Topic 4: Screening of siblings and offspring of patients with vesicoureteral reflux

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The sibling of a child with vesicoureteral reflux (VUR).

Introduction

Vesicoureteral reflux is a polygenic genetic disorder with an incidence of 1% in the general population.[1] Twinning studies demonstrate a 100% concordance in identical twins and 35-50% prevalence in fraternal twins when tested early in life.[2] Cystography of siblings and offspring of patients with VUR has shown a high prevalence of VUR.[3] Screening of offspring and siblings has been proposed as a means to detect a population at risk and allow timely treatment in order to reduce the risk of adverse outcomes associated with VUR, including urinary tract infections (UTI), pyelonephritis and renal scarring. In the 1997 VUR guideline,[4] a proposed future research goal was to determine the impact of sibling and offspring screening with early medical or surgical treatment on the risk of these outcomes.

Methodology

Literature Search, Data Extraction, and Evidence Combination

A meta-analysis of the existing literature was performed to develop recommendations for sibling and offspring screening. Outcomes included the VUR prevalence among siblings and offspring of VUR index cases who have been screened by cystography, and the prevalence of renal damage as determined by intravenous pyelogram (IVP) and technetium-99m-labeled dimercaptosuccinic acid (DMSA) scanning. The potential differences in the estimates of prevalence rates were stratified by the patient characteristics of age, sex, VUR grade, renal scarring and symptoms. Where possible, the effects of treatment were assessed in regards to resolution, infection and renal scarring.

Data from 22 articles (published between 1975 and 2006) were extracted and meta-analyzed. These reports included 3,201 children (2,957 siblings and 244 offspring); 3,040 children were screened with a cystogram (2,796 siblings and 244 offspring).

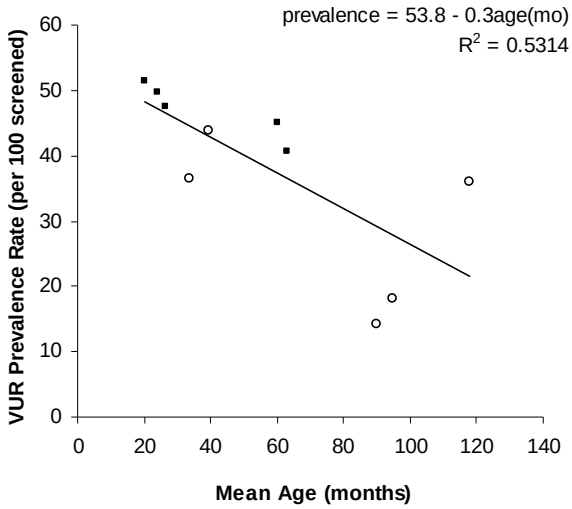
Outcomes Analysis

VUR Prevalence among Siblings and Offspring

Estimates of VUR prevalence among siblings ranged between 2.9% and 51.5%, for a mean estimate of 27.4 per 100 siblings screened (95% confidence interval [CI]: 19.6, 36.9). The VUR prevalence among mixed asymptomatic and symptomatic siblings was 27.7 per 100 (95% CI: 16.8, 42.2) siblings screened and 28.5 per 100 (95% CI 18.2, 41.7) asymptomatic siblings screened. For offspring, the prevalence of VUR ranged between 21.2% and 61.4%. The overall prevalence of VUR among the four studies was 35.7 per 100 (95% CI: 16.4, 61.0) offspring screened.

The influence of age at the time of screening was assessed to attempt to identify the causes of the wide variations in reported prevalence. The prevalence rate based on age at screening was estimated from the equation: Prevalence (per 100 screened) = 53.8 -0.3 x age (mo). The prevalence of VUR in siblings decreased with increasing age at screening by a rate of one screened person every 3 months (Figure 1), suggesting a higher prevalence in the youngest screened sibling (please refer to the Chapter 4 Technical Report for the derivation of this estimate).

Figure 1. VUR prevalence rate among siblings by average age at screening (open circles=asymptomatic; filled squares=mixed symptomatic and asymptomatic)



The VUR prevalence in siblings when stratified by sex is based on eight studies. The prevalence in screened male patients (21.3%) was not statistically different from that of females (26.4%); therefore, the sex of the sibling is not a selection criterion for screening.

VUR grade was assessed in 68% of the screened siblings. The overall prevalence in 11 studies that recorded VUR grade was 29.6 per 100 screened siblings. The prevalence for VUR grades I–II was 16.7 per 100 screened siblings and the prevalence for VUR for grades III–V was 9.8 per 100 screened siblings; these rates were not significantly different. Finally, laterality was assessed in screened siblings. Of those with VUR, there were similar percentages of unilateral and bilateral reflux (17.1 vs. 15.1 per 100 screened siblings, respectively).

Renal Cortical Abnormalities

Nine sibling studies provided information on both VUR and renal cortical abnormalities as diagnosed by either DMSA scanning or intravenous pyelogram (IVP). The prevalence of renal cortical abnormalities ranged between 11% and 54% for an overall estimate of 19.3 per 100 (95% CI: 10.9, 32.0) siblings with reflux. Among asymptomatic siblings, the prevalence of renal cortical abnormalities ranged between 0% and 100% for an overall

estimate of 14.5% (95% CI: 7.2, 27.3) and in studies where both symptomatic and asymptomatic siblings were examined, the overall estimate was 22.8% (95% CI: 7.2, 53.1). When evaluating only those studies in which 90% or more of the patients with VUR, or those initially screened for VUR, underwent DMSA scanning, the prevalence rate for renal scarring was 18.8% (95% CI: 9.8, 33.2). There was only one study that directly assessed the prevalence of renal cortical abnormalities among siblings with or without a prior history of UTI.[5] In this study the prevalence of renal cortical abnormalities was significantly different, with a rate of 35.2% (95% CI: 24.2, 47.8) among those with a prior history of UTI and 11.7% (95% CI: 6.2, 21.0) ($p < 0.05$) among those without a prior UTI.

There was limited information with which to assess the association between VUR grade and renal cortical abnormalities. Of the nine studies providing both rates of VUR and renal cortical abnormalities, only two assessed cortical abnormalities by VUR severity.[6, 7] In the 132 children (out of 144 total cases of VUR) who underwent a renal scan, 18 cases of scarring were found. Seven had grade II VUR, eight had grade III, and three had grade IV. The best association that can be estimated with the available data is at the aggregate level. Numerically, the association between the prevalence of VUR and the prevalence of renal cortical abnormalities by DMSA/IVP was moderate (Pearson $r = 0.45$, $p = 0.32$). However, the association across the seven studies providing information on both severity of VUR and renal cortical abnormalities was weak.

Recommendation: In siblings of children with VUR, a voiding cystourethrogram is recommended if there is evidence of renal scarring on ultrasound or if there is a history of urinary tract infection 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 urinary tract infection 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.

Option: Screening offspring of patients with VUR can be considered as similar to screening of siblings.

[Based on Panel consensus]

Summary

VUR was detected at an overall rate of 27 and 36 per 100 children screened among siblings and offspring, respectively, which is significantly greater than the 1% estimate in the general population.[1] There were no data to evaluate the immediate and long-term effects of treatment in the screened population of siblings. Consequently these recommendations are based on the assessment of present management and treatment, evaluation of the literature, and the results of this meta-analysis.

There were insufficient data to evaluate whether siblings with VUR are at greater risk of developing UTI than the general population or the rate of resolution in siblings with VUR. One report suggested that the grade-specific time to VUR resolution was shorter in asymptomatic siblings compared with symptomatic children.[8]

It is recognized that children with UTI and VUR are at increased risk for pyelonephritis. In this meta-analysis (see Chapter 1) children with VUR were found to be 2.8 times more likely to develop a renal scar (3.7 times more likely for the refluxing renal units) than children with pyelonephritis and no reflux. Only one study directly assessed the prevalence of renal damage and VUR among children with or without UTI at screening. In this study the prevalence of renal damage was significantly greater among those with a prior history of UTI and older age.[5]

In this Guideline, "congenital" renal cortical abnormalities were present in 19% of those with prenatal hydronephrosis without UTI. The rate of renal damage in infants with VUR diagnosed without UTI is 14%. In contrast, the rate of renal damage in screened siblings, some of whom were symptomatic, was 22.8%; this suggests that renal damage may be preventable in some cases. With treatment, either medical or surgical, new renal scarring has been estimated to occur in 5.2% to 31.4% of patients.[4] The rate of new scarring in medically observed, untreated

patients with VUR is under study but presently unknown; therefore, CAP treatment of the youngest (<1 year of age) screened sibling with VUR seems prudent at this time.

Parental preferences need to be considered when screening siblings and offspring. Parents with personal experience with VUR, VUR nephropathy, renal insufficiency, and hypertension will have specific opinions for their children. If one of their children has experienced a febrile UTI or pyelonephritis and is diagnosed with VUR this may influence their choice as to screening of offspring and siblings. Guidance as to how to perform screening and in whom, will be influenced by physician recommendations.

Due to the insufficiency of published data, the value of sibling screening for VUR cannot be determined; therefore, the following recommendations for improving the study design are proposed. All siblings must have an initial DMSA renal scan and a subsequent scan in the event of a documented UTI; the time to spontaneous resolution must be accurately recorded. The age at screening, the distinction between symptomatic and asymptomatic siblings, the presence and type of urinary infections, the duration of VUR, VUR grade and corresponding renal damage, if present, should be documented. Documentation of renal damage in all siblings at screening regardless of VUR status, if possible, is necessary. Genetic assessment of proband and siblings to determine the relative risk for UTI, VUR and renal scarring should be performed.

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