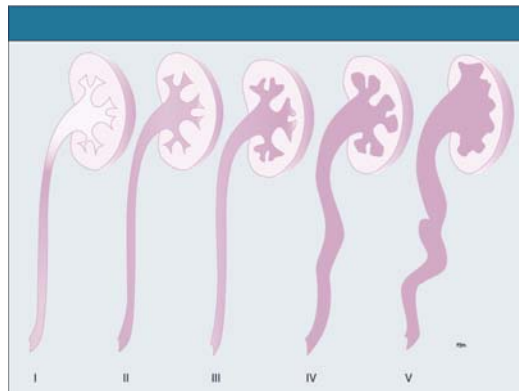


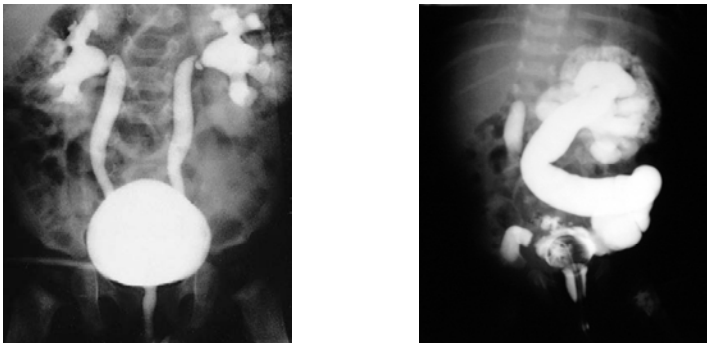
Management of Reflux Nephropathy: What is the Evidence

Tej K. Mattoo, MD, DCH, FRCP (UK)
Professor of Pediatrics
Wayne State University School of Medicine
Chief, Pediatric Nephrology & Hypertension
Children's Hospital of Michigan
Detroit, MI

Grades of VUR

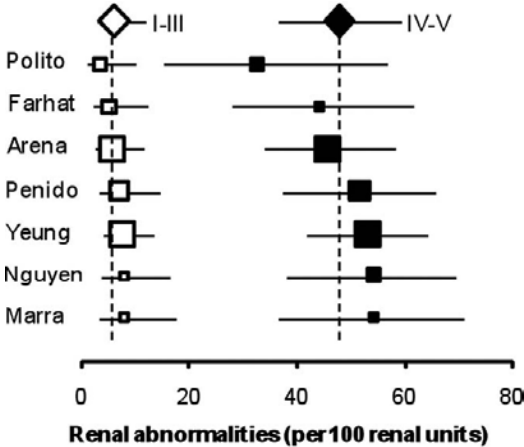


Grade V VUR



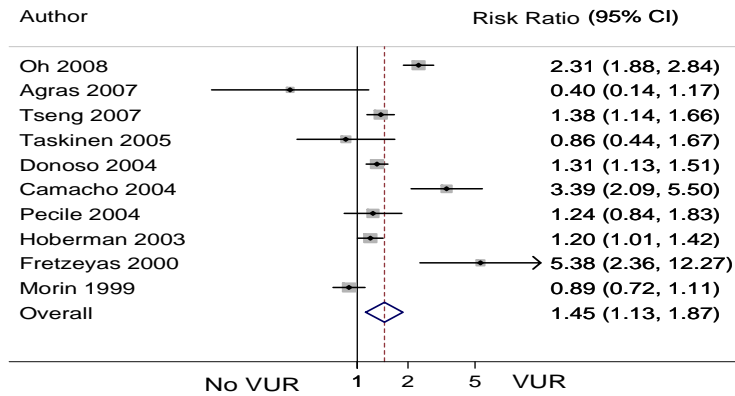
VUR and Renal Cortical Abnormalities (Without Prior UTI)

Skoog S et al, J Urology 2010; 184: 1145-51

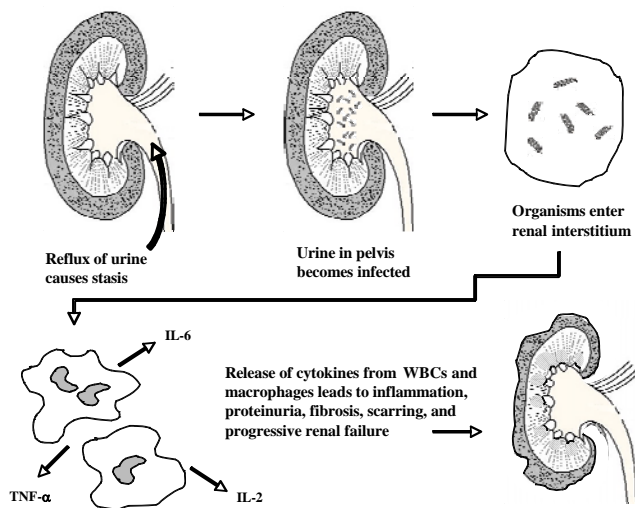


VUR Increases Risk of Acute Pyelonephritis

Shaikh N et al, Pediatrics (in press)



Renal Scarring with UTI ± VUR

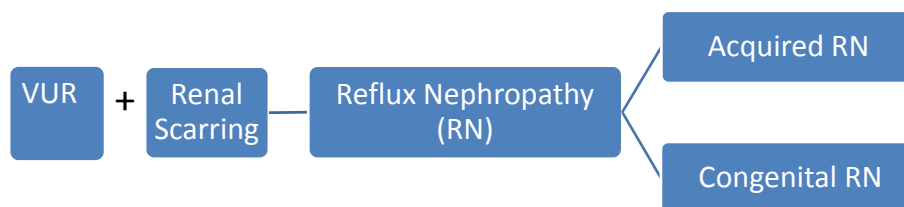


Mechanism for Progression of Renal Scars

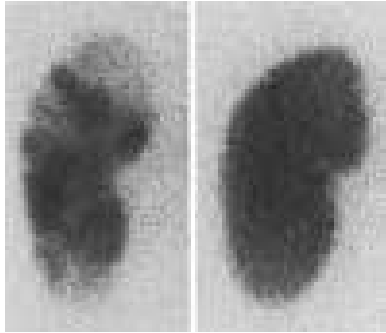
Cortan RS, KI 1982; 21:528-534

- Immunological injury
- Macromolecular trapping and mesangial dysfunction
- Vascular alterations and hypertension
- Hemodynamic alterations

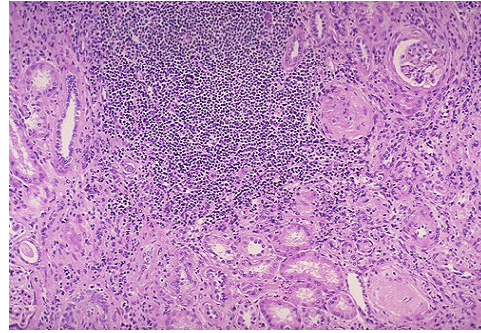
Reflux Nephropathy (RN)



Reflux Nephropathy (RN)



DMSA Renal Scan



Renal Biopsy

RN in Children

| Acquired RN | Congenital RN (Hypoplasia) |
|---------------------------------|----------------------------|
| ▪ UTI common before diagnosis | Preceding UTI is uncommon |
| ▪ Predominantly females (4-5:1) | Predominantly males |
| ▪ Low-grade VUR | High-grade VUR |
| ▪ Older children and adults | Younger children |

RN in adults

| | Males | Females |
|-------------------|----------------------|------------------------|
| UTI | Uncommon | Frequent |
| Plasma creatinine | Higher | Normal |
| ESRF | More common | Less common |
| VUR | High grade/bilateral | Low grade/unilateral |
| Proteinuria | Frequent/severe | Infrequent/Less severe |
| Hypertension | More common | Less common |

RN in Adults Why males are worse off?

1990

Dilution of severe cases (of RN) in females because of their earlier presentation due to recurrent UTI and pregnancy related complications, including UTI.

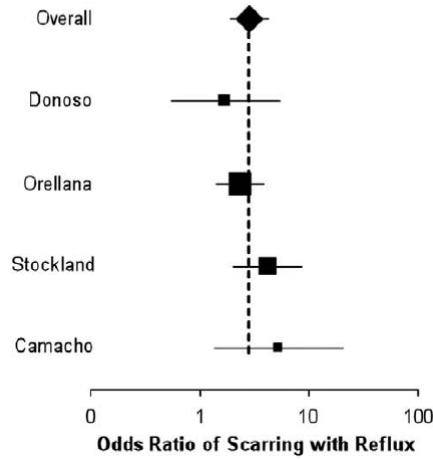
Williams DG, Editorial, Quarterly J of Med, 1990; 284:1205-1207

2010

Males are more likely to have congenital RN where as females mostly have acquired RN

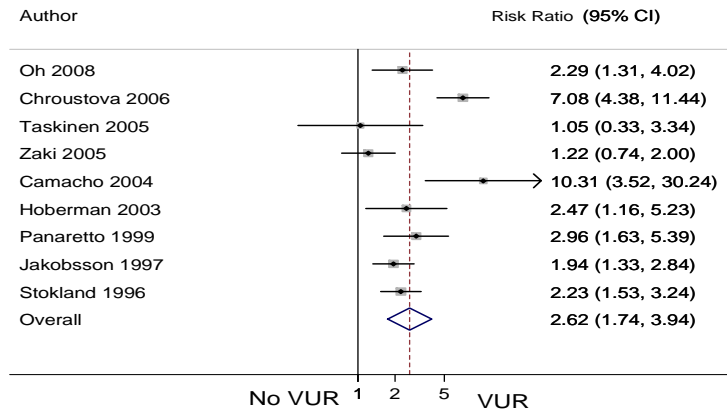
Odds Ratio of Renal Scarring with VUR

Peters CA et al, *J of urology* 2010; 184:1134-44

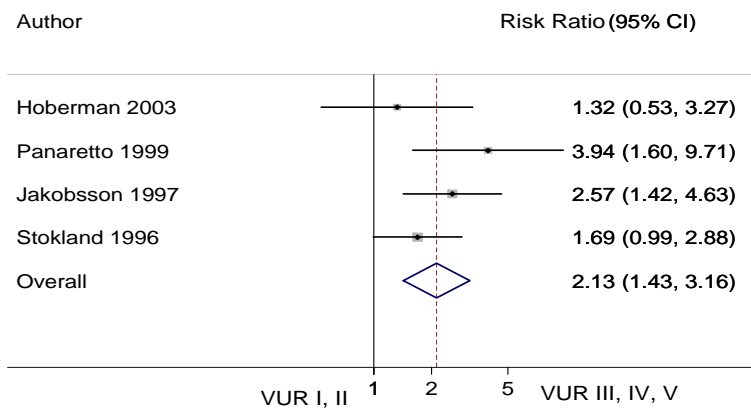


Risk of renal scarring according to presence or absence of vesicoureteral reflux

Shaikh N et al, *Pediatrics* (in press)

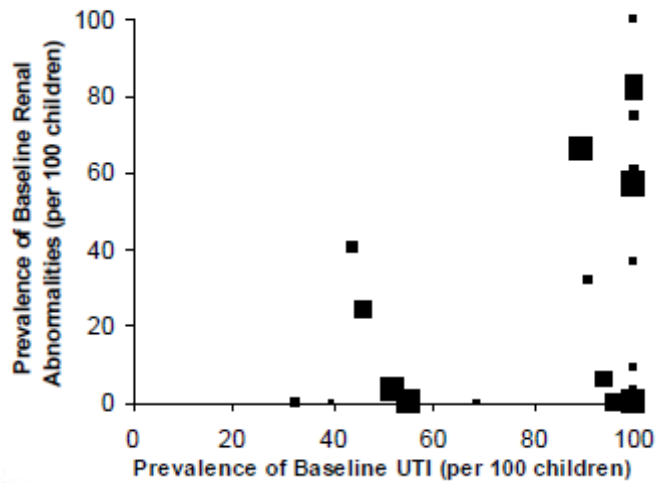


Risk of renal scarring according to the grade of vesicoureteral reflux



Greater Number of UTIs is Associated with Increased Renal Scarring

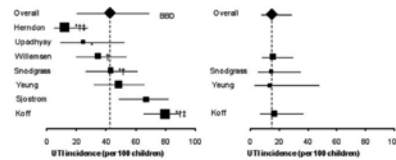
Peters CA et al, J of urology 2010; 184:1134-44



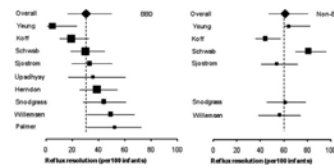
Bladder Bowel Dysfunction (BBD) and VUR

Peters CA et al, J of urology 2010; 184:1134-44

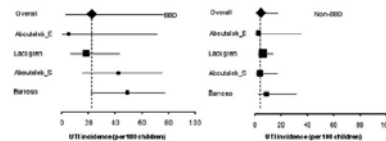
UTI Incidence



VUR Resolution with Prophylaxis



UTI Incidence after Surgical Intervention



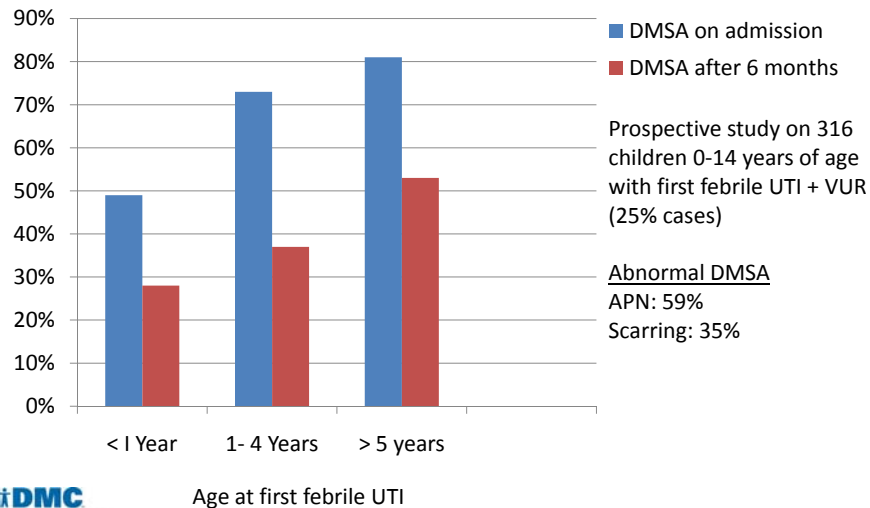
Dimercaptosuccinic acid (DMSA) Renal Scan in the Evaluation of Hypertension in Children

Ahmed M, Eggleston D, Kapur G, Jain A, Valentini RP, Mattoo TK
Pediatric Nephrology (2008) 23:435-438

- Renal scars found in 21% (33/159) of otherwise healthy children (Median age of 11 years) who were evaluated for newly diagnosed hypertension
- 22 patients had unilateral and 11 had bilateral scarring

Renal Injury After First Febrile UTI

Pecile P et al, Pediatrics 2009



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of Michigan

Age Offers No Immunity Against Renal Scarring

Adult pig kidneys scar as quickly as those of piglets with VUR and UTI

Coulthard et al, Pediatr Nephrol 2002; 17:481-4

Adult transplanted kidneys are also vulnerable to RN

Howie et al, Pediatr Nephrol 2002; 17:485-90

Some studies have reported increased risk of renal scarring in older children

Benador et al, Lancet 1997

Lin et al Pediatric Nephrology 2003

Ataei N et al, Pediatric Nephrology 2005

Hewitt IK et al, Pediatrics 2008

Coulthard M et al, Pediatric Nephrology 2009

Pecile P et al, Pediatrics 2009

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Complications of RN

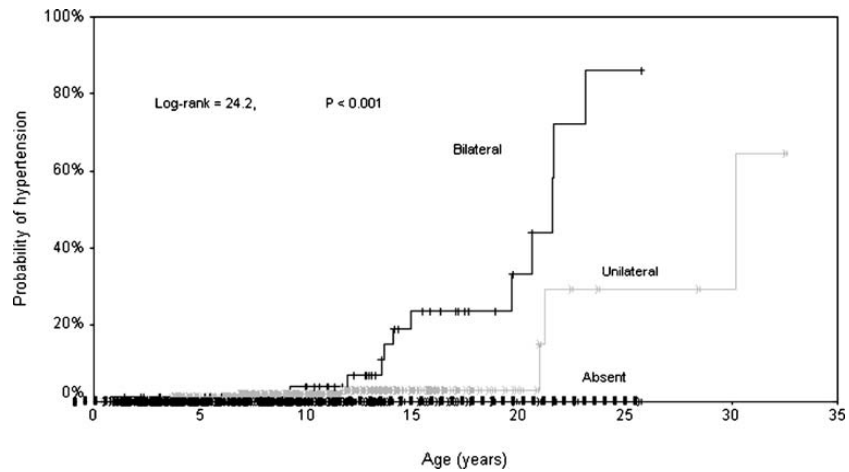
- Hypertension
- Proteinuria/FSGS
- Pregnancy related complications
- Renal calculi
- Progressive CKD/ESRF

Hypertension (VUR diagnosed in Childhood)

| First Author, Year | Number of Patients | Duration of FU | Hypertension (%) |
|--------------------|--------------------|--------------------|------------------|
| Lenaghan, 1976 | 102 | 5-18 Yrs | 10% |
| Wallace, 1978 | 156 | 13 Yrs (average) | 12.8% |
| Bailey, 1984 | 19 (neonates) | 17 yrs (average) | 10/17% |
| Beetz, 1989 | 189 | 10.8 yrs (average) | 11.5% |
| Jacobson, 1989 | 30 | 27 years | 7/30 (%) |
| Hinchliffe, 1994 | 86 | None | 10.4% |
| Goonasekera, 1996 | 100 | 15 years | 18% |
| Smellie, 1998 | 226 | 18-35 years | 7.5% |

Risk of HTN in Primary VUR

Simoes e Silva et al, Pediatr Neph, 2007; 22:459-62



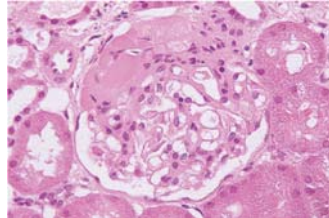
Hypertension (VUR Diagnosed in Adults)

| First Author, Year | Number of Patients (Mean age) | Duration of Follow-Up | Hypertension (%) |
|--------------------|--------------------------------|-----------------------|-----------------------------------|
| Torres, 1983 | 67 (30 Years) | At diagnosis | 34% |
| El-Khatib, 1990 | 147 (31 Years) | 6.9 ± 3.6 Years | 47% |
| Zhang, 1995 | 294 (17.3 Years) | 14 Years | 38% |
| Kohler, 2003 | 115 (28 Years) | 16 years (average) | 58%-bilateral RN 33%-unilat RN |

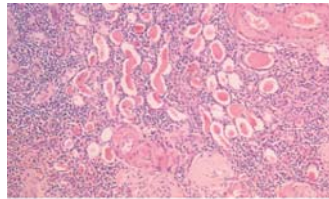
RN and Proteinuria

FSGS

- Sustained glomerular hyperfiltration?
- Autoimmune process?
- Both?
- Other factors?

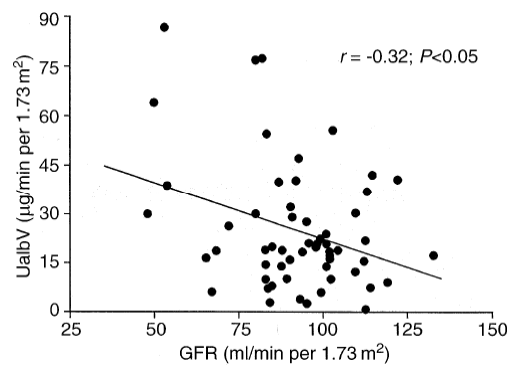


Reflux Nephropathy/
Chronic Pyelonephritis



Microalbuminuria in RN

30%-50% of patients with RN



Correlation between
urine albumin and
GFR in 57 children
(9.8 ± 4.2 years of
age) with RN

*Karlen J et al,
Pediatr Nephrol
1996; 10:705-8*

Pregnancy with RN

Higher risk of

- Pyelonephritis
- HTN
- Proteinuria
- Preeclampsia
- Low birth weight babies
- Miscarriage

End-Stage Renal Failure

5-10% ESRF in children

5-20% ESRF in adults

Treatment Objectives

Decrease the progression of renal disease and prevent target organ damage

Management of Reflux Nephropathy

1. Antibiotic prophylaxis
2. Surgical intervention
3. Management of hypertension /proteinuria
4. Management of voiding dysfunction (DES/BBD)
5. Counseling for pregnancy-related complications
6. Appropriate management of progressive CKD

Limitations of Published Data

- Retrospective studies
- Methodological flaws
- Small number of patients
- Variable inclusion/exclusion criteria
- Definition of scarring
- Imaging methods (IVP/DMSA)
- Duration of follow-up

Recent Randomized Studies on UTI/VUR

| Study | Blinded | Ages | VUR Grade | Urine collection | Outcome | Follow-up |
|-----------------------------|---------|---------------|-----------|--|-----------------|-----------|
| Garin (2005) | No | 1 mo – 18 yrs | I-III | Cath / Clean voided | UTI | 12 mo |
| Roussey (2008) | No | 1-36 mo | I-III | Bag | UTI | 18 mo |
| Pennesi (2008) | No | 0-30 mo | II-IV | Bag | Febrile UTI | 24 mo |
| Montini (2008) | No | 2-84 mo | I-III | Bag | Febrile UTI | 12 mo |
| Craig (2009) | Yes | 0-18 yrs | I-V | Suprapubic/ Cath/ Clean voided | Symptomatic UTI | 12 mo |
| Swedish Reflux Trial (2010) | No | 1-2 yrs | III & IV | Midstream Bag Bladder aspiration | Febrile UTI | 24 mo |

Renal Scarring in Recent Randomized Studies on UTI ± VUR

| Study | Patients with DMSA Renal Scan | Patients Included | VUR Grade | Renal Scarring on DMSA | | Relative Risk % (95% CI) |
|---------------------------|-------------------------------|-------------------|------------|------------------------|----------------------|----------------------------|
| | | | | Prophylaxis | No Prophylaxis | |
| Garin et al, 2005 | 113 | UTI + VUR | I-III | 5/55 (9.0%) | 2/58 (3.4%) | 2.6 (0.53 to 13.02) |
| Pennesi et al, 2008 | 100 | UTI + VUR | II-IV | 22/50 (44%) | 18/50 (36%) | 1.22 (0.75 to 1.9) |
| Montini et al, 2009 | 295 | UTI ± VUR | I-III | 50/187 (26.8%) | 33/108 (30.5%) | 0.87 (0.60 to 1.26) |
| Craig et al, 2009 | 154 | UTI ± VUR | I-V | 35/71 (49%) | 38/83 (46%) | 1.07 (0.77 to 1.50) |
| Swedish Reflux Trial 2010 | 136 | UTI+VUR +AD | III-IV | 40/68 (59%) | 45/68 (66%) | 0.88 (0.68 to 1.15) |
| COMBINED | 798 | UTI + VUR | 1-V | 152/431 (35.2%) | 136/367 (37%) | 0.97 (0.82 to 1.15) |

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“Big Bang” Effect

Ransley and Risdon

Kidney International, 1981

Scarring may result from a single episode of pyelonephritis, especially in very young patients.

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Medical Versus Surgical management of VUR with RN

- No difference in medical versus surgical treatment for-
 - New renal scar formation
 - New areas of parenchymal thinning
 - Progression of existing scars
 - Renal growth

Surgical Correction of VUR

- Patient age
- Grade of VUR
- ineffectiveness of antimicrobial prophylaxis
 - Breakthrough UTIs
 - New scars
- Patient/parent compliance
- Patient/Parent preference

Treatment of HTN

- To keep BP at < 90th percentile for age, height and gender.
- ACEI/ARB best, especially if proteinuria is present
- Nephrectomy, if RN is unilateral and differential renal function is acceptable.

Functional Voiding Disorders

- Constipation- diet \pm medication
- Voiding every 2-3 hours
- Age-appropriate toilet seats
- Medications: Anticholinergics, Alpha-blockers
- Biofeedback therapy
- Also, Botox, neuromodulation
- CIC in extreme cases

Randomized Intervention for Children With Vesicoureteral Reflux (RIVUR) Study

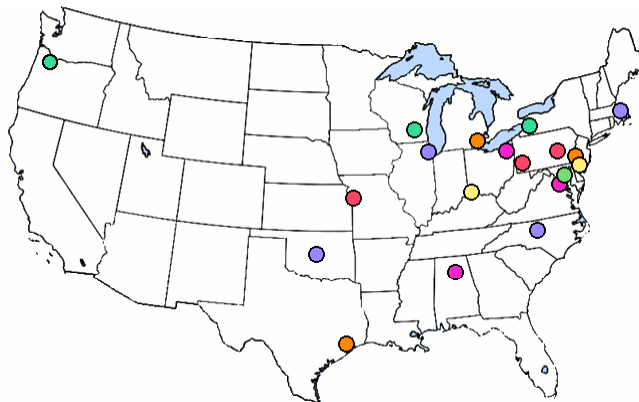


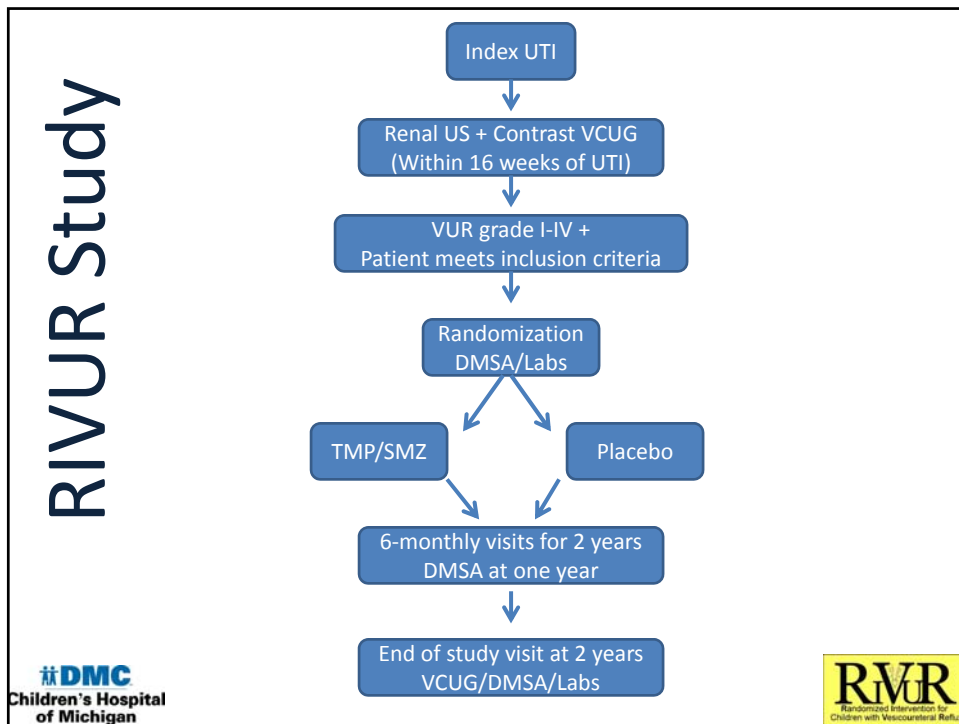
NIDDK
National Institute of Diabetes and
Digestive and Kidney Diseases

Year 2005



Other Participating Sites





Conclusion

- Reflux nephropathy is an increasingly recognized renal pathology in children and adolescents.
- Decreasing the progression of renal disease and preventing target organ damage are the main treatment objectives.
- Well-designed prospective studies are needed to define its clinical outcome in all age groups, children as well as adults.
- Evidence-based guidelines are needed in appropriate management of patients with reflux nephropathy.

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