The Evolving Role of Antibiotic Prophylaxis for Vesicoureteral Reflux

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Objectives

- Review literature establishing the value of antibiotic prophylaxis in the treatment of vesicoureteral reflux (VUR)
- Understand the impact and consequences of antibiotic prophylaxis
- Discuss recent literature demonstrating no benefit to antibiotic prophylaxis in select patients with VUR in the short term
- Discuss the future of antibiotic prophylaxis in the treatment of VUR

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Vesicoureteral Reflux (VUR)

- VUR affects 1% of otherwise normal children
- ~30-50% of children who present with urinary tract infection have VUR
- 10% of children with prenatally diagnosed hydronephrosis have VUR

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International classification of VUR (Campbell's 9th edition)

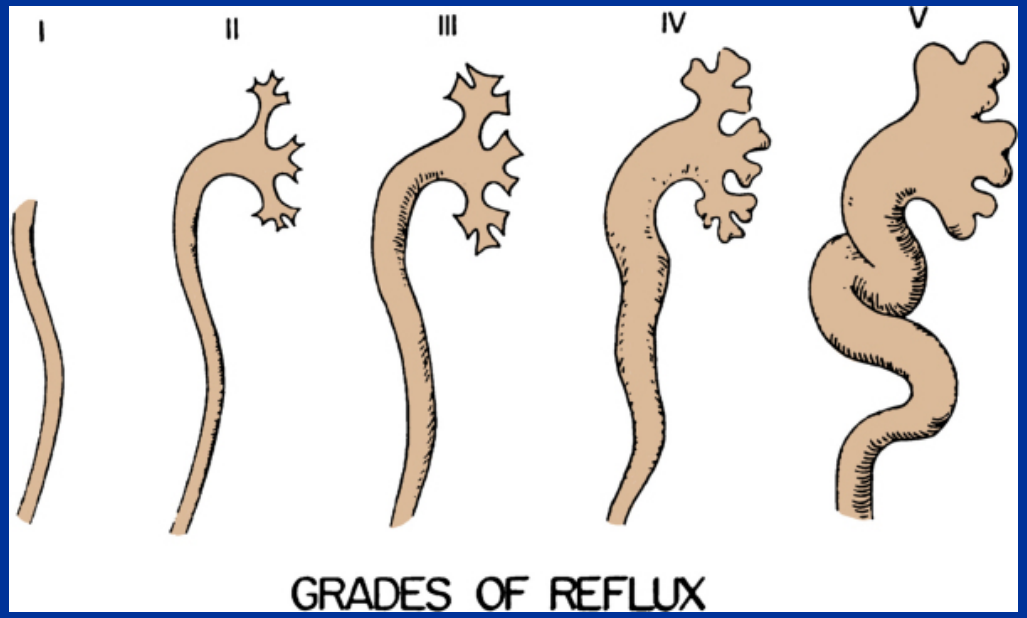


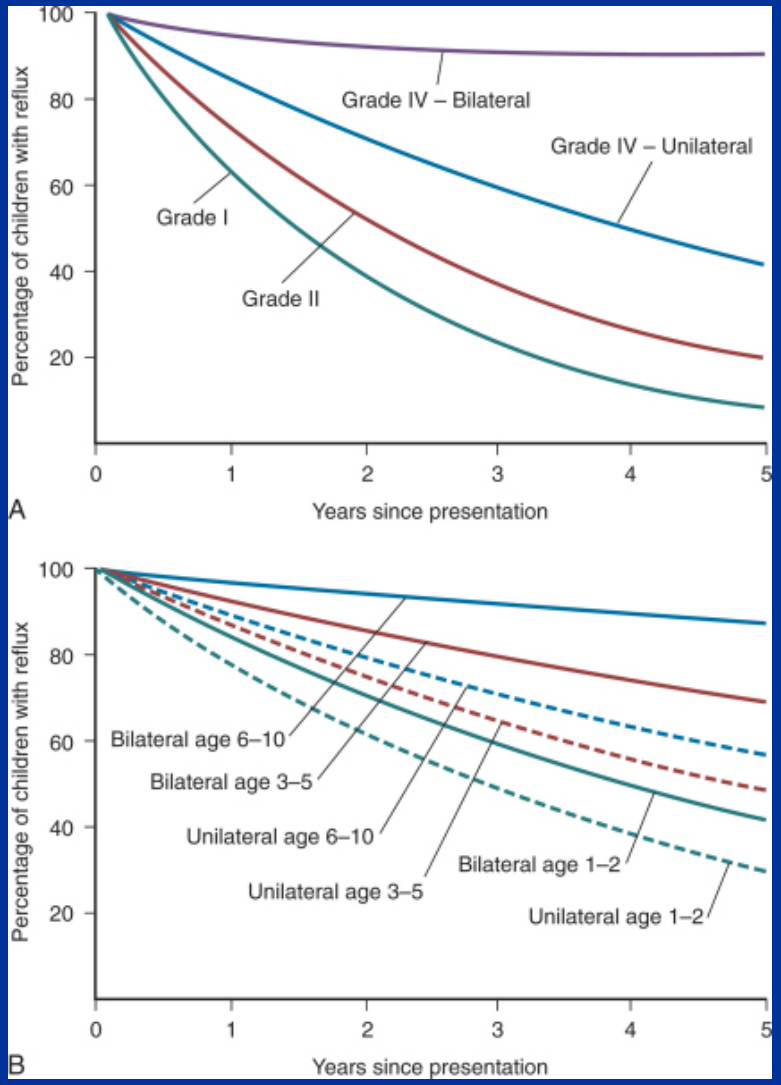
Figure 117-2

	Description
I	Into a nondilated ureter
II	Into the pelvis and calyces without dilatation
III	Mild to moderate dilatation of the ureter, renal pelvis, and calyces with minimal blunting of the fornices
IV	Moderate ureteral tortuosity and dilatation of the pelvis and calyces
V	Gross dilatation of the ureter, pelvis, and calyces; loss of papillary impressions; and ureteral tortuosity

Table 117-3 -- International Classification of **Vsicoureteral Reflux**

VUR Resolution Campbell's 9th Edition

- *From American Urological Association: Report on the Management of Vesicoureteral Reflux in Children. Baltimore, American Urological Association, Pediatric Vesicoureteral Reflux Clinical Guidelines Panel, 1997.*



VUR not just a benign disease - ESRD

- Incidences of CRI and ESRD difficult to assess
  - Ardissino et al (Pediatrics 2003) - contends it is the leading cause of CRI in children
  - Holland et al, J Ped 1990 - 3rd most common etiology of CRI

- However, the prevalence of reflux nephropathy in adults with a history of VUR is markedly lower in more recent series than in older series (Gargollo and Diamond, Nature Clin Prac 2007)

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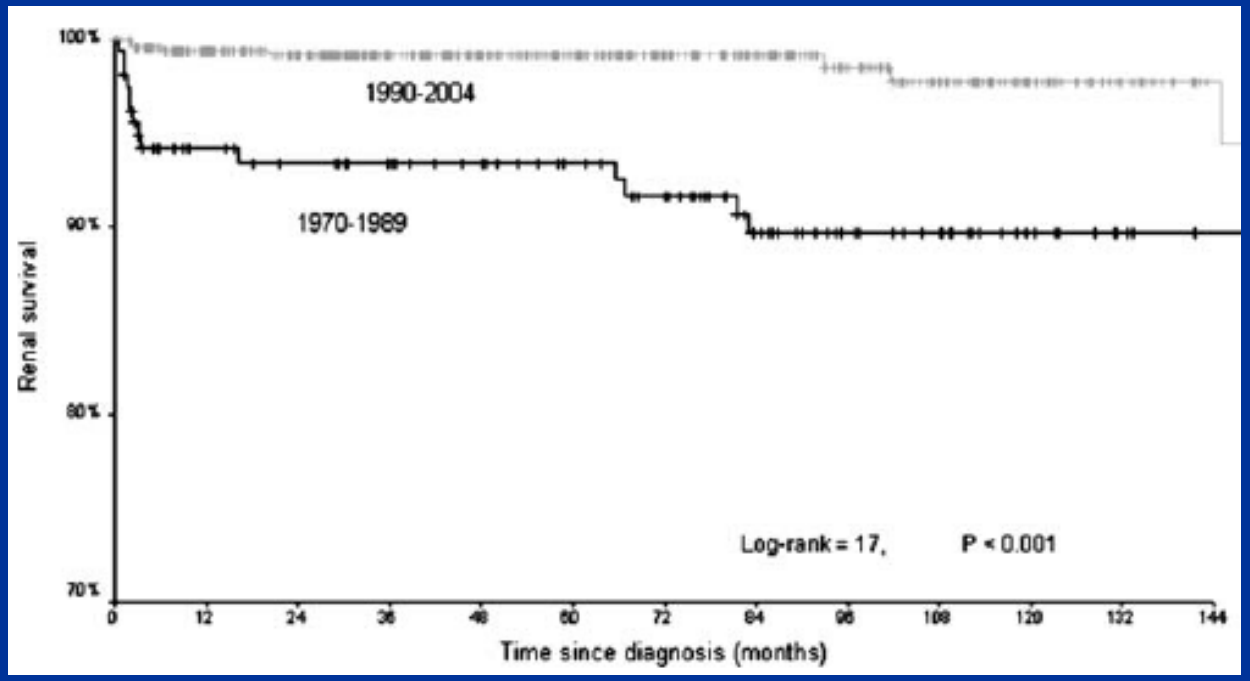
Renal Insufficiency and VUR - last 40 years



- Silva et al, Pediatr Nephrol 2006 – 735 children with VUR
- The probability of chronic kidney disease (GFR < 75ml/min per 1.73 m^2) 11% for patients diagnosed before 1990 and only 2% for children diagnosed after 1990

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VUR not just a benign disease - HTN

- Reflux nephropathy: renal scarring due to VUR
  - Most common cause of severe hypertension in children
  - Affects up to 30% of children with established renal scars

(Wan et al, J Urol 1996; Noe HN, J Urol 1992; Smellie and Normand, *Reflux Nephropathy* 1979; Ardissino et al, Pediatrics 2003)

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How have we arrived upon the current standards for management of VUR?

Foundations of Current Management of VUR

- International Reflux Study (IRS)
- American Urologic Association (AUA) Guidelines for VUR

IRS:
5 year results from European Arm

- "Five- year study of medical or surgical treatment in children with severe reflux: radiological renal finding." Smellie et al, Ped Nephrol 1992.
- 306 children with 8 European centres entered into IRS with UTI and Grade III or IV VUR with GFR >70mL/min followed for 5 years randomized to:
  - Medical treatment - 155
  - Surgical treatment - 151

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IRS:
5 year results from European Arm

- 272 (89%) completed follow-up
- New renal scars (IVU repeated at 6, 18, and 54 months):
  - 19 from medically treated
  - 20 from surgically treated
- 34/39 with scarring had grade IV VUR
- No new scars developed in the non-refluxing renal units among the 69 children with unilateral VUR

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IRS:
5 year results from US Arm

- 132 children with same inclusion criteria randomized as in European arm:
  - 68 assigned to medical therapy
  - 64 assigned to surgical group
- Same duration of f/u

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IRS:
5 year results from US Arm

- No difference in new renal scarring in the two groups:
  - 22% of medical and 31% of surgical patients ($p<0.4$)
- Similar rates of UTI for medical (29.4%) and surgical (32.8%) groups ($p<0.9$)
- Pyelonephritis occurred in 15 medical patients and 5 surgical patients ($p<0.05$)
- No difference in GFR

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IRS – 10 year results From European Arm

- Jodal et al, Pediatric Nephrol (2006)
- F/U planned for 5 years but extended to 10 years
  - 223/252 patients had follow-up imaging
- Renal scarring
  - 5 years: 40 new scars seen (1 discovered too late for print in original article)
  - 10 years: Only 2 new scars seen in next 5 years

IRS – 10 year results From European Arm

- Renal growth and UTI recurrence rate were similar, except that medically treated patients had more febrile infections:
  - 21% of medical patients had febrile UTIs versus 11% surgical patients ($p<0.01$)
- No difference in somatic growth or renal function
- 3 patients developed hypertension requiring treatment
- With close supervision, children with GFR ≥ 70mL/min progressed well with either medical or surgical management

AAP approved 1997 AUA Guidelines

Box 1 American Academy of Pediatrics Antibiotic Prophylaxis Guidelines for Children with Vesicoureteral Reflux.

According to guidelines set forth in 1997 by the Pediatric Vesicoureteral Reflux Guidelines Panel of the American Urological Association, which were endorsed and accepted by the American Academy of Pediatrics, the following patients should receive antibiotic prophylaxis for vesicoureteral reflux.

Children without renal scarring at diagnosis

- Infants (i.e. <1 year of age) with grades I–V reflux
- Children aged 1–5 years with unilateral or bilateral reflux grades I–IV, or unilateral reflux grades III–V
- Children aged 6–10 years with unilateral or bilateral reflux grades I–II. Note that some advocate not treating patients in this group as most are at low risk of developing UTIs and pyelonephritis (provided there is no voiding dysfunction or constipation)

Children with renal scarring at diagnosis

- Infants (i.e. <1 year of age) with grades I–V reflux
- Children aged 1–5 years with unilateral or bilateral reflux grades I–II, unilateral reflux grades III–IV, or bilateral reflux grades III–IV
- Children aged 6–10 years with unilateral or bilateral reflux grades I–II. Higher grades of reflux in patients in this age group should be treated by surgical correction

Gargollo PC and Diamond DA: "Therapy Insight: what nephrologists need to know about primary vesicoureteral reflux." Nature Clinical Practice Nephrology, October 2007.

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AAP approved 1997 AUA Guidelines Highlights

- Renal scarring:
  - Four prospective trials of medical therapy versus surgical correction
  - Birmingham reflux study 1987, Elo et al 1983, Olbing et al 1992, and Weis et al 1992
  - None of these trials showed a significant difference in renal scarring

- Urinary tract infection:
  - 41 articles reviewed for comparison of the incidence of UTI in medical therapy versus ureteral reimplantation
  - Incidence of pyelonephritis is approximately 2.5x higher in medical therapy than ureteral reimplantation
  - Incidence of cystitis is not significantly different in the two groups

AAP approved 1997 AUA Guidelines Highlights

- Ureteral Reimplantation
  - Overall success rate of ureteral reimplantation is 95%
  - Morbidity with surgery
    - postoperative obstruction – range 0 to 9.1 percent with a combined rate of 2%
    - contralateral VUR – 9% and generally resolves within 1 year following surgery

New AUA guidelines are under review but not yet completed

Is there any evidence that VUR should be managed differently?

Meta-analysis of randomized controlled trials (RCTs) for VUR

- "Antibiotics and surgery for vesicoureteral reflux: a meta-analysis of randomised controlled trials"
  - Wheeler et al, Arch Dis Child 2003

- Random effects model used to measure: UTI, new or progressive renal damage, renal growth, hypertension, and GFR

Meta-analysis of RCTs for VUR Wheeler et al 2003

- Relevant abstracts were reviewed independently by 2 authors, and any disagreement was resolved by a third author
- Data extraction was performed independently by 3 authors, and any disagreement was resolved by a fourth author
- The methodological quality of RCTs was evaluated based on randomization method, allocation concealment, standardization and blinding of outcome assessment, intention to treat analysis, and losses of follow up.

Meta-analysis of RCTs for VUR Wheeler et al 2003

- 11 RCTs were identified, and 3 were excluded
  - 2 trials compared injection materials for subureteric injection
  - 1 unable to differentiate randomized from non-randomized patients

Table 1 Characteristics of trials of interventions for children with vesicoureteric reflux

Study	Country	No. enrolled/ no. evaluated	Participants	Inclusion criteria	Intervention	Duration of antibiotics	Outcomes
Holland (1982)[20]	USA	10/10	Children 2 months – 10 years (mean 4.75 years) Source: not stated	Reflux grade* II–IV, with normal renal function and blood pressure	Antibiotic: trimethoprim-sulphamethoxazole or nitrofurantoin 1 mg/kg Combined: reimplantation (not specified) and antibiotics	Both groups: 5 month – 36 months (mean 17 months)	• UTI – culture positive • Renal damage† • Adverse effects of antibiotics
BRS (1987)[21–23]	UK	179/161	Children <15 years Source: GP, paediatrician referrals, hospital casualty	Reflux grade II with scarring or grade III, IV, V in absence of UTI within last 12 months	Antibiotic: trimethoprim or nitrofurantoin 1–2 mg/kg Combined: PL or Cohen reimplantation and antibiotics	Antibiotic: 2 year if resolution of reflux or 5 years Combined: 2 years	• UTI – culture positive • Renal damage† • GFR‡ • Resolution of reflux • Renal length
Morris (1991)[19]	New Zealand	138/118	Children 6 months – 10 years Source: not stated	Reflux grade III–IV, no major urological abnormality	Antibiotic: type and dose not stated Combined: Cohen reimplantation and antibiotics	Antibiotic: 2 years Combined: 3 months	• UTI – culture positive • GFR • Resolution of reflux
IRS Europe (1992)[12,24–32]	Europe	321/302	Children 6 days – 11 years Source: university teaching hospitals	Reflux grade III or IV, no major urinary tract abnormality, no previous urinary tract surgery, creatinine normal	Antibiotic: nitrofurantoin or trimethoprim 1–2 mg/kg Combined: PL, Cohen, LG reimplantation and antibiotics	Antibiotic: resolution of reflux or 5 years Combined: 6 months	• UTI – culture positive • Renal damage† • Obstruction post-op • Resolution of reflux • Renal length
IRS US (1992)[33–35]	USA	142/132	Children <10 years Source: university teaching hospitals	Reflux grade III or IV, no major urinary tract abnormality, no previous urinary tract surgery, creatinine normal	Antibiotic: nitrofurantoin or trimethoprim 1–2 mg/kg Combined: PL, Cohen, or other reimplantation and antibiotics	Antibiotic: resolution of reflux or 5 years Combined: 6 months	• UTI – culture positive • Renal damage† • Resolution of reflux • Renal area
Reddy (1997)[18]	USA	43/29	Children: age range not stated Source: university teaching hospital	Reflux grade not stated, newly diagnosed	Antibiotic prophylaxis: antibiotic not specified No treatment: daily urine nitrate Intermittent antibiotics 3 times per wk	Antibiotic: 1 year	• UTI • Renal damage¶ • Resolution of reflux
Smellie (2001)[24]	UK	53/50	Children 1–12 years Source: university teaching hospitals	Reflux grade III–V with bilateral abnormal IVP, no major urological abnormality	Antibiotic: nitrofurantoin or trimethoprim or trimethoprim-sulphamethoxazole 1–2 mg/kg Combined: Cohen and antibiotics	Antibiotic: variable Combined: 6 months	• UTI – culture positive • Renal damage† • GFR (change) • Renal length (change)
Capozza (2002)[5]	Italy	61/60	Children > 1 year Source: university teaching hospital	Reflux grade II–IV for ≥6 mth, no major urological abnormality, no recurrent UTI	Antibiotic: Not specified Combined: Dx/HA copolymer implantation and antibiotics	Antibiotic: 1 year Combined: 1 month	• UTI • Renal damage§¶ • GFR (change) • Resolution of reflux

*Grade of reflux standardised to the International Reflux Study. †On intravenous pyelogram. ‡Glomerular filtration rate. §On renal ultrasound.
¶On 99m-technetium dimercaptosuccinic acid scan.
PL, Politano-Leadbetter procedure; LG, Lich-Gregoir procedure; Dx/HA copolymer, dextranomer/hyaluronic acid copolymer.

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Meta-analysis of RCTs for VUR Wheeler et al 2003

- Similar outcomes noted as AUA Guidelines:
  - No difference in overall UTI rates
  - Lower rate of febrile UTI in surgery group
  - No difference in renal scarring in the two groups

- Reddy et al, Proceedings of the AAP 1997
  - 29 patients with antibiotics and observation arm
  - No difference in risk of UTI or renal scarring in two groups

Meta-analysis of RCTs for VUR Wheeler et al 2003

- Conclusions:
  - It is uncertain whether we benefit children with VUR at all with the current standard management
  - Additional benefit of surgery over antibiotics alone is small
  - With an assumed UTI rate of 20% on abx for 5 years, 9 ureteral re-implantations would be required to prevent 1 febrile UTI with no reduction in the number of non-febrile UTIs or renal damage

- Without observation arm in a prospective, randomized trial, true benefit or lack of benefit is unknown

- Does antibiotic prophylaxis affect the rate of recurrent UTIs?

Recurrent UTIs in Children Conway et al, JAMA 2007

- Large retrospective cohort of children 6 years or younger diagnosed between 2001-06
- Records searched from 27 primary care pediatric practices that share EMR
- 74,974 patients identified, 775 with recurrent UTIs

Recurrent UTIs in Children
Conway et al, JAMA 2007

- Antibiotic prophylaxis NOT associated with decreased risk of recurrent UTI

- Large inherent limitations of study:
  - Retrospective
  - 65% of chldren did not have VCUGs
  - Circumcision status unknown in 47% of male patients

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Smellie 1978 Lancet

- 45 children studied in a randomized open study of antibiotic prophylaxis versus none after first or recurrent UTI

- Number of UTIs after 10 months:
  - Prophylaxis – none
  - No prophylaxis – 11 UTI

Cochrane Study 2006

Long-term antibiotics for preventing recurrent UTIs

- Williams, Wei, and Craig
- Databases searched for randomized comparisons of antibiotics with other antibiotics, placebo, or no tx to prevent recurrent UTI
  - Two authors independently assessed and extracted information
  - Model used to estimate relative risk (RR) and risk difference (RD) for recurrent UTI (95% CI)

Cochrane Study 2006

- The following studies were identified and selected:

  Brendstrup 1990, Carlsen 1985, Lettgen 2002, Lohr 1977, Montini 2004, Savage 1975, Smellie 1978,Stansfield 1975

- 5/8 studies compared antibiotics with placebo or no treatment with varied duration of treatment (10 wks to 12 mos)

Results: Cochrane Study 2006

- Antibiotics reduced the risk of repeat positive urine culture compared to placebo/no treatment (RR 0.44, RD -30%)

- Comparison of antibiotics:
  - Nitrofurantoin more effective than trimethoprim (RR 0.48, RD -18%) but less well tolerated
  - Cefixime more effective than nitrofurantoin (RR 0.74, RD -3%) but 62% vs 26% patients taking respective medication had adverse effects

Is it necessary to give antibiotic prophylaxis to patients while being followed for VUR?

Garin et al, Pediatrics, March 2006

- "Clinical Significance of Primary Vesicoureteral Reflux and Urinary Antibiotic Prophylaxis After Acute Pyelonephritis"

- Conducted at 4 centers: University of South Florida; Universidad Austral, Valdivia, Chile; Hospital de Nuestra Senora de la Candelaria, Tenerife, Spain; and Hospital Materno Infantil, Gran Canaria, Spain

- Patients 3 months to 18 years of age who had acute pyelonephritis were randomized to either antibiotic prophylaxis or no antibiotic prophylaxis

Garin et al, Pediatrics, March 2006

- Monitored every 3 months for 1 year
- DMSA scans repeated every 6 months or if there was a febrile UTI
- UA/Urine cx repeated at each visit
- RUS/VCUG repeated after 1 year of monitoring
- 218/236 completed the study

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Garin et al, Pediatrics, March 2006

TABLE 1 Distribution of Demographic Characteristics in the Different Groups

Characteristic	Patients With VUR		Patients Without VUR	
	Prophylaxis	No Prophylaxis	Prophylaxis	No Prophylaxis
No.	55	58	45	60
Female/male	46/9	45/13	36/9	51/9
Age				
Median	3 y	2 y	2 y	2 y
Range	3 mo to 12 y	3 mo to 9 y	3 mo to 15 y	6 mo to 17 y
Degree of VUR, *n* (%)				
Grade I	9 (16.2)	10 (17.2)		
Grade II	28 (51.1)	29 (50.0)		
Grade III	18 (32.5)	19 (32.7)		

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Garin et al, Pediatrics, March 2006

TABLE 2 Rate and Type of UTI Recurrence in the Different Groups

Type	*n* (%)			
	Patients With VUR		Patients Without VUR	
	Prophylaxis	No Prophylaxis	Prophylaxis	No Prophylaxis
Asymptomatic	0 (0.0)	3 (5.1)	1 (2.2)	4 (6.6)
Cystitis	6 (9.2)	9 (15.5)	1 (2.2)	8 (13.8)
Acute pyelonephritis	7 (12.9)	1 (1.7)	2 (4.5)	2 (3.3)
None	42 (79.6)	45 (75.6)	41 (91.1)	46 (76.7)

TABLE 3 Rate of Renal Scars After Acute Pyelonephritis in the Different Groups

	Patients With VUR		Patients Without VUR	
	Prophylaxis	No Prophylaxis	Prophylaxis	No Prophylaxis
Renal scars, *n* (%)	5/55 (9.0)	2/58 (3.4)	2/45 (4.5)	4/60 (6.6)

UTIs on prophylaxis – 17

UTIs off prophylaxis - 27

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Garin et al, Pediatrics, March 2006

- Results:

  No statistically significant difference was observed with respect to rate of recurrent UTI, type of recurrence, recurrence of pyelonephritis, and rate of renal scarring

RIVUR Study

- Sponsored by National Institute of Diabetes and Digestive and Kidney Diseases
- Purpose: to learn whether all children with VUR should be treated with antibiotics
- Primary Outcome Measures: recurrent febrile or symptomatic urinary tract infection during 2-year follow-up
- Secondary Outcome Measures: renal scarring based on DMSA scan performed 1 and 2 years after enrollment

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RIVUR Study

- Study started in May 2007 and expected completion in April 2011

- Multicenter, randomized, double-blind, placebo-controlled trial with enrollment of 600 children

RIVUR Study Eligibility Criteria

2 months of age or greater but less than 6 years at time of randomization, a diagnosed first febrile UTI or symptomatic UTI within 70 days prior to randomization, and presence of Grade I-IV based on voiding cystourethrogram

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RIVUR Study Exclusion Criteria

- UTI diagnosis more than 70 days prior to randomization
- For patients less than 6 months of age at randomization, gestational age less than 34 weeks
- Co-morbid urologic anomalies
- Hydronephrosis, SFU Grade 4
- Ureterocele
- Urethral valve
- Solitary kidney
- Profoundly decreased renal size unilaterally on ultrasound,(based on 2 standard deviations below the mean for age and length) performed within 70 days after diagnosis of index UTI
- Multicystic dysplastic kidney
- Neurogenic bladder
- Pelvic kidney or fused kidney
- Known sulfa allergy, inadequate renal or hepatic function, G6PD deficiency or other conditions that are contraindications for use of TMP/SMZ
- History of other renal injury/disease
- Unable to complete the study protocol
- Congenital or acquired immunodeficiency
- Underlying anomalies or chronic diseases that could potentially interfere with response to therapy such as chronic gastrointestinal conditions (i.e., malabsorption, inflammatory bowel disease), liver or kidney failure, or malignancy.
- Complex cardiac disease as defined in the Manual of Procedures.
- Any known syndromes associated with VUR or bladder dysfunction
- Index UTI not successfully treated
- Unlikely to complete follow-up
- Family history of anaphylactic reaction to sulfa medications

**** There are many nuances to the evaluation and treatment of VUR**

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Not all VUR the same – *Renal Scarring*…

- Silva et al (Pediatric Nephrology 2006)
  - 735 children with primary VUR
  - Retrospective analysis of patients followed between 1970 and 2004
- Renal units with scarring stratified by grade

Table 2 Distribution of reflux grades and renal damage (RD) according to gender (n=1,116 renal units)

Grade of VUR	Male		Female		Total
	RD(+)	RD(−)	RD(+)	RD(−)	
I	1	20	2	49	72
II	6	63	39	266	374
III	23	63	92	171	349
IV	56	35	109	44	244
V	36	16	22	3	77
Total	122	197	264	533	1,116

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Renal Scarring: IRS vs Garin et al

- Overall rate of renal scarring in IRS (at 5 years): 60/438 (14%)
  - 40/306 in European arm (13.1%)

- Overall rate of renal scarring in Garin et al (at 1 year in VUR patients): 7/113 (6.2%)

Renal Scarring: IRS vs Garin et al

- Overall scars per VUR grade in IRS European arm:
  - Grade 3: 5/56 (8.9%)
  - Grade 4: 34/250 (13.6%)
  - Unknown: 1
  - * Grade 3 comprises 18.3% of patients in this study

- Overall scars per VUR grade in Garin et al
  - 1/19 (5.3%) with grade 1
  - 3/57 (5.2%) with grade 2
  - 5/37 (13.5%) with grade 3
  - * Grade 3 comprises 32.7% of patients in this study

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Renal Scarring and Animal Models

- Arnold et al, BJU 1993: In female piglets with unilateral VUR and ecoli inoculation into the bladder, bacterial cultures from renal parenchyma positive in:
  - 33% of refluxing kidneys with pyelonephritic scars
  - 23% of refluxing kidneys without scars
  - 21% of non-refluxing kidneys

Renal Scarring and Animal Models

Treatment with antibiotics significantly improved early histological changes in the pig model (Ransley and Risdon, Kidney Int 1981)

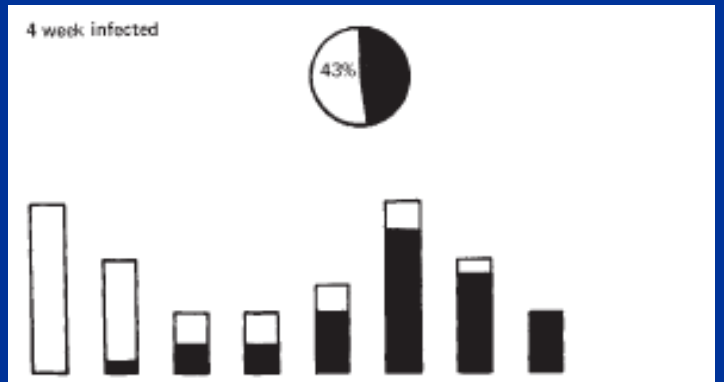

Fig. 8. *Extent of parenchymal damage in the control animals.* Each *bar chart* indicates the total area at risk in the kidney subjected to infected VUR in individual animals; that is, the height represents the number of refluxing papillae. The *shaded portion in each bar chart* indicates the extent of the damage observed. The *pie charts* summarize the information for each group.

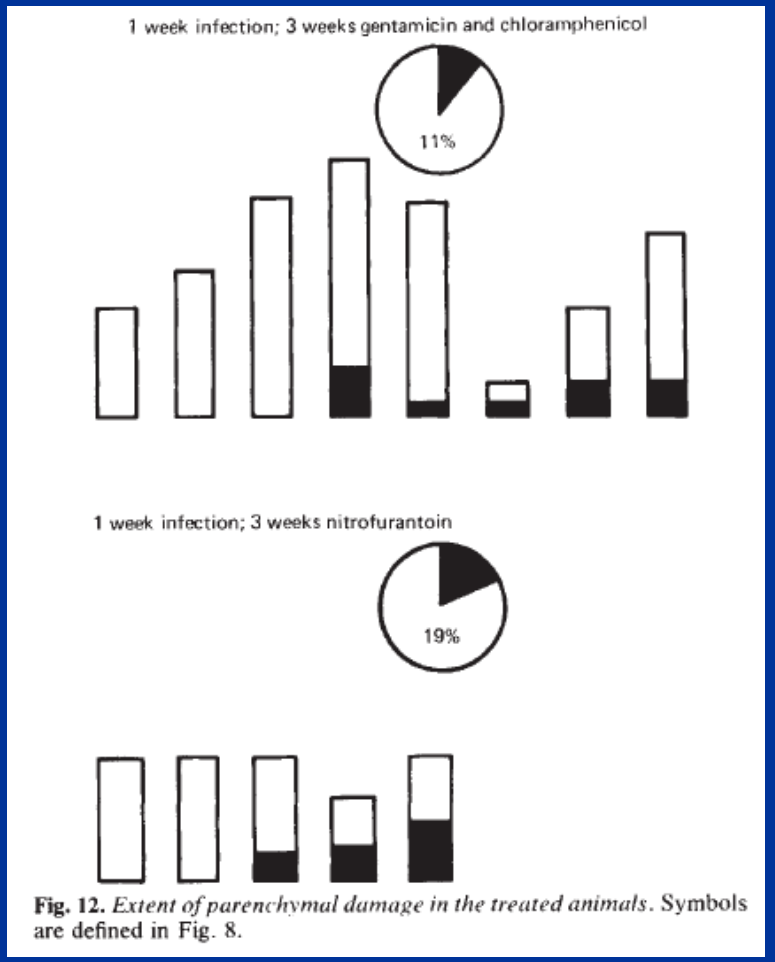

Fig. 12. *Extent of parenchymal damage in the treated animals.* Symbols are defined in Fig. 8.

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Renal Scarring and Animal Models

- VUR plays a role in the pathogenesis of renal scarring
- Antibiotic therapy can reduce renal scarring in animal models

Miscellaneous considerations about renal scarring not discussed but worth mentioning

- Can be caused by obstruction
- Appears to more readily occur in young children
- Renal dysplasia is indistinguishable from renal scarring and has been observed in infants without a history of UTI

Conclusions

- Progress has been made in the understanding and treatment of VUR
- Antibiotic prophylaxis is generally well tolerated with very limited major side effects
- Surgical management (ureteral reimplantation) is largely successful in correcting VUR and reducing the risk of recurrent febrile UTIs
- Hypertension and renal scarring are not common following long term management of VUR with either medical or surgical management

Conclusions

- No reduction in renal scarring with medical or surgical management of VUR has been demonstrated
  - Long-term (>10 years) results and expectations with these treatment modalities are known

- Evidence exists that antibiotic prophylaxis is beneficial in the treatment of recurrent UTIs

Conclusions

- Emerging data now exists which challenges the need for antibiotic prophylaxis in the settings of recurrent UTIs and low grade VUR
- Renal scarring is more likely in higher grades of VUR
- VUR has been linked to the pathogenesis of renal scarring in animal models

Conclusions

- It may be appropriate to withhold antibiotic prophylaxis in some patients with VUR with close observation
  - However, many nuances and varieties of VUR exist
  - May lead to avoidable renal scarring

- Most importantly - larger, randomized controlled studies are needed to:
  - Evaluate the impact of antibiotic prophylaxis in the setting of recurrent UTIs
  - Evaluate the significance of antibiotic prophylaxis in patients with VUR