Vesikoureteraler Reflux (VUR)

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State of the (Swedish) art 2011

Nephrologie und Urologie

W-Neuh-Vorträge-Luzern

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The Swedish Reflux Trial in Children: I. Study Design - Population Characteristics

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- **Part I to V: Journal of Urology 2010;184: pp 274-304**

Evidenz – Studien – EBM – GL ?!

- **Evidenz** = **Augenscheinlichkeit, Klarheit**
  = **Beweismittel, Daten, randomisierte Studien**

- **Evidenz = Studien ≒ Evidenz-basierte Medizin (EBM)**
  = **1 wichtiges Element von EBM**

- **EBM ≒ Guidelines (GL)**
  = **1 wichtiges Element von Guidelines**

Elemente der EBM (1)

- **1° Voraussetzung: Evidenz = randomisierte Studien**
  - „Randomized controlled trials (RCTs), which generate the most rigorous evidence on treatment efficacy, generally examine only one type of intervention in a selected population with one dominant health problem …
  - obwohl in Pädiatrie „oft“ singuläres Problem: HWI, INS ..
    → Studiensetting, Ein- und Ausschlusskriterien
    → in Praxis nicht „einfach“ 1:1 umsetzbar
- ***EBM ist mehr / umfassender → weitere Elemente***

Elemente der EBM (2)

- **Persönliche ärztliche Erfahrungen**
- **Lokale Umstände in Praxis / Spital**
  - Verfügbarkeit von Techniken (Skills) / Geräten
  - Sozio-Kultur: z.B. Deutsch-CH vs Romandie vs Tessin
- **Kosten**
- **Nationale und kantonale Gesetze**
  - KVG (z.B. Kantonsgrenzen vs Qualitätskriterien …)

Elemente der EBM (3)

- **Somatische Krankheit**
  - verläuft per se oft „regelhaft“: Pyelonephritis, Asthma …
- **Dennoch: Medizin ist …**
  - = keine exakte Wissenschaft
  - = eine intuitive Heilkunst
- **Und: Individuum …**
  - Jeder Patient ist ein Individuum mit eigenen Empfindungen seiner Symptome / Beschwerden, Wertvorstellungen, „Variabeln“ und „Geschichte“

Purpose of "The Swedish Reflux Trial in Children"

We compared the

1. vesicoureteral reflux (VUR) resolution
2. rates of febrile urinary tract infection (UTI)
3. kidney damage

in children with VUR grade III-IV/V treated in 3 ways:

1. antibiotic prophylaxis
2. endoscopic therapy
3. surveillance with antibiotics only for symptomatic UTI

Materials and Methods

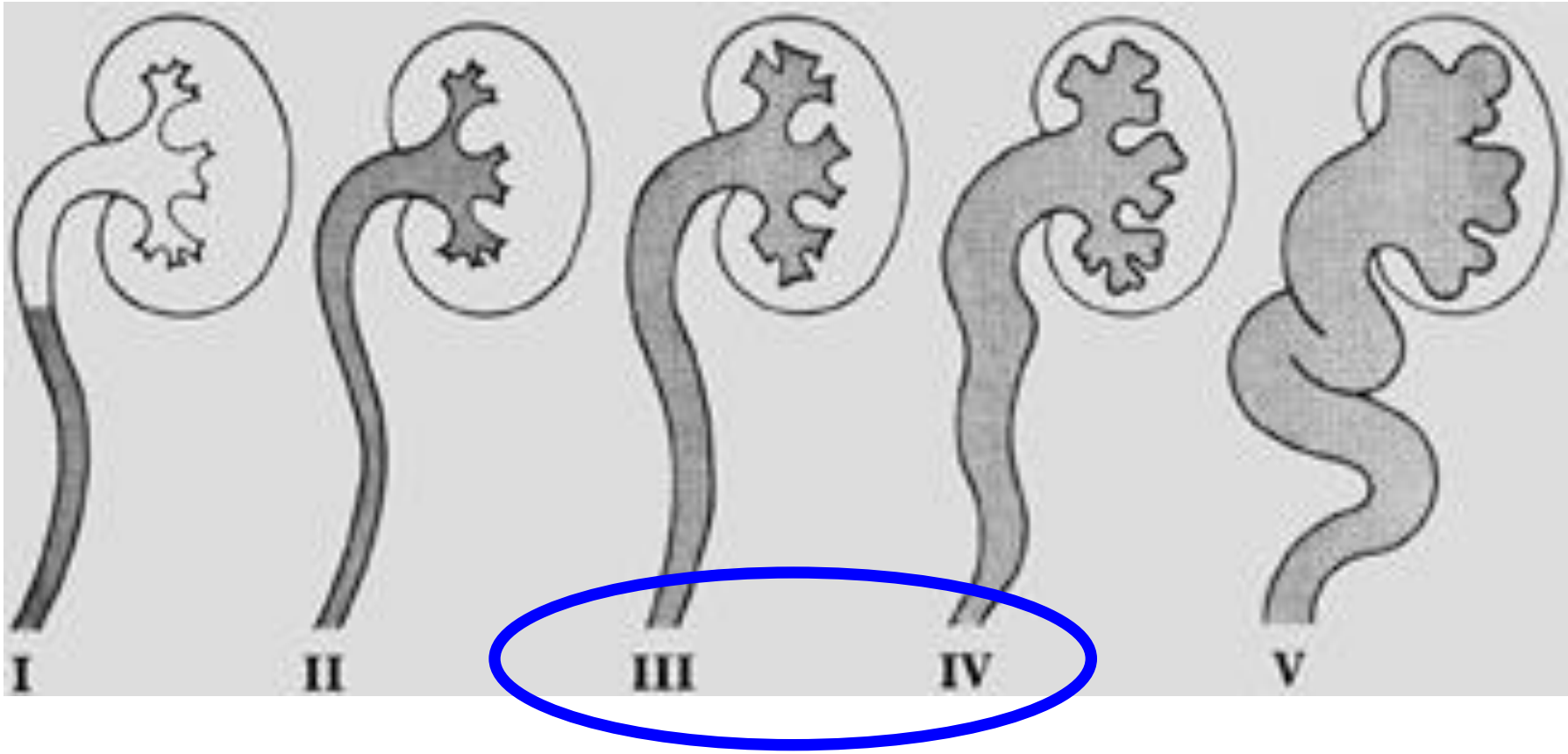
Children of **1 - 2 years with grade III–IV/V VUR** were recruited into this prospective, open, randomized, controlled, multicenter study and followed for 2 years after randomization.

The main study end points

1. VUR status
2. recurrent febrile urinary tract infection
3. renal status on DMSA scintigraphy

Outcomes were analyzed by the intent to treat principle.

VUR Gradierung I – V / V

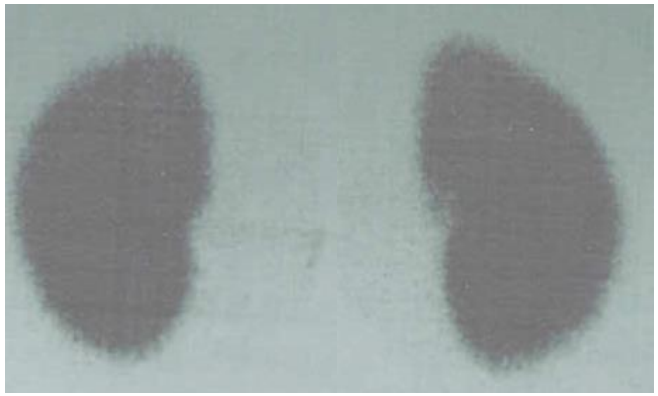


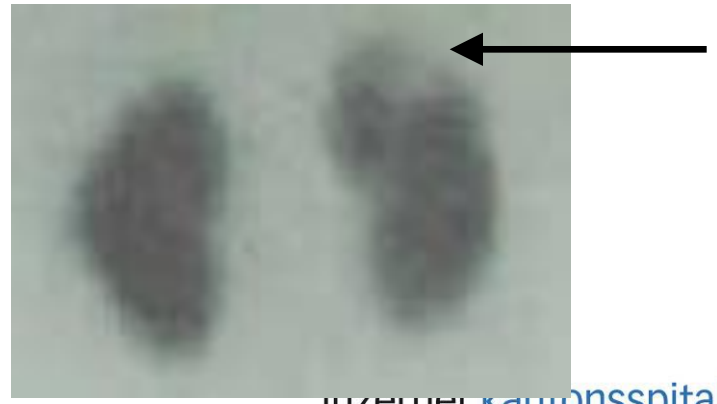
DMSA-Szintigraphie

- Akutstadium: Oberpol rechts
  Läsion = Photondefekt =
  Perfusionsausfall durch
  Pyelonephritis

- Verlauf nach 6 Monaten:

geheilt vs Narbe rechter Oberpol





Group 1: Antibiotic prophylaxis

Children randomized to the prophylaxis group were prescribed **0.5 to 1 mg/kg trimethoprim once daily** as the first choice.

Other options were 1 mg/kg nitrofurantoin and 5 mg/kg cefadroxil, each given once daily. The choice of agent was left to local physician discretion.

Questions on adherence to prophylaxis were asked at each contact, but not otherwise tested.

Group 2: Endoscopic injection

We used **dextranomer/hyaluronic acid copolymer** for endoscopic injection.
Patients in the endoscopic group received prophylaxis until a new VCU showed absent VUR or improvement to grade I–II.

Group 3: Surveillance

No specific preventive measures were done.

All study groups

Parents were made aware of UTI symptoms and told to seek medical advice early if recurrence was suspected, especially if the child had high fever.

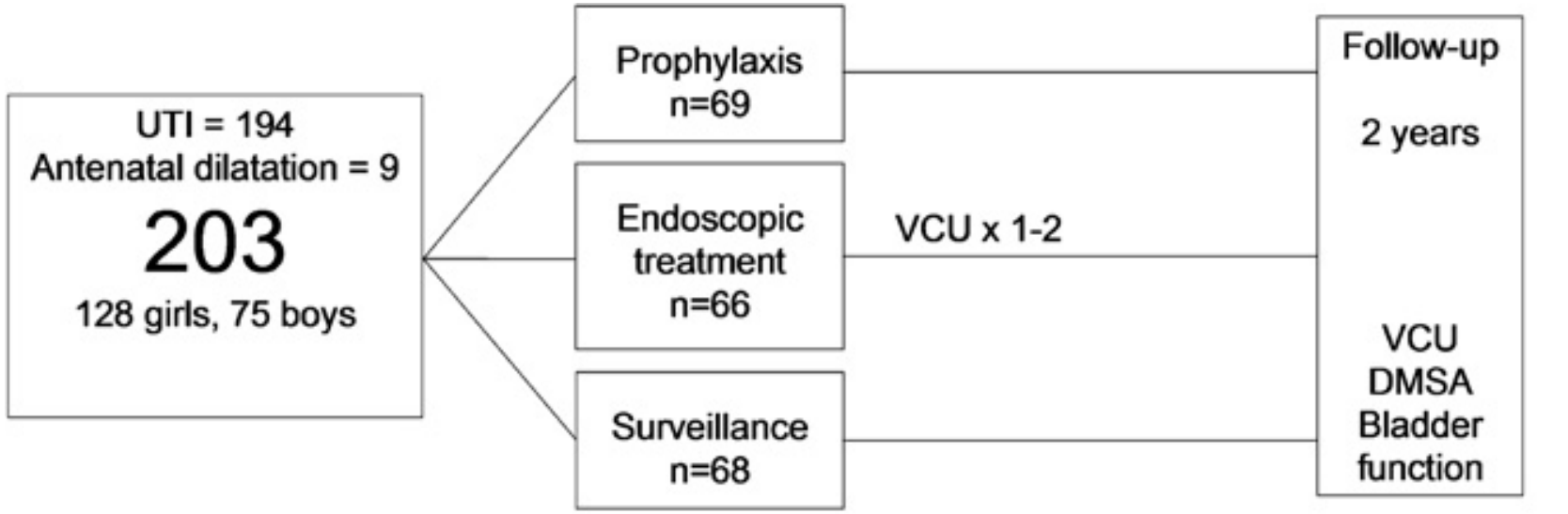

UTI = 194
Antenatal dilatation = 9
203
128 girls, 75 boys
Prophylaxis
n=69
Endoscopic
treatment
n=66
Surveillance
n=68
VCU x 1-2
Follow-up
2 years
VCU
DMSA
Bladder
function
Study start Dec 2000 – inclusion of patients stopped Feb 2007 – last follow-up Apr 2009

Table 1. *VUR status at study entry in 203 children*

VUR Status	No. Girls	No. Boys	Total No.
IV–IV	5	3	8
IV–III	7	10	17
IV–II	6	7	13
IV–I	6	1	7
IV–0	16	16	32
III–III	21	10	31
III–II	20	11	31
III–I	2	2	4
III–0	45	15	60
Totals	128	75	203

Results

- During a 6-year period **128 girls and 75 boys (total n = 203)** entered the study. In 96% VUR was detected after UTI.
- Recruitment was slower than anticipated, but adherence to the protocol was good.
- 93% followed for intended 2 years without treatment arm change
- 201 (= all except 2) completed 2-year follow-up scintigraphy

Conclusions

- Recruitment was difficult, but > 200 children were entered and randomly assigned to 3 groups with similar basic characteristics.
- Good adherence to the protocol made it possible to address the central study questions.

The Swedish Reflux Trial in Children: II. VUR Outcome: Results

- Reflux status improved in all 3 treatment arms
- Of patients in the **prophylaxis**, **endoscopic** and **surveillance** groups **39%**, **71%** and **47%**, respectively, had VUR resolution or downgrading to grade I–II after 2 years.
  - significantly more in the endoscopic than in the prophylaxis and surveillance groups (p 0.0002 and 0.003).
- After 1 or 2 injections 86% of patients in the endoscopic group had no or grade I–II VUR, but recurrent dilating (= III-IV) VUR was seen in 20% after 2 years.

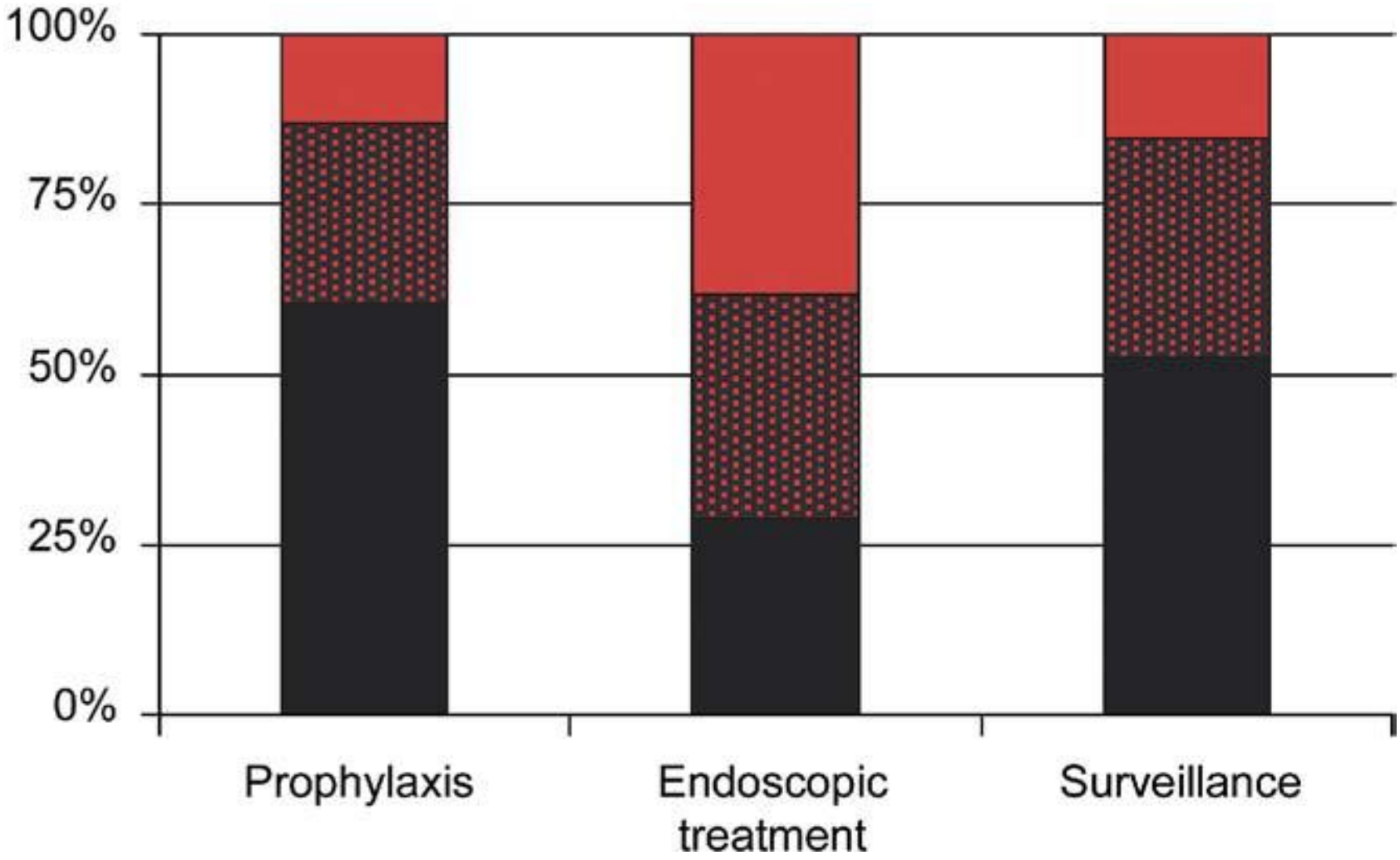


Figure 1. VUR status after 2 years in treatment groups. Red bars indicate no VUR. Red and black bars indicate grade I–II VUR. Black bars indicate grade III–IV VUR.

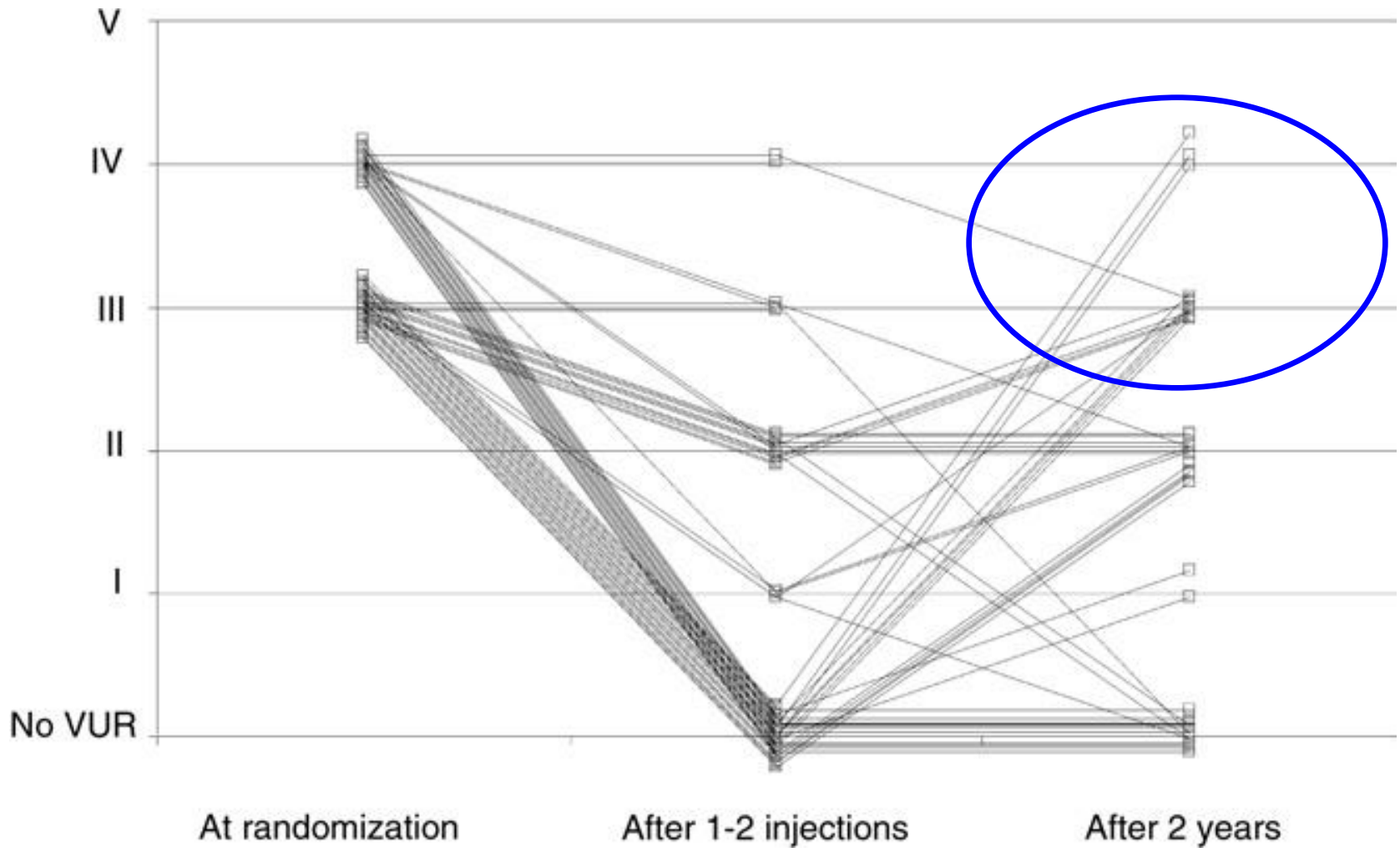


Figure 3. VUR grade at randomization, after 1 or 2 injections and after 2 years in 66 children with endoscopic treatment.

The Swedish Reflux Trial in Children: II. VUR Outcome: Conclusions

- Endoscopic treatment resulted in dilating (= III-IV) VUR resolution or downgrading in most treated children.
- After 2 years endoscopic treatment results were significantly better than the spontaneous resolution rate or downgrading in the prophylaxis and surveillance groups.
- However, of concern is the common reappearance of dilating VUR after 2 years.

The Swedish Reflux Trial in Children: III. UTI Pattern: Results

- 67 febrile recurrences in 42 girls and 8 in 7 boys (p=0.0001)
- Difference in the recurrence rate among treatment groups in girls with febrile infection
  - in 8 of 43 (19%) on prophylaxis
  - 10 of 43 (23%) with endoscopic therapy
  - 24 of 42 (57%) on surveillance (p=0.0002)
- In girls, recurrence rate associated with persistent VUR after 2 years (p=0.0095). However, VUR severity (grade III or IV) at study entry did not predict recurrence.

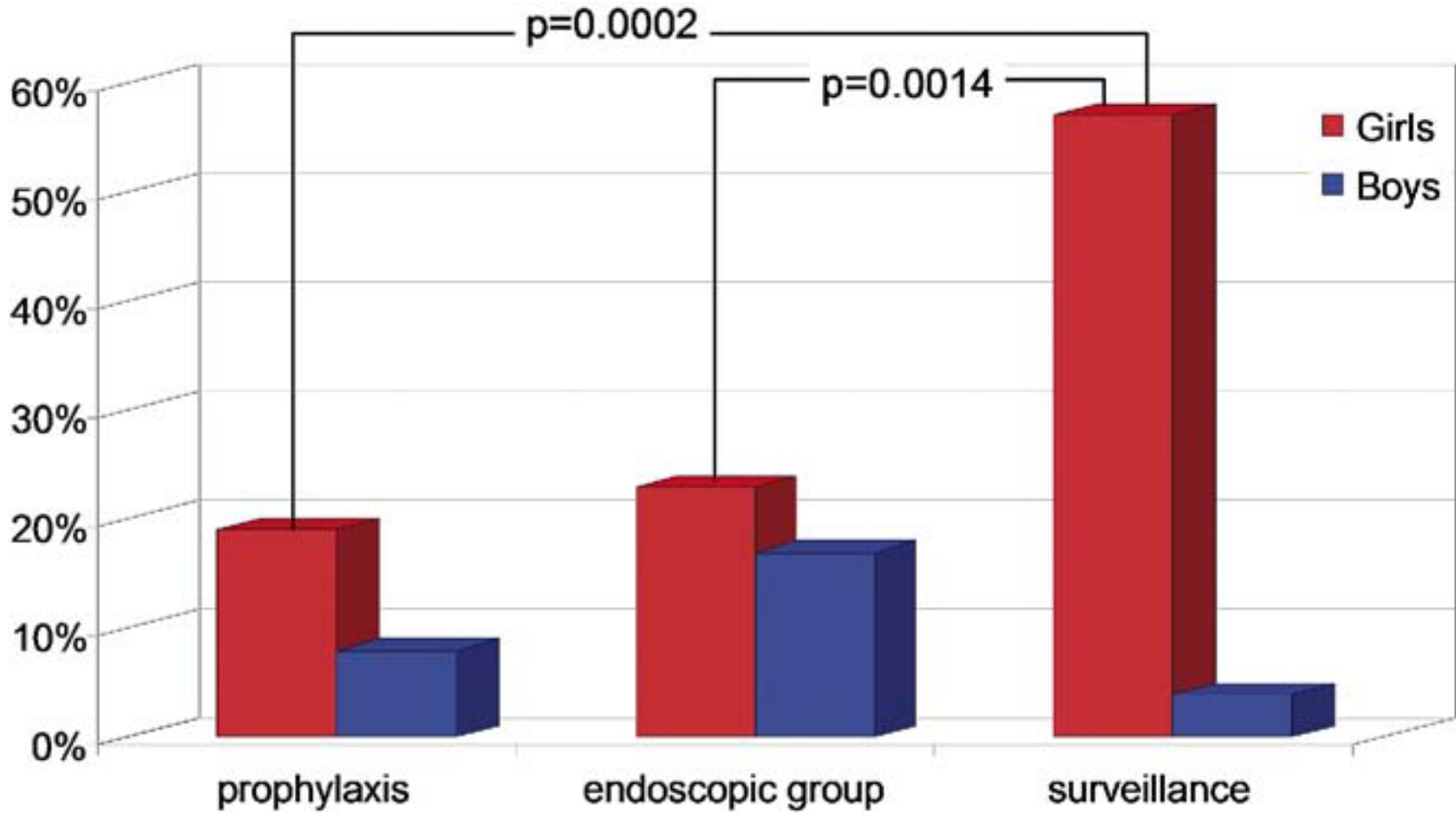
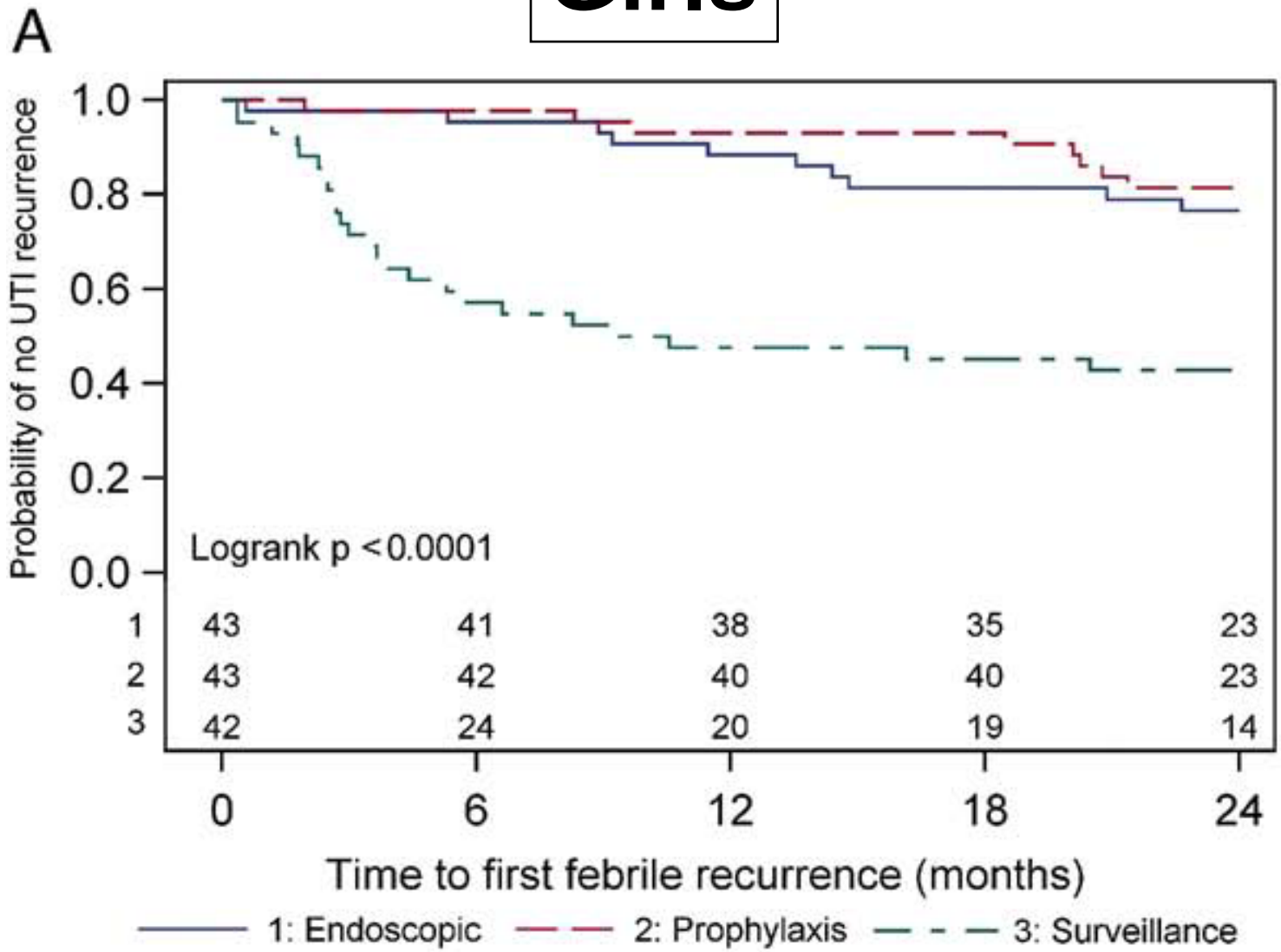


Figure 1. Febrile UTI recurrence rate by gender and treatment group

Girls



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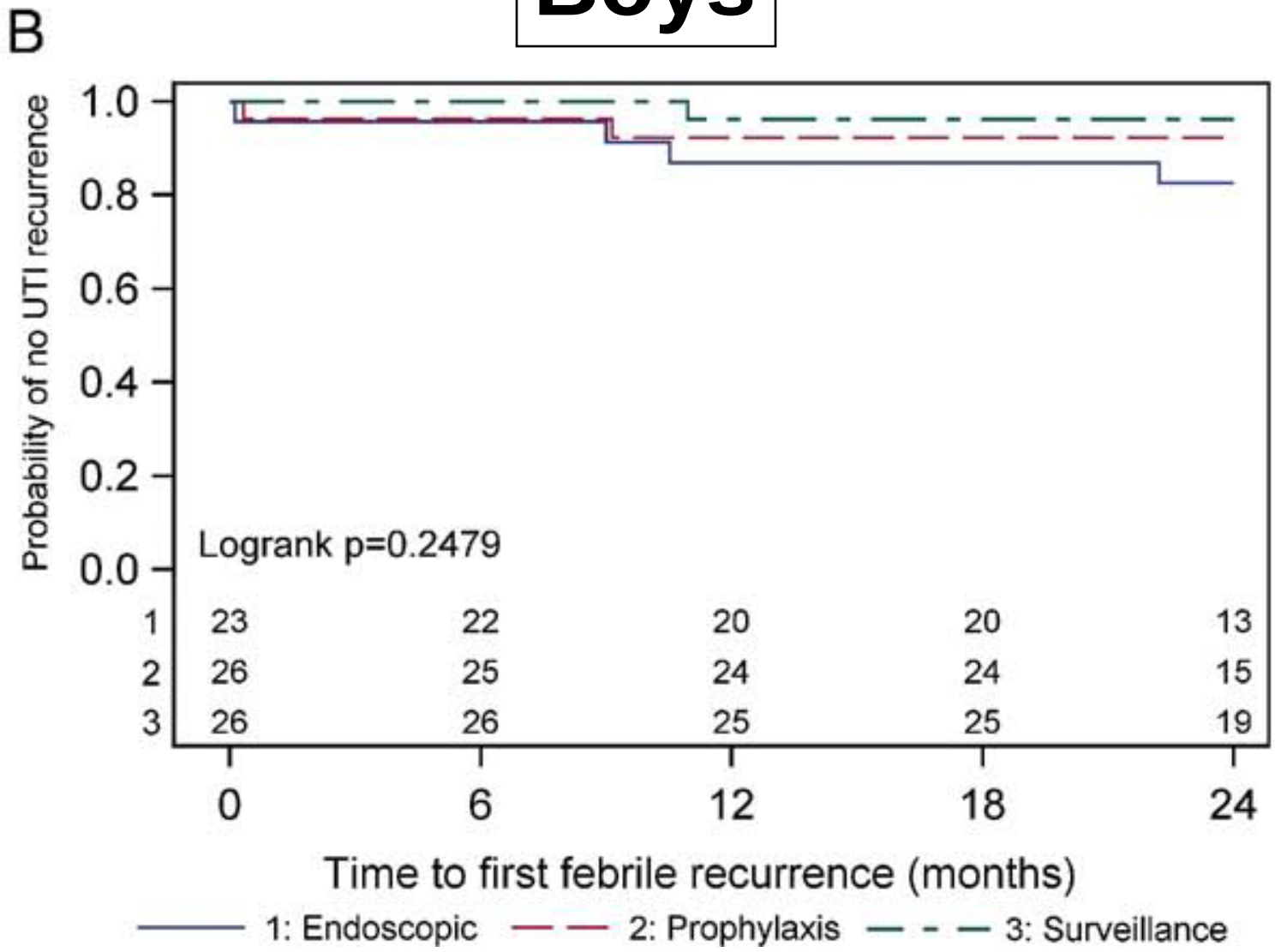
Boys



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The Swedish Reflux Trial in Children: III. UTI Pattern: Conclusions

- In this randomized, controlled trial there was a high rate of recurrent febrile UTI
  - in girls >1 year with dilating (= III-IV) VUR
  - but not in boys
- Antibiotic prophylaxis and endoscopic treatment decreased the UTI rate as compared to surveillance.

The Swedish Reflux Trial in Children: IV. Renal Damage: Results

- New renal damage in a previously unscarred area was seen in 13 girls and 2 boys:
  - 8 were on surveillance
  - 5 received endoscopic therapy
  - 0 was on prophylaxis (p=0.0155)
- New damage more common (p<0.0001) in children
  - with recurrence of (febrile) UTI: 11 of 49 (= 22%)
    - than without UTI: 4 of 152 (= 3%)

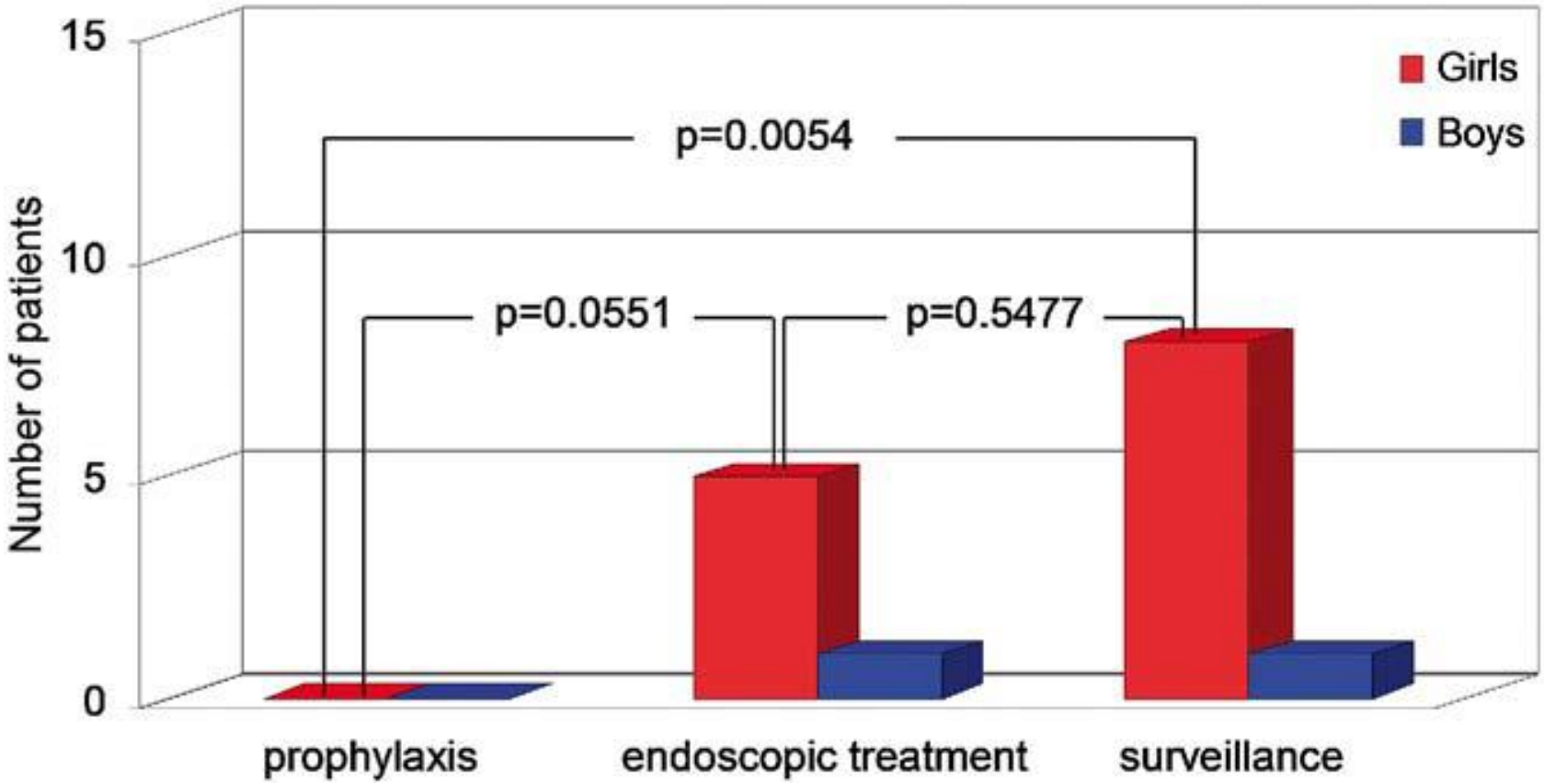


Figure 1. New renal damage in children with dilating VUR by treatment arm

Table 2. *VUR at study entry*

VUR Grade	No. Kidneys*	No. Progression	No. New Damage
No VUR	92	0	0
I	11	0	0
II	44	0	1
III	173	7	10
IV	83	6	5
Totals	402	13	16

1/147 = <1%

29/256 = 11%

* Followup DMSA scan not done in 2 patients.

The Swedish Reflux Trial in Children: IV. Renal Damage: Conclusions

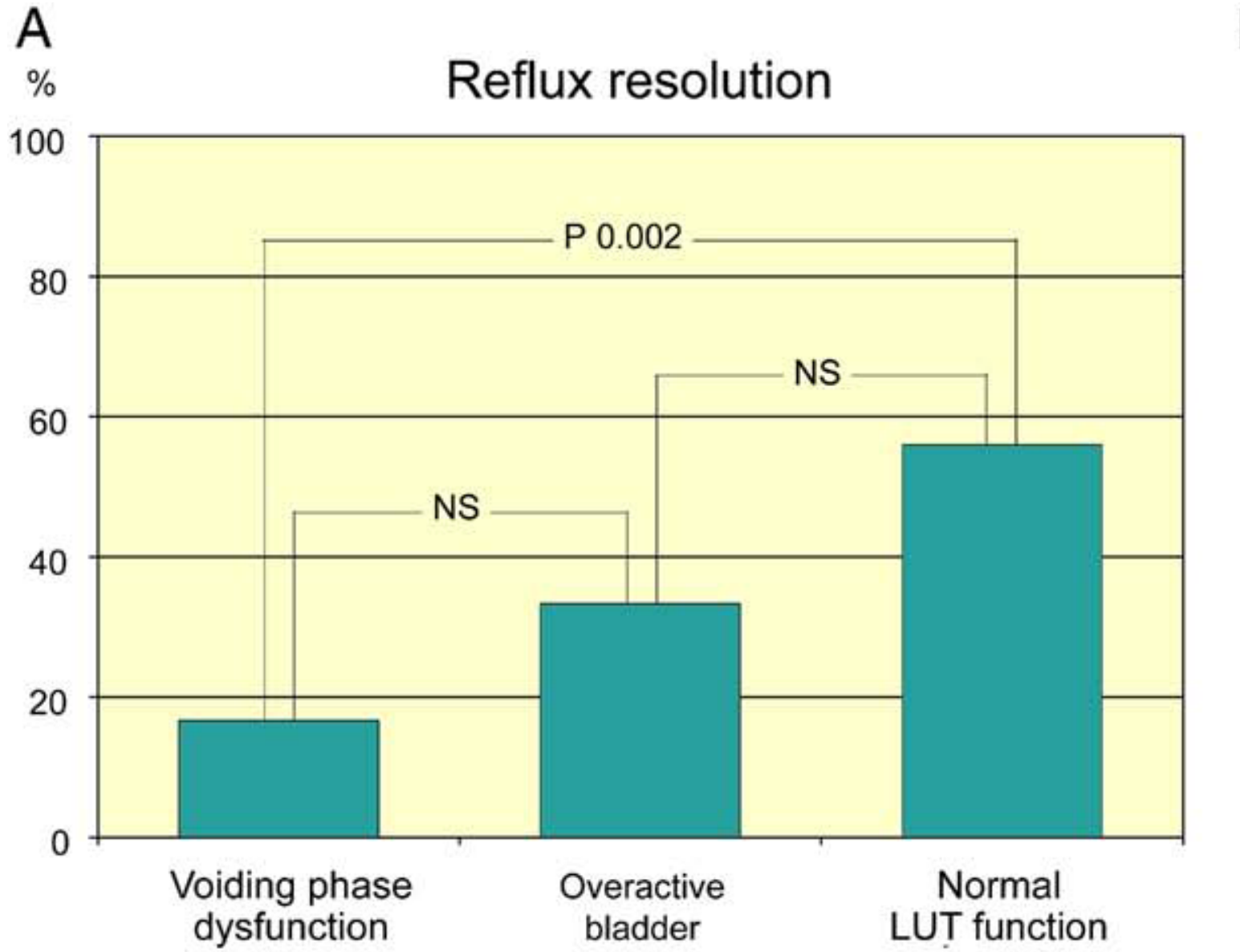
- Renal damage progression may be a consequence of new insults to the kidney or a long-term process in a damaged kidney that does not reflect events that occur during the study period.
- In boys the rate of new renal damage was low.
- It was significantly higher in girls and most common in the control surveillance group.
- Strong association between recurrent febrile UTI and new renal damage in girls.

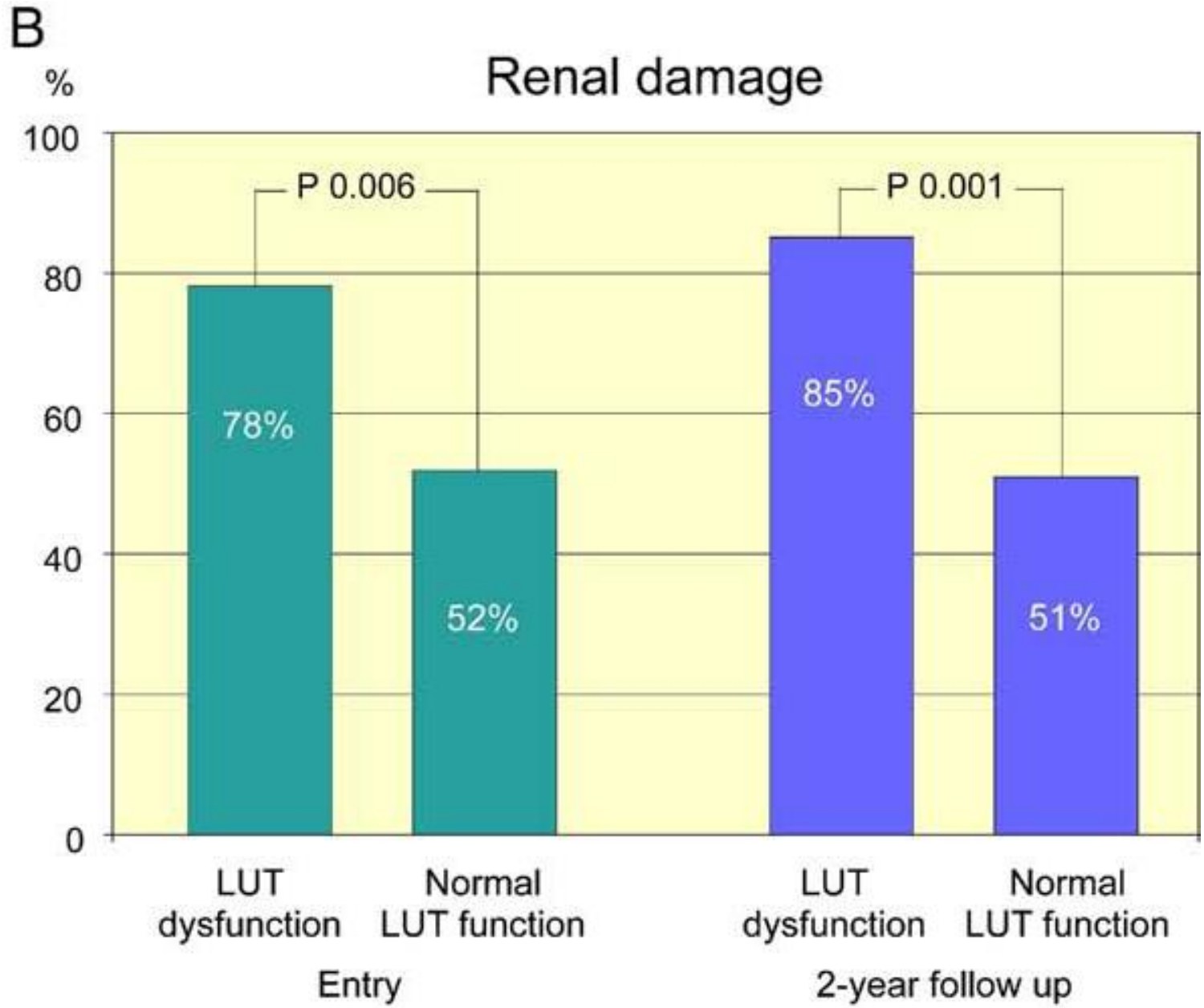
The Swedish Reflux Trial in Children: V. Bladder Dysfunction: Methods

- Lower urinary tract function was investigated by noninvasive methods
  - at study entry with 4-hour voiding observation in 148 patients
  - at 2 years by structured questionnaire and post-void residual flow measurement in 161 patients

The Swedish Reflux Trial in Children: V. Bladder Dysfunction: Results

- Bladder / lower urinary tract (LUT) dysfunction
  - high bladder capacity / increased post-void residual urine
    - at study entry: 20%
    - at 2 years: 34% (overactive bladder / voiding phase)
- Recurrent UTI: 33% with vs 20% without bladder dysfunction (p=0.084)
- VUR resolution: negative correlation with dysfunction at 2 years (p=0.002)
- Renal damage: positive correlation with dysfunction at study entry and at 2 years (p=0.001)


A
%
Reflux resolution
100
80
60
40
20
0
P 0.002
NS
NS
Voiding phase dysfunction
Overactive bladder
Normal LUT function



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The Swedish Reflux Trial in Children: V. Bladder Dysfunction: Conclusions

- After toilet training
  - a third of children with dilating VUR had lower urinary tract dysfunction, mainly voiding phase problems
  - Dysfunction was associated with persistent VUR and renal damage

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Version 03/10

Harnwegsinfektionen und vesikoureteraler Reflux

1. Allgemeines

Der Begriff Harnwegsinfektion (HWI) beinhaltet Pyelonephritis (PN), Zystitis oder asymptomatische Bakteriurie. Ein differenziertes Vorgehen ist nötig. Jede PN ist ein Notfall. HWI treten in den ersten 3 Lebensmonaten bei Knaben, danach bei Mädchen viel häufiger auf. Bei Fieber ohne Fokus ist immer an eine HWI zu denken (bei onkologischen Patienten mit Fieber ohne Fokus mit gleichzeitiger Aplasie: immer Urinkultur).

2. Diagnostik der HWI

2.1. Kriterien für Diagnose HWI

1) Allgemein-Symptome (z.B. Fieber, reduzierter AZ, Erbre-chen).
2) Lokal-Symptome (Schmerzen, Dysurie, Pollakisurie, Einnässen).
3) Erhöhtes CRP.
4) Leukozyturie.
5) Bakteriurie
6) in besonderen Situationen DMSA-Szintigraphie. Im klinischen Alltag gehen wir davon aus, dass eine febrile HWI (Temperatur axillär >38,5°, rektal >38,0°) eine PN ist.

5. Weitere Abklärungen nach der ersten Pyelonephritis (nicht nach Cystitis)

5.1. Alle Kinder:

- **Ultraschall** der Nieren und ableitenden Harnwege innerhalb der ersten 3-(5) Tage
- Kinder mit HWI, die bei uns diagnostiziert werden, sollen den Ultraschall ambulant im Kinderspital erhalten (individuelle Ausnahmen und nach Rücksprache mit dem Hausarzt); die Röntgenabteilung reserviert nach Möglichkeit am Morgen um 8.30 Uhr einen Notfalltermin
- **DMSA-Szintigraphie** nur ausnahmsweise

5.2. < 3 Jahre:

- **MCUG** 2 - 8 Wochen nach HWI bei allen Kindern (Frage nach: VUR = vesikoureteraler Reflux, Ureterocele, Pathologie der Blase, posteriore Urethralklappen)

5.3. > 3 Jahre: MCUG (nach Rücksprache mit OA) nur wenn

- US der Nieren/Harnwege pathologisch
- Knaben mit auffälliger Miktion tagsüber

5.4. Szintigraphie (DMSA oder MAG-3), MR oder IVP: nicht routinemässig

Neu ab Juli 2008
Bei isoliertem VUR Grad I - II/V erfolgt primär keine Prophylaxe mehr. Kontrollierte Studien haben keinen signifikanten Vorteil = Reduktion der Re-Infektionsrate gezeigt.

VUR höheren Grades = Grad III - V/V ist weiterhin eine Indikation für eine antibiotische Langzeitprophylaxe. Da bei Knaben >2 Jahren und bei Mädchen >4 Jahren selbst bei persistierendem VUR das Risiko einer PN mit Narbenbildung gering ist, wird die Prophylaxe in der Regel bei Knaben mit 2 J., bei Mädchen mit 2 - 4 J. gestoppt. Operationsindikationen sind Durchbruchsinfektionen oder Non-compliance.

6.1. Dosierung der Antibiotikaprophylaxe bei VUR und Megaureter

Verabreichung bei Kindern, die noch nicht trocken sind, in 2 Dosen; sobald trocken in 1 Dosis abends:

- Cotrimoxazol (SMX + TMP): 9 mg/kg Cotrimoxazol (oder 1,5 mg/kg Trimethoprim-Anteil) pro dosi
- Nitrofurantoin: 0,75 - 1,0 mg/kg pro dosi: Kapseln können über Apotheke LUKS bestellt werden: Dosis pro Kapsel von 1 bis 150 mg; Kapseln können auch geöffnet werden und Inhalt (Pulver) per os.

- **cave: Alter < 2 Monate: Amoxicillin (Clamoxyl): Dosis 10mg/kg per os; 2 Dosen/d**

6.2. Dauer der Antibiotikaprophylaxe bei VUR und Megaureter

- Knaben: < 2 J: 1 Jahr lang, jedoch mind. bis zum Alter von 2 J.
  > 2 J: 3 – 6 Monate
- Mädchen: < 4 J: Bis zum Alter von **2 - 4** J., resp. bis zum Verschwinden des VUR
  > 4 J: 6 – 12 Monate

VUR 2011

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state of the Swedish and Swiss art

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