Preventive Antibiotic Treatment in Vesicoureteral Reflux (VUR): The Debate

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“P. & A. Kyriakou” Children’s Hospital, Athens, Greece
Why we should use preventive antibiotic treatment in children with VUR
Preventive Antibiotic Treatment

VUR III-V → Febrile UTI → Renal Scars
What do we know about VUR in relation to recurrent UTI and scarring?
VUR → Febrile UTI
VUR in general population

2-3 % of children

Pediatrics 1999 AAP (results from 54 studies)
Febrile UTIs and VUR

? % of children with a history of febrile UTI have VUR
30-40% of children with a history of UTI have VUR

Pediatrics 1999 AAP (results from 54 studies)
VUR occurs in 2-3% of normal children

VUR occurs in 30-40% of children with febrile UTIs

VUR is a major factor in the pathogenesis of febrile UTIs
VUR and the risk of recurrence of UTI


Matti Nuutinen · Matti Uhari

Recurrence and follow-up after urinary tract infection under the age of 1 year

262 children (134 girls, 128 boys)

161 recurrences in:

43 (32%) girls

45 (35%) boys
Recurrence and follow-up after urinary tract under the age of 1 year

Cumulative incidence (%)
775 children from a network of 27 primary care pediatric practices with a common electronic health record.

EHR was managed by The Children’s Hospital of Philadelphia.
Recurrent Urinary Tract Infections in Children: Risk Factors and Association With Prophylactic Antimicrobials

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


74,974 Children aged 6 years or younger with at least 2 clinic visits

775 With record of urinary tract infection

164 Excluded
   91 Previous UTI
   55 Observation time <24 d
   17 Comorbid conditions
   1 UTI diagnosed by bag specimen

611 With first UTI included in analysis

83 With recurrent UTI 13%
Relative Risk of Recurrent UTI

Reference: 1.0
VUR I II III: 1.17 (0.52-2.66)
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)
Risk of Renal Scarring in Children With a First Urinary Tract Infection: A Systematic Review

Nader Shaikh, Amy L. Ewing, Sonika Bhatnagar and Alejandro Hoberman

*Pediatrics* published online Nov 8, 2010;
Meta-analysis of 33 studies

1533 references identified
  546 from Medline
  949 from Embase
  38 from review of references

1205 references excluded based on the title/abstract

328 references retrieved

295 references excluded
  90 UTI not required for inclusion
  59 Not first UTI
  34 DMSA timing did not meet criteria
  30 Insufficient data to calculate prevalence
  27 Duplicate studies
  21 Urine culture criteria not met
  9 Case series (n < 25)
  8 Loss to follow-up >15%
  8 Study included adults
  5 Used SPECT DMSA
  5 Results according to kidney, not child

33 references included in analysis
Children with VUR were significantly more likely to develop acute pyelonephritis.

RR (relative risk): 1.5 [95% CI: 1.1–1.9]
Children with a history of UTI and dilated VUR are more likely to develop recurrent febrile UTIs than children with no VUR or no dilated VUR.
VUR III-V → Febrile UTI → Renal Scars
Girls

- Acquired lesions after recurrent UTIs
- Diagnosed in older age
- Usually with low grades of VUR (or no VUR)
- Bladder dysfunction
VUR III-V  Febrile UTI  Congenital Renal Scars
"Bud" theory

4th week of gestation

Ureteric bud

Metanephric mesenchyme

Urogenital truck

Caudal displacement of the ureteric bud

Short intravesical ureter

VUR

Abnormal interaction with metanephric mesenchyme

Renal hypoplasia-dysplasia
Boys

- Congenital
- Usually with high grades of VUR
- At low risk to develop acquired lesions
Primary Vesicoureteric Reflux as a Predictor of Renal Damage in Children Hospitalized with Urinary Tract Infection: A Systematic Review and Meta-Analysis

ISKY GORDON,* MARIA BARKOVICS,* SIMA PINDORIA,† TIM J. COLE,† and ADRIAN S WOOLF†

*Department of Radiology, Great Ormond Street Hospital for Children NHS Trust, London; †Centre for Paediatric Epidemiology and Biostatistics, and the ‡Nephro-Urology Unit, Institute of Child Health, London, United Kingdom.
VUR and renal lesions

Original search 838

185 papers + 10 abstracts = 235 studies

643 excluded as no imaging included

25 studies included (includes 2 with follow-up data; total data sets 27)

210 excluded*

Hospitalized patients only

12 studies included

Data reported as ‘Children’

7 studies

Data reported as ‘Kidneys’

7 studies

Non-hospitalized patients

13 studies excluded
VUR and renal lesions

The odds of the presence of renal lesions after a febrile UTI are roughly doubled in children with VUR i.e. the presence of VUR increases the chance of a positive scan by about 20%
<table>
<thead>
<tr>
<th>DMSA</th>
<th>no VUR</th>
<th>grade I II</th>
</tr>
</thead>
<tbody>
<tr>
<td>normal</td>
<td>120</td>
<td>20</td>
</tr>
<tr>
<td>abnormal</td>
<td>103 (46%)</td>
<td>24 (54%)</td>
</tr>
</tbody>
</table>

Hansson S et al. J Urol 2004
# Early DMSA in children with febrile UTI

<table>
<thead>
<tr>
<th></th>
<th>no VUR</th>
<th>grade I II</th>
<th>grade III-V</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N=303</strong></td>
<td>223</td>
<td>44</td>
<td>36</td>
</tr>
<tr>
<td><strong>DMSA</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>normal</td>
<td>120</td>
<td>20</td>
<td>7</td>
</tr>
<tr>
<td>abnormal</td>
<td>103 (46%)</td>
<td>24 (54%)</td>
<td>29 (80%)</td>
</tr>
</tbody>
</table>

_Hansson S et al. J Urol 2004_
Prevalence of renal defects on DMSA scan

Joo Hoon Lee · Chang Hee Son · Moo Song Lee · Young Seo Park

Vesicoureteral reflux increases the risk of renal scars: a study of unilateral reflux


48 children 0–5 years with unilateral VUR diagnosed after the first pyelonephritis
Vesicoureteral reflux increases the risk of renal scars: a study of unilateral reflux


<table>
<thead>
<tr>
<th>DMSA scan</th>
<th>Initial</th>
<th>Six months later</th>
</tr>
</thead>
<tbody>
<tr>
<td>VUR (+) renal units</td>
<td>34 units (70.8%)</td>
<td>23 units (47.9%)</td>
</tr>
<tr>
<td>VUR (−) renal units</td>
<td>13 units (27.1%)</td>
<td>7 units (14.6%)</td>
</tr>
<tr>
<td>( P )-value</td>
<td>(&lt;0.01)</td>
<td>(&lt;0.01)</td>
</tr>
<tr>
<td>Odds ratio</td>
<td>6.54</td>
<td>5.39</td>
</tr>
<tr>
<td>95% CI(^a)</td>
<td>2.68~15.9</td>
<td>2.02~14.38</td>
</tr>
</tbody>
</table>

\(^a\)Confidence interval
Risk of Renal Scarring in Children With a First Urinary Tract Infection: A Systematic Review
Nader Shaikh, Amy L. Ewing, Sonika Bhatnagar and Alejandro Hoberman
Pediatrics published online Nov 8, 2010;
Children with vesicoureteral reflux (VUR) were significantly more likely to develop renal scarring compared with children with no VUR.

RR: 2.6 (95% CI: 1.7–3.9)
Children with **VUR grades III or higher** were more likely to develop scarring than children with **lower** grades of VUR

RR: **2.1** (95% CI: 1.4–3.2)  
53% vs 25%; P < .001
Renal scarring in children with febrile UTI
Acquired permanent renal lesions (scars)

UTI with fever

VUR

Genetic background

Renal scars
What do modern studies on prophylactic antibiotics after a UTI tell us?
Ineffectiveness of Preventive Antibiotic Treatment

The use of prophylaxis in VUR seemed very rational for four decades.

2001: Most published studies comparing antibiotics with placebo or no treatment for preventing UTI in children with VUR have been poorly designed, with biases known to overestimate the true treatment effect.

There were only three trials \((n = 151)\) comparing antibiotics with placebo/no treatment till 2006.

Ineffectiveness of Preventive Antibiotic Treatment

218 children with a history of febrile UTI and positive findings on DMSA

Antibiotic prophylaxis:
Sulfamethoxazole/trimethoprim (1–2 mg/kg trimethoprim) or Nitrofurantoin (1.5 mg/kg once daily).

versus

No antibiotic prophylaxis

Garin EH et al., Pediatr 2006
### Ineffectiveness of prophylaxis

#### Patients With VUR

<table>
<thead>
<tr>
<th></th>
<th>Prophylaxis</th>
<th>No Prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic</td>
<td>0 (0.0)</td>
<td>3 (5.1)</td>
</tr>
<tr>
<td>Cystitis</td>
<td>6 (9.2)</td>
<td>9 (15.5)</td>
</tr>
<tr>
<td>Acute pyelonephritis</td>
<td>7 (12.9)</td>
<td>1 (1.7)</td>
</tr>
<tr>
<td>None</td>
<td>42 (79.6)</td>
<td>45 (75.6)</td>
</tr>
</tbody>
</table>

#### VUR III 32%

#### Patients Without VUR

<table>
<thead>
<tr>
<th></th>
<th>Prophylaxis</th>
<th>No Prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic</td>
<td>1 (2.2)</td>
<td>4 (6.6)</td>
</tr>
<tr>
<td>Cystitis</td>
<td>1 (2.2)</td>
<td>8 (13.8)</td>
</tr>
<tr>
<td>Acute pyelonephritis</td>
<td>2 (4.5)</td>
<td>2 (3.3)</td>
</tr>
<tr>
<td>None</td>
<td>41 (91.1)</td>
<td>46 (76.7)</td>
</tr>
</tbody>
</table>
### Ineffectiveness of prophylaxis

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Montini et al.</th>
<th>Antibiotic prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>tot</td>
</tr>
<tr>
<td>No VUR</td>
<td>129</td>
<td>5</td>
</tr>
<tr>
<td>VUR grade I</td>
<td>19</td>
<td>1</td>
</tr>
<tr>
<td>Grade II</td>
<td>37</td>
<td>3</td>
</tr>
<tr>
<td>Grade III</td>
<td><strong>26</strong></td>
<td><strong>6</strong></td>
</tr>
<tr>
<td>Grade IV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td><strong>211</strong></td>
<td><strong>15</strong></td>
</tr>
</tbody>
</table>

+ : Nr or children with febrile UTIs
### Ineffectiveness of prophylaxis

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pennesi et al.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Antibiotic prophylaxis</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>tot</td>
<td>+</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>No VUR</th>
<th>VUR grade I</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade II</td>
<td>Grade III</td>
<td>Grade IV</td>
<td>All patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>22</td>
<td>17</td>
<td>50</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>9</td>
<td>8</td>
<td>18</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>24</td>
<td>16</td>
<td>50</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>7</td>
<td>8</td>
<td>15</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

+ : Nr or children with febrile UTIs
<table>
<thead>
<tr>
<th>Study Reference and Subjects’ Grade of Vesicoureteral Reflux</th>
<th>Number of Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Garin et al.</td>
<td>218</td>
</tr>
<tr>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Grades I through III</td>
<td>225</td>
</tr>
<tr>
<td>Roussey-Kesler et al.</td>
<td>225</td>
</tr>
<tr>
<td>Grades I through III</td>
<td></td>
</tr>
<tr>
<td>Pennesi et al.</td>
<td>100</td>
</tr>
<tr>
<td>Grades II through IV</td>
<td></td>
</tr>
<tr>
<td>Montini et al.</td>
<td>338</td>
</tr>
<tr>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Grades I through III</td>
<td></td>
</tr>
</tbody>
</table>

*Hobermann A, Keren R. NEJM 2009*
<table>
<thead>
<tr>
<th>Study Reference and Subjects’ Grade of Vesicoureteral Reflux</th>
<th>Number of Subjects</th>
<th>Blinded Study</th>
<th>Age of Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Garin et al.⁶</td>
<td>218</td>
<td>No</td>
<td>1 mo–18 yr</td>
</tr>
<tr>
<td>None</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grades I through III</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Roussey-Kesler et al.⁷</td>
<td>225</td>
<td>No</td>
<td>1–36 mo</td>
</tr>
<tr>
<td>Grades I through III</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pennesi et al.⁸</td>
<td>100</td>
<td>No</td>
<td>0–30 mo</td>
</tr>
<tr>
<td>Grades II through IV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Montini et al.⁹</td>
<td>338</td>
<td>No</td>
<td>2–84 mo</td>
</tr>
<tr>
<td>None</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grades I through III</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

_Hobermann A, Keren R  NEJM 2009_
<table>
<thead>
<tr>
<th>Study Reference and Subjects’ Grade of Vesicoureteral Reflux</th>
<th>Method of Diagnosis</th>
<th>Duration of Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Garin et al.(^6)</td>
<td>Bladder catheterization or clean voided collection</td>
<td>12 mo</td>
</tr>
<tr>
<td>None</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grades I through III</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Roussey-Kesler et al.(^7)</td>
<td>Bag collection</td>
<td>18 mo</td>
</tr>
<tr>
<td>Grades I through III</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pennesi et al.(^8)</td>
<td>Bag collection</td>
<td>24 mo</td>
</tr>
<tr>
<td>Grades II through IV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Montini et al.(^9)</td>
<td>Bag collection</td>
<td>12 mo</td>
</tr>
<tr>
<td>None</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grades I through III</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Hobermann A, Keren R. NEJM 2009*
The lack of an observed reduction in the risk of recurrent UTI may have resulted from insufficient statistical power.

To detect a reduction of 10% in the absolute risk of recurrent UTIs, a study would need to enrol 600 children.
Misclassification of UTIs with specimens from bag collections children may have diluted any actual benefit of antimicrobial prophylaxis.

The inclusion criteria of several studies also limit their generalizability.
Antibiotic Prophylaxis and Recurrent Urinary Tract Infection in Children

Antibiotic Prophylaxis and Recurrent Urinary Tract Infection in Children

<table>
<thead>
<tr>
<th>Maximum grade of vesicoureteral reflux</th>
<th>Group 1</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>119 (41)</td>
<td>115 (40)</td>
</tr>
<tr>
<td>I or II</td>
<td>57 (20)</td>
<td>57 (20)</td>
</tr>
<tr>
<td>III to V</td>
<td>65 (23)</td>
<td>64 (22)</td>
</tr>
<tr>
<td>Unknown</td>
<td>47 (16)</td>
<td>52 (18)</td>
</tr>
</tbody>
</table>
14 children would need to be treated to prevent one case of urinary tract infection.

P = 0.02 (log-rank test)

36 of 288 patients (13%)

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Antibiotic</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>288</td>
<td>278</td>
<td>288</td>
</tr>
<tr>
<td>273</td>
<td>271</td>
<td>271</td>
</tr>
<tr>
<td>273</td>
<td>264</td>
<td>248</td>
</tr>
<tr>
<td>271</td>
<td>261</td>
<td>242</td>
</tr>
<tr>
<td>264</td>
<td>261</td>
<td>232</td>
</tr>
<tr>
<td>264</td>
<td>257</td>
<td>225</td>
</tr>
<tr>
<td>257</td>
<td>216</td>
<td>208</td>
</tr>
</tbody>
</table>
Antibiotic Prophylaxis and Recurrent Urinary Tract Infection in Children

In children with a single symptomatic UTI, prophylaxis should be considered but not routinely recommended.
OC034
RECURRENT FEBRILE URINARY TRACT INFECTIONS IN CHILDREN RANDOMIZED TO PROPHYLAXIS, ENDOSCOPIC INJECTION OR SURVEILLANCE. RESULTS FROM THE SWEDISH REFLUX STUDY.
S. Hansson*, P. Brandström¹, U. Jodal¹
¹Pediatric Uronephrologic Center, PUNC, The Queen Silvia Children’s Hospital, Göteborg, ²Pediatrics, Ryhov County Hospital, Jönköping, Sweden
Swedish study

Randomized controlled trial from 23 Swedish centers

203 children (128 girls 75 boys, 1-2 yrs) from 23 centers

VURIII:126

IV: 77

Age 1-2 years

History of a febrile urinary tract infection (194) or prenatal screening (9).

Incidence of recurrent UTI

67 febrile recurrences in
33% girls
10% boys (p = 0.0001)

Incidence of recurrent UTI

- Prophylaxis: 14%
- Endoscopic: 21%
- Surveillance: 37%

\[ p = 0.0002 \]
Kaplan-Meyer curves from time of randomization to the first febrile UTI

New renal damage in a previously unscarred area was seen in 13/128 girls and 2/75 boys.

8/13 surveillance

5/13 endoscopic therapy

0/13 prophylaxis (p = 0.0155)

545 Children with VUR on preventive antibiotic treatment

<table>
<thead>
<tr>
<th>Grade</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>6.6%</td>
</tr>
<tr>
<td>II</td>
<td>54.2%</td>
</tr>
<tr>
<td>III</td>
<td>31.6%</td>
</tr>
<tr>
<td>IV</td>
<td>5.7%</td>
</tr>
<tr>
<td>V</td>
<td>1.9%</td>
</tr>
</tbody>
</table>

Only 0.5% developed new scars or deteriorated previous lesions

Multicenter, doubleblind, randomised, placebo controlled trial designed to evaluate the effectiveness of antimicrobial prophylaxis
– after first UTI
– VUR grades I – IV
– age 2 months – 6 years
– aiming at 600 children
Why we should use prophylactic antibiotics in children with VUR?
Natural history of VUR

Population of 1,000,000 children

Mcllroy 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

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

80%

Mcllroy 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

VUR 30,000

UTI 6,000
Recurrent UTI 2,000

No UTI 24,000

Renal “scarring” 10,000

McIlroy PJ et al.  
*J Paediatr Child Health* 36 : 569 –573, 2000  
http://jasn.asnjourrnals.org/cgi/content/full/19/5/847
Natural history of VUR

VUR 30,000

UTI 6,000
Recurrent UTI 2,000

No UTI 24,000

Renal “scarring” 10,000

Hypertension?

ESRD 5

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

http://jasn.asnjournals.org/cgi/content/full/19/5/847
The high frequency of preserved renal function in patients with scarring is a consequence of special attention to UTI and adequate supervision during childhood.

Sverker Hansson, Göteborg, Sweden
VUR is not a benign condition

Is reflux nephropathy preventable, and will the NICE childhood UTI guidelines help?

Malcolm G Coulthard

*Arch. Dis. Child.* 2008;93;196-199; originally published online 4 Oct 2007; doi:10.1136/adc.2006.100529
Prophylactic antibiotics (PA)

VUR III-V $\rightarrow$ Febrile UTI $\rightarrow$ Renal Scars
Prophylactic antibiotics (PA)

VUR III-V → Febrile UTI → Renal Scars

Voiding dysfunction

Early diagnosis and treatment
## Balance between benefit and harm of PA

<table>
<thead>
<tr>
<th>Benefit</th>
<th>Harm</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Prevention of febrile UTIs</td>
<td>• Side effects</td>
</tr>
<tr>
<td>• Prevention of the development of renal scars</td>
<td>• Antimicrobial resistance</td>
</tr>
<tr>
<td></td>
<td>• Cost</td>
</tr>
</tbody>
</table>
Current evidence is unable to identify subgroup(s) of children who may benefit from antibiotic prophylaxis.

Most trials excluded children with complex congenital malformations and/or higher grades of VUR.
The benefit of antimicrobial prophylaxis in children at greater risk of complications might be higher from those children included in clinical trials.

Lack of compliance could apparently reduce the beneficial effect of prophylaxis.
Prophylactic antibiotics in children with VUR

No Yes
The same management for all children with VUR?

**Procrustean solution**

Procrustes had a bed in which he invited people to spend the night, and then with his hammer stretched them to fit. If the guest proved too tall, he would amputate the excess length.
Children with VUR and risk for renal lesions

- High risk
- Low risk
Children with VUR and risk for renal lesions

**High risk**

- VUR grade > III
- History of febrile UTI with acute DMSA renal lesions
- History of recurrent febrile UTIs

**Low risk**

- VUR grade I and II
- Girls toiled trained
- Boys > 2 years old
3 years old girl
3 years old boy
3 years old boy
Might not be beneficial for:
• boys > 2 year of age with VUR
• children with VUR I and II

Should be recommended in girls with VUR until successful toilet training is achieved
Until the results of appropriately designed, placebo-controlled, prospective studies become available, VUR should be considered a risk factor for renal scarring and treat each patient on an individual basis.
Hippocrates (460-377 AC)

Do not harm