

Imaging of Urinary Tract Infection in Children: A Tale of Two Paradigms

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Paradigms

There are two dominant and distinct paradigms for imaging of UTI in children. One places emphasis on the demonstration of **VUR**, the other on the documentation of **APN**. Both assume that UTIs can be associated with serious immediate problems related to urosepsis as well as long-term complications related to renal scarring and subsequent HTN, renal insufficiency and ESRD.

Cute Dog Picture

Discussion regarding the performance and interpretation of DMSA scans, RNCs and VCUG can be found in standard pediatric imaging textbooks.



VUR Paradigm

VUR is frequently associated with APN and subsequent scarring. Thus, the detection of VUR provides useful information for the clinician.

VUR Paradigm: Assumptions

VUR is relatively rare in normal children.

VUR can be accurately and reliably detected.

There are effective treatments for VUR.

VUR and APN are related such that the presence of VUR is an independent risk factor for APN and renal scarring and the absence of VUR reduces the child's risk for APN and long-term renal damage.

APN Paradigm

The documentation that the locus of a UTI is in the kidney, APN, rather than in the bladder, cystitis, allows patients to be stratified allowing for more appropriate treatment and follow up strategies.

APN Paradigm: Assumptions

APN is not rare in children.

APN cannot be reliably and accurately detected based on clinical findings and can only be made with imaging.

APN requires more intensive treatment than cystitis in order to decrease scarring and prevent complications from permanent renal damage.

VUR need not be detected/treated in the absence of APN.

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VUR: What do we think know?

The incidence of VUR in childhood has been quoted as 1-2%.

VUR Frequency

Indications	Incidence of VUR
Normal	17%
UTI	31%
prenatal HN ipsi/contra	20/20%
UPJ ipsi/contra	16/20%
MCKD ipsi/contra	9/11%
Siblings female/male	36%/25%

Sargent Pediatr Radiol 2000

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VUR: Detection

Does a single negative cystogram exclude VUR?

VUR: Detection

Jequier (1989) using VCUG, found VUR with the 2nd cycle only (SCR) in 11/177 patients. Discrepancies between the two cycles were found in 22/177 patients with respect to grade, side or presence.

AJR 1989

VUR: Detection

Neel using RNC studied 85 children whose VUR was felt to have resolved based on a negative RNC in the previous 12 months and found recurrent VUR in 25 (29%) patients.

J Urol 2000

VUR: Detection

Paltiel found the addition of a second cycle as part of a VCUG detected VUR in 11/142 children under three years in whom the initial cycle was negative. The frequency of SCR was 12% in those studied supine compared to 4% in those studied prone. All but one of the cases was Grade I or II.

Radiology 1992

VUR: Detection

Polito using VCUG, found SCR in 45/96 children (1 mo to 16 years) including 8 patients with Grade IV or V VUR. Upgrading to > Grade III occurred in an additional 7 patients. Age did not significantly effect the frequency of SCR nor in upgrading of VUR

Pediatric Nephrology 2000

VUR: Detection

Papadopoulou using VCUG, found SCR in 50/275 children (<2 years) including 5 with Grade IV or V VUR. Reflux was detected in only 18 children during the initial cycle.

European Radiology 2002

VUR: Frequency of SCR

Jequier	6%
Neel	29%
Paltiel	8%
Polito	47%
Papadopoulou	18%
Average	22%

VUR: Can continuous monitoring improve detection?

Single vs Cyclic
VCUG vs RNC

VUR: Detection Rates

Kogan(1986) reported 10 children in whom VUR was strongly suspected and the VCUG was normal and RNC positive.

VCUG RNC

Dikshit(1993) 87% = 96% High grade VUR missed on 2 VCUG, 1 RNC.

Merrick(1995) 47% < 78% Indirect RNC

Polito(2000) 55% < 94% Cyclic VCUG 1st, high grade missed only with VCUG in 17/27 KUU.

McLaren(2001) 43% < 91% RNC first. High grade VUR missed on 41 VCUG, only 1 RNC

Unver(2006) 85% = 69% VCUG 1st, High grade VUR missed on 3 VCUG, 4 RNC.

VUR: VCUG vs RNC

The general trend in the literature indicates similar to somewhat greater sensitivity for VUR with RNC compared to VCUG. VUR can be missed with either technique; more frequently low grade with RNC and higher grade with VCUG.

VUR: Do the Results of VCUGs and RNCs have the same accuracy for predicting of APN or Scarring?

APN Prediction: VCUG vs RNC

McLaren correlated VUR detected with VCUG or RNC, but missed with the other technique, with DMSA results.

DMSA + VCUG + 48%

RNC + 92%

APN Prediction: VCUG vs RNC

Sulkan correlated VUR detected with VCUG or RNC, but missed with the other technique, with DMSA results.

DMSA + VCUG + 43% RNC + 71%

RNC +/VCUG -

DMSA + in 80%

VCUG +/RNC -

DMSA + in 50%

Scar Prediction: VCUG vs RNC

There is indication that the VUR detected with RNC is more likely to be associated with renal scarring than that demonstrated with VCUG.

Scar Prediction: VCUG vs RNC

Merrick followed 3646 children with UTI a mean of 7.4 years and found children with a normal VCUG were statistically more likely to develop chronic renal scarring than the children with a normal RNC.

VUR: VCUG vs RNC

The odds ratio for the development of renal scarring based on the presence or absence of VUR was of 14 with RNC and 4 VCUG. These numbers indicate statistically significant predictive power for scarring based on the RNC result but not with the VCUG result.

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VUR has short term stability and can be accurately and reliably detected.

There are effective treatments for VUR.

VUR and APN are related such that the presence of VUR is an independent risk factor for APN and ESRD and the absence of VUR reduces the child's risk for APN and long-term renal damage.

VUR: Natural History

What would happen if you did nothing?

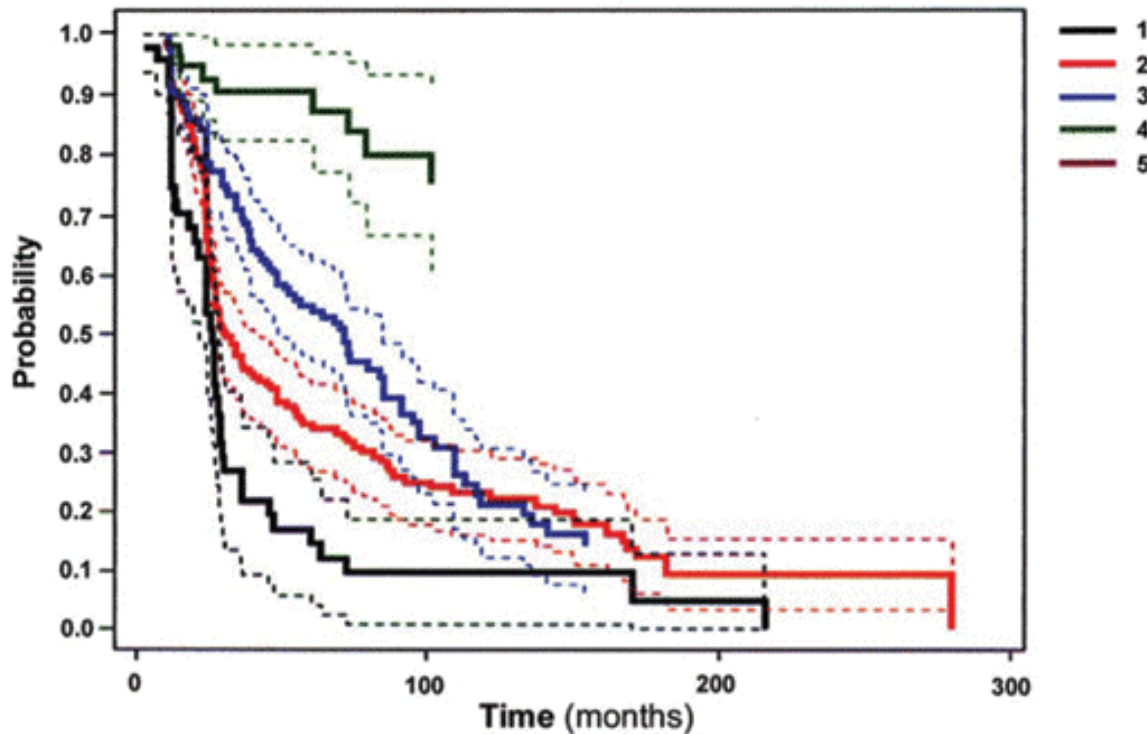


Figure 3 – Kaplan-Meier survival curves with 95% of confidence interval showing the probability of vesicoureteral reflux resolution, in months, according to grade.

VUR: Natural History

For newly diagnosed unilateral Grade III or IV VUR, the spontaneous resolution rate is 11%/yr.

Tamminen-Mobius J Urol 1992

VUR: Treatment

Antibiotic prophylaxis vs surgical repair show **equivalent** renal scar formation and renal function (GFR) in children with Grade III and IV VUR.

There was an **increase** incidence of re-infection in the medically treated group.

Weiss J Urol 1992

VUR: Treatment

Why? Non-compliance
On-going VUR

VUR: Treatment Non-compliance

Prophylactic antibiotics have not conclusively been shown to reduce frequency of clinically relevant recurrent UTIs (Williams J Pediatrics 2001).

UTI recurrence rate is independent of VUR incidence in patients on antibiotic prophylaxis (Wald Pediatrics 2006).

Prophylactic antibiotics increase the risk of UTI in patients with VUR and often the recurrent infection is resistant to the prophylactic antibiotics given (Garrin Pediatrics 2006).

VUR: Stopping Treatment

Cessation of antibiotic prophylaxis in children with persistent reflux has been investigated. Patients are typically selected based on normal voiding function and normal anatomy, ability to verbalize symptoms, and expectation for close follow up.

VUR: Stopping Treatment

Cooper (J Urol 2000) identified 51 patients retrospectively and found only 5 febrile UTI during 204 patient-years in follow up.

Houston (J Urol 2001) identified 196 patients from their clinics in whom Abx had been stopped. Scarring was found in 5 patients on Abx and 7 off. (3/7 stopped Abx AMA)

Georgiaki-Angelaki (Scan J Inf Dis 2005) compared APN rates in 54 patients during the two years before and after ABx. They found similar rates of recurrent UTI and APN in both groups.

VUR: Treatment

“Although there are associations between VUR, UTI and renal damage, the assumption that VUR is a modifiable risk factor is not based on strong empiric evidence.... It is uncertain whether the identification and treatment of children with VUR confers clinically important benefit.”

Wheeler 2003 Arch Dis Child

VUR Paradigm: Assumptions

VUR is relatively rare in normal children. **False**

VUR has short term stability and can be accurately and reliably detected. **False**

There are effective treatments for VUR. **True/False**

VUR and APN are related such that the presence of VUR is an independent risk factor for APN and ESRD and the absence of VUR reduces the child's risk for APN and long-term renal damage.

APN Paradigm: Assumptions

APN is not rare in children.

APN cannot be reliably and accurately detected based on clinical findings and can only be made with imaging.

APN requires more intensive treatment than cystitis in order to decrease scarring and prevent complications from permanent renal damage.

VUR need not be detected/treated in the absence of APN.

Incidence of APN in UTI

51% Preda J Pediatric 2007 (<1yr)

70% Tseng J Pediatric 2007 (<2yr)

51% Hansson J Urol 2004 (<2yr)

80% Ataei Pediatr Nephrol 2005 (>5yr)

61% Vanderfoille Ped Neph 1998 (>5yr)

63% Benador Lancet 1997 (0-16yrs)

86% Jakobsson Arch Dis Child 1994 (0-16yr)

66% Majd Sem Nuc Med 1992 (0-19yr)

65% Goldraich Ped Neph 1995 Meta-analysis

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APN Diagnosis:

Based on clinical findings alone, APN and cystitis are difficult to distinguish. As many as 50% of children with cystitis will be felt to have APN based on clinical grounds. Importantly, up to 1/3 of children with APN will present clinically with signs suggestive of cystitis instead.

The imaging diagnosis of APN is extremely accurate using DMSA planar/pinhole or SPECT techniques with very high inter-observer agreement.

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APN: Treatment

There is only indirect data to suggest that APN requires more intensive treatment than cystitis:

Renal scars develop more frequently if the diagnosis or treatment of UTI is delayed.

Cochrane Review(2008) found all strategies of antibiotic treatment (IV only, IV to oral, oral only) to be equally effective.

APN Paradigm: Assumptions

APN is not rare in children.

True

APN cannot be reliably and accurately detected based on clinical findings and can only be made with imaging.

True

APN requires more intensive treatment than cystitis in order to decrease scarring and prevent complications from permanent renal damage.

?

VUR need not be detected/treated in the absence of APN.

APN and VUR Paradigm Assumptions

VUR and APN are related such that the presence of VUR is an independent risk factor for APN and ESRD and the absence of VUR reduces the child's risk for APN and long-term renal damage.

VUR need not be detected/treated in the absence of APN.

VUR% in Patients w/ and w/o APN

Stockland	47	39
Jacobsson	34	58
Rosenberg	40	9
Majd	37	21
Hansson	34	34
Ataei	13	29
Tseng	30	12
Preda	30	15
Benador	38	37

VUR Paradigm: VUR and APN

Gordon reviewed 838 articles in a meta-analysis of reports regarding APN and VUR. They identified 12 studies including 537 hospitalized children with UTI who had DMSA scans and VCUG. They found no statistically significant positive or negative predictive value of the VCUG in the diagnosis of APN.

Gordon(2003) J Am Soc Nephrol

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VUR Paradigm: VUR and APN

A positive VCUG increased the likelihood of APN in this patient group by 20%. A negative VCUG decreased the likelihood of APN by only 8%.

There was insufficient data to breakdown these figures by VUR grade.

Gordon(2003) J Am Soc Nephrol

VUR Paradigm: VUR and APN

“Thus, it can be concluded that the identification or exclusion of VUR lacks sufficient predictive value to be useful in the diagnosis of APN.”

VUR and APN: False Negatives

Numerous studies have demonstrated that the majority of children with DMSA-documented APN do not have reflux and are thought to have non-reluxing ascending pyelonephritis.

Identification of these children is not felt to be important under the VUR paradigm.

VUR and APN: False Positives

But what about the false positives, i.e., children with VUR but no APN?

Because dilating reflux is felt to be a risk factor for future scarring, it is important to identify children with VUR grades III-V.

Does the DMSA do this?

APN Paradigm: Identification of Dilating VUR

Do children with UTI and high grade VUR have abnormal DMSA scans? Yes in 134/150 reported patients.

Stockland	19/25	missed 6 Grade III
Jacobsson	14/15	
Rosenberg	7/8	but HN on US
Majd	21/21	
Hansson	29/36	2yr f/u NL DMSA in 6, NL VCUG in 5 Gr I in 2
Ataei	3/3	
Tseng	21/21	
Preda	26/27	
Moorthy	1/1	

APN Paradigm: Assumptions

APN is not rare in children.

True

APN cannot be reliably and accurately detected based on clinical findings and can only be made with imaging.

True

APN requires more intensive treatment than cystitis in order to decrease scarring and prevent complications from permanent renal damage.

?

VUR need not be detected/treated in the absence of APN.

True

VUR Paradigm: Assumptions

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VUR has short term stability and can be accurately and reliably detected. **False**

There are effective treatments for VUR. **True/False**

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VUR has short term stability and can be accurately and reliably detected. **False**

There are effective treatments for VUR. **True/False**

VUR and APN are related such that the presence of VUR is an independent risk factor for APN and **ESRD** and the absence of VUR reduces the child's risk for APN and **long-term renal damage.**

VUR and the Development of Renal Scarring

What are the benefits to the patient derived from the reduction of grade or complete elimination of VUR? Specifically, is there a decreased incidence of renal scarring?

VUR and the Development of Renal Scarring

Jakobsson reported a renal scar rate of 24% two years after APN in a group of 76 children. The incidence of scar formation increased significantly with increasing grade of VUR.

Grade 0	19%
Grade 1-2	29%
Grade 3-5	56%

But 23/37 scarred kidneys had no reflux.

VUR and the Development of Renal Scarring

Stokland reported a renal scar rate of 38% at one year after APN in a group of 157 children. The incidence of scar formation increased significantly with VUR and with increasing grade.

	DMSA +	DMSA -
VUR +	28	27
VUR-	31	71

Would Elimination of VUR Reduce The Development of Renal Scars?

If VUR was an independent risk factor for renal scarring, patients treated with surgical repair of VUR would be expected to show decreased scar formation compared to patients with medically observed VUR.

The International Reflux Study attempted to confirm this.

Surgical vs Medical Treatment of VUR

Patients with grade III or IV VUR randomized as to treatment, highly standardized inclusion and diagnostic criteria.

European: 287 patients 5 Yr	302 patients 10 Yr
140 surgery 147 medical	149 surgery 153 medical

New scars	23	25	21	19
Baseline NL DMSA	7	1	12	13

New scars more common in Grade IV VUR than III

Piepsz 1998 Eur J Pediatr
Olbing 2003 Pediatr Neph

Surgical vs Medical Treatment of VUR

Patients with grade III or IV VUR randomized as to treatment, highly standardized inclusion and diagnostic criteria.

American: 5 year 132 patients

	64 surgery	68 medical	
New scars	31%	22%	(significantly less)
APN	5	15	(significantly more)

No difference in renal growth, GFR, or increase in GFR over the follow up period between the two groups.

VUR and the Development of Renal Scarring

Results from a meta-analysis of five studies that compared surgical vs medical treatment of VUR found no difference in the development of new or progressive scars between the two treatment options.

	Surgery	Medical
New scars		
at 2 years	5/82	5/89
at 4 years	57/281	58/291
Progressive scars		
at 2 years	16/82	16/89
at 4 years	44/226	48/244

Is it important to identify of VUR?

Thus, there is some indication that in the presence of APN, higher grades of VUR are associated with increased scarring when compared to no or low grade VUR. It is not clear how much of this is due to pre-existing renal damage in the setting of high grade VUR.

Is it important to identify of VUR?

Additionally, since there have been no large scale prospective studies comparing standard surgical or medical treatment of VUR with observation only, the negative effect of prophylactic antibiotics on the long term scarring rates are unknown. The on-going RIVUR study is attempting to address these issues.

Is it important to identify of VUR?

Additionally, there is indication that the DMSA scan more specifically identifies children at risk for renal scarring than a reflux study.

Prediction of Renal Scarring: DMSA vs VCUg

Merrick: 3646 children w/ UTI followed for 2-16 years.
On follow up between 2-16 years. VUR was
identified in 395 patients

	RNC		VCUG	
TP	307/395		187/395	
	+	-	+	-

Prediction of Renal Scarring: DMSA vs VCUg

Progressive renal damage was found in 29 kidneys. All children with progressive renal damage had recurrent infections. What best predicted progressive renal damage?

VUR was present 20/29 initially and in 660 kidneys that did not show progressive damage.

DMSA was positive for APN in 20/29 kidneys initially and in 149 kidneys that did not show progressive renal damage.

Arch Dis Child 1995

Summary

APN paradigm is based on assumptions that appear to be more correct than those of the VUR paradigm. The demonstration of APN not only identifies children who may require more intensive treatment of their infection, but also accurately identifies children at risk for higher grades of VUR that may be associated with an increased risk of renal scarring. In these patients, a reflux study can be obtained.

Summary

The VUR paradigm suffers from the inability to reliably identify all cases of VUR. Additionally, many children without APN will undergo unnecessary imaging because of the demonstration of VUR unassociated with APN. Many children with APN and at risk for renal scarring will not be identified with this imaging paradigm. Lastly, the meaningfulness of the identification of VUR has come into question as the role of prophylactic antibiotics and surgical repair come under further scrutiny.

Summary

But.....There are many unanswered questions.

Would the IRS had substantially different results with a prophylactic antibiotic arm? With Deflux instead of UNC?

To what extent are DMSA defects due to renal dysplasia associated with prenatal VUR/voiding dysfunction and precede UTIs?

Does aggressive anti-reflux/prophylactic antibiotic therapy impact long-term renal health?

To what extent do local factors (continuity of care, tort reform) dictate practice?