

Pediatric Vesicoureteral Reflux Guidelines Panel Summary

Report: Clinical Practice Guidelines for Screening Siblings of Children With Vesicoureteral Reflux and Neonates/Infants With Prenatal Hydronephrosis

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From the American Urological Association Education and Research, Inc.

Purpose: The American Urological Association established the Vesicoureteral Reflux Guideline Update Committee in July 2005 to update the management of primary vesicoureteral reflux in children guideline. The Panel defined the task into 5 topics pertaining to specific vesicoureteral reflux management issues, which correspond to the management of 3 distinct index patients and the screening of 2 distinct index patients. This report summarizes the existing evidence pertaining to screening of siblings and offspring of index patients with vesicoureteral reflux and infants with prenatal hydronephrosis. From this evidence clinical practice guidelines are developed to manage the clinical scenarios insofar as the data permit.

Materials and Methods: The Panel searched the MEDLINE® database from 1994 to 2008 for all relevant articles dealing with the 5 chosen guideline topics. The database was reviewed and each abstract segregated into a specific topic area. Exclusions were case reports, basic science, secondary reflux, review articles and not relevant. The extracted article to be accepted should have assessed a cohort of children, clearly stating the number of children undergoing screening for vesicoureteral reflux. Vesicoureteral reflux should have been diagnosed with a cystogram and renal outcomes assessed by nuclear scintigraphy. The screening articles were extracted into data tables developed to evaluate epidemiological factors, patient and renal outcomes, and results of treatment. The reporting of meta-analysis of observational studies elaborated by the MOOSE group was followed. The extracted data were analyzed and formulated into evidence-based recommendations regarding the screening of siblings and offspring in index cases with vesicoureteral reflux and infants with prenatal hydronephrosis.

Results: In screened populations the prevalence of vesicoureteral reflux is 27.4% in siblings and 35.7% in offspring. Prevalence decreases at a rate of 1 screened person every 3 months of age. The prevalence is the same in males and females. Bilateral reflux prevalence is similar to unilateral reflux. Grade I–II reflux is estimated to be present in 16.7% and grade III–V reflux in 9.8% of screened patients. The estimate for renal cortical abnormalities overall is 19.3%, with 27.8% having renal damage in cohorts of symptomatic and asymptomatic children combined. In asymptomatic siblings only the rate of renal damage is 14.4%. There are presently no randomized, controlled trials of treated vs untreated screened siblings with vesicoureteral reflux to evaluate health outcomes as spontaneous resolution, decreased rates of urinary infection, pyelonephritis or renal scarring.

Abbreviations and Acronyms

CAP	= continuous antibiotic prophylaxis
DMSA	= dimercaptosuccinic acid
PGC	= Practice Guidelines Committee
PNH	= prenatal hydronephrosis
RPD	= renal pelvic diameter
SFU	= Society for Fetal Urology
US	= ultrasound
UTI	= urinary tract infection
VCUG	= voiding cystourethrogram
VUR	= vesicoureteral reflux

The complete Guideline is available at <http://www.auanet.org/content/guidelines-and-quality-care/clinical-guidelines.cfm>.

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In screened populations with prenatal hydronephrosis the prevalence of vesicoureteral reflux is 16.2%. Reflux in the contralateral nondilated kidney accounted for a mean of 25.2% of detected cases for a mean prevalence of 4.1%. In patients with a normal postnatal renal ultrasound the prevalence of reflux is 17%. The prenatal anteroposterior renal pelvic diameter was not predictive of reflux prevalence. A diameter of 4 mm is associated with a 10% to 20% prevalence of vesicoureteral reflux. The prevalence of reflux is statistically significantly greater in females (23%) than males (16%) ($p=0.022$). Reflux grade distribution is approximately a third each for grades I–II, III and IV–V. The estimate of renal damage in screened infants without infection is 21.8%. When stratified by reflux grade renal damage was estimated to be present in 6.2% grade I–III and 47.9% grade IV–V ($p < 0.0001$). The risk of urinary tract infection in patients with and without prenatal hydronephrosis and vesicoureteral reflux could not be determined. The incidence of reported urinary tract infection in patients with reflux was 4.2%.

Conclusions: The meta-analysis provided meaningful information regarding screening for vesicoureteral reflux. However, the lack of randomized clinical trials for screened patients to assess clinical health outcomes has made evidence-based guideline recommendations difficult. Consequently, screening guidelines are based on present practice, risk assessment, meta-analysis results and Panel consensus.

Key Words: vesico-ureteral reflux, kidney, ureter, hydronephrosis, child

SCREENING of siblings of index patients with vesicoureteral reflux and patients with prenatally diagnosed hydronephrosis for VUR has been proposed to detect a population at risk, potentially allowing treatment to decrease adverse outcomes associated with VUR, including urinary tract infections, pyelonephritis and renal scarring. The goal for the Panel was to conduct a comprehensive review of the literature and meta-analysis of published outcomes data on the screening of known populations with increased prevalence of VUR. From this analysis and recognizing its limitations, the Panel developed guidelines for screening of siblings and children of index patients with VUR and patients with PNH which reflect the level of evidence available. A “standard” is the most rigid treatment policy, a “recommendation” has significantly less rigidity and an “option” has the least rigidity. Definitions are available in the complete document.

METHODOLOGY

The AUA Pediatric Vesicoureteral Reflux Guidelines Panel developed 5 clinical questions frequently asked about VUR management, 2 of which dealt with screening for VUR in siblings and children of index patients with VUR, and screening of patients with PNH. Articles were included based on specific criteria relevant to screening for VUR (for details see Technical Articles 4 and 5 at <http://www.auanet.org/content/guidelines-and-quality-care/clinical-guidelines.cfm>). After extraction data were conditioned in 2 steps, including verification of completeness and screening for repeated or overlapping reports. A quality score was developed and used descriptively to identify possible relationships between estimates and study quality. Guidelines for reporting meta-analysis of observational studies elaborated by the MOOSE (Meta-analysis Of Observational Studies in Epidemiology) group were used.¹

Sibling Screening

The 22 articles selected for extraction were published between 1975 and 2008, and comprised patients studied from 1959 to 2003. These reports included 3,201 children (2,957 siblings and 244 offspring), of whom 3,040 (2,796 siblings and 244 offspring) were screened with a cystogram. The potential differences in the estimates of prevalence rates were stratified by age, sex, VUR grade, renal scarring and symptoms. When possible, the effects of treatment were assessed in regard to resolution, infection and renal scarring. Based on these data and data from the other 4 clinical questions addressed, the Panel developed recommendations for screening of siblings.

Prenatal Hydronephrosis

Of 6,579 infants with PNH in 43 studies published between 1991 and 2008 selected for meta-analysis VUR was present in 4,756 (34 studies), renal abnormalities were present in 302 (5) and UTI was present in 616 (8). Outcomes were stratified by prenatal or postnatal RPD or PNH severity. Pre-defined RPD threshold criteria for the PNH diagnosis (eg ≥ 4 mm during the 2nd trimester and ≥ 7 during the 3rd trimester were used).² PNH confirmed in the neonatal period via US, pre-defined threshold criteria for the postnatal US diagnosis and postnatal cystography (preferably voiding) within the first 3 months of life were assessed.

There was large variability across these studies regarding the definition of PNH, indications and timing of postnatal evaluation, and therefore the percentage of patients undergoing renal ultrasonography, cystography, or other investigations. The major limitations of the review similar to what was found in the sibling and offspring screening index case, are: (1) limited number of studies providing information detailing the presence of factors thought to modify the risk of VUR, in particular the RPD threshold; (2) potential selection bias within the samples examined as not all the prenatally detected cases underwent postnatal screening; and (3) variation in performance of renal scintigraphy for the patients with reflux, and (4) variable reporting of findings by renal unit and patients.

Limitations of Literature

Among the major limitations of the conducted review of sibling screening are 1) limited number of studies providing information regarding factors thought to modify the risk of VUR, 2) limited evaluation and separation of screened siblings who were symptomatic and asymptomatic, 3) unequal stratification by age impeding calculation of age specific VUR rates, 4) retrospective design with incomplete data sets and incomplete renal damage measurements, and 5) intermingling data on patients and renal units. There are no studies that prospectively measured the outcomes of sibling screening.

RESULTS

Sibling Screening

Twinning studies demonstrate a 100% concordance in identical twins and 35% to 50% prevalence in fraternal twins when tested early in life.³ Screening of siblings and offspring of patients with VUR has demonstrated an increased prevalence of VUR. The prevalence of VUR determined from this meta-analysis is 27.4 (2.9–51.9)/100 siblings screened and 35.7 (16.4–61)/100 screened offspring (fig. 1).

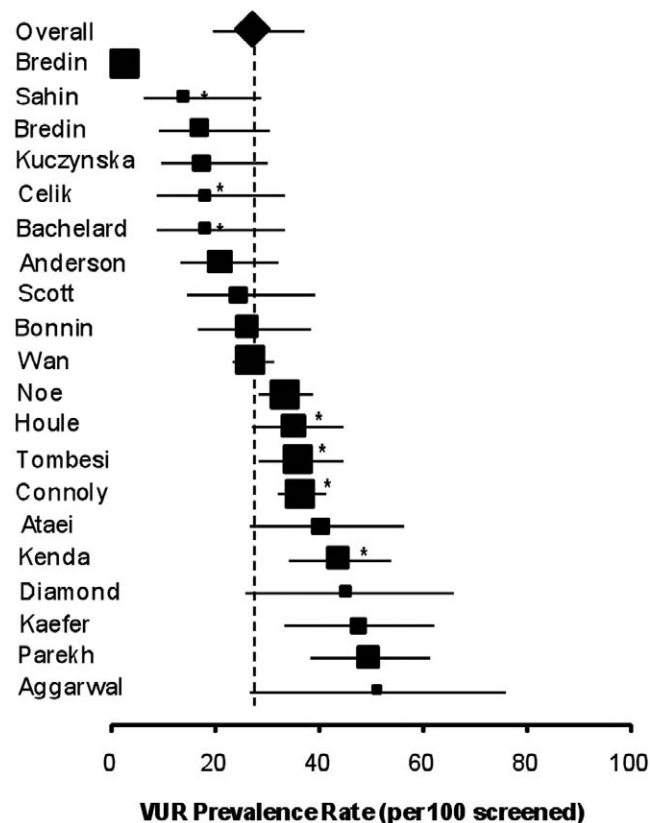


Figure 1. Forest plot of VUR prevalence in screened siblings. Size of rectangle is proportional to number of screened patients in study. Specific study is listed on y-axis. Asterisk indicates studies in which only asymptomatic siblings were screened.

Table 1 summarizes the general characteristics of the samples across the studies. Siblings were on average 4 years older than offspring, and more siblings than offspring were screened. The proportions of males and females were similar with an increased percentage of females being screened.

Analysis of the effect of age at screening on the prevalence of detecting VUR is shown in figure 2. This equation indicates that the prevalence of VUR decreases with the age of the cohort at a rate of 1/100 screened persons approximately every 3 months. This rate corresponds to an annual resolution rate of 4%, and can aid in assessing the need for screening based on patient age.

Table 2 summarizes the VUR prevalence stratified by sex and grade. The prevalence was slightly higher among female than male siblings but not significantly so. There was a higher prevalence of grade I–II than grade III–V VUR. Dilating VUR (grade III–V) was estimated in 9.8/100 screened siblings.

Renal Cortical Abnormalities

Assessment of renal cortical abnormalities required pooling of information from DMSA scanning and intravenous pyelography (IVP). Renal damage in screened patients without prior urinary infection ranged between 0% and 100% for an overall estimate of 14.5% (95% CI 7.2, 27.3). When symptomatic and asymptomatic siblings were examined the overall estimate was 22.8% (95% CI 7.2, 53.1).

VUR grade and associated renal cortical abnormalities were assessed. The association between the prevalence and severity of VUR, and prevalence of renal cortical abnormalities by DMSA/IVP was moderate (Pearson $r = 0.45$, $p = 0.32$). This estimate was affected by the scarcity of one-on-one information between VUR grade and renal cortical abnormalities extracted from the literature.

PNH Screening

The prevalence of VUR in patients with PNH was reported in 34 studies, in which the mean percentage of neonates/infants screened by cystography was 78% (range 11% to 100%). Reflux was detected in 7% to 35% of patients undergoing cystography (average 16.2%, fig 3). Reflux per renal unit with PNH was determined from 15 studies, yielding a mean of 12.6% (95% CI 8, 18). If postnatal selection was eliminated and 100% of patients with PNH underwent cystography (even if no hydronephrosis is detected postnatally), the prevalence of reflux was 18 (95% CI 13, 25)/100 infants. VUR into the nondilated kidney accounted for a mean of 25.2% detected reflux (95% CI 17.6, 34.7). Considering the total of 3,082 renal units screened, mean prevalence of VUR in a nondilated kidney was 4.1% (95% CI 2.3, 7.4). In 9 studies in children with PNH and a normal postnatal ultrasound mean prevalence of reflux was 17% (95%

Table 1

Characteristic	Siblings			Offspring		
	Mean ± SD (No. studies)	Min	Max	Mean ± SD (No. studies)	Min	Max
Av age (mos)	51.9 ± 36.5 (11)	1.7	118	2.5 ± 2.5 (3)	1	5.4
% Males	44.5 ± 8.6 (14)	27.3	56.8	41.4 ± 10.7 (3)	30.6	51.9
% Females	56.0 ± 9.7 (14)	43.2	72.7	58.6 ± 10.7 (3)	48.1	69.4
No. VUR screened	140 ± 169 (20)	11	532	48.8 ± 28.7 (5)	12	79
No. DMSA screened	49 ± 58 (12)	4	167	—	—	—

CI 10, 27). Consequently a normal postnatal ultrasound does not rule out the presence of VUR.

Table 3 summarizes VUR estimates based on sex, and prenatal and postnatal RPD. The prevalence of VUR is significantly greater in females than males (p = 0.022). Increasing RPD did not predict an increased likelihood of VUR. A RPD of only 4 mm was associated with VUR in approximately 10% to 20% of screened neonates. Other factors that might influence the prevalence of VUR were investigated, including trimester of PNH assessment, timing of postnatal evaluation (1 to 3 months) and percentage of patients screened. None of these factors correlated with findings of reflux.

The approximate distribution of reflux grade was I–II in a third, grade III in a third and grade IV–V in a third, based on maximum grade in patients and renal units. Reflux grade was significantly associated with renal damage. Renal abnormalities occurred in a mean of 6.2% vs 47.9% of those with grade I–III vs IV–V reflux (p <0.0001, fig. 4). Renal

abnormalities before UTI occurred ranged from 2% to 63% (mean 21.8%) of patients with VUR and 26% to 42% (mean 32.3%) of renal units.

The efficacy of prophylactic antibiotics in preventing UTIs and renal damage was assessed in patients with PNH. Only 8 studies reported UTI data during the postnatal screening period. There was considerable variability in antibiotic administration, with some instituting prophylaxis in all patients after delivery, while others only prescribed antibiotics to those with VUR and/or hydronephrosis. Agents used were not uniformly reported. Consequently the risk of UTI in patients with PNH with or without VUR cannot be determined, nor can the possible impact of antibiotic prophylaxis. Given these limitations, the incidence of UTI during the postnatal period ranged between 0.5 and 21.3/100 infants under surveillance for an overall incidence of 4.2 (95% CI 0.9, 17.9)/100 infants, the majority with reflux.

DISCUSSION

This meta-analysis provided significant information about the prevalence of VUR, epidemiological data on sex, grade distribution and renal damage in patients screened for VUR. It has documented a much higher prevalence of VUR in siblings, offspring and children with PNH than might be expected in the general population. We have shown that the degree of RPD is not associated with postnatal VUR prevalence in screened patients with PNH. Age at the time of screening siblings for VUR is important as prevalence will decrease at a rate of 4% per year. Gender is relevant in screening decisions with no effect on siblings but a statistically significant increased prevalence in females with PNH.

The prevalence of congenital reflux nephropathy is approximately 14.5% in siblings and offspring and 21.8% in PNH screened patients. In patients with PNH congenital reflux nephropathy was associated with grade in screened siblings with VUR and was statistically significantly greater with grade IV–V reflux. Few studies have provided evidence of the value of screening and efficacy data regarding spontaneous resolution or prevention of UTIs or renal damage, and this meta-analysis was not able to provide these data. However, we can glean some per-

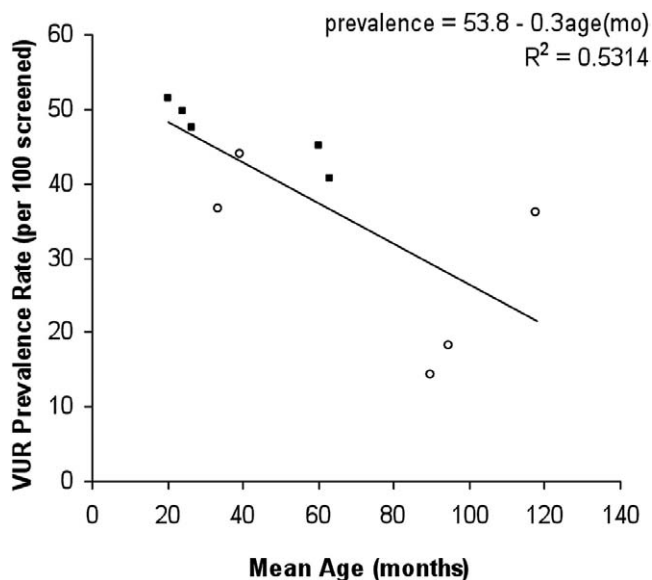


Figure 2. VUR prevalence varied with average age at screening. Open circles represent screened asymptomatic siblings and closed rectangles represent screened asymptomatic and symptomatic siblings.

Table 2

Factor	% Overall (95% CI)	% Category 1 (95% CI)	% Category 2 (95% CI)
Gender:	23.3 (15.6, 33.3)	Males 21.3 (14.3, 30.7)	Females 26.4 (16.2, 40.1)
No. siblings	1,267	554	713
IRS grade (1,891 siblings)	29.6 (21.6, 39.1)	I-II 16.7 (10.3, 25.8)	III-V 9.8 (5.3,17.4)
IRS grade (1,414 siblings)*	28.1 (18.1-40.9)	I-II 16.5 (8.6, 29.2); III 5.0 (1.2,18.2)	III-V 8.0 (3.5,17.2); IV-V 2.1 (1.4,3.2)

* Estimates from studies that provided information on grade III reflux.

spective from our results, information in the literature and clinical practice.

It is well recognized that children with UTI and VUR are at increased risk for pyelonephritis. Children with VUR are 2.6 times more likely to have a renal scar (3.9 times more likely for the refluxing renal units) than those with pyelonephritis and no reflux (see Results and chapter 1 of the VUR clinical practice guideline at <http://www.auanet.org/content/guidelines-and-quality-care/clinical-guidelines.cfm>).⁴ Although this finding has not been proven in a screened population there is no evidence to suggest

a different pattern. An increased risk of renal damage being detected is present with dilating VUR and at a younger screening age. Asymptomatic and symptomatic screened siblings presumably have a similar risk of renal damage. Only 1 study assessed directly the prevalence of renal damage and VUR among children with and without UTI at screening. In that study the prevalence of renal damage was significantly greater among those with a history of UTI, suggesting the value of preventing UTI in asymptomatic screened patients.

VUR resolution depends on numerous factors including gender, age at presentation, grade, laterality, scarring and bladder volume at the time of VUR; mode of presentation; and presence of voiding dysfunction. The 1997 guideline provided graphs and recommendations based on estimates of resolution to assist the clinician in decision making, which has been replicated more recently by others. Again not proven, there is no reason to assume that patients presenting as screened siblings or with PNH and VUR will behave differently. A recent nomogram has shown that the resolution rate is improved for patients with PNH and VUR.⁵

Detection and treatment of reflux in the youngest patient population have been outlined in chapter 2 of the VUR clinical practice guideline (<http://www.auanet.org/content/guidelines-and-quality-care/clinical-guidelines.cfm>). Early detection of a febrile UTI is critical in infants, who are unable to verbally communicate lower urinary tract symptoms. Detection of VUR by screening infants in at risk populations before presentation with febrile UTI is laudable but its outcomes remain unknown. Primary VUR diagnosed during infancy and managed nonoperatively with CAP is likely to resolve by 12 to 48 months in approximately half of all children. No evidence is available that either supports or refutes the idea that infants with VUR presenting after UTI are different than those presenting with PNH or as screened siblings in regard to resolution or risk of renal damage.

Recent doubt about the efficacy of continuous antibiotic prophylaxis in patients with VUR has influenced decisions regarding reflux screening and detection. CAP has not been proven to reduce the incidence of febrile UTI in children or in screened populations with

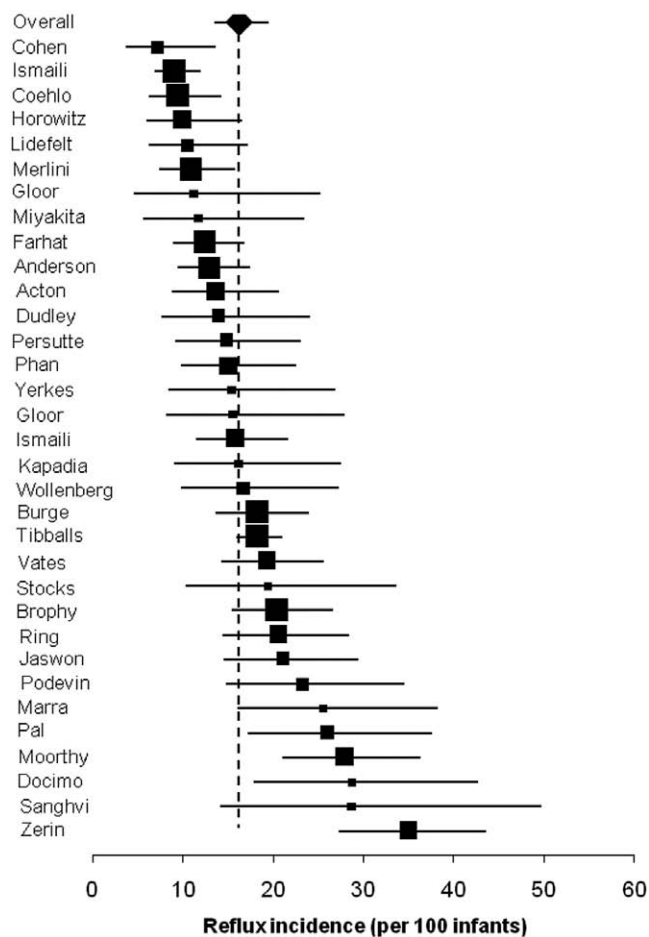


Figure 3. Forest plot estimates of VUR prevalence in PNH screened patients. Size of rectangle is proportional to number of screened patients in study. Specific study is listed on y-axis.

Table 3. Stratified VUR prevalence rate per 100 infants screened

Factor	% Overall (95% CI)	% Group 1 (95% CI)	% Group 2 (95% CI)
Gender:	18.2 (11.6, 27.4)	Males 16.1 (9.9, 25.1)	Females 23.0 (14.2, 35.0)
No. siblings	1,300	911	389
Laterality (2,379 siblings)	16.2 (11.5, 22.3)	Unilat 7.7 (5.4, 10.7)	Bilat 8.0 (5.4, 11.5)
Postnatal US (1,337 siblings)*	16.2 (10.7, 23.7)	Normal or RPD <5 mm 17.0 (10.7, 25.8)	Abnormal or RPD ≥5 mm 15.6 (10.0, 23.6)
Postnatal US + 100% VCUg (909 siblings)	16.1 (8.9, 27.3)	Normal or RPD <5 mm 13.3 (7.0, 24.0)	Abnormal or RPD ≥5 mm 18.6 (10.3, 31.4)

* Not all underwent VCUg.

VUR. This fact challenges the core of current expectant therapy of VUR with prophylactic antibiotics, yet the general applicability of these new data remains uncertain. Methodological issues in study design, patient selection, reflux grade, methods of urine collection and, most importantly, underpowered design to evaluate differences between treatment groups does not allow at this time indiscriminate application to all infants and children with VUR. Consequently until these specific populations of patients are studied in a prospective fashion, CAP is considered to provide infants with protection against UTIs while awaiting spontaneous resolution.

The use of prophylactic antibiotics in a plan anticipating spontaneous resolution is recommended in the infant with VUR presenting with a UTI (summary, chapter 2 of VUR clinical practice guideline). However given the uncertainties in screened populations, it is an option at this time, as is a program of no CAP with treatment of UTI if one occurs. In this scenario VUR has been diagnosed by screening VCUg. It is unknown if it is sufficient to know the increased prevalence of VUR in at risk populations and counsel parents as to

later diagnosis of VUR after a symptomatic UTI. There are insufficient data to make a recommendation for either approach in these unscreened children.

Therefore, recommendations for screening are limited by the uncertainty of any potential benefit gained by identifying VUR. Identification of VUR may increase the awareness of parents and health providers to the potentially increased risk of pyelonephritis and renal scarring. Given the information at hand and the results of the meta-analysis, the specific clinical practice guideline and its basis with regard to screening of siblings and patients with PNH are listed below.

SUMMARY GUIDELINES

Screening Guidelines for Siblings of VUR Patients and Patients With Prenatal Hydronephrosis

“Recommendation: In siblings of children with VUR, a VCUg or radionuclide cystogram is recommended if there is evidence of renal cortical abnormalities or renal size asymmetry on ultrasound or if there is a history of UTI in the sibling who has not been tested [Based on Panel consensus].”

“Option: Given that the value of identifying and treating VUR is unproven, an observational approach without screening for VUR may be taken for siblings of children with VUR, with prompt treatment of any acute UTI and subsequent evaluation for VUR [Based on Panel consensus].”

“Option: Sibling screening of older children who are toilet trained may be offered, although the value of identification of VUR is undefined [Based on Panel consensus].”

“Option: Ultrasound screening of the kidneys in the sibling of a child with VUR may be performed to identify significant renal scarring and to focus attention on the presence and potential further risk of VUR [Based on Panel consensus].”

“Option: Screening offspring of patients with VUR can be considered as similar to screening of siblings [Based on Panel consensus].”

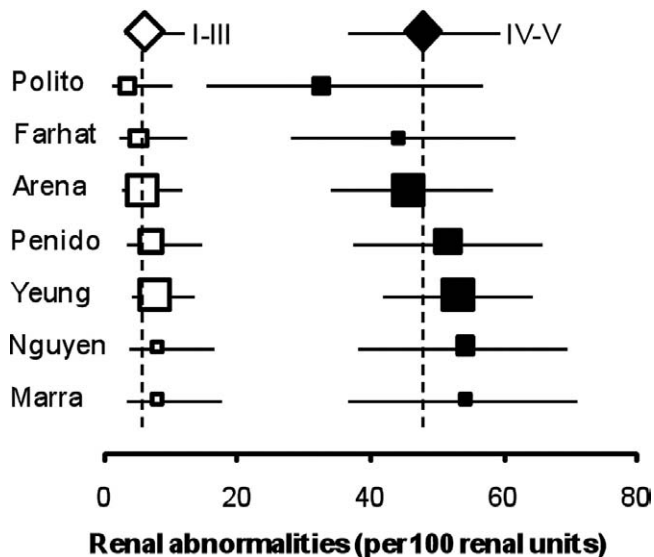


Figure 4. Forest plots of renal cortical abnormalities estimates based on grade of VUR without prior UTI.

“Recommendation: VCUg is recommended for infants with high-grade hydronephrosis (SFU Grades 3-4), hydroureter or abnormal bladders on ultrasound, or who develop a UTI on observation [Based on review of data and Panel consensus].”

“Option: An observational approach without screening for VUR, with prompt treatment of any UTI, may be taken for children with PNH (SFU Grades 1-2), given the unproven value of identifying and treating VUR. It is also considered an option to perform a VCUg in these patients to screen for VUR [Based on Panel consensus].”

Research Priorities

Future studies regarding the screening of siblings with PNH, and children in general for VUR and renal damage should be designed in such a way that 1) the age at screening is specified, preferably in standard ranges; 2) a clear distinction between symptomatic and asymptomatic children is reported; 3) assessment of renal damage is performed in all children with VUR and in all children screened if feasible; 4) severity of VUR by grade is reported; 5) renal outcomes are reported by patient and each kidney; 6) treatment options including CAP, observation and surgery are prospectively assigned and all outcomes are measured in each treatment group; and 7) genetic assessment of the proband and siblings to determine the relative risk for UTI, VUR and renal scarring is done.

ACKNOWLEDGMENTS, DISCLAIMERS AND DISCLOSURES

The supporting systematic literature review and drafting of this document were conducted by the Pediatric Vesicoureteral Reflux Clinical Guidelines Panel (the Panel) created in 2006 by the American Urological Association Education and Research, Inc. The Practice Guidelines Committee of the AUA selected the Panel chair and vice chair, who in turn appointed the additional Panel members with specific expertise in this disease. The mission of the Panel was to develop either analysis or consensus based recommendations, depending on the type of evidence available and Panel processes, to support optimal clinical

practices in the management and screening of primary vesicoureteral reflux in children.

This document was submitted to approximately 75 urologists and other health care professionals for peer review. After revision of the document based on the peer review comments, the report was submitted to and approved by the PGC and the AUA Board of Directors. Funding of the Panel and PGC was provided by the AUA, although Panel members received no remuneration for their work.

This document provides guidance only and does not establish a fixed set of rules or define the legal standard of care. As medical knowledge expands and technology advances, the document may change. Today it represents not an absolute mandate but rather current proposals or recommendations for treatment under the specific conditions described. For all of these reasons, the document does not preempt physician judgment in individual cases. Also, treating physicians must take into account variations in resources, and patient tolerances, needs and preferences. Conformance with the recommendations reflected in this document cannot guarantee a successful outcome.

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All Panel members completed conflict of interest disclosures. (C) indicates compensation was received and (U) indicates no compensation was received. Scientific Study or Trial: Jack S. Elder, QMed Scandinavia (U); Meeting Participant or Lecturer: Billy Arant, Novartis (C); Other: Jack S. Elder, FSC Laboratories (U); Investment Interest: Antoine E. Khoury, Covalon (U), Interface Biologics (U); Owner: Ellen Shapiro, Medical Reviews (C); Linda E. Whetter, Zola Associates (C).

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