

# The Pathogenesis And Management Of Renal Scarring In Children With Vesicoureteric Reflux And Pyelonephritis

Mahmood R. Khazaei, MD

Associate professor of Pediatric Nephrology

Islamic Azad University – Mashhad Branch

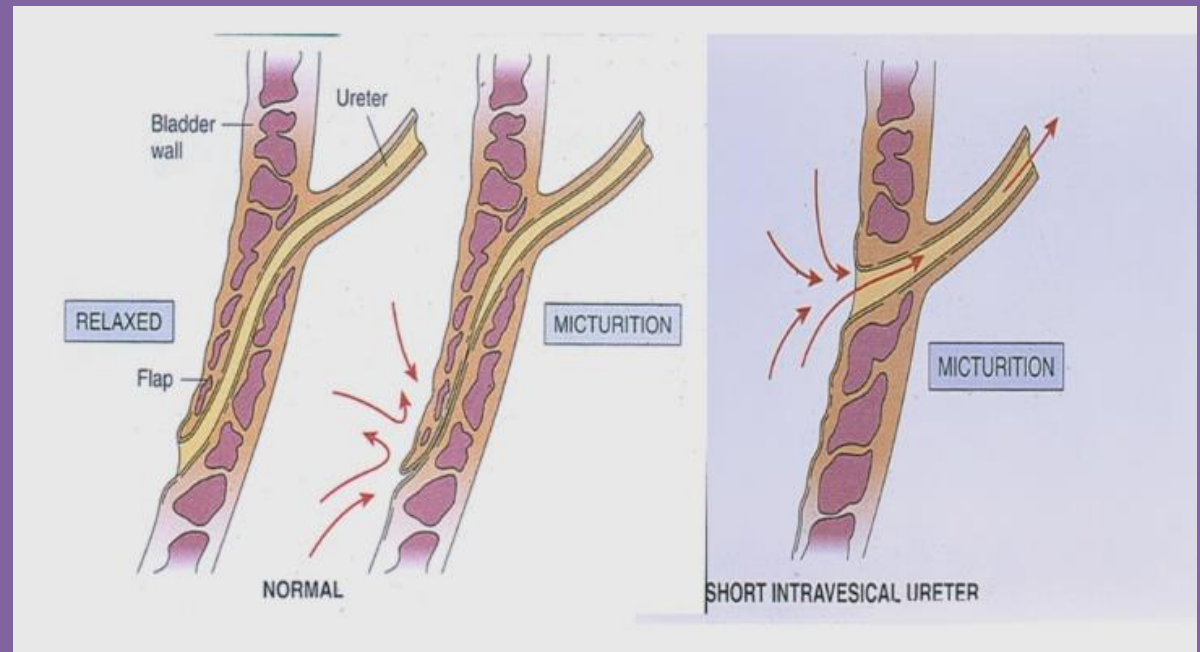
# Basic concepts

- **Most common anatomical condition leading UTI**
  - VUR found in 50% of children with UTI.
  - Reflux nephropathy is leading cause of 1/3 childhood ESRD
- **Affects 1% of all children.**
- **Boys typically dx with higher grades than girls.**
- **F/M ratio is 6:1**
- **10 times more common in whites vs blacks**
- **Hereditary components / Family history !**
  - ✓ parent: 50% / sibling 33-45%

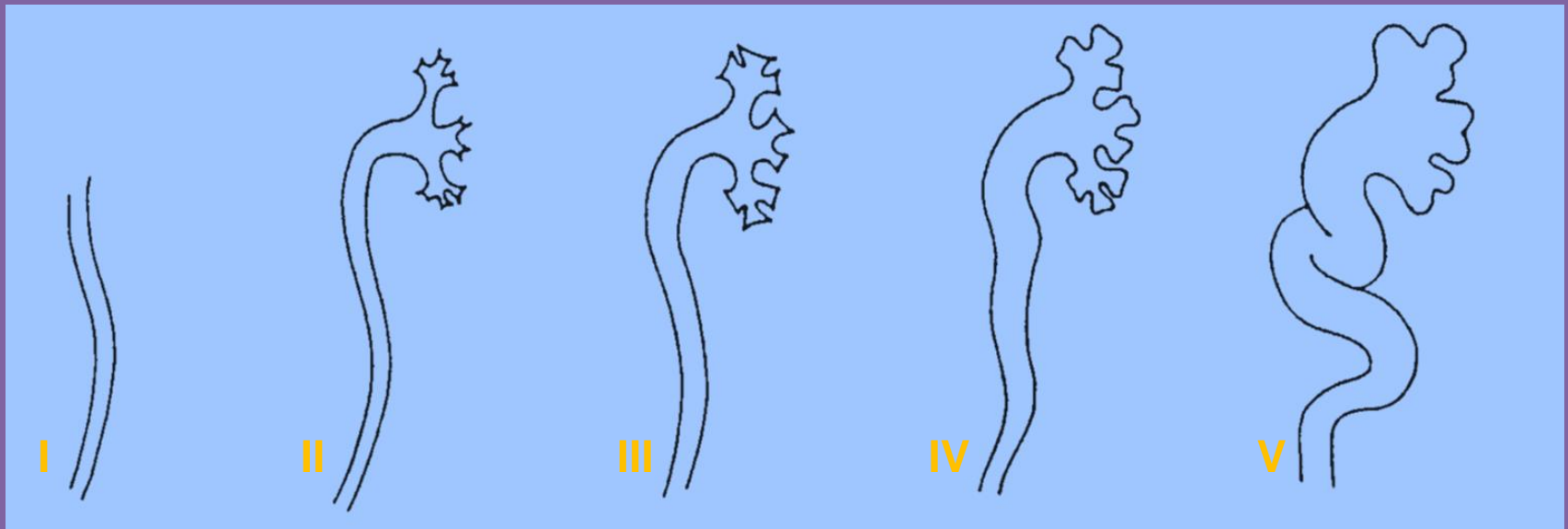
# Definition: VUR

Abnormal flow of urine backward from the bladder

- Primary
- Secondary
  - Functional
  - Anatomical

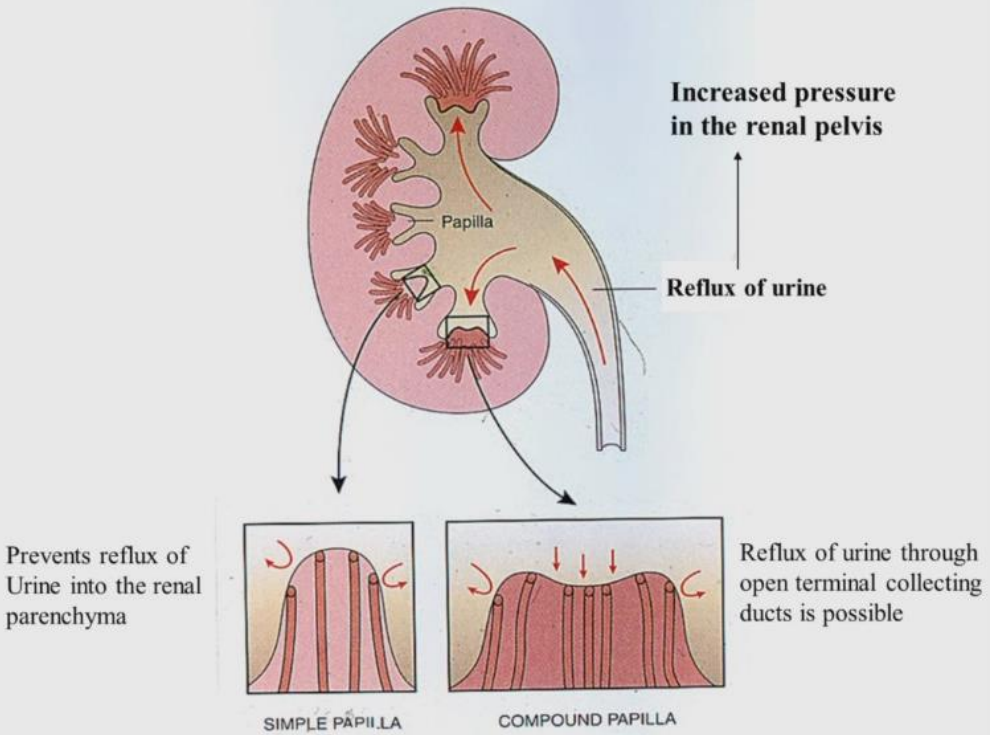


# International Reflux Study grading



International Study Classification (Williams & Wilkins © 1981)

# Definition: IRR



S Kanumakala et al. Arch Dis Child 2004;89:692

# Renal scarring / pathogenesis

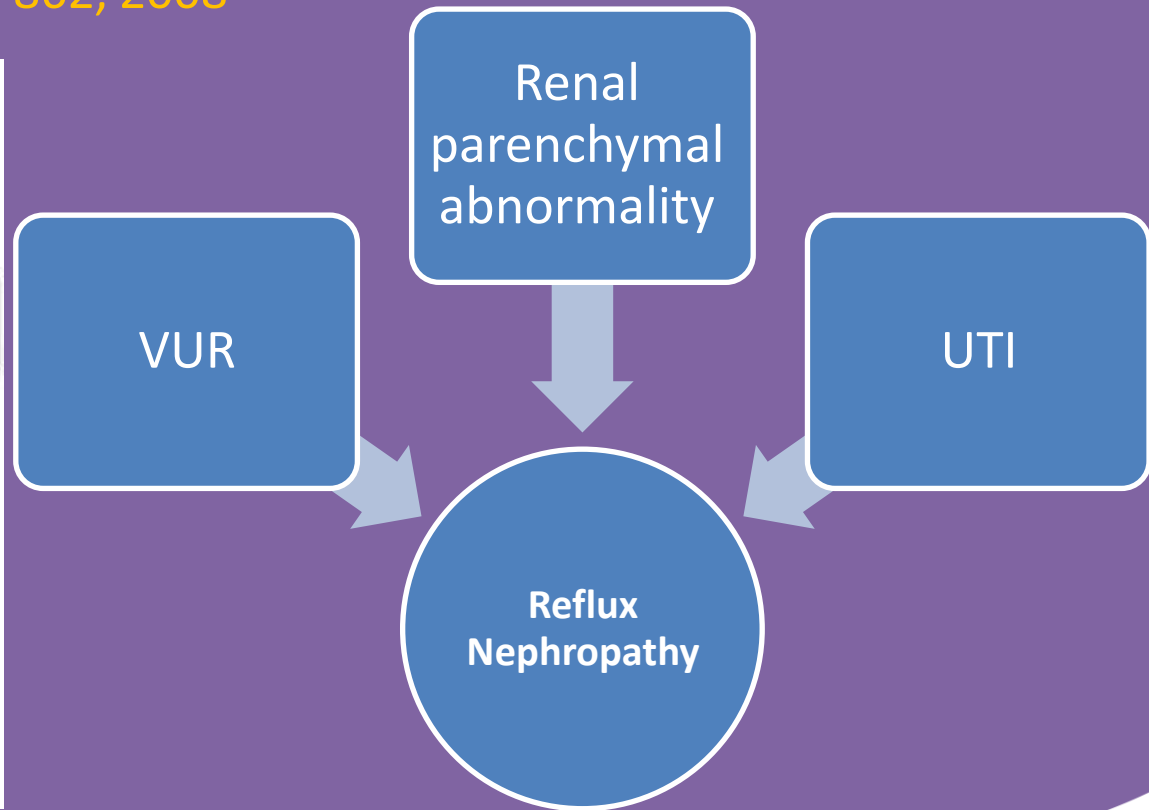
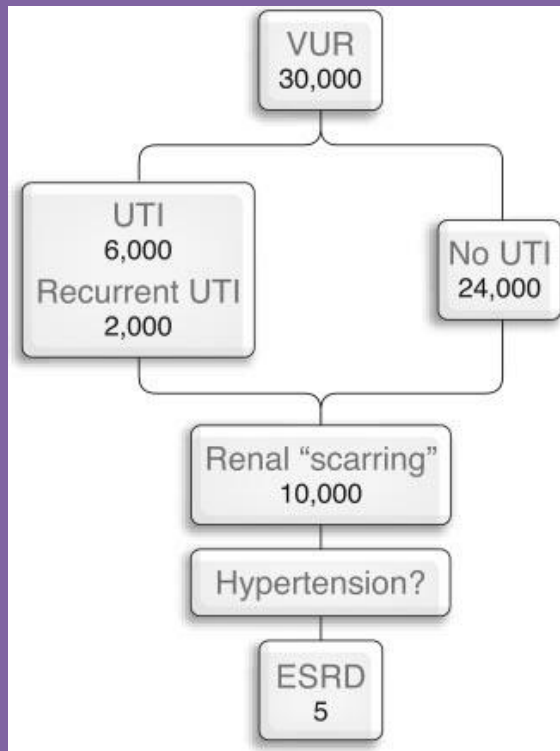
- Infection
- Backpressure associated
- Congenital embryonic VUR + metanephric mal-development

# Vesicoureteral Reflux

Gabrielle Williams,\*† Jeffery T. Fletcher,† Stephen I. Alexander,† and Jonathan C. Craig\*†

\*School of Public Health, University of Sydney, and †Centre for Kidney Research, The Children's Hospital at Westmead, New South Wales, Australia

*J Am Soc Nephrol* 19: 847–862, 2008



# RN Incidence

Condition	reference	Rate
Antenatal VUR (Cong. RN)	Yeung CK, et al. The characteristics of primary vesico-ureteric reflux in male and female infants with pre-natal hydronephrosis. Br J Urol;. 1997; 80: 319-27	30%
	Ismaili K, et al. Primary vesicoureteral reflux detected in neonates with a history of fetal renal pelvis dilatation: a prospective clinical and imaging study. The Journal of pediatrics. 2006; 148: 222-7	60%
UTI + VUR	Rushton HG. The evaluation of acute pyelonephritis and renal scarring with technetium 99m dimercaptosuccinic acid renal scintigraphy: evolving concepts and future directions. Pediatric Nephrology. 1997; 11:108–20.	36%
	Doganis D, et al. Does early treatment of urinary tract infection prevent renal damage? Pediatrics. 2007; 120:e922–8.	56%
UTI ± VUR	Shaikh N, Ewing AL, Bhatnagar S, Hoberman A. Risk of renal scarring in children with a first urinary tract infection: a systematic review. Pediatrics. 2010; 126:1084–91	12%

It is not clear

if the VUR and its severity have a **causative role** in the formation of renal scars  
 or whether it is a **marker for** congenital mal-development such as  
 hypoplasia/dysplasia



# RN risk factors

VUR are more likely to develop pyelonephritis & scar formation

Higher grades of VUR

VUR + UTI

bladder bowel dysfunction (BBD):

delay in the treatment of febrile UTI (more than 48 hrs after the onset of fever)

Hewitt IK, et al. Early treatment of acute pyelonephritis in children fails to reduce renal scarring: data from the Italian Renal Infection Study Trials. Pediatrics. 2008;


Young age:

Some recent studies have reported that the age may not be a risk factor for renal scarring and the risk in older children is the same or even higher as compared to the younger children

## Evaluation of acute pyelonephritis with DMSA scans in children presenting after the age of 5 years

Authors

[Authors and affiliations](#)

Neamatollah Ataei , Abbas Madani, Reza Habibi, Mosa Khorasani

In conclusion, data did not confirm the conventional opinion that the risk of renal scarring after pyelonephritis is low in children over the age of 5 years.

# PEDIATRICS®

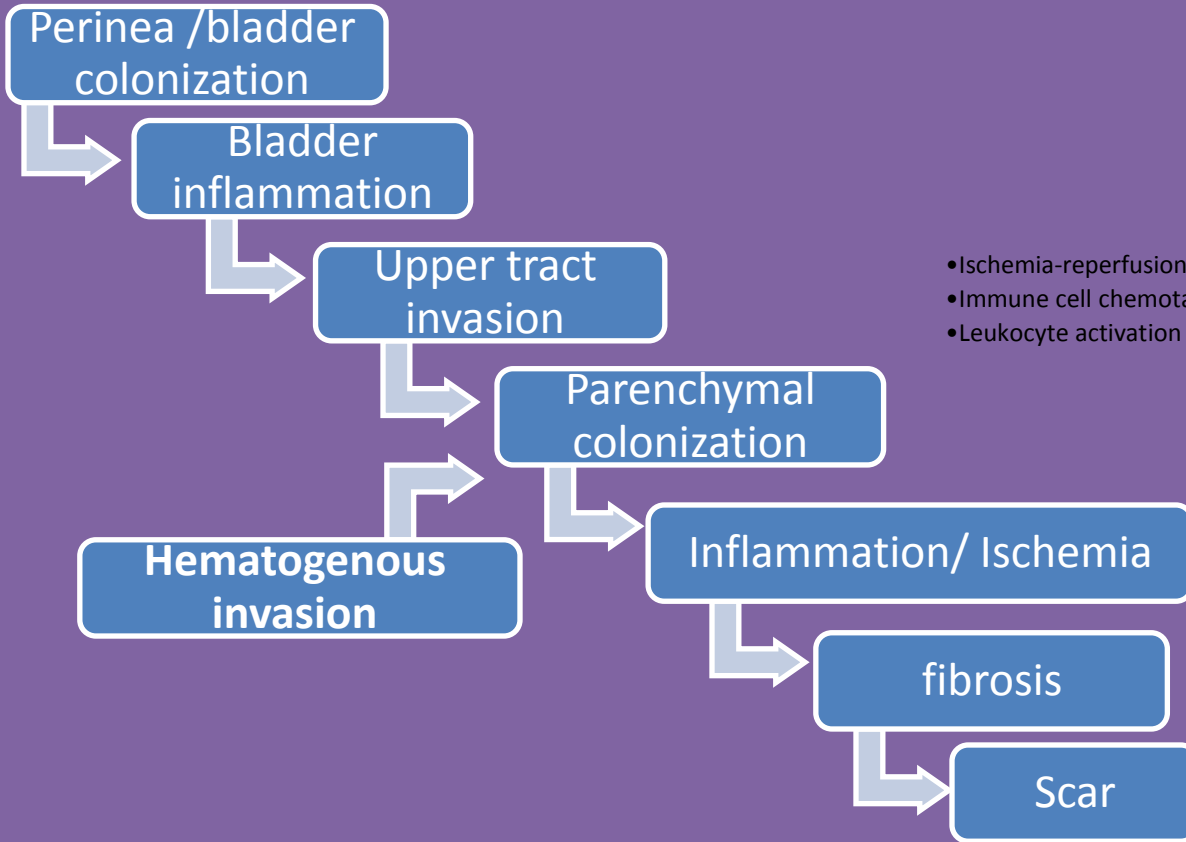
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

## Age-Related Renal Parenchymal Lesions in Children With First Febrile Urinary Tract Infections

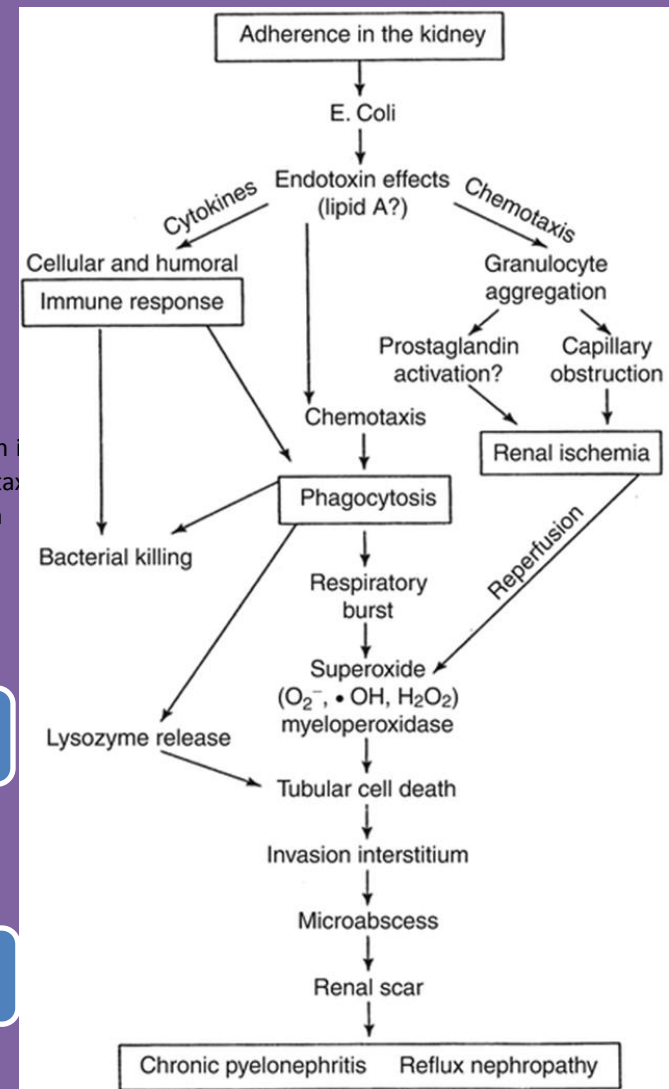
Paolo Pecile, Elisabetta Miorin, Carla Romanello, Enrico Vidal, Marzia Contardo, Francesca Valent and Alfred Tenore

*Pediatrics* July 2009, 124 (1) 23-29; DOI: <https://doi.org/10.1542/peds.2008-1192>

Children <1 year of age with febrile urinary tract infections have a lower risk of parenchymal localization of infection and renal scarring.



- Ischemia-reperfusion injury
- Immune cell chemotaxis
- Leukocyte activation



# Interplay between vesicoureteric reflux and kidney infection in the development of reflux nephropathy in mice

Samantha E. Bowen<sup>1,\*</sup>, Christine L. Watt<sup>2,\*</sup>, Inga J. Murawski<sup>2</sup>, Indra R. Gupta<sup>2,3</sup> and Soman N. Abraham<sup>1,4,5,6,‡</sup>

## SUMMARY

Vesicoureteric reflux (VUR) is a common congenital defect of the urinary tract that is usually discovered after a child develops a urinary tract infection. It is associated with reflux nephropathy, a renal lesion characterized by the presence of chronic tubulointerstitial inflammation and fibrosis. Most patients are diagnosed with reflux nephropathy after one or more febrile urinary tract infections, suggesting a potential role for infection in its development. We have recently shown that the C3H mouse has a 100% incidence of VUR. Here, we evaluate the roles of VUR and uropathogenic *Escherichia coli* infection in the development of reflux nephropathy in the C3H mouse. We find that VUR in combination with sustained kidney infection is crucial to the development of reflux nephropathy, whereas sterile reflux alone fails to induce reflux nephropathy. A single bout of kidney infection without reflux fails to induce reflux nephropathy. The host immune response to infection was examined in two refluxing C3H substrains, HeN and HeJ. HeJ mice, which have a defect in innate immunity and bacterial clearance, demonstrate more significant renal inflammation and reflux nephropathy compared with HeN mice. These studies demonstrate the crucial synergy between VUR, sustained kidney infection and the host immune response in the development of reflux nephropathy in a mouse model of VUR.

DMM


## Child Health Update

# Corticosteroids for renal scar prevention in children with acute pyelonephritis

Teeranai Sakulchit MD   Ran D. Goldman MD FRCPC

### Conclusion

Corticosteroids are effective as an adjunctive therapy in addition to standard treatment of children with acute pyelonephritis, in order to prevent subsequent renal scarring. However, research is extremely limited, especially in

children, and more studies are needed to confirm these findings before steroids can be used in practice as an acceptable treatment to reduce risk of scarring. 

### Competing Interests

None declared

### Correspondence

VOL 63: APRIL • AVRIL 2017 | *Canadian Family Physician* • *Le Médecin de famille canadien* 287

# Scar & Immunomodulators

[Pediatr Nephrol.](#) 2013 Feb;28(2):277-83. doi: 10.1007/s00467-012-2308-4. Epub 2012 Oct 7.

## The effect of vitamin E or vitamin A on the prevention of renal scarring in children with acute pyelonephritis.

[Sobouti B](#)<sup>1</sup>, [Hooman N](#), [Movahed M](#).

### ⊕ Author information

#### Abstract

**BACKGROUND:** Numerous factors may contribute to renal tissue injury after urinary tract infection. We have evaluated the effects of vitamins A or E supplementation in combination with antibiotics for the prevention of renal scarring in acute pyelonephritis.

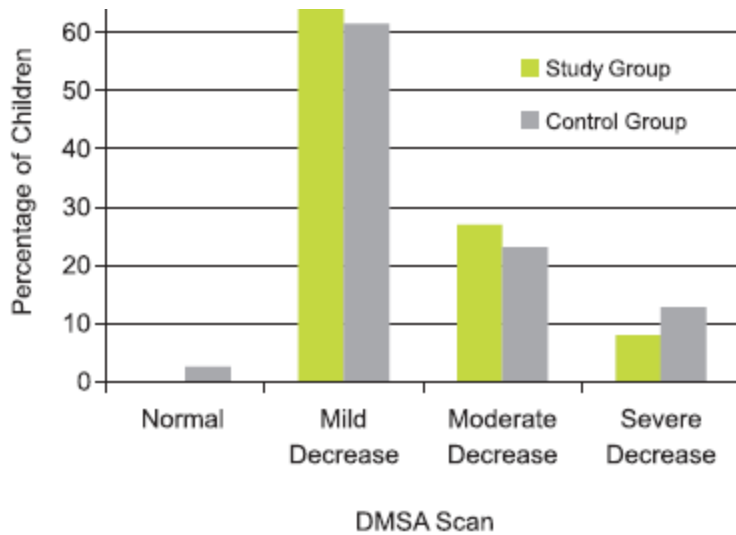
**METHODS:** A simple non-blind randomized clinical trial was conducted on 61 children aged 1 month to 10 years between 2004 and 2006. The inclusion criteria were positive urine culture, clinical findings, and 99mTc-dimercaptosuccinic acid (DMSA) scintigraphy-based evidence in favor of acute pyelonephritis. The children were randomized into three treatment groups: 10-day treatment with only antibiotics (control group; n = 25) and 10-day treatment with supplements of vitamin A (n = 17) or vitamin E (n = 18) in addition to antibiotics during the acute phase of infection. The final analysis was performed after excluding male patients. Each patient was evaluated twice by 99mTc-DMSA scintigraphy performed at least 6 months apart.  $P < 0.05$  was considered to be statistically significant.

**RESULTS:** The analysis included 108 kidney units. The frequency of inflammation at the beginning of therapy was not significantly different in the three groups (63.3 % in vitamin A, 61 % in vitamin E, and 76.2 % in the control group). A worsening of lesions, based on the second 99mTc-DMSA scan, was observed in 42.5, 0, and 23.3 % of the control, vitamin E, and vitamin A patients, respectively (LR = 26.3,  $P < 0.001$ ).

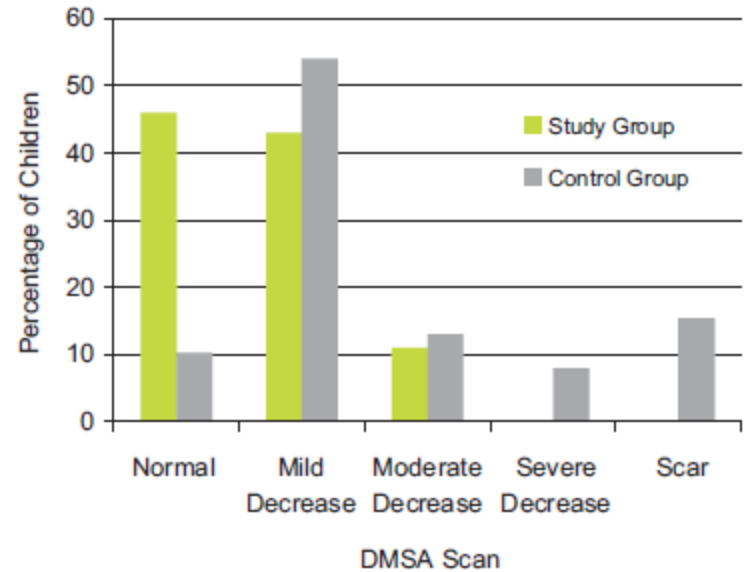
**CONCLUSION:** Vitamins A or E supplements were effective in reducing renal scarring secondary to acute pyelonephritis.

# Role of Vitamin A in Preventing Renal Scarring After Acute Pyelonephritis

Reza Dalirani, Mojtaba Yousefi Zoshk, Mostafa Sharifian, Masoumeh Mohkam, Abdollah Karimi, Alireza Fahimzad, Mona Varzandefar



**Figure 1.** Baseline technetium Tc 99m dimercaptosuccinic acid (DMSA) renal scans in children of the study and control groups. Scan results are categorized as normal and mild, moderate, and severe decrease in kidney cortical function.



**Figure 2.** Secondary technetium Tc 99m dimercaptosuccinic acid (DMSA) renal scans in children of the study and control groups. Scan results are categorized as normal; mild, moderate, and severe decrease in kidney cortical function; and scar presentation.

# Scar formation predictor: pNGAL

Original Article  
Clinical Chemistry

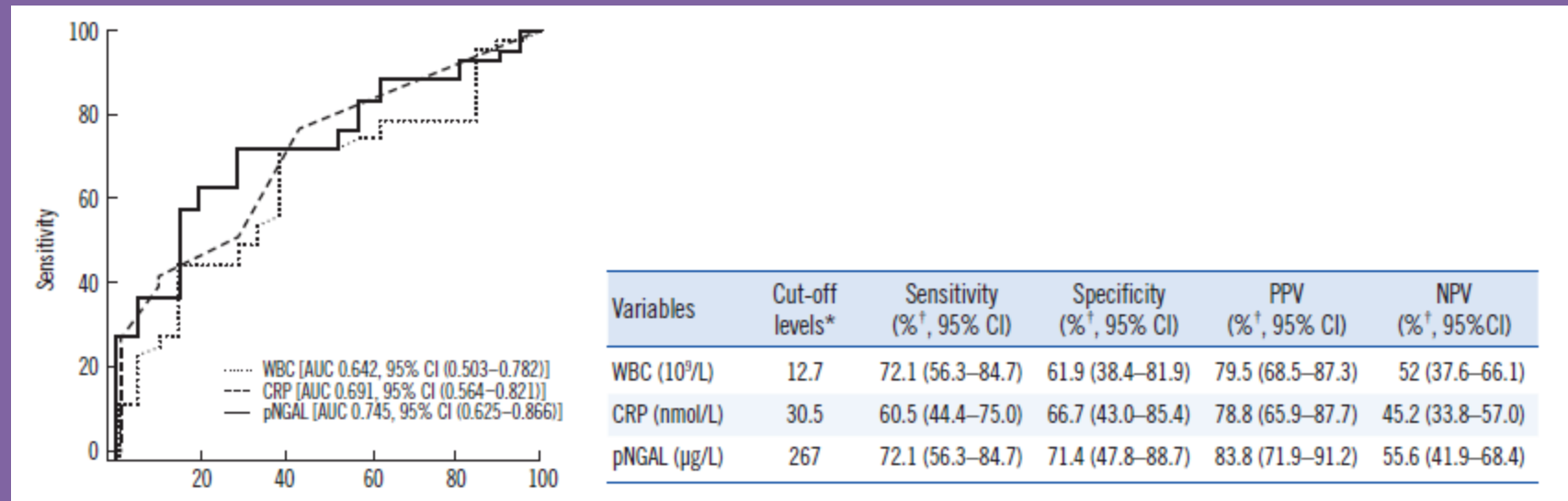


Ann Lab Med 2018;38:425-430  
<https://doi.org/10.3343/alm.2018.38.5.425>  
ISSN 2234-3806 • eISSN 2234-3814

ANNALS OF  
LABORATORY  
MEDICINE

## Plasma Neutrophil Gelatinase-Associated Lipocalin as a Predictor of Renal Parenchymal Involvement in Infants With Febrile Urinary Tract Infection: A Preliminary Study

Bo Ae Yun, M.D., Eun Mi Yang , M.D., and Chan Jong Kim , M.D.





# Scar formation predictor: procalcitonin

17<sup>th</sup> International Congress of Nephrology, Dialysis, and Transplantation

Tabriz, Iran 19-22 November 2019



International Society of Nephrology



Iranian Society of Nephrology

# Management: Prophylaxis Vs No Prophylaxis

## PEDIATRICS®

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

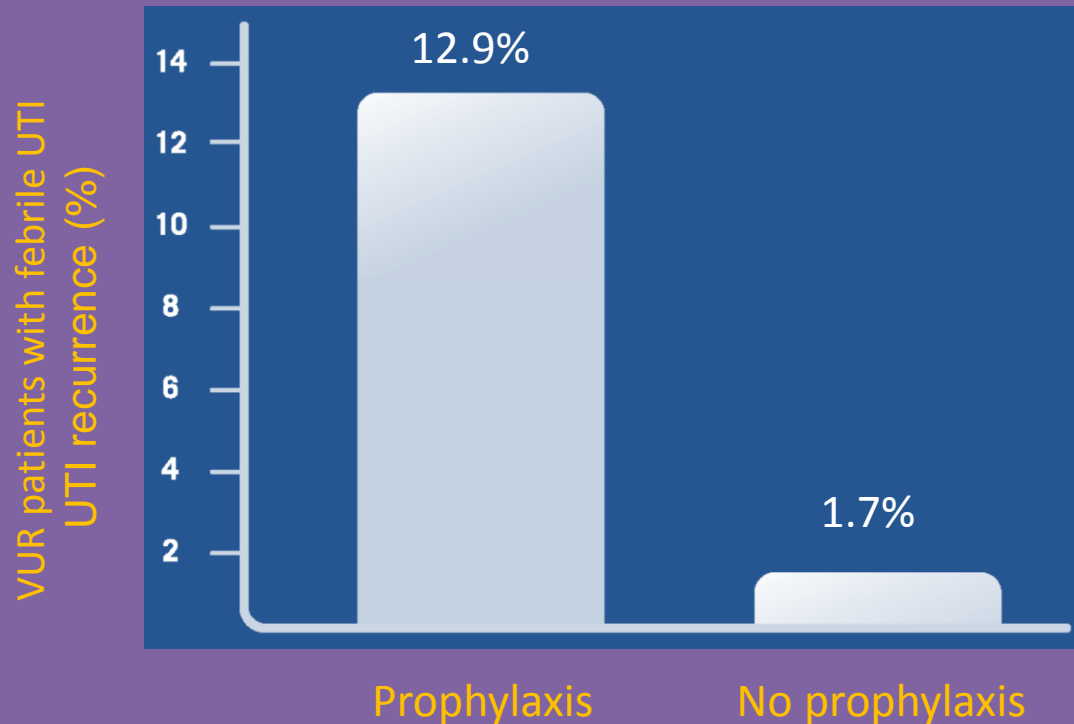
### Clinical Significance of Primary Vesicoureteral Reflux and Urinary Antibiotic Prophylaxis After Acute Pyelonephritis: A Multicenter, Randomized, Controlled Study

Eduardo H. Garin, Fernando Olavarria, Victor Garcia Nieto, Blanca Valenciano, Alfonso Campos and Linda Young

Pediatrics March 2006, 117 (3) 626-632; DOI: <https://doi.org/10.1542/peds.2005-1362>

- 236 pts aged 3m -18yrs with APN enrolled
- Randomized into 2 groups (c/s CAP); F/U=1 yr
- K U/S & VCUG @ 1<sup>st</sup> m & 12<sup>th</sup> m ; DMSA @ 6<sup>th</sup> & 12<sup>th</sup> mo
- **Conclusion:**
  - mild/moderate VUR does not increase the incidence of UTI, pyelonephritis, or renal scarring after acute pyelonephritis.
  - Moreover, a role for urinary antibiotic prophylaxis in preventing the recurrence of infection and the development of renal scars is not supported by this study

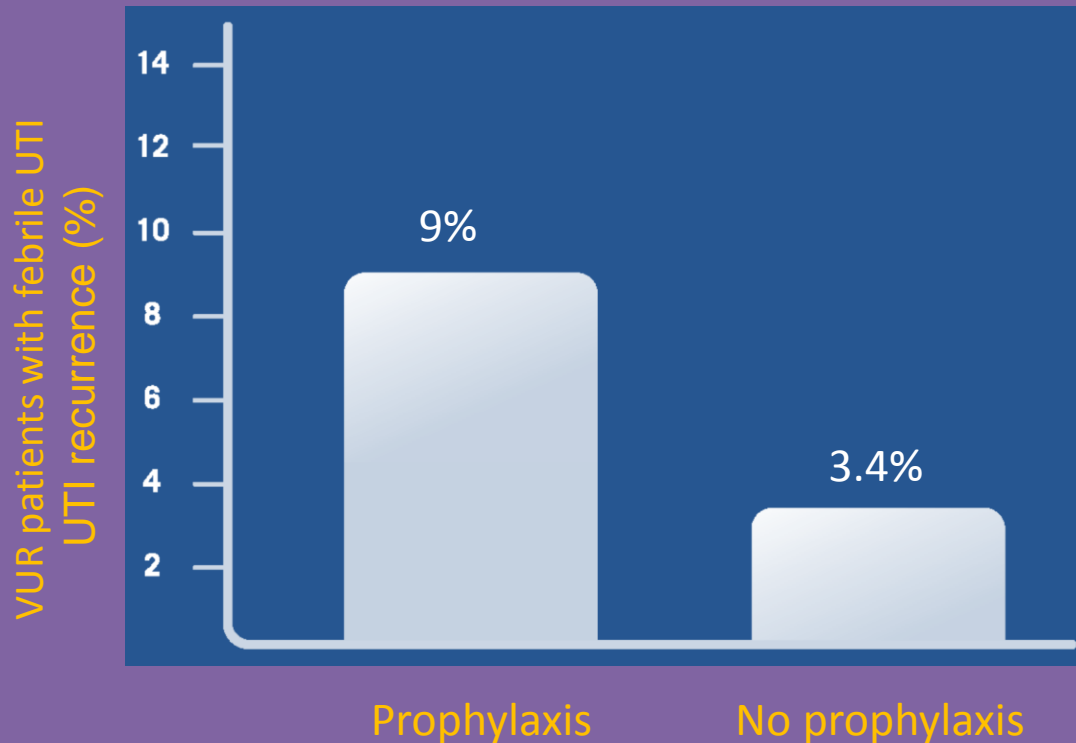
# Rate of febrile UTIs higher with antibiotic prophylaxis than with no treatment at all



$P=0.0291$  A 1-year, follow-up, randomized, urinary antibiotic prophylaxis-controlled study of 218 patients aged 3 months to 18 years with documented acute pyelonephritis to determine antibiotic efficacy of febrile UTI management.<sup>1</sup>

Garin EH, et al. Clinical significance of primary vesicoureteral reflux and urinary antibiotic prophylaxis after acute pyelonephritis: a multicenter, randomized, controlled study. *Pediatrics*. 2006;117(3):626-632.

# Rate of renal scarring *higher* with antibiotic prophylaxis



Incidence of renal scarring increased approximately 3 fold in patients on antibiotic prophylaxis<sup>1</sup>

Garin EH, et al. Clinical significance of primary vesicoureteral reflux and urinary antibiotic prophylaxis after acute pyelonephritis: a multicenter, randomized, controlled study. *Pediatrics*. 2006;117(3):626-632.

# Ab. Prophylaxis & infancy

- American Urological Association (AUA) 2010 meta-analysis:
- 21 studies, 1323 infants
- Outcomes:
  - rate of VUR resolution
  - Incidence of UTI
  - Incidence of renal cortical abnormalities
- Recommendation:
  - VUR (any grade)+ Hx of feb. UTI: CAP recommended
  - VUR III-V : CAP recommended
  - VUR I-II & no UTI: CAP offered
  - Male + VUR + UTI: circumcision considered with permission

# VUR correction

- Evidence of benefit for treating VUR is inadequate regarding recurrence of UTI or renal scarring
  - International Reflux Study Olbing H, et al. Radiology. 2000; 216:731–7.
  - Birmingham Study Birmingham Reflux Study Group. Br Med J (Clin Res Ed). 1987;
  - Swedish Reflux Trial Holmdahl G, et al. The Swedish reflux trial... J Urol. 2010; 184:280–5.
- Surgically treatment options:
  - surgical reimplantation (gold standard) 98% success rate
  - Laparoscopic surgery
  - Intrauterine or subureteral jel injection

## Indicated and recommended in patients with:

high grade VUR (IV and V),  
ineffective CAP

breakthrough UTI's

patients allergic to antimicrobials

poor patient compliance

worsening of scars

parental preference

girls with VUR @ puberty approaches.

# Key points

- Many children with VUR do not benefit from either diagnosis or treatment of their condition
- Prospective studies have not demonstrated utility of antibiotic prophylaxis in preventing urinary tract infections in many children with VUR
- Prospective studies generally showed no difference in renal function or growth, progression or development of new scars, or urinary tract infections in those treated by operative intervention versus prophylactic antibiotics
- increasing grades of reflux and renal scars identify a higher risk group for subsequent renal damage and long-term clinical sequelae
- Management decisions are complex and require an individualized approach, taking into account numerous variables