Clinical and laboratory indices of severe renal lesions in children with febrile urinary tract infection

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Cumulative incidence of symptomatic UTIs

Association between urinary symptoms at 7 years old and previous urinary tract infection

A Hellström, E Hanson, S Hansson, K Hjälmås, U Jodal

At the age of 7 years (1982)
3553 children

Girls: 8.4%
Boys: 1.7%

Febrile UTI: 37%

Cumulative incidence of UTIs

At the age of 7 years (1982) 3627 children entered school in Goteborg (Sweden)

3553 questionnaires were completed

At the age of 7 years (1982) 3627 children entered school in Goteborg. 3553 questionnaires were completed.

Previous UTI was reported in:

- 274 children
- 177 with bacteriuria: 145 girls
- 66 with acute pyelonephritis
Febrile UTIs

- Acute pyelonephritis (APN) or upper UTI
- Acute cystitis (AC) or lower UTI
- Unspecified

The nonspecific nature of symptoms makes the clinical differentiation difficult.

DMSA scan: the gold standard for APN diagnosis
Boys (225)

Number of patients

Unspecified
AC
APN

Age (years)

Age at the first recognized UTI

Uncircumcised

Boys (225)

Girls (952)

Acute pyelonephritis

50%–80% of children with febrile UTI have lesions at the DMSA

Rushton HG Pediatr Nephrol 1997

Normal

APN
After 6 months, 9.5% of 275 children had renal scars found only in children with abnormal findings on the acute DMSA scan.

Can we predict the development of renal lesions?

The goal: identification of children at high risk of severe renal lesions after febrile UTI.

Selective imaging investigation and management.

Siomou E, Stefanidis CJ Ped Nephrol 2007
Can we predict the development of renal lesions?

Clinical findings
- Duration of fever
- Other

Biochemical findings
- Raised s. creatinine

Imaging
- VCUG
- DMSA
- Renal US

Biomarkers of kidney inflammation
- WBCs
- CRP
- PCT
Vesicoureteral reflux (VUR) and renal lesions

VUR is rare in normal children (2%)

VUR is frequent in children with UTIs (30-40%)

VUR was considered the major factor in the pathogenesis of febrile UTI and renal scaring
Long term complications of VUR

Primary care pediatricians

- UTI(s)
- VUR

Pediatric nephrologists

- Renal Scarring
- Hypertension
- CKD
VUR and APN

- Bacteria in pelvis
- Bacteria in renal parenchyma
- Inflammation of renal parenchyma
- Scarring of renal parenchyma
Pathophysiology of acute pyelonephritis

E. Coli with p.fibria

Lipopolysaccharide

Toll-like receptor

CD14

Uroepithelial cell

Inflammation of renal parenchyma

Pathophysiology of acute pyelonephritis

E. Coli with p.fibria
Lipopolysaccharide

Toll-like receptor
CD14

Uroepithelial cell

Activation of nuclear factor κB

Pathophysiology of acute pyelonephritis

Cytokines and chemokines

Nuclear factor κB

Pathophysiology of acute pyelonephritis.

Nuclear factor κB

Cytokines and chemokines

Interleukin-8

↑ Neutrophil recruitment

Pathophysiology of acute pyelonephritis

Cytokines and chemokines

Nuclear factor κB

Cytokines and chemokines

Interleukin-8

TNF-α

↑ Neutrophil recruitment

↑ Vascular permeability and inflammation

Pathophysiology of acute pyelonephritis

Cytokines and chemokines

Nuclear factor κB

Cytokines and chemokines

Interleukin-8

TNF-α

TGF-β

Prostaglandins

↑ Neutrophil recruitment

↑ Vascular permeability and inflammation

↑ Scar formation

Permanent renal lesions related with fUTIs

Girls

Acquired lesions after recurrent UTIs
Usually diagnosed in older age
Usually with low grades of VUR (or no VUR)
Bladder dysfunction

Normal → APN → Scar
Boys

Congenital renal lesions

Usually diagnosed < 1<sup>st</sup> year of age

Usually with high grades of VUR

At low risk to develop acquired lesions
VUR is a risk factor for APN?
**Association high grade VUR/APN**

<table>
<thead>
<tr>
<th>Author</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agras 2007</td>
<td>0.33 (0.07, 1.60)</td>
</tr>
<tr>
<td>Aktas 2008</td>
<td>9.96 (2.35, 42.19)</td>
</tr>
<tr>
<td>Belhadj-tahar 2008</td>
<td>13.62 (0.78, 237.21)</td>
</tr>
<tr>
<td>Bressan 2009</td>
<td>0.98 (0.10, 9.64)</td>
</tr>
<tr>
<td>Castello-girona 1995</td>
<td>3.95 (1.47, 10.64)</td>
</tr>
<tr>
<td>Ditchfield 1994</td>
<td>3.29 (1.77, 6.13)</td>
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<tr>
<td>Donoso 2004</td>
<td>6.26 (0.35, 110.91)</td>
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<tr>
<td>Farnsworth 1991</td>
<td>1.92 (0.99, 3.69)</td>
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<tr>
<td>Fouzas 2010</td>
<td>4.36 (2.21, 8.60)</td>
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<td>Galetto-lacour 2003</td>
<td>1.74 (0.09, 35.39)</td>
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<td>Herz 2010</td>
<td>1.24 (0.55, 2.78)</td>
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<td>ilias 2002</td>
<td>2.52 (0.70, 9.09)</td>
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<td>Jakobsson 1992</td>
<td>4.46 (0.58, 35.90)</td>
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<td>Karavanaki 2007</td>
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<td>Kotoula 2009</td>
<td>0.98 (0.32, 3.06)</td>
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<tr>
<td>Lee 2009</td>
<td>22.29 (8.27, 60.11)</td>
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<td>Lee 2009</td>
<td>3.35 (2.22, 5.07)</td>
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<td>Lin 2007</td>
<td>12.90 (3.95, 42.10)</td>
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<td>Muga zuriarrain 2008</td>
<td>40.01 (2.20, 726.71)</td>
</tr>
<tr>
<td>Preda 2007</td>
<td>29.59 (3.96, 221.29)</td>
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<td>Sheu 2006</td>
<td>11.07 (1.33, 92.07)</td>
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<tr>
<td>Siomou 2009</td>
<td>1.97 (0.63, 6.16)</td>
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<tr>
<td>Stokland 1996</td>
<td>8.16 (3.76, 17.72)</td>
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<tr>
<td>Tuerlinckx 2005</td>
<td>2.40 (0.27, 21.16)</td>
</tr>
<tr>
<td>Wallin 1993</td>
<td>12.21 (0.68, 217.85)</td>
</tr>
<tr>
<td>Wang 2005</td>
<td>7.57 (0.42, 136.98)</td>
</tr>
<tr>
<td>Overall (I-squared = 61.0%, p = 0.000)</td>
<td>4.05 (2.81, 5.86)</td>
</tr>
</tbody>
</table>

Relative Risk of APN

<table>
<thead>
<tr>
<th>Reference</th>
<th>VUR</th>
</tr>
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<tbody>
<tr>
<td>1.0</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>(1.8-2.3)</td>
</tr>
</tbody>
</table>
Association high grade VUR/APN

Relative Risk of APN

- Reference: 1.0
- VUR: 2 (1.8-2.3)
- VUR IV V: 4.1 (2.8-5.9)
VUR is a risk factor for recurrent fUTIs?
VUR and the risk of recurrence of UTI

Recurrence urinary tract infections in children: Risk factors and association with prophylactic antimicrobials

Patrick H. Conway; Avital Cnaan; Theoklis Zaoutis; et al.


Relative Risk of Recurrent UTI

<table>
<thead>
<tr>
<th>Reference</th>
<th>VUR I II III</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0</td>
<td>1.17 (0.52-2.66)</td>
</tr>
</tbody>
</table>

VUR I II III
VUR and the risk of recurrence of UTI

**Relative Risk of Recurrent UTI**

- **Reference**: 1.0
- **VUR I II III**: 1.17 (0.52-2.66)
- **VUR IV V**: 4.59 (1.36-15.47)
VUR is a risk factor for renal lesions?
Dilating VUR (grade III, IV, V) is a risk factor for the development of renal lesions
UTI 1970-79 in Gothenburg, Sweden

1221 children followed from first febrile UTI (fUTI) scarring in 10% (urography)

Follow-up after 16-26 years

Renal function well preserved (> GFR 70 ml/min/1.73m²)


No increased risk of hypertension

Wennerström et al  J Hypertension 2000;18:485-91
1221 children followed from first UTI

Mean follow-up 41 years

Renal function kidney function decreases from a mean of 93 ml/min/1.73m² to 81 ml/min/1.73m²

This was found in women with severe bilateral renal scarring

Natural history of VUR: population of 1,000,000 children

McIlroy PJ et al.
*J Paediatr Child Health* 36: 569–573, 2000

http://jasn.asnjournals.org/cgi/content/full/19/5/847
Natural history of VUR: population of 1,000,000 children

VUR 30,000

UTI 6,000
Recurrent UTI 2,000

No UTI 24,000

3%

McIlroy PJ et al.
*J Paediatr Child Health* 36: 569–573, 2000

http://jasn.asnjournals.org/cgi/content/full/19/5/847
Natural history of VUR: population of 1,000,000 children

- VUR (30,000)
  - UTI (6,000)
    - Recurrent UTI (2,000)
  - No UTI (24,000)
  - Renal “scarring” (10,000)

3%
Natural history of VUR: population of 1,000,000 children

McIlroy PJ et al.  
*J Paediatr Child Health* 36 : 569 –573, 2000

http://jasn.asnjournals.org/cgi/content/full/19/5/847
Can we predict the development of renal lesions?

**Clinical findings**
- Duration of fever
- Other

**Biochemical findings**
- Raised s. creatinine

**Imaging**
- VCUG
- DMSA
- Renal US

**Biomarkers of kidney inflammation**
- WBCs
- CRP
- PCT
Urinary tract infection in children

Urinary tract infection in children: diagnosis, treatment and long-term management

Issue date: August 2007
Definition of atypical UTI

Clinical findings
- Seriously ill. Septicaemia
- Abdominal or bladder mass
- Poor urine flow

Biochemical findings
- Raised serum creatinine

Evidence of non-\textit{Ecoli} UTI
- Infection with non-\textit{E. coli} organisms
- Failure to respond to treatment with suitable antibiotics within 48 hours
Clinical predictors of scarring after fUTI

Do systemic symptoms predict the risk of kidney scarring after urinary tract infection?

<table>
<thead>
<tr>
<th>Groups of children</th>
<th>(1) &lt;6 months</th>
<th>(2) 6 months to 3 years</th>
<th>(3) &gt;3 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children with scars</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boys</td>
<td>6</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Girls</td>
<td>3</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Total</td>
<td>9</td>
<td>21</td>
<td>21</td>
</tr>
<tr>
<td>Children without scars</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boys</td>
<td>9</td>
<td>20</td>
<td>15</td>
</tr>
<tr>
<td>Girls</td>
<td>11</td>
<td>43</td>
<td>42</td>
</tr>
<tr>
<td>Total</td>
<td>20</td>
<td>63</td>
<td>57</td>
</tr>
</tbody>
</table>

Coulthard MG et al. Arch Dis Child 2009
Clinical predictors of scarring after fUTI

Do systemic symptoms predict the risk of kidney scarring after urinary tract infection?  

<table>
<thead>
<tr>
<th>Age group</th>
<th>Vomiting, anorexia, malaise</th>
<th>Hospitalised</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sensitivity</td>
<td>Specificity</td>
</tr>
<tr>
<td>(1) &lt;6 months</td>
<td>0.78 (0.60)</td>
<td>0.25</td>
</tr>
<tr>
<td>(2) 6 months–3 years</td>
<td>0.62 (0.58)</td>
<td>0.56</td>
</tr>
<tr>
<td>(3) &gt;3 years</td>
<td>0.43 (0.33)</td>
<td>0.81</td>
</tr>
</tbody>
</table>

Low specificity of clinical findings

Coulthard MG et al. Arch Dis Child 2009
Clinical predictors of scarring after fUTI

Clinical and laboratory indices of severe renal lesions in children with febrile urinary tract infection

Medical records with the diagnosis of “febrile UTI” (period 2002 – 2004)  
n = 290 children

- Missing data (n = 10)
  - n = 280
    - Obstructive uropathy (n = 10)
      - n = 270
        - Missing acute DMSA (n = 96)
          - n = 174
            - Previous episode of UTI (n = 26)

Total number of patients  
n = 148 children

Clinical predictors of scarring after fUTI

Among several common symptoms associated with febrile UTI shivering was the only clinical sign predictive (Odds Ratio = 4.3) of acute renal lesions in DMSA scan.
Clinical predictors of scarring after fUTI

Clinical findings:
Gastrointestinal (vomiting, diarrhea) and/or Neurological symptoms (irritability, seizures)
Fever (≥38°C)

<table>
<thead>
<tr>
<th>Age</th>
<th>DMSA positive</th>
<th>DMSA negative</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>3–6 months</td>
<td>18</td>
<td>15</td>
</tr>
<tr>
<td>6–12 months</td>
<td>12</td>
<td>19</td>
</tr>
<tr>
<td>12–18 months</td>
<td>1</td>
<td>18</td>
</tr>
<tr>
<td>18–24 months</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Total</td>
<td>33</td>
<td>58</td>
</tr>
</tbody>
</table>

*DMSA* dimercaptosuccinic acid renal scan

Clinical predictors of scarring after fUTI

Do systemic symptoms predict the risk of kidney scarring after urinary tract infection? **No**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>DMSA positive</th>
<th>DMSA negative</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (months)</td>
<td>8.9±5.8</td>
<td>7.0±5.9</td>
<td>0.019</td>
</tr>
<tr>
<td>Fever</td>
<td>39.6±0.7</td>
<td>39.2±1.2</td>
<td>0.114</td>
</tr>
<tr>
<td>GI symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>10 (11%)</td>
<td>21 (22%)</td>
<td>0.038</td>
</tr>
<tr>
<td>Vomiting</td>
<td>32 (35%)</td>
<td>31 (33%)</td>
<td>0.753</td>
</tr>
<tr>
<td>Irritability</td>
<td>12 (13%)</td>
<td>7 (7%)</td>
<td>0.198</td>
</tr>
<tr>
<td>Seizures</td>
<td>4 (4%)</td>
<td>7 (7%)</td>
<td>0.380</td>
</tr>
<tr>
<td>URI symptoms</td>
<td>10 (11%)</td>
<td>16 (17%)</td>
<td>0.237</td>
</tr>
</tbody>
</table>

Low specificity of clinical findings

Renal inflammatory changes were developed in 41% of the infants treated < 24 hours since the onset of fever, versus 75% of those treated > day 4. This difference was significant.

Once the kidney is involved, the risk of development of scarring is independent of the timing of therapy.
The predictor of new/progressive renal scar formation was the presence of previous renal scarring and greater number of UTIs.
Can we predict the development of renal lesions?

Clinical findings
- Duration of fever
- Other

Biochemical findings
- Raised s. creatinine

Imaging
- VCUG
- DMSA
- Renal US

Biomarkers of kidney inflammation
- WBCs
- CRP
- PCT
627 children from 10 studies

Cutoff value: 0.5 to 0.6 ng/mL
Pooled diagnostic odds ratio of serum PCT for APN: 14.25 (95% confidence interval, 4.70 to 43.23).
Association of Procalcitonin With Acute Pyelonephritis and Renal Scars in Pediatric UTI

290 abstracts identified by electronic search, compiling PCT with child (with all medical subject heading terms and text words)

→ 261 excluded after reading abstract

19 articles considered for inclusion, representing 15 centers

→ 1 excluded because no DMSA scan

18 articles included, representing 13 centers
Biomarkers APN Renal scars

Cut off value: 0.5 ng/mL

OR 7.9 (5.8–10.9)
71% sensitivity
72% specificity

OR: 3.4 (2.1–5.7)
79% sensitivity
50% specificity
Validation studies are needed to derive an evidence-based clinical decision rule to identify children at high risk of renal scarring after UTI and selectively perform late DMSA-scan.
Procalcitonin, C-reactive protein, and erythrocyte sedimentation rate for the diagnosis of acute pyelonephritis in children (Review)

Shaikh N, Borrell JL, Evron J, Leeflang MMG
Diagnostic accuracy of PCT and CRP for APN

A low CRP < 20 mg/L appears to be somewhat useful in ruling out APN (decreasing the probability of APN to < 20%),

The PCT seems better suited for ruling in APN, but the limited number of studies and the marked heterogeneity between studies prevents us from reaching definitive conclusions.

Shaikh N et al. Cochr libr 2015
At present, we do not find any compelling evidence to recommend the routine use of any of these tests in clinical practice.

Absence of evidence is not evidence of absence.

Absence of evidence means simply that there is no adequate information.

Altman DG et al. BMJ 1995
Can we predict the development of renal lesions?

Clinical findings
- Duration of fever
- Other

Biochemical findings
- Raised s. creatinine

Imaging
- VCUG
- DMSA
- Renal US

Biomarkers of kidney inflammation
- WBCs
- CRP
- PCT
Predictors of scarring after the first UTI

Identification of Children and Adolescents at Risk for Renal Scarring After a First Urinary Tract Infection
A Meta-analysis With Individual Patient Data

Single meta-analytic logistic regression model with data of 1280 patients

Patients: 1280 children with first diagnosed UTI

<table>
<thead>
<tr>
<th>Source</th>
<th>No. of Children</th>
</tr>
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<tbody>
<tr>
<td>Bressan et al, 2009</td>
<td>72</td>
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<td>Craig et al, 1998</td>
<td>304</td>
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<td>Hoberman et al, 1999</td>
<td>309</td>
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<td>Kotoula et al, 2009</td>
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<td>Levtchenko et al, 2001</td>
<td>80a</td>
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<tr>
<td>Montini et al, 2007</td>
<td>450b</td>
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<td>Prat et al, 2003</td>
<td>77</td>
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<tr>
<td>Taskinen and Rönnholm, 2005</td>
<td>62c</td>
</tr>
<tr>
<td>Tuerlinckx et al, 2005</td>
<td>68d</td>
</tr>
</tbody>
</table>
Factors associated with renal scarring

(listed in descending order of importance)

Grade IV or V VUR
(22 times higher than in children with no VUR)

Abnormal ultrasonographic findings

C-reactive protein (>40mg/L)

Temperature (>39°C)

Organism other than E coli

Polymorphonuclear cell count (>60%)

Take home messages

Children at risk to develop renal lesions after fUTIs:

- Increased serum CRP (>40 mg/L)
- PCT (>1 ng/ml)

The combination of:
- abnormal renal ultrasonography
- an etiologic organism other than E. coli
- fever > 39°C
Take home messages

High risk group to develop renal lesions after fUTIs:

Children with: dilating vesicoureteral reflux recurrent fUTIs acquired renal scarring
High risk group to develop long term complications are children with extensive bilateral lesions