Infants with urinary tract infection

- renal damage and risk factors

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Abstract

Background Identification of infants with urinary tract infection (UTI) who are at risk of renal scarring is an important clinical challenge with considerable economic consequences. Few issues in pediatric practice today have been so debated as the appropriate investigation of an infant with UTI. The widespread investigation model with ultrasonography (US), voiding cystourethrography (VCU) and renal scintigraphy is extensive and has lately been questioned. Minimising the work-up protocol is an important goal.

Aims The general purpose was to identify risk factors and to reduce the work-up protocol for infants with UTI with maintained clinical safety. Specifically, to assess replacement of VCU by renal scintigraphy and the value of standard US in the primary investigation of infants with UTI, to evaluate risk factors for permanent renal damage including the usefulness of urinary biomarkers in children with UTI.

Methods 290 consecutive infants with first time symptomatic community acquired UTI were included in this population-based 3-year study. US and dimercaptosuccinic acid (DMSA) scintigraphy were performed within a few days from diagnosis and VCU within 2 months. A late DMSA scan one year later was scheduled for patients with abnormal acute scan and for those having a febrile UTI recurrence during the follow-up. Investigations, treatment and management followed the guidelines of the hospital. In addition, analysis of urinary proteins was made in 52 children <2 years with UTI and in 23 controls with elevated serum CRP (s-CRP) >20 mg/L due to an acute non-UTI infection.

Results Vesicoureteral reflux (VUR) was found in 52 infants. DMSA scan was abnormal in 149 children (51%) and the rate of abnormality increased with VUR grade ($p<0.001$). Only 1 of the 27 patients with dilating VUR (grade III-V) had normal DMSA scan. Abnormality on US was associated with presence and severity of abnormality on DMSA scan ($p=0.006$). Renal length was associated with CRP and temperature ($p<0.0001$).
Important structural abnormality including dilating VUR was found in 40 infants and permanent renal damage in 71. 25 children had febrile UTI recurrence. Renal damage was significantly associated with febrile UTI recurrence. S-CRP, serum creatinine, leukocyturia, and anterior-posterior diameter of the renal pelvis (APD) were identified as independent predictors of permanent renal damage.
S-CRP was positively correlated with temperature and all the other urinary proteins. Urinary retinol binding protein (u-RBP) and Clara cell protein (u-CC16) were significantly higher in children with UTI than in control children.

Conclusion Acute DMSA scintigraphy was abnormal in infants with UTI when there was dilating VUR. A normal DMSA scan makes VCU unnecessary in the primary examination of infants with UTI. US detected most infants with structural abnormality with the exception of reflux grade III. More children with structural

abnormality were diagnosed after UTI than after antenatal diagnosis or because of other clinical symptoms. US is therefore essential in the work-up after UTI, especially when there is no systematic third trimester organ screening.
CRP is useful as predictor of permanent kidney damage in infants with UTI and may together with APD on US serve as basis for an imaging algorithm. The low molecular weight proteins u-CC16 and u-RBP showed an association with renal uptake defects visualized in acute DMSA scans. The levels of u-RBP and u-CRP were significantly higher in children with UTI compared to children with fever of non-UTI conditions. A combination of biomarkers may be useful in the clinical assessment of children with UTI.

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Contents

List of publications

This thesis is based on the following articles:

I. **Preda I, Jodal U, Sixt R, Stokland E and Hansson S**
Normal dimercaptosuccinic acid scintigraphy makes voiding cystourethrography unnecessary after urinary tract infection.
*J Pediatr. 2007; **151**: 581-4.*

II. **Preda I, Jodal U, Sixt R, Stokland E and Hansson S**
Value of ultrasonography in work-up of infants with first-time urinary tract infection.
J Urol. 2010 (May), in press.

III. **Preda I, Jodal U, Sixt R, Stokland E and Hansson S**
Imaging strategy in infants with urinary tract infection – a new algorithm.
Manuscript.

IV. **Andersson L, Preda I, Mirjana Hahn-Zoric, Hanson L Å, Jodal U, Sixt R, Barregård L and Hansson S**
Urinary proteins in children with urinary tract infection.
*Pediatr Nephrol. 2009; **24**: 1533-8.*

Abbreviations and acronyms

A1M	alpha 1-microglobulin
APD	anterior-posterior diameter
AUC	area under the curve
CC16	Clara cell protein
CI	confidence interval
CRP	C-reactive protein
DMSA	^{99m}Tc-dimercaptosuccinic acid
LMWP	low-molecular-weight proteins
MAG3	mercapto-acetyltriglycine
RBP	retinol-binding protein
ROC	receiver operating characteristic
SD	standard deviation
SDS	standard deviation score
US	ultrasonography
UTI	urinary tract infection
VCU	voiding cystourethrography
VUR	vesicoureteral reflux

Introduction

The low glomerular filtration rate of the newborn is rapidly changing during the first months of life. Nephrogenesis is complete at birth, but the maturation of the glomerular and tubular function continues during the first two years, through both cellular proliferation and enlargement.[1] After the first 2 years the glomerular filtration rate remains unchanged when normalized for body surface area. The kidneys have been considered particularly vulnerable to damage during the first years of life.

UTIs affect 2% of the infants and are not a homogenous entity but rather a spectrum of conditions from asymptomatic bacteriuria to fulminant sepsis. In infants and small children the symptoms are diffuse (eg irritability, failure to thrive, nausea and vomiting, decreased appetite, diarrhoea) while older children may be able to localize pain. Fever is the main symptom leading to the diagnosis of UTI. Differentiating a lower from an upper UTI in infants is of clinical importance but may be difficult. The kidney inflammation in acute upper UTI (pyelonephritis) with fever and increase of acute phase reactants may result in impaired function and permanent renal damage.

The extent of renal damage required for long-term consequences - hypertension, proteinuria and impaired renal function – is not well known and their frequency in patients with pyelonephritic scarring is uncertain.[2-7] Population based long-term studies into adulthood have shown a low rate of complications associated with renal damage in comparison with earlier calculations based on selected series from tertiary centers. Thus, in young adults with renal scarring followed for 2 decades, hypertension was seen in only 3 of 54 (6%) born in the 1950s and 60s, and in 5 of 53 (9%) from the 70s.[4,8]

Risk factors for scarring are obstructive malformation, VUR, number of pyelonephritic attacks, and delay of treatment of acute infections. [9-13]

VUR is the backward leakage of urine from the bladder to the ureter and is considered an abnormal phenomenon in humans, although normal in several animal species. It is usually prevented by a valve-like mechanism in the vesico-ureteral junction. VUR is more common in infants with a prevalence in normal children of 0.4 – 1.8%, and about equal frequency in boys and girls. VUR has a high rate of spontaneous resolution during childhood by “maturation” of the valve mechanism. VUR is graded on a five-grade scale - from I with reflux only to the ureter, to V with gross dilatation of the renal pelvis and papillary impressions not any longer visible in the majority of the calyces (figure 1). VUR may enhance the bacterial ascendance from the bladder to the kidney increasing the risk of renal infection. There is also an association between bladder dysfunction, UTI, VUR and renal damage.[14]

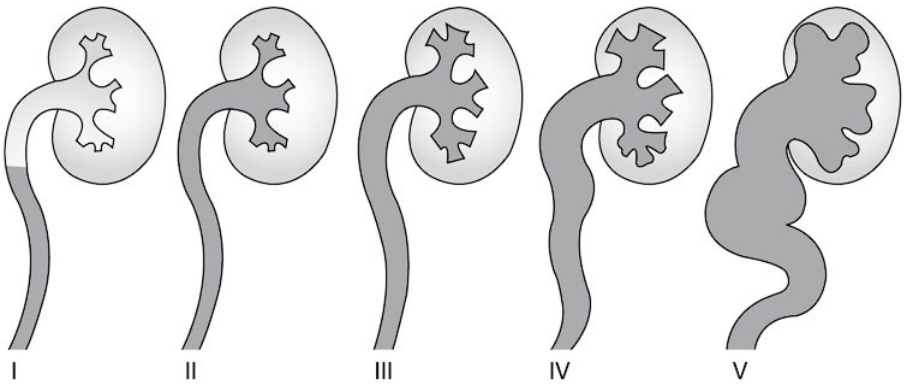

Figure 1. International grading of VUR.

Much attention has been paid to reflux nephropathy which alludes to the association of VUR and renal damage.[9] This term has covered the end-result of different pathophysiological processes. It has been speculated that irreversible renal damage is associated with the reflux of sterile fetal urine or an embryological defect and also with the reflux of infected urine (postnatally acquired). Hodson and Edwards described patients with VUR and renal damage with or without associated UTI.[15] This for many years motivated the search for VUR and the associated renal scarring by VCU and urography, respectively. The latter was for long time the standard method for the detection of renal scarring but it could take up to two years for the scars to be visible on urography. The DMSA scintigraphy was introduced in the 1980s and is clearly superior to urography due to its high sensitivity for the detection of both acute and late renal damage.[16]

Few issues in pediatric practice today have been so debated as the appropriate investigation of an infant with UTI. The widespread investigation model with US, VCU and renal scintigraphy is extensive[17,18] and has lately been questioned. The concept with focus on identification of VUR as a major risk factor has been challenged since more than half of the children with UTI associated renal damage do not have VUR.[19,20] However, the rate of renal damage is related to the grade of VUR, and VUR with dilatation (grade III to V) is a significant risk factor.[21]

The standard method for detecting acute pyelonephritis and renal scarring is static scintigraphy with DMSA.[22] The uptake of DMSA will be reduced in acutely inflamed or scarred kidney areas. Renal damage, congenital or acquired, is characterised by fibrosis giving various degrees of irregular outline of the kidney, distortion of the local anatomy and a focal reduction of kidney function.

US is noninvasive and has good ability to visualise the upper urinary tract, to detect anatomic abnormalities and dilatation but does not provide information about the renal function.

Fetal organ screening by US is common in many countries while most centers in Sweden perform a single examination at the 18th week of pregnancy. An early fetal US does not allow the identification of the same number of abnormalities as when

a 3rd trimester US is added. When late pregnancy US is performed, most major anomalies will be picked up and the value of a repeat investigation in children with UTI has been questioned.[23-25]

VCU is the standard method for diagnosis of VUR. VCU requires that contrast medium is instilled into the bladder through a catheter in the urethra, which is invasive and painful. It gives anatomical and functional information about the bladder and urethra and allows grading of VUR.[26]

The clinical challenge in the differentiation between UTI with and without renal involvement has fuelled the quest for sensitive and specific test for early diagnosis of acute pyelonephritis and determination of the severity of renal parenchymal involvement. CRP is formed mainly in the liver by the hepatocytes, but recent studies have shown that it is also produced at other sites, such as cardiovascular locations, adipose tissue and the kidney. The concentration of serum CRP (s-CRP) during an inflammatory process increases exponentially. The elimination rate of CRP is constant, and since the local production at other sites is low, the concentration of s-CRP is regulated by liver synthesis. The CRP molecule is too large to be excreted by glomerular filtration. Therefore an increased urinary excretion of CRP is the result of local production and secretion of this protein from kidney tissue rather than from glomerular filtration.

LMWPs are becoming increasingly studied, especially in environmental medicine, because the method is non-invasive and may provide early detection of kidney problems.

Some investigations have monitored proteinuria in UTI patients but most of these have used non-specific reagent strips or measured microalbuminuria. Few have investigated LMWPs with specific immunoassays. Increased excretion of LMWPs has been found in children with glomerular disease and abnormal acute DMSA scintigraphy in children with UTI were shown to relate to the urinary excretion of A1M.[27]

CC16 is produced by the nonciliated, nonmucous secretory Clara cells of the pulmonary airways but also by similar epithelial urogenital cells and was previously called "human urinary protein 1".[28] RBP is freely filtered in the glomerulus and almost completely reabsorbed and catabolised by the proximal tubular cells. An increased urinary excretion of RBP indicates a proximal tubular dysfunction.

The contentious background described above and the urge to reduce the number of investigations raised the aims of this study with focus on renal damage and risk factors.

Aims of the study

The general purpose of this work was to identify risk factors and to reduce the work-up protocol for infants with UTI with maintained clinical safety.

The specific aims were:

a. To assess the replacement of VCU by renal scintigraphy in the primary investigation of infants with UTI

b. To assess the value of standard US examination in infants with UTI

c. To evaluate risk factors for permanent renal damage in infants with UTI

d. To assess the usefulness of urinary biomarkers in children with UTI

Patients and Methods

Definitions

UTI diagnosis required significant bacteriuria defined as any growth of bacteria in urine from a suprapubic bladder aspiration or ≥100,000 per mL colony-forming units of a single strain in urine from two midstream or bag samples. Febrile UTI was defined by rectal temperature of at least 38.5°C.

Inclusion and exclusion criteria

Paper I, II and III

All infants <1 year of age with UTI at our hospital were prospectively recorded during a 3-year period (June 2002 to June 2005). Infants living within the primary catchment area of the hospital and diagnosed with a first symptomatic community acquired UTI at the Emergency Room were eligible for the study. Children with known urogenital or anorectal malformation or neurologic disease were excluded.

Paper IV

Children eligible for the study were <2 years of age with febrile UTI, who attended the hospital emergency room when the study team was available and fulfilling the same inclusion and exclusion criteria as above. Controls were children with elevated s-CRP >20 mg/L due to an acute infection in an organ other than the urinary tract (i.e. negative urine culture). Children who had a chronic inflammation or disease were excluded.

Ethical approval

The study was approved by the Research Ethics Committee of University of Gothenburg (Ö118-02).

Investigation and further management

Investigations, treatment and further management followed the hospital guidelines. The highest values of the measured rectal temperature, s-CRP, serum creatinine and leukocyturia were used in the analysis. Infants with symptomatic UTI were treated 10 days with co-trimoxazole or a cephalosporin. The parents were informed about UTI signs and encouraged to visit the emergency room or other outpatient clinic in case of fever or other symptoms compatible with UTI. At the end of the study the parents were questioned specifically about recurrences, and the files and microbiology reports of all children included in the study were searched for new episodes of UTI.

Imaging

The imaging protocol included US of the urinary tract and DMSA scintigraphy as acute investigations and VCU within 2 months after the diagnosis. Additional examinations, such as intravenous urography, dynamic renal scintigraphy, or computerized tomography were performed on an individual basis according to findings at the primary investigation.

US was carried out as a standard clinical procedure and included transverse and longitudinal images of both kidneys. US was considered abnormal when the AP diameter was >7 mm, when there was dilatation of calyces or ureters irrespective of AP diameter, when renal length was >2SDS or <-2 SDS, when one kidney was >15% longer than the other, when signs consistent with duplication were found and when there was increased renal echogenicity. Renal length measurements were transferred into SDS using the reference material by Vujic et al.[29] The US was performed at a median of 1 day (0-20 days) after the diagnosis of UTI, and 96% of the patients were investigated within 1 week.

The VCUs were performed according to standard procedures of the pediatric radiology department. VUR was graded I to V according to the recommendation of the International Reflux Study in Children.[26]

The DMSA scan was performed in accordance with the guidelines of the Pediatric Committee of the European Association of Nuclear Medicine.[30] Static renal scintigraphy was performed 3 to 4 hours after injection of DMSA in a dose of 1 MBq/kg body weight (minimum, 15 MBq). Images were obtained in 1 posterior and 2 oblique projections, with 300,000 counts in the posterior view. A focal reduction or absence of uptake in one or more areas in the kidney was considered abnormal. A kidney with relative function <45% was also classified as abnormal. The extent of kidney damage was graded arbitrarily on the DMSA scan (class 1: abnormal uptake with relative function >45%, class 2: relative function 40-44% irrespective of uptake, class 3: relative function <40% irrespective of uptake). In case of bilateral involvement the kidneys were individually classified according to extent of damage. In the analysis the kidney with the more pronounced involvement was used to characterize the patient.

DMSA scan was performed a median of 5 days after admission (range 0-22 days), 74% within 1 week and 97% within 2 weeks. Patients in whom DMSA scan was delayed ≥30 days were not included in the analysis.

A late DMSA scan about one year after inclusion was scheduled for patients with abnormal acute DMSA scan and for those having a febrile UTI recurrence during the follow-up. The children were followed until the late scintigraphy was performed, i.e. for at least one year.

MAG3 renography was chosen to follow patients with markedly dilated renal pelvis. MAG3 renography was performed in accordance with the guidelines of the Pediatric Committee of the European Association of Nuclear Medicine.[31]

All scintigraphies were evaluated by an experienced specialist in pediatric nuclear medicine and all US and VCUs were reevaluated by an experienced specialist in pediatric radiology without knowledge of other data.

Paper IV
The investigation program was the same as above. In addition, a spot sample for analysis of urinary proteins was obtained within 3 days of diagnosis. CRP, A1M, RBP and CC16 were measured in urine by commercial high-sensitivity enzyme-linked immunosorbent assays (ELISAs) using polyclonal rabbit antibodies against human proteins coated onto the wells of the micro-titre plates. The excretion of each urinary protein was expressed as the ratio between the concentration of the respective protein and the urinary creatinine.

Statistical methods

Statistical significance was reached with a p-value <0.05.

Paper I
For comparisons between dichotomous values, the Fisher exact test was used, and for ordered values, the Mantel–Haenszel χ^2 test was used. The capacity of DMSA scintigraphy to detect children with VUR ≥III was determined by calculating sensitivity, specificity, negative and positive predictive values, and likelihood ratios with 95% CIs. Likelihood ratio positive was defined as Sensitivity/(1-Specificity), and likelihood ratio negative was defined as (1-Sensitivity)/Specificity.

Paper II
For comparisons between ordered values the Mantel–Haenszel χ^2 test was used and for nonparametric correlation analyses the Spearman's rank correlation coefficient.

Paper III
For comparisons between two groups regarding dichotomous variables, the Fisher's exact test was used, and for ordered categorical variables, the Mantel–Haenszel χ^2 test. The association of DMSA scan results with continuous variables was assessed using Spearman's rank correlation test and with ordered categorical variables with the Mantel–Haenszel χ^2 test. In order to select independent predictors for kidney damage, variables with a p-value <0.05 were entered into a stepwise multiple logistic regression model. The accuracy of the selected model from the logistic procedure was evaluated with the area under the ROC curve. All tests were two-tailed.

Paper IV
Since the distribution of urinary proteins were not normal, group comparisons were performed using the non-parametric Kurskal-Wallis test and correlations between variables using Spearman´s rank correlation coefficient. Stepwise logistic regression (using the cumulative logit model) was used for multivariate purposes.

Patient groups

Paper I, II and III

The Children's hospital has a primary uptake population of 0.7 million residents. Almost all infants with UTI are diagnosed at the hospital.[32] During the 3-year period 324 infants with UTI were eligible and consecutively recorded. 34 did not fulfil the imaging protocol (Table I). 290 fulfilled the complete study protocol, 161 boys with median age 2.7 months, and 129 girls with median age 7.4 months (figure 2). No boy was circumcised.

Table I. Description of infants with incomplete imaging investigation.

Eligible children	**324**
VCU not performed	11[a]
• parent decision	7
• protocol violation	3
• catheter failure	1
DMSA scan not performed within 30 days	23
• performed later	20[b]
• MAG3 scan instead	3[c]
Total	**290**

[a] DMSA scan performed in 10, all with normal findings
[b] VCU performed in all, VUR grade IV and grade I in one infant each
[c] all 3 with uptake defects

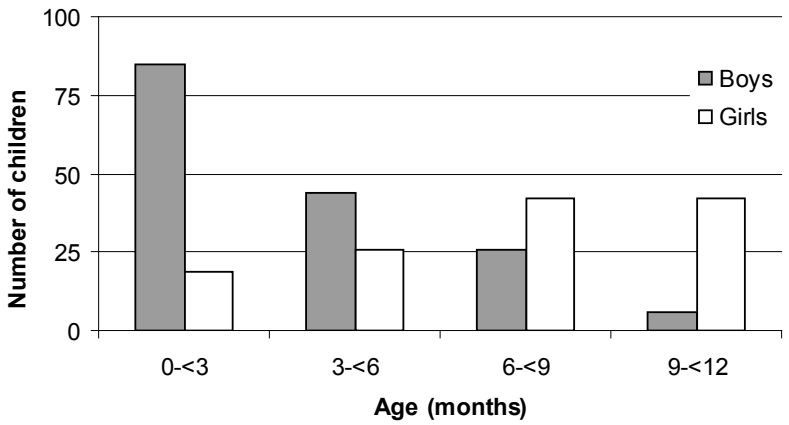

Figure 2. Age distribution of 161 boys and 129 girls with first known UTI.

The median temperature was 39.3°C (range, 36.5- 41.1°C); ≥38.5°C was seen in 229 infants (79%). The median CRP level was 72 mg/L (range, 0-360 mg/L); 231 infants (80%) had CRP levels ≥20 mg/L. The bacteriuria was caused by *Escherichia coli* in 265 cases (91%), *Klebsiella/Enterobacter* in 11 cases, Enterococci in 4, Proteus in 3, and 1 case each of coagulase negative staphylococci, *Staphylococcus aureus*, *Citrobacter*, *Haemophilus parainfluensae*, *Serratia*, *Pseudomonas,* and beta-hemolytic streptococci.

Paper IV

The patient group comprised 52 children <2 years of age with first-time UTI, 26 boys (median age 0.2 years, range 12 days – 1.0 year) and 26 girls (median age 0.9 years, range 1.5 months – 1.9 years). Fever of ≥38.5°C was recorded in 44 (85%) children. Non-febrile children had other symptoms (failure to thrive, poor weight gain, irritability or vomiting), and were generally <3 months of age. The bacteriuria was caused by *Escherichia coli* in 47 (90%) cases, *Klebsiella* in three, coagulase-negative staphylococci (one) and *Proteus* (one).

Controls were 23 children (11 boys) slightly older than the UTI patients, with a median age of 1.8 years, range 0.2–2.8 years. They had an acute infection in another organ than the urinary tract: five had X-ray-verified pneumonia, ten upper respiratory tract infection, three otitis and five other infections. The control children were collected at two different occasions since 13 control children were added 3 years later to enlarge this group.

Methodological considerations

DMSA and MAG3 scintigraphy

DMSA scan was the method of choice but MAG3 renography was performed to follow patients with markedly dilated renal pelvis when obstruction or poor drainage could be expected. The renal side distribution, expressed as split function in per cent of the total activity, is obtained in both scintigraphic methods but the MAG3 dynamic tracer gives less sensitivity for renal parenchymal abnormality than the static DMSA tracer. DMSA is taken up by the tubular cells directly from the tubular vessels and particularly reveals cortical abnormality. In a kidney with severe hydronephrosis the static tracer may accumulate in the renal cavities and the reading of the cortical images becomes more difficult which might generate a falsely high differential function.[30]

Although objections might be raised against the use of two scintigraphic methods, it reflects the clinical reality and comparative studies of MAG3 and DMSA scintigraphies in children showed that inflammatory lesions in acute pyelonephritis and during recovery are reliably semiquantitatively and qualitatively identified by MAG3.[33,34]

Patients with uptake defects at an acute DMSA are mostly regarded as having an inflammatory process of the renal parenchyma, i.e. acute pyelonephritis. An alternative situation is that the uptake defects depict areas of fibrous tissue that were either

antenatally acquired or caused by a previous renal infection (scarring). There may have been some patients with this type of renal damage in the study group, but the low age and the lack of previous history of UTI make it unlikely that the proportion of patients with previous infection was large. Whatever the uptake defects represent, they depict areas of decreased renal function which may be clinically important to detect.

Laboratory sampling

The inclusion of the control patients (paper IV) in our study would have been ideally made in one and not two different periods with a 3 years interval, as the storage of the frozen urine samples before analysis was of different length. The results given by the analysis of samples from the controls may be influenced by this different length of prolonged storage. According to the literature, the concentrations of LMWPs (such as RBP, CC16 and A1M) in urine tend to decrease with long-term storage without preservatives.[35-38] However, unpublished data (Lena Andersson et al) have shown CC16 to be stable even after 3 years of storage. It may be assumed that the protein concentrations have decreased somewhat after 3 years of storage.

Results

Paper I

Renal status, bacterial type and VUR

Fifty-two of the 290 infants had VUR, 27 with dilatation (grade III-V). VUR grade according to sex is shown in table II.

Abnormal acute DMSA scan was seen in 149 children (51%), 77 of 161 boys (48%) and 72 of 129 girls (56%). The rate of abnormality increased with VUR grade ($p < 0.001$; table III). Only 1 of the 27 patients with dilating VUR had normal DMSA scan results. This was a boy who at the age of 2 weeks had failure to thrive, no fever, CRP 12 mg/L, and growth of *E coli* in suprapubic aspirate. US and DMSA scan (Figure 3) were normal. On VCU, there was unilateral VUR with moderate calyceal dilatation (grade III). During follow-up, there was 1 febrile UTI recurrence, but a repeat DMSA scan 2 years later was normal.

Table II. VUR grade according to sex in 290 infants with UTI.

	No of boys	**No of girls**	**Total**
	n=161	**n=129**	
No VUR	136 (84%)	102 (79%)	238
VUR	25 (16%)	27 (21%)	52
grade I	4	4	8
II	7	10	17
III	5	8	13
IV	5	5	10
V	4	0	4

Table III. VUR grading according to renal status at DMSA scan.

	Normal scan	**Abnormal scan**
	n=141	**n=149**
No VUR	133	105
I to II	7	18
III to V	1	26

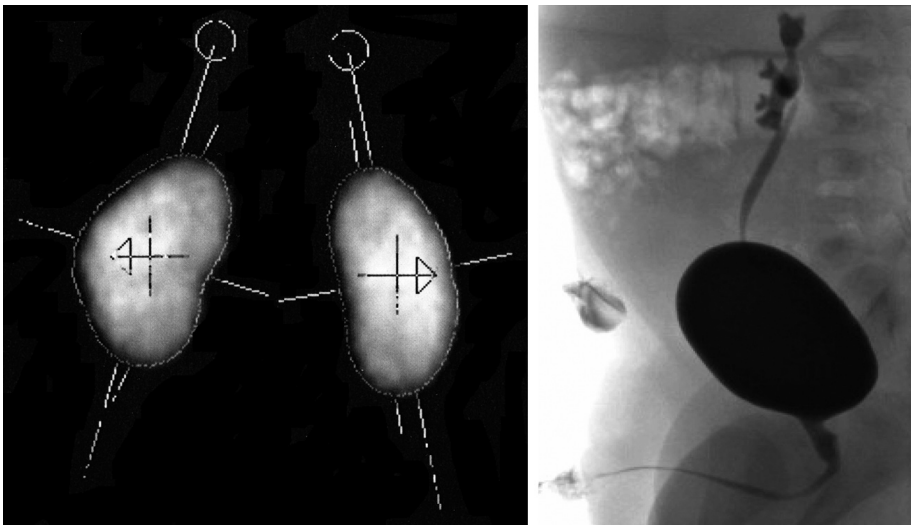

Figure 3. The only patient with dilating VUR and normal acute DMSA. **Left***, DMSA scan posterior view.* **Right***,VCU with dilating VUR, grade III.*

The ability of acute DMSA scan to identify children with VUR ≥III had a sensitivity of 96% (95% CI 81-100), specificity 53% (95% CI, 47-59), positive predictive value of 17% (95% CI 12-25), negative predictive value of 99% (95% CI 96-100), positive likelihood ratio 2.06 (95% CI 1.77 – 2.39), negative likelihood ratio 0.07 (95% CI 0.01 – 0.48).

Non-*E coli* UTI was found in 14 of 238 children without VUR (6%), in 3 of 25 children with grade I to II VUR (12%), and in 8 of 27 children with grade III to V VUR (30%). This increasing frequency according to VUR grade was significant in both boys and girls (p<0.01 and <0.001, respectively).

Paper II

Abnormal US findings

The results of US are shown in table IV. Abnormal US examination was seen in 120 (41%) of the 290 children. AP diameter >7 mm occurred in 27 (9%) infants and calyceal or ureteral dilatation with AP <8 mm in a further 17 (6%). Renal length measurements of both kidneys were available in 288 patients (one with missing films and one with solitary kidney). The median length of the longer kidney in each patient was 1.3 SDS (-2.4 to 7.1) and of the shorter kidney 0.7 SD (-4.1 to 4.6); 82 patients had renal length >2 SDS (bilateral in 39) and 6 patients <-2 SDS (bilateral in 3). In 33 children one kidney was >15% longer than the other (11 additional cases). Increased echogenicity was found in 6 patients of whom 2 had this as the only abnormality. Duplication was suspected in 10 patients (1 additional case). There was also one infant with a pelvic kidney and one with a solitary kidney. Thus these 120 patients had altogether 183 abnormal findings on US.

Table IV. Findings at acute US in 290 infants with UTI.

Normal	170
AP diameter >7 mm	27
Calyceal or ureteral dilatation	17
Renal length >2 SDS	82
Renal length <-2 SDS	6
Renal size difference	33
Increased echogenicity	6
Duplication	10
Pelvic kidney	1
Solitary kidney	1
Total number of abnormalities	**183**

US findings and VUR

The relation between US findings and VUR is shown in table V. Abnormal US was significantly correlated to the presence and severity of VUR (p=0.0022). Of 27 patients with dilating VUR (grades III to V) 17 had abnormal US. Grade IV-V VUR was seen in 14 patients of whom 12 had abnormal US findings (dilatation in 9, renal length >2 SDS in 1, renal length difference >15% in 1 and duplication in 1). Only 5 of 13 children with VUR grade III were identified (dilatation in 2, renal length >2 SDS in 2, and renal length difference >15% in 1).

Table V. Findings on US versus VUR grade in 290 infants with symptomatic UTI, 52 with VUR.

		Grade of VUR				
US	**No VUR**	**I**	**II**	**III**	**IV**	**V**
Normal (n=170)	147	5	8	8	2	0
Abnormal (n=120)	91	3	9	5	8	4
Total	**238**	**8**	**17**	**13**	**10**	**4**

US findings and abnormal acute DMSA scan

There was a significant relation between abnormality on US and presence and severity of abnormality on DMSA scan (p=0.006; table VI). Of the children with class 3 defects 63% had abnormal US; the corresponding figure for class 2 defects was 54% and for class 1 defects 38%. The sensitivity and specificity of US to detect DMSA abnormalities was 48% (95% CI, 40-57) and 66% (95% CI, 57-74), respectively. Positive and negative predictive values were 60% (95% CI, 51-69) and 55% (95% CI, 47-62), respectively. By excluding discrete changes on the DMSA scan (class 1) the sensitivity of ultrasound to detect DMSA scan abnormality increased from 48% to 58%.

Table VI. Findings on renal US versus grade of abnormality on the DMSA scan in 290 infants with symptomatic UTI.

	Grade of abnormality on scintigraphy			
		DMSA class		
US	No abnormality	1	2	3
Normal (n=170)	93	43	22	12
Abnormal (n=120)	48	26	26	20

Renal length in relation to temperature, CRP and DMSA scan abnormality

There was a significant relation between the length of the longer kidney in each patient (expressed as SDS) and inflammatory parameters such as temperature ($p<0.0001$) and CRP ($p<0.0001$; table VII). The renal length was also related to the presence of acute DMSA scan abnormality ($p<0.0001$).

Table VII. Temperature, CRP and frequency of abnormal DMSA scan according to length of the longer kidney (SDS) at US of 288 children with first UTI.*

	Renal length				P value
	<0 SDS	0-<1 SDS	1-≤2 SDS	>2 SDS	
	(n=37)	(n=80)	(n=89)	(n=82)	
Temperature (°C)	38.5	39.0	39.4	39.5	<0.0001
CRP (mg/L)	38	75	91	115	<0.0001
Abnormal DMSA scan (%)	22	43	57	67	<0.0001

* missing information in 2 patients

Important structural abnormality

Using US, DMSA scan and VCU, and when needed further imaging investigations such as urography, dynamic renal scintigraphy or computerized tomography, a total of 40 infants, 21 boys and 19 girls, with important structural abnormality including VUR grades III-V were found. Table VIII illustrates the ability of US, VCU and DMSA scan, respectively, to identify these infants. DMSA scan was abnormal in all but 3 cases.

Table VIII. Abnormal findings at US, VCU and DMSA scan in 40 infants with first UTI and important structural abnormality including dilating VUR (grade III to V).

	US abnormal	VCU abnormal	DMSA scan abnormal
Pelvi-ureteral junction stenosis (n=4)	4	0	4
Distal ureteral stenosis (n=5)	5	1*	4
Ureterocele (n=2)	2	0	1
Pelvic kidney (n=1)	1	0	1
Renal aplasia (n=1)	1	0	1
VUR grades III to V (n=27)	17	27	26
Total	**30**	**28**	**37**

*Dilated distal ureter and VUR grade I

Mode of detection of important structural abnormality

During the 3-year study period 28 infants from the area were diagnosed with important structural abnormality outside the UTI study; 15 were diagnosed from antenatal dilatation on US and 13 postnatally (table IX). The latter were investigated for various reasons: UTI diagnosed at the hospital but inclusion criteria not fulfilled (4), UTI diagnosed outside the hospital (3), abdominal mass (3), poor urine stream (1), abdominal US screening because of irritability (1) and severe prematurity (1). Surgery was performed in 7 of the patients with antenatally known conditions and in 7 of the others.

Table IX. Infants with important structural abnormality in the urinary tract living in the primary uptake area of the hospital according to mode of detection.

	Outside UTI study		In UTI study	Total
	Antenatal	Postnatal		
	n=15	n=13	n= 40	**n=68**
Pelvi-ureteral junction stenosis	8	5	4	**17**
Distal ureteral stenosis	0	2	5	**7**
Ureterocele	2	1	2	**5**
Posterior urethral valves	2	3	0	**5**
Pelvic kidney	0	0	1	**1**
Multicystic kidney	2	1	0	**3**
Renal aplasia	0	0	1	**1**
VUR grades III to V	1	1	27	**29**

Paper III

A late DMSA scan was performed in 130 children at a median of 1.1 years after the UTI. There were 126 patients with normal acute scintigraphy and no recurrence who therefore did not require a late scan. In 13 children MAG3 renography was done at follow-up instead of DMSA scan because of marked dilatation of the upper urinary tract. These MAG3 scans all showed renal uptake defects. In the remaining 21 children the protocol was violated and a late DMSA was not performed; in 17 because of doctors's decision (in 14 without UTI recurrence and minimal changes on the acute scan, and in 3 with UTI recurrence and normal acute scan), and in 4 with abnormal acute DMSA scan (in 2 cases the families moved abroad and in 2 the parents did not allow a repeat investigation). Thus, 269 of 290 patients (93%) had endpoint data, 71 with and 198 without kidney damage.

For continuous variables, body temperature was mean 39.5°C (SD 0.8) in patients with and 39.0°C (SD 1.0) without kidney damage, CRP 134 mg/L (SD 70) and 69 mg/L (SD 68), and serum creatinine 27 µmol/L (SD 10) and 22 µmol/L (SD 7), respectively. For ordered variables, table X shows clinical data at inclusion compared with the results of the late scan. CRP ($p<0.0001$), serum creatinine ($p<0.0001$), body temperature ($p=0.0002$), leukocyturia ($p<0.0012$), type of bacteria ($p=0.0002$), and APD <10/≥10 mm ($p<0.0001$) were all significantly associated with permanent renal damage.

Table X. Ordered clinical data according to permanent renal damage (n=71) at the last isotope scan (endpoint result).

			n (%)	p-value
Sex	boys	(n=148)	37 (25%)	
	girls	(n=121)	34 (28%)	0.5669
Leukocyturia	0	(n=25)	4 (16%)	
	1	(n=22)	2 (9%)	
	2	(n=56)	12 (21%)	
	3	(n=56)	11 (20%)	
	4	(n=108)	41 (38%)	0.0012
Bacteria	E. coli	(n=245)	57 (23%)	
	Non-E. coli	(n=24)	14 (58%)	0.0002
APD	<10 mm	(n=250)	55 (22%)	
	≥10 mm	(n=19)	16 (84%)	<0.0001
VUR	0	(n=218)	40 (18%)	
	I-II	(n=24)	8 (33%)	
	III-V	(n=27)	23 (83%)	<0.0001
Febrile recurrences	no	(n=249)	60 (24%)	
	yes	(n=20)	11 (55%)	0.0026

During follow-up there were 25 children (14 boys) with febrile UTI recurrence. Four infants had more than one recurrence (2 boys). Kidney damage was associated with febrile UTI recurrence (p=0.0026).
In a stepwise multiple logistic regression model CRP (p<0.0001), serum creatinine (p=0.0078), leukocyturia (p=0.0101) and APD <10/≥10 mm (p=0.0001) were identified as independent predictors of permanent renal damage (table XI). When the effect of CRP alone was included in a model, the area under the ROC curve was 0.77, with CRP and APD (<10/≥10 mm) it was 0.81, and with all 4 variables the AUC was 0.84 (figure 4).

Table XI. Bivariate and multiple logistic regression analysis with odds ratio, AUC, adjusted odds ratio and adjusted p-values.

	Bivariate analysis		**Multiple logistic regression analysis**	
	Odds ratio (95% CI)	AUC* (95% CI)	Adjusted odds ratio (95% CI)	Adjusted p-value
CRP (in intervals of 50 mg/L)	1.84 (1.50-2.26)	0.77 (0.70-0.89)	1.90 (1.51-2.40)	p<0.0001
AP dilatation	18.90 (5.32-67.23)	0.60 (0.55-0.65)	15.54 (3.77-64.03)	p=0.0001
Serum creatinine	1.07 (1.03-1.11)	0.67 (0.59-0.74)	1.06 (1.01-1.10)	p=0.0078
Leukocyturia	1.48 (1.16-1.89)	0.63 (0.57-0.71)	1.47 (1.10-1.98)	p=0.0101

* for the multiple model with all 4 variables included the area under the ROC curve was 0.84 (0.78-0.89)

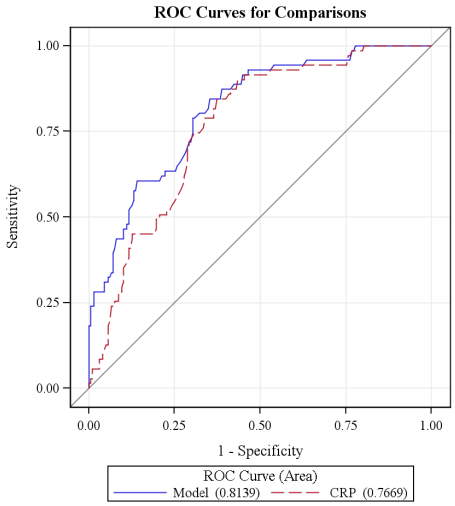

Figure 4. ROC curves for prediction of permanent renal damage with CRP only and CRP and APD (model) using logistic regression.

To construct a practical decision rule for imaging, different CRP levels in combination with APD were evaluated. Sensitivity and specificity values for kidney damage for CRP above selected cut-points or APD ≥10 mm were calculated from the ROC curves as shown in table XII. To simplify the decision rule and to construct an algorithm for investigation of infants with UTI we chose CRP ≥70 mg/L or APD ≥ 10 mm as threshold for further imaging. According to this algorithm, infants with CRP <70 mg/L and APD <10 mm do not need further investigation with either DMSA scan or VCU. In infants with CRP ≥70 mg/L or APD ≥10 mm, acute DMSA scan is recommended and in case of abnormality a VCU is added. In this patient material, such an algorithm would have spared 173 VCU's and 137 acute DMSA scans. Of the 137 infants who would not be investigated with DMSA scan according to the algorithm, only 7% had permanent renal damage compared to 43% of the 157 investigated children.

Table XII. Different cut-off levels of CRP in combination with AP dilatation ≥10 mm.

CRP (mg/L) or AP ≥10 mm	Sensitivity (95% CI)	Specificity % (95% CI)
60	89% (78-95)	57% (49-64)
70	87% (77-94)	59% (51-65)
80	85% (74-92)	62% (55-69)
90	80% (69-88)	68% (61-74)

Paper IV

US examination of kidneys and bladder was performed within 1–2 days and showed dilatation of the urinary tract compatible with distal ureteral stenosis in 5 cases, and pelvo-ureteral stenosis in one. VCU was performed within 1–2 months in 48 patients and showed VUR in 7, 4 of whom had dilatation.
Acute DMSA scan showed abnormal uptake in 36 patients (69%). The urinary excretion of LMWPs in the control children and in children with UTI, stratified by DMSA class, is shown in Table XIII and Figure 5.

Table XIII. Highest recorded temperature, s-CRP, u-CRP, u-A1M, u-RBP, U-CC16 in children with acute UTI and in control children with febrile non-UTI infections.

	Controls n=23 median range	**DMSA 0** n=16 median range	**DMSA 1** n=12 median range	**DMSA 2** n=15 median range	**DMSA 3** n=9 median range
[a)]Temperature (°C)	40.0 38.6–41.0	39.2 37.0–40.3	40.0 37.0–40.4	40.0 39.0–41.0	39.3 38.2–41.0
[b)]s-CRP (mg/L)	96 21–243	42 <LoD–142	110 <LoD–247	130 64–300	169 92–224
u-CRP (µg/g creatinine)	27 <LoD–177	42 <LoD–5916	308 3–8000	88 7–5407	511 55–3114
u-A1M (mg/g creatinine)	4.9 0.6–35	3.1 1.1–23	2.6 0.4–18	6.6 2.0–51	10.5 <LoD–108
[c)]u-RBP (µg/g creatinine)	110 <LoD–2935	141 <LoD–1975	289 10–1981	386 <LoD–7620	2502 172–7792
[d)]u-CC16 (µg/g creatinine)	6.3 <LoD–303	5.7 <LoD–177	97 <LoD–384	105 1–476	488 91–904

a) p=0.04 for association between DMSA class and temperature (Kruskal Wallis test)
b) p=0.0003 for association between DMSA class and s-CRP (Kruskal Wallis test)
c) p=0.002 for association between DMSA class and u-RBP (Kruskal Wallis test)
p<0.0001 for association between DMSA class and u-CC16 (Kruskal Wallis test)

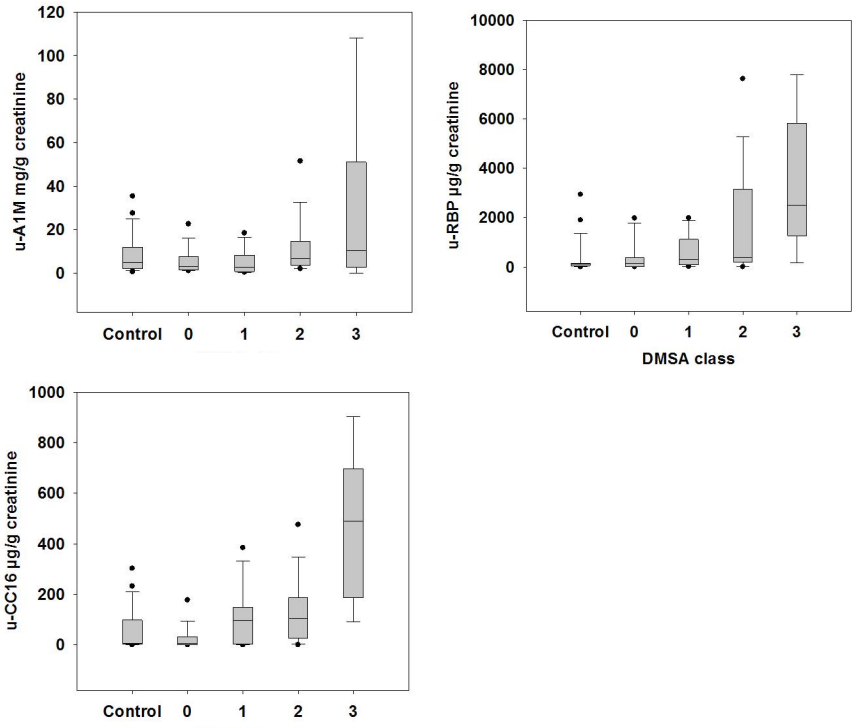

Figure 5. Levels of u-A1M , u-RBP, u-CC16 in patients with UTI categorized into DMSA scintigraphy classes 0-3 and in controls. Median values and 10, 25, 75 and 90 percentiles are given.

In UTI patients the acute phase protein s-CRP was positively correlated with temperature and all the other proteins (u-CRP, u-A1M, u-RBP and u-CC16). Urinary CRP and u-CC16 were positively correlated with all other proteins but not with temperature. Urinary A1M and u-RBP were not significantly associated with temperature, but with each other. U-CRP was higher in children with UTI compared with control children ($p<0.001$, Figure 6) but it was not associated with DMSA class ($p=0.23$).

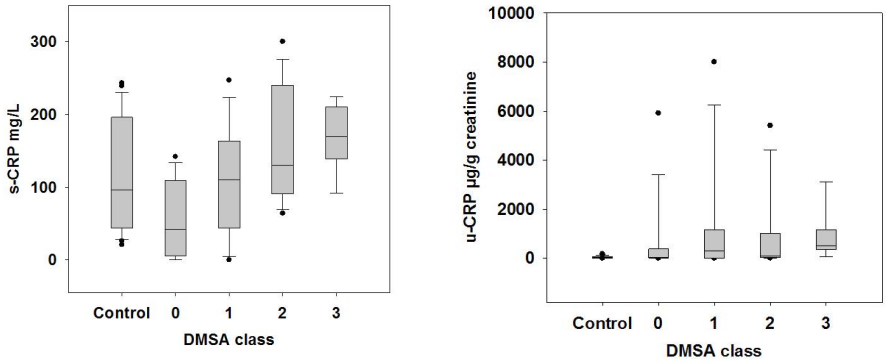

Figure 6. Levels of s-CRP and u-CRP in patients with UTI categorized into DMSA scintigraphy classes 0-3 and in controls. Median values and 10, 25, 75 and 90 percentiles are given.

Urinary RBP and u-CC16 were significantly higher in children with UTI than in control children (p=0.005 and p=0.04, respectively). Furthermore, children without scintigraphic signs of renal involvement (DMSA class 0) had lower urinary protein excretion than those with such signs (DMSA class 1–3) in terms of u-CC16 ($p<0.001$), u-RBP (p=0.008) but not for u-A1M (p=0.25). There was also a correlation between DMSA class and s-CRP ($p<0.001$).

U-CC16, u-RBP and s-CRP and temperature were included in a stepwise logistic regression model and u-CC16 and s-CRP were found to be independent predictors of the degree of renal involvement according to DMSA scintigraphy ($p<0.001$ and $p<0.016$, respectively).

General discussion

This population-based 3-year prospective study consecutively included infants with symptomatic community acquired UTI. They constitute a representative group of infants with UTI in our area. Of 324 included patients, 290 (90%) fulfilled the acute investigation protocol and 269 fulfilled the entire protocol. As in earlier population-based studies, the boys were significantly younger than the girls.

Identification of infants with UTI who are at risk of renal scarring is an important clinical challenge with considerable economic consequences. Permanent kidney damage shown by a late DMSA scintigraphy was chosen as the endpoint for the analysis in paper III. There are few studies that have used late DMSA scan findings to test the ability of clinical variables to predict renal damage.[16,39-42] A limitation of these studies is the relatively small number of patients while our study population is larger.

The frequency of VUR, 16% in boys and 21% in girls, is lower than in most other publications, but similar to the figures in the material from our hospital in the 1990s (16% in boys and 25% in girls).[43] The reason for this low frequency of VUR is unclear, but may be related to a high detection rate of UTI, with less severe cases also being diagnosed. Dilating VUR was seen in 56 % of boys and 48 % of girls with VUR. Grade V was seen exclusively in boys. Higher grades of VUR were seen more frequently in children with UTI caused by organisms other than *E coli*, as in earlier studies.[21,44]

Acute DMSA scanning was performed early in the course of the UTI, at a median of 5 days after the start of treatment, and abnormality was found in 51% of the children. The frequency of abnormality increased with VUR grade, as previously shown in prospective studies with acute febrile UTI.[45,46] However, children without VUR also had a high frequency of abnormality - in our study 44%. There was a high sensitivity (96%), a high negative predictive value (99%), and a low likelihood ratio negative (0.07) of acute DMSA abnormality to detect VUR grade III or more, demonstrating a low risk of dilating VUR in children with normal DMSA scan.

In a retrospective study of children <2 years old with acute UTI from our center[21], it was shown that 147 of 303 VCUs (49%) could have been avoided if only children with abnormal acute DMSA scan were investigated; 7 cases with VUR grade III would have been missed, but only one of them had permanent renal damage at a repeat DMSA scintigraphy. These findings were repeated in another retrospective study of 142 children ≥2 years where dilating VUR was seen in 21, all with abnormal DMSA scan.[47] The results of our prospective study convincingly support the concept of not performing VCU routinely in infants with UTI. If VCU had been performed only in infants with abnormal DMSA scintigraphy, 140 invasive VCUs would have been avoided, with only 1 patient with dilating VUR (grade III) being missed. A selective approach focusing on renal status rather than on the presence or absence of VUR not only selects those children with VUR who are at greatest risk for renal scarring, but will also make it possible to avoid half the VCUs routinely performed in the work-up of children with UTI.

The value of performing US in children with UTI has been questioned.[23-25] Montini

et al studied the diagnostic accuracy of routine US and VCU for predicting long-term renal damage after a first febrile UTI in 300 children ≤2 years of age, all with normal antenatal US. US was recommended only when not performed prenatally, in children with poor response to antibiotic treatment and in children with complicated or recurrent infections.[25] Other authors have expressed diverging opinions and concluded that US remains necessary in the evaluation of infants after febrile UTI.[48,49]

A crucial point regarding the role of US is how important structural abnormality is identified (table IX). In our uptake area, like in many other centers in Sweden, routine antenatal US is performed as a single examination around the 18th week of pregnancy, not allowing identification of the same number of abnormalities as when a late pregnancy US is added. In our 3-year study there were actually more structural abnormalities of the urinary tract identified by the work-up after UTI than after antenatal US or by the postnatal investigation because of other clinical symptoms. However, the most severe type of malformation, posterior urethral valves, was detected by US in 5 infants, antenatally in 2, postnatally in 3 but in no case after UTI.

In our study (paper II) US was abnormal in 120 patients (41%) and 30 of 40 children with structural abnormality were identified. Of 14 children with VUR grades IV to V, US was abnormal in 12 (86%). VUR grade III was missed in the majority of cases. Thus, of 290 infants with symptomatic UTI, US detected major findings in 30 (10%). When late antenatal US is not performed, US of infants with UTI provides information that may influence the further management and is an important part of the investigation.

Renal length was above +2 SDS in 28% of the patients which indicates that infants with acute pyelonephritis have enlarged or swollen kidneys, a finding previously described. Dinkel et al found on US that kidney volume in acute pyelonephritis was increased to an average of 175% of normal, most impressively so during the first year of life, and that in 50% of cases there was a bilateral increase in kidney size.[50] Johansson et al performed repeated investigations that revealed a significant successive decrease in renal size in the first four to five weeks after acute pyelonephritis.[51] The relation between renal length on US and inflammatory parameters (fever, CRP and acute DMSA scan changes) shown in paper II is of great interest and should be further addressed in prospective studies.

Guidelines for work-up of children with UTI have been debated for many years but no consensus has been reached. The focus has traditionally been on identification of VUR, and VCU has been widely recommended although the value of investigating for VUR as predictor of renal damage has been questioned.[20] Of the 71 children in our study who had renal damage at late DMSA scan, only one third had dilating VUR. Primary focus on the kidneys and use of VCU only in children with abnormal DMSA scan as we proposed in paper I has been called the "top-down" approach.[52]

A radical reduction of imaging was proposed in the guidelines published by the National Institute for Health and Clinical Excellence (NICE).[53] US is recommended as routine procedure only in infants <6 months of age, with imaging of older children based on identification of risk factors. Unfortunately, no analysis of the detection

rate of different types of urinary tract anomalies was shown. In a recently published study from Hong-Kong, Tse et al validated the NICE guidelines by retrospective analysis of 134 infants <6 months of age with UTI.[54] Of 98 infants with normal US, 22 had scarred kidneys that would have been left undiagnosed. They concluded that this protocol may not be optimal for infants less than 6 months of age.

In the study by Montini et al the benefit of performing early US, DMSA scan or VCU was minimal, and the only imaging that was suggested was a DMSA scan after 6 months to detect scarring.[25] The conditions in Sweden are different with only one early antenatal US not always focused on organ screening. Thus, in our country a higher rate of infants with dilatation of the urinary tract would be expected to present with UTI.

The conclusion that US is important in the imaging of infants with UTI was reinforced by the results presented in paper III. With stepwise multiple logistic regression analysis CRP, APD, serum creatinine and leukocyturia were identified as independent predictors. The two last variables contributed only marginally to improve the ROC curve, however, and increased the AUC from 0.81 to 0.84. Therefore, these variables were excluded when the algorithm for imaging was constructed. The algorithm is thus based on cut-off levels of ≥70 mg/L for CRP and ≥10 mm for APD. With this design the algorithm is easy to use and only 9 of 71 children with ultimate renal damage would have been missed. Of these, 5 had relative kidney function >45% which means limited damage.

The algorithm has the advantages of being based on US which is non-invasive and on CRP which is easy to perform, inexpensive and rapidly available. The increase in serum CRP at a serious infection is exponential, doubling every 8–9 hours with a half-life of 13–16 hours.[55] Since febrile infants often attend the emergency room early, CRP may still be low in the increasing phase. Therefore it may be of value to repeat the CRP testing.

Other US findings and clinical conditions that are additional indications for further imaging are listed in Table XIV.

Table XIV. Indications for supplementing the US with further imaging in infants with UTI.

Clinical findings
weak urine stream
palpable mass
Laboratory results
elevated serum creatinine
US findings
kidney aplasia/ectopy
marked difference in kidney size
marked dilatation
ureterocele
suspected posterior urethral valves

The choice of a cut-off level at CRP ≥70 mg/L is supported by a study by Wang et al. They investigated 45 febrile children aged 9 days to 9.8 years and found a correlation between CRP ≥70 mg/L at UTI and renal scarring. They concluded that US is useful in predicting the development of renal scarring when laboratory parameters was taken into account.[41]

Identification of biomarkers may improve detection of risk patients and allow for further simplification of the imaging algorithm. In our study, the urinary excretion of CRP was increased in children with UTI, but there was no clear association of u-CRP with the extent of renal changes assessed by acute DMSA scintigraphy. U-CC16, u-RBP and s-CRP, on the other hand, were significantly associated with the severity of DMSA scan abnormality.

Previous studies indicate that tubular proteinuria is common in acute pyelonephritis, and occasionally also albuminuria, as reviewed by Carter et al.[56] Such proteins are potential biomarkers for prediction of renal involvement in children with UTI. In order to quantitatively assess the sensitivity and specificity of these markers, optimal cut-off limits are needed, based on studies in larger groups of children. There is also a need for data on normal levels of these proteins and their kinetics in infants although data on RBP in somewhat older children are available.[57]

U-CRP, which is not a LMWP, was not clearly associated with DMSA class, but its level was significantly increased in UTI patients compared with non-renal fever controls (Figure 6 A-B). This finding is similar to that by Chiou et al, who observed that the albumin excretion was increased in UTI patients compared with controls with fever not caused by UTI.[58] Although we obtained a statistically significant difference between our two groups, it should be noted that our patient material was small. Our findings need to be validated in a larger study. If they are confirmed, a combination of several urinary biomarkers may be useful in the evaluation of febrile children. Such a procedure would be non-invasive and relatively rapid since u-CRP, u-RBP and u-CC16 can be analysed with commercially available ELISA kits.

Conclusions

Paper I
In 26 of 27 infants with UTI and dilating VUR, the acute DMSA scintigraphy was abnormal. Thus, a normal DMSA scan makes VCU unnecessary in the primary imaging of infants with UTI.

Paper II
US detected most infants with structural abnormality with the exception of reflux grade III. More children with structural abnormality were diagnosed after UTI than after antenatal diagnosis or because of other clinical symptoms. US is therefore an essential part of the work-up of infants with UTI when there is no third trimester organ screening.

Paper III
CRP is useful as predictor of permanent renal damage in infants with UTI and may together with dilatation on US serve as basis for a new algorithm that further reduces the imaging protocol.

Paper IV
The low molecular weight proteins u-CC16 and u-RBP were associated with renal uptake defect on acute DMSA scan. The levels of u-RBP and u-CRP were significantly higher in children with UTI compared to those with fever of non-UTI conditions. A combination of biomarkers may be useful in the clinical assessment of children with UTI.

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Errata

Paper I, page 582, left column, table I and last paragraph: the number of eligible infants should be 324 instead of 325 as written. Also, DMSA scan not performed within 30 days should be 23 instead of 24 and DMSA performed later 20 instead of written 21.