Vesico-ureteric Reflux: management

M. J. Kemper
Hannes
40 weeks gestation
Pregnancy normal
Icterus (1 day FT)
discharge day 5
10th day
Fever
Diarrhea
Labs: CRP 80, Leuc 20000
Septical Work-up:
  LP normal
  Urine +++Leucos
  St. epidermidis

Father: Pediatrician in 2nd year of training
Vesicoureteric (-renal) Reflux

Backflow of urine from bladder
• Auf Dauer hat der der vesicoureterale Reflux einen deletären Einfluß auf das Nierenparenchym (Druckatrophie, aszendierende Pyelonephritis usw.).

• In the long run VUR is deleterious for the renal parenchyma (pressure atrophy, ascending pyelonephritis)
EDITORIAL COMMENTARY

Vesicoureteral reflux, a benign condition

Mika Venhola • Matti Uhari

EDITORIAL COMMENTARY

Vesicoureteric reflux is not a benign condition

Malcolm G. Coulthard
VESICO-URETERIC REFLUX
Reflux Nephropathy (vs. Dysplasia)

Abb. 3a–d. Gradeinteilung von Nierenparenchymnarben nach Smellie.
a Nicht mehr als zwei Narben. b Mehr als zwei Narben, aber einige Areale zumindest annähernd normaler Nierenparenchymdicke erhalten. c Diffuse Verdünnung des Parenchys mit generalisierter Kelchektsie. d Kleine Niere ohne verbliebenes normales Parenchym. (Gedruckt mit Erlaubnis von: Smellie J, Edwards D, Hunter N, Normand ICS, Prescod N [8])
VUR = Refluxnephropathy = Chronic kidney disease?

- 1970ies VUR most frequent cause of ESRD in children (mix up with PUV etc.)
- Recent data:
  - Incidence of ESRD 4%
  - Craig 14% ESRD, scars 17-20%
    - Hypertension 6%
  - Proteinuria
New paradigm CAKUT: Definition

- Congenital
- Anomalies of the
- Kidney and
- Urinary
- Tract

VUR and dysplasia are (mainly) determined antenatally.
The life of the human kidney before birth: its secrets unfolds (A. Woolf)

Metanephros
VESICO-URETERIC REFLUX

Prevalence:
- 30% of children with pyelonephritis
- Newborns: 0,4 - 1,8% (?)
- African Americans < White
- Clustering in families:
  - siblings 30 - 40%
  - parents to children up to 65%
- the earlier investigated the higher the frequency
- Question MJK: how many patients with VUR but without UTI
VESICO-URETERIC REFLUX

Causes:

-Primary: -maturation disturbed, usually grade I and II; disappears in 80%

-«anomaly» usually grade ≥ III; dissappears only in 10%; associated with dysplasia

-«Secondary»: -distal obstruction
- neuropathic bladder (Prune Belly)
-voiding dysfunction
BBD: Blader & Bowel Dysfunction
Risk factors for Reflux Nephropathy/Scars:

![99m-Tc DMSA Renal Scan](image)

- **Differential Function**
  - **LT Kidney = 95 %**
  - **RT Kidney = 7 %**

- **Pinholes**
### Individual Risk Factors: Girls
- White race
- Age < 12 mo
- Temperature ≥ 39°C
- Fever ≥ 2 d
- Absence of another source of infection

<table>
<thead>
<tr>
<th>Probability of UTI</th>
<th>No. of Factors Present</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤1%</td>
<td>No more than 1</td>
</tr>
<tr>
<td>≤2%</td>
<td>No more than 2</td>
</tr>
</tbody>
</table>

### Individual Risk Factors: Boys
- Nonblack race
- Temperature ≥ 39°C
- Fever > 24 h
- Absence of another source of infection

<table>
<thead>
<tr>
<th>Probability of UTI</th>
<th>No. of Factors Present</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤1%</td>
<td>Uncircumcised: a</td>
</tr>
<tr>
<td></td>
<td>Circumcised: No more than 2</td>
</tr>
<tr>
<td>≤2%</td>
<td>Uncircumcised: None</td>
</tr>
<tr>
<td></td>
<td>Circumcised: No more than 3</td>
</tr>
</tbody>
</table>

**FIGURE 2**
Probability of UTI Among Febrile Infant Girls\(^2\) and Infant Boys\(^2\) According to Number of Findings Present. aProbability of UTI exceeds 1% even with no risk factors other than being uncircumcised.
Figure 3. Presence or Absence of Renal Scarring after Six Months According to Demographic and Clinical Characteristics of Children with a First Urinary Tract Infection.

VUR denotes vesicoureteral reflux, and VCUG voiding cystourethrogram.
FIGURE 4
Relationship between renal scarring and number of bouts of pyelonephritis. Adapted from Jodal.59
Further risk factors: Swedish Reflux Study and RIVUR: increased risk for scars with dilating VUR

<table>
<thead>
<tr>
<th>Number of kidneys</th>
<th>VUR grade</th>
<th>Totals(^a)</th>
<th>New damage</th>
</tr>
</thead>
<tbody>
<tr>
<td>No VUR</td>
<td>92</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>11</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>44</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>173</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>83</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Totals</td>
<td>402</td>
<td>16</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Follow-up DMSA-scan not done in 2 patients.
Swedish Reflux Study: increased risk for scars in girls

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Girls</th>
<th>Boys</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. patients with UTI/total No. patients (No. UTIs)</td>
<td></td>
</tr>
<tr>
<td>Prophylaxis</td>
<td>8/43 (11)</td>
<td>2/26 (2)</td>
</tr>
<tr>
<td>Endoscopic</td>
<td>10/43 (14)</td>
<td>4/23 (4)</td>
</tr>
<tr>
<td>Surveillance</td>
<td>24/42 (42)</td>
<td>1/26 (2)</td>
</tr>
<tr>
<td>Totals</td>
<td>42/128 (67)</td>
<td>7/77 (8)</td>
</tr>
</tbody>
</table>
What can we do to prevent scars?

Treatment Options in VUR

- Detect and treat pyelonephritis immediately
- Advise parents to contact pediatrician immediately in case of
  - Fever
  - Lethargy, poor feeding
  - Symptoms of sepsis
  - Loin pain (even if no fever) or excessive crying
Diagnosis of febrile UTI (pyelonephritis)

-Gold Standard: Suprapubic aspiration

-Silver Standard: Catheterization

-Bronze Standard: Clean Catch

-Iron Standard: Urine bag

-Important: send for culture immediately
How should be treat pyelonephritis?


Randomised trial of oral versus sequential intravenous/oral cephalosporins in children with pyelonephritis

• Thomas J. Neuhaus et al

• 6 months-16 y.
• Oral ceftibuten vs. Intravenous cetriaxon for 3 days, followed by oral ceftibuten: same outcome (scars) after adjustment
• High risk for scars: increased CRP and high degree of VUR
• <6 months and if very ill: hospitalise (ampicillin/cephalosporin)
What else can we do to prevent scars?  
Treatment Options in VUR

<table>
<thead>
<tr>
<th>Conservative Management</th>
<th>Surgical Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Prophylaxis</td>
<td>- Lich- Gregoir</td>
</tr>
<tr>
<td>- No Prophylaxis</td>
<td>- Cohen ...</td>
</tr>
<tr>
<td>(=watchful waiting)</td>
<td>- Laparoscopic</td>
</tr>
<tr>
<td>- Bladder training (girls!)</td>
<td>- Injection (STING)</td>
</tr>
</tbody>
</table>
Treatment of VESICO-URETERIC REFLUX

International Reflux Study (Olbing, Smellie et al)

• Antibiotic Prophyaxis equivalent to surgery, no increased incidence of scars
• Including high Grade VUR
• Risk factors for persistence of VUR
  • Grade IV and bilateral VUR
International Reflux Study: Surgery vs prophylaxis: 10 year results
(Ped Nephrol 2006)

252/306 children with follow-up

- Up to 5 y. FU: 40 scars
- 5-10 y: additional 2 scars
- GFR<70: n=1
- Hypertension n=3
Cochrane Analysis (2004, 2007)

- 11 studies of 1148 children
  - Risik of infections equal in conservatively managed vs. operated groups
  - Combined approach
  - Reduction UTI 50%, formation of scars unchanged
- “Additional benefit of surgery is small at best”
  - If 20% UTI-risik: 9 reimplantations prevent 1 febrile UTI
Which antibiotic prophylaxis?

1-4 weeks of age: cephalosporin
>4 weeks trimethoprim (SMX)
>12 moths: nitrofurantoin
2008: Times are changing
VUR: concepts in diagnosis and treatment prior 2008

1980-1990:
MCUG in all UTI
and prophylaxis if VUR
Is Antibiotic Prophylaxis in Children With Vesicoureteral Reflux Effective in Preventing Pyelonephritis and Renal Scars? A Randomized, Controlled Trial

What This Study Adds

This multicenter, open-label, randomized, controlled trial demonstrates that continuous antibiotic prophylaxis is ineffective in reducing the rate of pyelonephritis recurrence and the incidence of renal damage in children who are younger than 30 months and have VUR grades II through IV.

Marco Pennesi, MD, Laura Travani, MD, PhD, Leopoldo Peratoner, MD, Andrea Bordugo, MD, Adriano Cattaneo, MD, Luca Ronfani, MD, PhD, Silvia Minisini, MD, Alessandro Ventura, MD, for the North East Italy Prophylaxis in VUR study group

P Bennesi et al, Pediatrics 2008
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Prophylaxis ($n = 50$)</th>
<th>No Prophylaxis ($n = 50$)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with at least 1 pyelonephritis recurrence in the first 2 y of follow up, $n$ (%)</td>
<td>18 (36)</td>
<td>15 (30)</td>
<td>.50</td>
</tr>
<tr>
<td>First year after enrollment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of episodes, mean (SD)</td>
<td>0.6 (1.1)</td>
<td>0.4 (0.8)</td>
<td>.29</td>
</tr>
<tr>
<td>Patients with recurrence, $n$ (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 episode</td>
<td>10 (20)</td>
<td>7 (14)</td>
<td></td>
</tr>
<tr>
<td>2 episodes</td>
<td>3 (6)</td>
<td>2 (4)</td>
<td></td>
</tr>
<tr>
<td>≥3 episodes</td>
<td>4 (8)</td>
<td>3 (6)</td>
<td></td>
</tr>
<tr>
<td>Patients without recurrence, $n$ (%)</td>
<td>33 (66)</td>
<td>38 (76)</td>
<td></td>
</tr>
<tr>
<td>Second year of follow-up</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of episodes, mean (SD)</td>
<td>0.2 (0.6)</td>
<td>0.3 (0.9)</td>
<td>.71</td>
</tr>
<tr>
<td>Patients with recurrence, $n$ (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 episode</td>
<td>7 (14)</td>
<td>4 (8)</td>
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<td>3 (6)</td>
<td></td>
</tr>
<tr>
<td>≥3 episodes</td>
<td>1 (2)</td>
<td>1 (2)</td>
<td></td>
</tr>
<tr>
<td>Patients without recurrence, $n$ (%)</td>
<td>41 (82)</td>
<td>42 (84)</td>
<td></td>
</tr>
<tr>
<td>Parameter</td>
<td>Prophylaxis ($n = 50$), $n$ (%)</td>
<td>No Prophylaxis ($n = 50$), $n$ (%)</td>
<td></td>
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<tr>
<td>-------------------------------</td>
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<tr>
<td>Persistent VUR at the end</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>second year grade of VUR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>3 (6)</td>
<td>4 (8)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>10 (20)</td>
<td>12 (24)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>15 (30)</td>
<td>20 (40)</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>3 (6)</td>
<td>4 (8)</td>
<td></td>
</tr>
<tr>
<td>Persistent VUR at the end</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>fourth year grade of VUR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>3 (6)</td>
<td>3 (6)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>7 (14)</td>
<td>5 (10)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>13 (26)</td>
<td>14 (28)</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>3 (6)</td>
<td>3 (6)</td>
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</tr>
</tbody>
</table>
should be performed to detect anatomic abnormalities. Data from the most recent 6 studies do not support the use of antimicrobial prophylaxis to prevent febrile recurrent UTI in infants without vesicoureteral reflux (VUR) or with grade I to IV VUR. Therefore, a voiding cystourethrography (VCUG) is not recommended routinely after the first UTI.

VCUG is indicated if renal and bladder ultrasonography reveals hydronephrosis, scarring, or other findings that would suggest either high-grade VUR or obstructive uropathy and in other atypical or complex clinical circumstances. VCUG should also be performed if there is a recurrence of a febrile UTI. The recommendations in this guideline do
The Swedish reflux trial: Review of a randomized, controlled trial in children with dilating vesicoureteral reflux

Per Brandström, Ulf Jodal, Ulla Sillén, Sverker Hansson
Conclusions

For girls above 1 year of age with dilating VUR, there was benefit from active medical and surgical treatment in reducing recurrence rate. We also showed that in girls prophylaxis reduced the risk of new renal damage. On the other hand, boys older than 1 year with dilating VUR did not benefit from active treatment.

New assessment at 4 years of age

Figure 5  Management strategies for children >1 year of age with dilating VUR. *No evidence in study for prophylaxis or endoscopic injection being superior.
CONCLUSIONS

Among children with vescicoureteral reflux after urinary tract infection, antimicrobial prophylaxis was associated with a substantially reduced risk of recurrence but not of renal scarring. (Funded by the National Institute of Diabetes and Digestive and Kidney Diseases and others; RIVUR ClinicalTrials.gov number, NCT00405704.)

EFFECT MODIFIERS

Children with grade III or IV reflux at baseline were more likely to have febrile or symptomatic recurrences than were children with grade I or II reflux (64 of 280 children [22.9%] vs. 46 of 322 [14.3%], P=0.003). Hazard ratios for recurrences
Swedish Reflux Study & RIVUR: impact on management?

• AAP recommendation no longer supported?
  • Prophylaxis useful
  • VUR is risk factor
  • VUR present even if ultrasound is normal
VUR: concepts in diagnosis and treatment

1980-1990:
MCUG in all UTI and prophylaxis if VUR

2011: AAP No MCUG and no prophylaxis

2015: MCUG and prophylaxis if VUR, surgery?
Summary VUR (and UTI)

- VUR is frequent and associated with UTI and scars
- If you do not perform MCUG you will not find VUR
- If you do not perform DMSA you will not detect scars
- Scars: risk increased with VUR III-IV (especially girls)
- Recurrent UTIs must be prevented
- Antibiotic prophylaxis in boys until 1 and in girls until 4 or until normal bladder and bowel function
- If prophylaxis fails: surgery (after 1st fUTI on prophylaxis)
- Long-term follow-up necessary (especially girls)
Future Directions UTI/VUR: Individualised approach?
Vesicoureteric reflux is a benign condition, if you treat it properly and prevent complications

Markus Kemper