Epidemiology of paediatric renal stone disease in the UK

R J M Coward, C J Peters, P G Duffy, D Corry, M J Kellett, S Choong, W G van’t Hoff

Background: The previous epidemiological study of paediatric nephrolithiasis in Britain was conducted more than 30 years ago.

Aims: To examine the presenting features, predisposing factors, and treatment strategies used in paediatric stones presenting to a British centre over the past five years.

Methods: A total of 121 children presented with a urinary tract renal stone, to one adult and one paediatric centre, over a five year period (1997–2001). All children were reviewed in a dedicated stone clinic and had a full infective and metabolic stone investigative work up. Treatment was assessed by retrospective hospital note review.

Results: A metabolic abnormality was found in 44% of children, 30% were classified as infective, and 26% idiopathic. Bilateral stones on presentation occurred in 26% of the metabolic group compared to 12% in the infective/idiopathic group (odds ratio 2.7, 95% CI 1.03 to 7.02). Coexisting urinary tract infection was common (49%) in the metabolic group. Surgically, minimally invasive techniques (lithotripsy, percutaneous nephrolithotomy, and endoscopy) were used in 68% of patients.

Conclusions: There has been a shift in the epidemiology of paediatric renal stone disease in the UK over the past 30 years. Underlying metabolic causes are now the most common but can be masked by coexisting urinary tract infection. Treatment has progressed, especially surgically, with sophisticated minimally invasive techniques now employed. All children with renal stones should have a metabolic screen.

The last British epidemiological study of paediatric nephrolithiasis, performed in 1973,1 concluded that stones were principally secondary to urinary tract infections, particularly Proteus, that recurrence occurred if there was inadequate eradication of infection,2 and that open surgery was the favoured treatment option. To examine if these findings are still relevant we have studied children presenting to the same centres over the past five years.

METHODS

Since 1997, all children presenting with a renal stone to either Great Ormond Street Hospital or St Peter’s Hospital (within the Middlesex Hospital) were referred for a metabolic evaluation. Each child was reviewed by a consultant paediatric nephrologist (WVH) in a dedicated paediatric renal stone clinic, using a specific list of questions and a paediatric nephrologist (WVH) in a dedicated paediatric evaluation. Each child was reviewed by a consultant nephrologist (WVH) in a dedicated paediatric renal stone clinic, using a specific list of questions and a paediatric nephrologist (WVH) in a dedicated paediatric evaluation.

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Hyperoxaluria. A raised spot oxalate:creatinine (Ox:Cr) ratio greater than the 95th centile age related normal reference values (birth 0.2 mmol/mmol; 5 years 0.14 mmol/mmol; 10 years 0.85 mmol/mmol; 15 years 0.06 mmol/mmol)5 was used as an initial screen. Repeated abnormalities were confirmed by a 24 hour urine collection into an acidified container and urine was also sent for determination of urinary glycolate and t-glyceraldehyde concentrations. In cases with persistent hyperoxaluria, primary hyperoxaluria was suspected and a liver biopsy performed to determine levels of alanine glyoxylate aminotransferase (for primary hyperoxaluria type 1) and glyoxylate transferase reductase (for type 2).

Cystinuria. Quantitative urinary amino acid determination by ion exchange chromatography showed levels of cystine above 18 mg/g creatinine together with isolated increases of the other dibasic amino acids (ornithine, lysine, arginine).

Hyperuricosuria. Repeated increased spot urines of urate:creatinine level greater than age specific reference values (1.6 mmol/mmol at <6 months of age decreasing to 0.4 mmol/mmol in adolescence).6 These were then confirmed with 24 hour collections against age specific references.7

The aetiology of the stone was considered infective if no metabolic abnormality was detected and the child presented with, or had a past history of urinary tract infection (UTI).
Epidemiology of paediatric renal stone disease

Age at presentation, sex distribution, and aetiological type of paediatric stones presenting to Great Ormond Street and the Middlesex hospital 1997–2001. (A) Males (n = 82). (B) Females (n = 39).

<table>
<thead>
<tr>
<th>Age at presentation</th>
<th>Random Ca:Cr ratio, 95th centile (mmol/mmol)</th>
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<tr>
<td>&lt;7 months</td>
<td>1.96</td>
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<tr>
<td>8–18 months</td>
<td>1.4</td>
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<tr>
<td>19 months–6 years</td>
<td>0.78</td>
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<tr>
<td>6–16 years</td>
<td>0.56</td>
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Statistics
When comparing groups for risk factors, odds ratios with 95% CI were used in the Instat software package. In defining the population characteristics the median age was used as this was considered most representative.

RESULTS
Incidence, age, and sex at presentation
One hundred and twenty one patients (82 boys and 39 girls; 2.1:1 boys:girls), were included over the five year period (fig 1). The median age of presentation was 36 months for males (range 3–180 months) and 48 months (range 4–137 months) for females.

Presenting features
Presentation with the classic combination of renal colic and macroscopic haematuria was uncommon. Sixty six (55%) children had macroscopic haematuria, 61 (50%) abdominal pain, but only 36 (30%) patients had both symptoms. In 21 (17%) patients the stones were apparently asymptomatic and fortuitously detected. Interestingly the median height and weight of children on presentation was lower than average, on the 25th centile in 93 children (77%) who were measured (range 0.4th to 91st centile).

A positive family history of renal stones was present in 19 (16%) first degree relatives, rising to 40 (33%) if both first and second degree relatives were considered. Sixteen (13%) children were born prematurely (<37 weeks), and in 10 (8%) there was a history of prolonged immobility, principally secondary to neurological impairment. In 58 (48%) there was a previous history of urinary tract infection. This study did not aim to address the frequency of congenital renal anomalies in the children with stones. However, at least eight (7%) were known to have vesicoureteric reflux, six (5%) had stenosis within the urinary tract, and one child bilateral renal cortical cysts (the cause of which remains under investigation). Of these 15, three were defined as metabolic, four infective, and eight idiopathic stone formers.

Aetiology
Fifty three (44%) had an underlying metabolic abnormality, 36 (30%) were classified as having an infective aetiology, and in 32 (26%) no aetiological factor could be detected. Metabolic stone formers presented throughout childhood, in contrast to infective aetiologies which were more common in the under 6 age group, with 89% presenting in this period (fig 1).

Metabolic aetiologies
Of the 53 patients with a metabolic abnormality: 30 had hypercalciuria (57%), 12 cystinuria (23%), one hyperuricosuria (2%), five intermittent hyperoxaluria (9%), four primary hyperoxaluria (8%), and one child an unclassified hypercalcaemic condition (2%).

Within the hypercalciuric group, one child from a consanguineous marriage had the hypomagnesaemia, hypercalciuria (Michaelis-Manz) syndrome. Immobility and prematurity contributed to eight cases. The remainder had idiopathic hypercalciuria, with no other obvious exacerbating factors such as calciiuric inducing medications. Interestingly, of these, 48% had a family history of nephrolithiasis. One child had persistent hypercalcaemia and an inappropriately raised parathormone level, but repeatedly normal 24 hour and spot urine calcium excretion (the underlying diagnosis in this boy is under ongoing investigation).

The hyperoxaluric group consisted of four children with primary hyperoxaluria: three with type 1 and one child with non-type 1/type 2 (none had type 2). Four children had enteric hyperoxaluria secondary to small bowel pathology. Three of these were born prematurely, two of whom had bowel resections for necrotising enterocolitis. One child who was born at term had bowel resected for a rhabdomyosarcoma. The single child with uric acid stones underwent further investigation of the purine metabolic pathways but no underlying defect was detected.

Excluding the single patient with hyperuricosuria, between 45% and 58% (total mean 49%) of children with each of the defined metabolic abnormalities had presented with a urinary tract infection. Children with a metabolic abnormality presented at a median of 40 months (range 3–168 months) compared to 36 months (range 6–180 months) in the infective/idiopathic group. There were proportionally more males in the infective/idiopathic (male:female, 2.6:1) compared to the metabolic group (male:female, 1.7:1). The risk of presenting with bilateral stones was increased significantly in children with an underlying metabolic abnormality, with 14 of 53 (26%) having bilateral stones in the metabolic group compared to 8 of 68 (12%) in the non-metabolic group (odds ratio 2.7, 95% CI 1.03 to 7.02).

Infective stones
These occurred in 36 patients with a median age of presentation of 30 months. The male to female ratio was 1.6:1. Boys presented at an earlier age than girls (median of 24 months compared to 48 months). Two children with multiple stones had xanthogranulomatous pyelonephritis, resulting in chronic renal failure.
Stone distribution
The stones were upper tract in 104 children (86%), unilateral on the left in 44 (36%), on the right in 38 (31%), and bilateral in 22 (18%). In four cases (3%) the stones were located in the bladder, and in seven (6%) in both the bladder and upper tract. In six (5%) the stones were passed, before determination of location.

Stone composition
The majority of stones analysed were composed of calcium oxalate or calcium phosphate (50%). Triple phosphate stones were detected in 32%; however in two cases (3%) of those analysed, the stone consisted of both triple phosphate and cystine, and both these children had cystinuria. These were diagnosed by virtue of their urinary investigations. In 44% of children stone analysis could not, or was, not undertaken (usually because they had undergone lithotripsy before metabolic evaluation and no fragments were available).

Stone removal
One hundred and eight (89%) children underwent a procedure to remove the stone(s) (fig 2). Commonly, a combination of techniques was used to achieve stone clearance. In 25 (21%) cases open surgery alone was performed. A review of the surgical management of a subset of these patients (treated between 1997 and 1999) has recently been presented.13

DISCUSSION
The epidemiology of paediatric nephrolithiasis appears to have changed in the past 30 years. This study does not address whether the incidence of stone disease in children has changed, which has been reported to account for between 0.13 and 0.94 cases per 1000 hospital admissions in the western world,14 but does indicate an apparent change in the aetiology of stone formation. Males continue to suffer more renal stones than females, a predominance that is confirmed aetiology of stone formation. Males continue to suffer more renal stones than females, a predominance that is confirmed

Figure 2 Surgical modalities of stone removal (n=121).

Figure 3 Underlying stone aetiologies. Comparison between previous study (1966–71) and present study (1997–2002).
We recommend that every child with a stone should have a metabolic evaluation, primarily to initiate preventive treatment early, but also to allow siblings to be screened if necessary.

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**REFERENCES**


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Problems after repair of aortic coarctation

S

ome years after repair of coarctation of the aorta, up to a third of patients are hypertensive and a similar proportion has developed recoarctation. Coarctation is often associated with a bicuspid aortic valve the clinical significance of which is uncertain. A study in Rotterdam (JW Roos-Hesselink and colleagues. Heart 2003;89:1074–7) has illustrated the long term problems.

Of 149 patients followed up in a clinic for adults with congenital heart disease, 124 had adequate echocardiographic data. They had had coarctation repair at a median age of 9 years (4–16 years) and were followed up for 18 years (13–25 years). Median age at last follow up was 28 years (20–36 years). Forty six of the 124 patients are reported to have had associated heart abnormalities recorded at operation (ventricular septal defect (n = 18), persistent ductus arteriosus (n = 16), atrial septal defect (n = 4), mitral valve abnormality (n = 4), transposition of the great arteries (n = 3), dextrocardia (n = 1)). Operative techniques included resection and end to end anastomosis (n = 91), subclavian flap (n = 14), and graftplasty (n = 10). (Surgical technique was not recorded in detail for nine patients.)

There were three deaths on follow up in the adults’ clinic, all between 14 and 20 years after repair. One was from acute aortic dissection, one during aortic arch surgery, and one from aortic valve endocarditis and massive acute aortic regurgitation. A bicuspid aortic valve was identified at echocardiography in 48 patients; 30 patients had a trileaflet valve, and the number of leaflets was uncertain for 46 patients. Seventy eight patients developed aortic valve disease (39 aortic stenosis, 36 aortic regurgitation, 3 both) and 27 had intervention for it (surgery for 25 and balloon dilatation for two). The proportion of patients with aortic valve disease was 63% overall and 70% in patients with a bicuspid valve. The ascending aorta was dilated in 26 of the 48 patients known to have a bicuspid valve and 9 of the remaining 76. Thirty had established aortic pathology (arch hyperplasia (n = 10), cervical aortic arch (n = 4), severe kinking of the aorta (n = 8), kinking plus cervical arch (n = 8)). Recurrence of coarctation occurred in 28 patients and was more frequent in patients who had had their first repair under the age of 6 years. Recoarctation was treated surgically in 10 patients and with balloon dilatation in 18, at an average of 16 years after the initial repair. Thirty patients were taking antihypertensive treatment at their last follow up visit. These patients were older at last follow up and had their initial repair at an older age than patients not receiving antihypertensive treatment.

Late problems are common in patients who have had repair of aortic coarctation. All patients should be followed up for life.
Euroaspirations

We read with interest the recent article of Papadopoulos et al.1 The Euro was accepted with remarkable alacrity by the peoples of the eurozone. The franc, mark, guider, lira, and other currencies were effectively replaced within one week in February 2002. The euro changeover was effective, efficient, and essentially painless. The currency has prospered with 20% growth since its introduction and is now worth approximately 70 pence sterling and one US dollar 15 cents.

In the first few months of the euro, we too noticed several children presenting to our emergency department having decided to see how well the euro went down. These were children in the oral exploratory ages of 1–3 years. As a consequence and for guidance to our emergency department colleagues, a “eurometer” was made (fig 1). Some of the euro coins are small and some ended up in the upper airway, the oesophagus, and the stomachs of toddlers and preschool children (fig 2). We have seen 22 such patients in first eight months of this year. A few euroentreval were required.

The UK’s euro debate sees the euro as a threat to the national pound. Has anyone else considered the euroaspiration? “Should the UK stay in or out of the euro?” ask the headlines? Sweden plunged into controversy when it consulted its people in a euro referendum. Denmark is sitting on the fence. All accident and emergency departments in the eurozone ought to be cognisant of the potential of the 1 cent coin to lodge in the oesophagus or sit in the upper airway. The differential diagnosis of any toddler with acute upper airway obstruction should, in the eurozone, include eurostridor.

We, like Dr Papadopoulos and colleagues, warn that if one aspires to euroconvert, one must accept euroaspirations.

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Reference

PostScript

Thrombocytopenia is predictive of lethality in severe childhood falciparum malaria

Moulin and others1 reported that thrombocytopenia was not a marker of severity in children suffering falciparum malaria. In a previously published study,2 we have shown a highly significant association between thrombocytopenia and either severity or prognosis in childhood falciparum malaria. To our knowledge, this association had not been noted or looked for before.

Our study took place from October 1997 to March 1999, in the paediatric department of the Hopital Principal in Dakar, Senegal, where clinical presentation, WHO criteria of severe malaria, and platelet count were prospectively recorded. Of 288 falciparum cases, 215 matched the 2000 WHO definition of severe malaria. Median platelet counts were lower (98 000/mm3 versus 139 000/mm3; p < 0.02) among severe cases than in mild cases, and in children who died (n = 26) than among those who recovered (68 500/mm3 versus 109 000/mm3; p < 0.002). In severe cases, children presenting with a platelet count <100 000/mm3 were more likely to die (20%, 22/110) than those with a higher platelet count (3.8%, 4/115; odds ratio (OR) 6.31, 95% confidence interval (CI) 2.0 to 26.0; p < 0.0003). Moreover, multivariate analysis identified thrombocytopenia as an independent predictor of death (OR 13.3, 95% CI 3.2 to 55.1; p < 0.0001)—that is, when the effect of cerebral malaria, respiratory distress syndrome, severe anaemia, and other severe malaria criteria was taken into account.

The absence of an association between thrombocytopenia and clinical malaria severity in the samples studied by Moulin and others does not prove its non-existence. Moreover, their study suffers from several limitations that may explain the discrepancy between their and our conclusions. First, they have observed only four deaths among 234 malaria cases. Their survey was consequently powerless to establish any association between thrombocytopenia and lethality.

The low level of lethality among severe cases (3.5%, 4/112) also suggests that clinical presentations observed in the Moulin et al study were less life threatening than in ours, even if 69 of their severe cases have been admitted in the same paediatric department where our study was conducted previously. It is well established that the case fatality rate varies according to clinical presentation and definition of severe falciparum malaria criteria. Thus any analysis of prognostic factors of malaria lethality must take into account the composition of the sampled cases in terms of clinical presentations, for example, analysing the different syndromes separately. In our study, the association between thrombocytopenia and lethality was significant among children with cerebral malaria or respiratory distress but not among children only presenting with severe anaemia, convulsions, or hypoglycaemia. It is possible that the composition of the severe cases sampled by Moulin and others may have confused the association. Age is another confounding factor that was not controlled in the Moulin et al study. We showed that age was associated with both lethality and thrombocytopenia.

Furthermore, the exposure of children to malaria may be not so different between the samples studied by Moulin and others. In large areas of Dakar, the level of transmission was very low, less than one clinical case in 10 years. It is thus likely that a significant proportion of the children from Dakar, and to a less extent from Libreville, had never been infected before by Plasmodium falciparum. Without reliable information about the exact location of their habitat, it is inappropriate to estimate their level of previous exposure to malaria in urban areas where the level of transmission is heterogeneous.

Finally, it must be stressed that in the studies of prognostic factors of lethality, the occurrence of death rather than substitute variables, for example, severe malaria criteria, is the variable of interest. Among children suffering severe falciparum malaria, thrombocytopenia (<100 000/mm3) should be considered as predictive of a fatal outcome, especially in those with cerebral malaria or respiratory distress.3

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References


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Judged by our legacy

Current global health strategies focus on important issues in child health, such as the eradication of polio by 2005 and the drastic reduction of child mortality by the year 2010. These short term goals are essential to provide the necessary political focus and public health impetus. However, the ultimate success of our current health initiatives will be measured by their ability to provide sustained health to present and future generations.

At the beginning of the third millennium we celebrated the tremendous strides that health care has taken in the past century, while rightfully reflecting on current global inequities in access to health care. Reflection also emphasises the unequalled human impact exerted on our planet in the 20th century and the environmental responsibility that faces health care providers in the 21st century.

As paediatricians we need to provide an articulate voice for all the children of our planet, both for current and future generations. Current initiatives stir more emotion and elicit more political commitment, but protecting the health of future generations is as much our ethical responsibility, as the reduction of present mortality. Short term goals are important, but we have to redefine what is meant by the attainment of child health for all, within the framework of sustainability. The real challenge facing our generation is to improve child health for all, now and in the future.

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Response to salbutamol by wheezy infants

We previously reported a randomised controlled trial of β2 agonist in wheezing infants.1 Within this paper we reported no measurable physiological response to 400 µg salbutamol. Pulmonary function tests were performed after the completion of a symptom diary study and prior to enrolment in a study of inhaled corticosteroid.1 Raw values of maximum flow at functional residual capacity (V’\textsubscript{maxFRC}) and bronchodilator response were reported as there were no suitable standard values for V’\textsubscript{maxFRC} available, either from our laboratory or internationally.

Subsequently, collaboration between centres in the UK and USA has produced enough data to allow calculation of standard deviation scores (Z scores) for V’\textsubscript{maxFRC}. We have now reanalysed our data in the light of this new information.

Of 29 subjects, seven had abnormal baseline V’\textsubscript{maxFRC} Z scores (< −2). In comparison with subjects with normal baseline V’\textsubscript{maxFRC} (Z score > −2), these patients showed a significantly greater response to salbutamol (see table 1). Six of seven subjects showed a significant change in V’\textsubscript{maxFRC} (≥12.5% or 2 > x group coefficient of variation) compared to 3/22 in the normal group (see fig 1).

This suggests that patients with identifiable obstruction at the time of testing are more likely to respond to inhaled salbutamol.

The evidence for efficacy of bronchodilators in early life is lacking. Although many intervention studies have been performed, the majority have suboptimal methodology or insensitive outcome measures. Infant pulmonary function studies are usually performed at a time the child is asymptomatic due to concerns of sedating ill patients, reducing the opportunity to measure a response. Due to the protocol design of our study, subjects could only have pulmonary function measured during a two week period2 and thus, although not acutely unwell, we have had a recent exacerbation or upper respiratory tract infection with persisting changes of airway obstruction. This may have allowed us to measure this response, although this was not apparent without the use of an appropriate reference standard.

Post hoc subgroup analysis of this kind should always be interpreted with caution. An alternative explanation for these findings could be regression towards the mean, with those with worst baseline function becoming more “normal”. While this data involves only small numbers and no control group, it does indicate a possible benefit of salbutamol in infants with demonstrable airway obstruction at the time of testing, and invites further studies using appropriate techniques and reference standards.

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The use of insulin pumps improves the metabolic control in children and adolescents with type 1 diabetes

We greatly appreciated the article by Torrance and colleagues’ about the use of insulin pumps and we agree with their conclusion that the benefits of continuous subcutaneous insulin infusion (CSII) outweigh the disadvantages. Our three year experience with CSII at the Juvenile Diabetes Regional Centre of Tuscany has shown that many doctors do not flexibly adjust insulin according to their patient’s needs. Continuous insulin administration enhances the compliance in children and teenagers with type 1 diabetes (T1DM), but it also represents an effective way to improve the metabolic control of our patients.

We studied the entire group of 34 (16 males, 18 females) T1DM patients aged up to 18 years followed at our centre, who in the period from January 2000 to November 2002 started CSII therapy and continued it for at least one year without interruption. At the time of attaching the pump the mean age was 14.4 years (range 9–17.8) and the mean duration of diabetes was 6.2 years (range 0.6–15.8). We found that the mean HbA1C values of the group decreased from 8.35% (SD 1.08) at the beginning of the treatment

<table>
<thead>
<tr>
<th>Table 1 Changes in pulmonary function following salbutamol in infants grouped by baseline V’\textsubscript{maxFRC} Z score</th>
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<tbody>
<tr>
<td><strong>Baseline Z score</strong></td>
</tr>
<tr>
<td>&lt; −2</td>
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<tr>
<td>≥ 2</td>
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<tr>
<td>Mean % change (SD) from baseline V’\textsubscript{maxFRC}</td>
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*p<0.05, *p<0.005

**Figure 1** Percentage change in V’\textsubscript{maxFRC} after 400 µg salbutamol in recurrently wheezy infants grouped by baseline V’\textsubscript{maxFRC} Z score.

**References**

with CSII, to 7.81% (SD 0.95) 12 months later (paired t test; p = 0.002). In addition, the mean daily insulin requirement of the patients dropped by 23.7%, from 58.2 IU (SD 15.3) to 44.4 IU (SD 11) (paired t test; p < 0.001); the mean body mass index did not vary significantly in the period (from 20.7 (SD 2.5) to 21.2 (SD 2.4)). During the period studied no episodes of hypoglycaemia occurred; one episode of ketoadiposis was caused by displacement of the cannula. No episode of local infection occurred. Three patients discontinued the CSII after the first year and one after the second year of treatment.

Our experience shows that use of an insulin pump improves the metabolic control of T1DM in children and adolescents, and reduces the daily insulin requirement.

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Reference

Read the label carefully

The figure shows the packaging of a “rice slice”, which a mother gave to her 23 month child, believing it to be free of any milk. The patient had an anaphylactic reaction shortly after ingesting a very small amount. On close inspection of the ingredients, casein is listed but not qualified as a milk protein.

The child initially presented at 8 weeks of age with a cutaneous reaction to cows’ milk formula on her second exposure, having previously been breast fed. She had raised specific IgE level to milk and a positive skin prick test (3 mm wheal with 6 mm erythema). Thereafter she was managed with an extensively hydrolysed formula and the erythema). Thereafter she was managed with antihistamine but not an adrenaline auto-injector.

The parents of 20 patients (age range 11 months to 13 years) on our regional paediatric oncology ward completed a questionnaire. Parents who had only recently received the diagnosis were excluded. Parents responded to five statements, with “strongly agree, agree, disagree, strongly disagree, or neither”.

(1) I object to having my child’s name and location on the board where everyone else can see it—17 disagreed (11 strongly), with 1 parent agreeing.

(2) I think that having the centrally placed name board helps the people looking after my child to quickly find out where my child is and who is looking after them—18 agreed (13 strongly), with 1 disagreeing.

(3) I think having my child’s name on the board represents a risk to their safety—18 disagreed (11 strongly), with no parents agreeing.

(4) I like to be able to look at the board to see which other patients whom we know are on the ward—18 agreed (13 strongly), with no disagreement.

(5) I would be happy for the name board to be reintroduced—19 agreed (15 strongly) with no disagreement.

Armed with these results, and mindful of various comments made by parents, the boards are back to their original place. On admission, the parents are asked whether they object to their child’s full name being placed on it. This appears to work well, with satisfaction among clinicians, parents, and managers—an unusual state of affairs!

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References

CORRECTION

The authors of the paper entitled Epidemiology of paediatric renal stone disease in the UK (Coward et al., Arch Dis Child 2003;88:962–965) would like to acknowledge the source of their data in Table 1. This table was adapted from data published in the paper by So et al (Pediatr Nephrol 2001;16:133–139).