging a well child from the follow up clinic. Altogether 77-6% of girls and 71-0%
of boys presenting before their first birthday had further infections confirmed, compared with 45.4% of girls and 39.3% of boys presenting after this anniversary. There were frequently multiple episodes in both sexes.

Ultrasound was not performed either during micturition or systematically both before and after micturition. A dilated collecting system was observed on the routine (full bladder) scan in 368 of the 2664 kidneys in whom the ultrasound report was available (table 1). Progressive scarring occurred more commonly in kidneys with reflux and in kidneys with a dilated collection system than in those without, the effects being cumulative. Renal or ureteric calculi were present in two. Twenty eight (1.2% of the children having ultrasound) came to surgery: 14 pyeloplasty, five partial nephrectomy, six nephrectomy, and three ureteric reimplantation. Two others, both with extensive cortical loss at presentation, have subsequently undergone renal transplantation, one of whom died nine years after presentation in chronic renal failure.

Both MCU and the IVS were performed within one month of each other in 609 of the children (table 2). Accepting that there is no absolute standard, that reflux may be intermittent and that some children were probably missed by both techniques, but regarding any discordance as a false negative gives MCU a sensitivity of 47% and an accuracy of 66% compared with 78% and 86% respectively for the IVS. Progressive renal damage occurred more commonly in girls of any age and boys over 1 year with reflux at presentation than in its absence (table 3). Reflux was the most important single factor identifying those girls under 1 year at risk of progressive renal damage, but was not statistically significant in boys. Seventy of the 151 kidneys in which progressive damage occurred were of normal size and without demonstrable scars at presentation and no reflux could be demonstrated in 23. Kidneys in which reflux was demonstrated on IVS were 13.5 times more likely to deteriorate than those in which no reflux was observed (table 4). In contrast kidneys with reflux on MCU were four times as likely to suffer progressive damage.

### Discussion

Urinary tract infection is common. In a general practice study 0.31% of girls and 0.17% of boys experienced one or more infections per year. Between 0.5% and 1% of women have reflux nephropathy, which carries a one in 1000 lifetime risk of progressing to end stage renal failure. There is a substantial body of evidence that most of the renal damage is initiated in childhood. The recommended practice in this area for the whole of the period under review has been for all children with a bacteriologically proved urinary infection to be referred to a paediatrician for investigation. Both paediatric units followed the same policy and there was close cooperation between surgeons and physicians. We abandoned the routine use of excretion urography in children with urinary tract infection in 1978, in favour of ultrasound and scintigraphy, because of the lower sensitivity and higher radiation dose of the older technique (approximately an order of magnitude greater than our current practice). Ureteric reimplantation was rarely performed for reflux not associated with recurrent infections or progressive scarring, and in this respect practice was at the conservative end of the contemporary spectrum. The ‘STING’ procedure was introduced only at the end of the period reviewed and did not influence the findings in this survey.

While we have no direct means of determining directly the degree of compliance by general practitioners with the recommendations of the hospital based paediatricians, there are well established links between general practice and the hospitals. Children whose imaging studies were normal at presentation and whose urine promptly became sterile with treatment were followed up by their general practitioners, but those subsequently returning to any paediatrician or referred to adult urologists or renal physicians in the area with recurrent infection were identified through the record system. The population is somewhat more stable than in many larger conurbations, while the small numbers of previously unknown cases of chronic pyelonephritis presenting to adult clinics in the relevant age groups are compatible with a reasonably consistent implementation of the recommended policy. We thus believe that this study is representative of contemporary clinical practice and that the population we have identified is as characteristic and comprehensive as it is practicable to achieve in the clinical environment. Nevertheless it is recognised that our data are likely to be incomplete and give a minimum estimate the true prevalence of progressive disease.

### Table 2 Correlation between MCU and IVS in individual kidneys; examinations performed within one month of each other

<table>
<thead>
<tr>
<th></th>
<th>Reflux on IVS</th>
<th>No reflux on IVS</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reflux on MCU</td>
<td>99</td>
<td>88</td>
<td>187</td>
</tr>
<tr>
<td>No reflux on MCU</td>
<td>208</td>
<td>214</td>
<td>422</td>
</tr>
<tr>
<td>Total</td>
<td>307</td>
<td>302</td>
<td>609</td>
</tr>
</tbody>
</table>

CI = confidence interval.

### Table 3 Associations between the presence or absence of reflux 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 reflux was observed | 74 | 3632 | | 134 | 1174 |
| No (%) which developed new or progressive scarring | 1 (1-4) | 49 (1-3) | | 5 (3-7) | 14 (1-2) |
| No of kidneys with reflux | 46 | 897 | | 51 | 265 |
| No (%) which developed new or progressive scarring | 9 (19-6) | 53 (5-9) | | 4 (5-6) | 16 (6-0) |
| Difference in % (95% CI) | 18-2 (6-5 to 30-0) | 4-6 (3-0 to 6-2) | | 1-9 (-4-4 to 8-2) | 4-8 (1-9 to 7-6) |
Previous long term series that considered the role of reflux have employed MCU. We used the IVS as the first investigation to detect reflux in children with bladder control and able to cooperate because it eliminates catheterisation and substantially reduces the radiation dose; otherwise MCU was performed. The higher sensitivity of IVS for detecting vesicoureteric reflux is well established, the substantial difference seen in this series confirming previous findings.8 11 No arbitrary age limit was set. Voiding was attempted at any age if the accompanying parent thought cooperation a possibility and diagnostic IVS studies were obtained in some 2 year olds. The long term significance of the abnormalities found by IVS or ultrasound has previously been inferred by extrapolation from earlier studies using MCU (the assumption being made that both revealed similar pathology) and has not been assessed separately. It is, however, sometimes argued that the IVS may have a higher error rate, be too sensitive, or that the information provided is not strictly comparable, leading to over or under treatment. It is thus important to follow up these children to establish the value of the tests employed.

Six hundred and nine of the children had both MCU and an IVS performed sufficiently close in time (one month) for direct comparison to be valid. As in previous studies IVS had a significantly higher sensitivity than MCU, possibly because continuous recording before and during micturition is normal practice, as it does not increase the radiation dose.8 11 In contrast it is usual to image intermittently when performing MCU in order to minimise radiation, the radiation dose being directly dependent on screening time. Consequently the ureters may be under observation for less than 10% of the total duration of the examination. Recognised disadvantages of the IVS are its inability to detect reflux during the filling phase and that the conventional grading of reflux is not applicable. MCU provides a ‘snap-shot’ which may catch urine below its maximum level and thus underestimate its severity, while ‘low grade’ reflux must always propel retrogradely non-opacified urine proximal to it in the ureters and collecting system. There is disagreement as to the frequency with which reflux during filling occurs as an isolated finding, in the absence of reflux during voiding. Reflux is moreover commonly intermittent, so that any single test is likely always to have a substantial false negative rate.18 These factors may jointly account for progressive scarring in children apparently without reflux. A priori it is reasonable to expect that any technique that is more sensitive at detecting reflux during voiding should be associated with fewer false negatives.

All direct comparisons between the IVS and MCU have shown a substantial discrepancy, sometimes interpreted as ‘false positive’ IVS, on the tenuous assumption that MCU is a reference standard.8 18 False positive IVS due to reciprocating urine in dilated ureters is recognised19 but dilated ureters were uncommon in the population who comprised this study. Follow up, however, reveals a much higher prevalence of progressive damage in children in whom MCU was considered normal than in those whose IVS was normal (table 4). Three of the children (two girls who presented in their first year and a boy in the second) who developed the most severe damage – from a normal kidney at presentation to an atropic kidney – did not have reflux demonstrated (on MCU) at presentation or any subsequent time, although one of the girls had a dilated collecting system on ultrasound.

The much higher sensitivity of IVS than MCU may contribute to the difference in risk of progressive damage between children with a normal IVS and those in whom reflux was demonstrated at IVS, when compared with those who had MCU, substantiates the validity and superiority of the IVS as a technique of detecting reflux. Progressive damage was not confined to dysplastic kidneys. These findings indicate either that reflux is not the important factor previously believed or, more plausibly, MCU has a significantly higher false negative rate than the IVS. Indeed, in view of the substantially lower sensitivity of MCU, it can no longer be considered as the reference against which other techniques are judged. It should now be regarded as an obselete technique for detecting vesicoureteric reflux in subjects with bladder control, because it is more invasive, gives more radiation, and has a higher error rate. Reflux can also be detected if ultrasound is performed during micturition, but too many children are inhibited by the presence of an adult with an ultrasound probe while they are attempting to urinate, making this rather impractical. The appearance of dilatation after voiding is also indicative of reflux but was not sought during the period in question. We have not compared the IVS with any direct ultrasound technique nor with the direct isotope voiding technique. The combination of dilatation on the resting ultrasound scan and reflux was associated with a high (26-8%) incidence of progressive damage, whereas dilatation without demonstrable reflux or reflux into a non-dilated system were associated with a lower risk (3-8% and 5-1% respectively). The absence of a dilated collecting system is thus of no value to exclude either reflux or the risk of progressive damage. The lowest rate of deterioration (<1%) was in children without dilatation who did not reflux.

Bacteriuria is more common in boys during the first few months of life; at all subsequent ages the prevalence is higher in females. In boys under 1 year, neither reflux nor recurrent urinary tract infection was associated with an increased risk of progressive renal damage. In contrast reflex was the most important risk factor in girls at this age. In older children reflux
and cortical loss were of similar predictive value, while subsequent infection was only marginally less significant. Considering only children with comprehensive follow up data, reflux was observed at presentation in 20 of the 29 kidneys which developed progressive damage, but also in 660 kidneys which did not. In the same group there was progressive damage in 20 (not all the same) of the 169 kidneys with scintigraphic evidence of cortical loss at presentation and in 12 of the 92 with ultrasound abnormalities. Thus tests for reflux have a lower specificity than the other modalities for predicting progressive damage. Further infections were documented in all but two of the children with reflux who deteriorated. If reflux, and in particular the IVS were to be used as the sole criterion for follow up it would be necessary to keep under review almost two thirds of the children investigated, but nevertheless a substantial percentage of those who do deteriorate would be missed. The IVS, or indeed any single test for reflux in isolation is thus not suitable as a screening test. The present study reaffirms the importance of reflux as a risk factor for progressive renal damage, but principally when associated with other risk factors, in particular further episodes of infection.

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