

Topic 2: Management of infants less than one year of age with vesicoureteral reflux

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Index patient

The infant less than one year of age who is diagnosed with primary vesicoureteral reflux (VUR) during the early postnatal period based on a diagnosis of prenatal hydronephrosis (PNH) or following the occurrence of a urinary tract infection (UTI).

Introduction

Vesicoureteral reflux in infants is usually diagnosed after a febrile UTI or during the postnatal work-up of a child with PNH. To prevent any detrimental impact on long-term renal function, early detection of a febrile UTI is critical in infants, who are unable to verbally communicate lower urinary tract symptoms. The management of infants with VUR has become increasingly controversial due to systematic reviews of the literature which support the protective role of circumcision and studies that question the time-honored value of prescribing continuous antibiotic prophylaxis (CAP). Moreover, there has been a relatively recent paradigm shift following the introduction of early treatment by endoscopic injection therapy. Management of infants with VUR should take into consideration the likelihood of spontaneous resolution, the likelihood of recurrence of UTI and the risk of developing renal parenchymal abnormalities.

Methodology

Literature Search, Data Extraction, and Evidence Combination

A meta-analysis of the existing literature was performed to determine the effects of nonoperative management (i.e., CAP) in children with VUR who are less than one year of age. Outcomes included the rates of VUR resolution, the incidence of UTI, and the incidence of renal cortical abnormalities. For inclusion, infants must have been diagnosed with VUR by cystography at or before one year of age and VUR resolution must have been assessed by at least one follow-up cystogram. Assessment by renal scintigraphy (technetium-99m-labeled dimercaptosuccinic acid, diethylenetriamine pentaacetate, or mercaptoacetyltriglycine) was required for studies reporting data on renal cortical abnormalities.

Twenty-one studies met the inclusion criteria (six were prospective), data were extracted and a meta-analysis was performed. Of these, four provided data on VUR resolution by sex, nine provided data on resolution rates by VUR grade (based on renal units), seven provided data on renal cortical abnormalities, and 15 provided data on occurrence of UTI (with varying criteria for UTI diagnosis) in patients receiving CAP. These reports included data on 1,323 infants managed with CAP; 81.0% had a diagnosis of PNH and 67.8% were male.

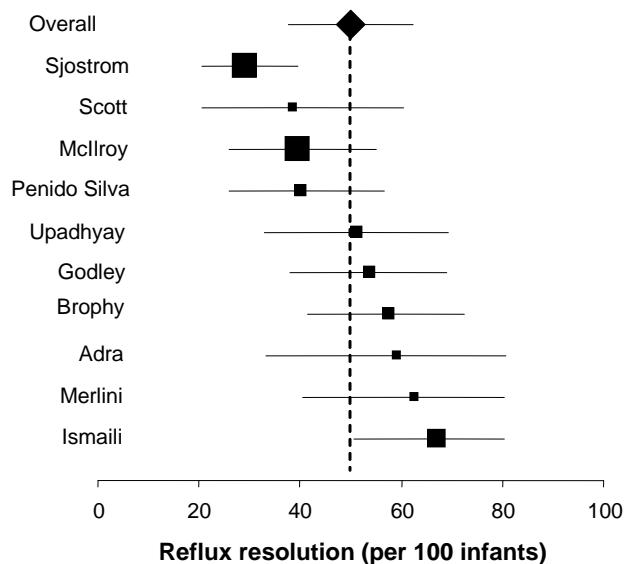
Outcomes Analysis

Vesicoureteral Reflux Resolution

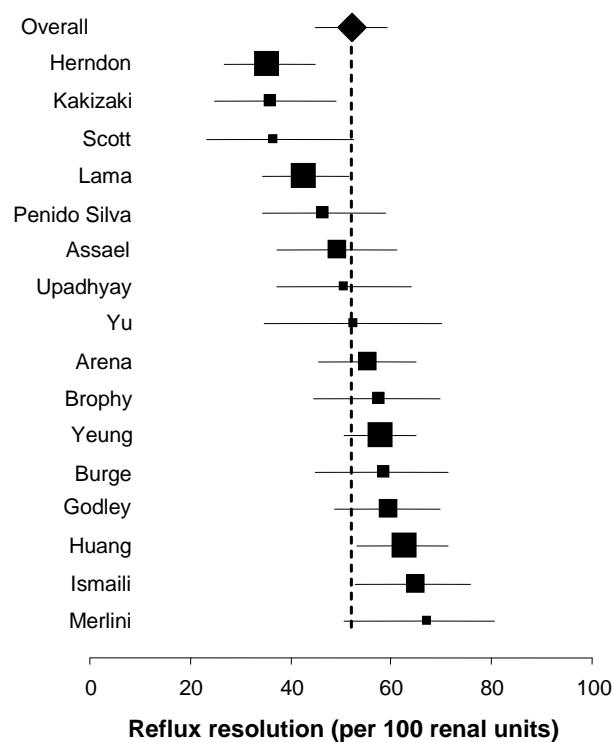
The resolution rate for infants with PNH or UTI at presentation was 49.9 per 100 patients and 52.0 per 100 renal units (Figure 1), with the range of follow-up times between 12 and 48 months. The resolution rate for studies with infants diagnosed prenatally (no prior UTI) was 59.2 per 100 infants, representing a 20% greater VUR resolution compared to the rate for all infants.

Figure 1. Forest plot of VUR resolution rates among infants (A) per patient and (B) per renal unit.

A.



B.

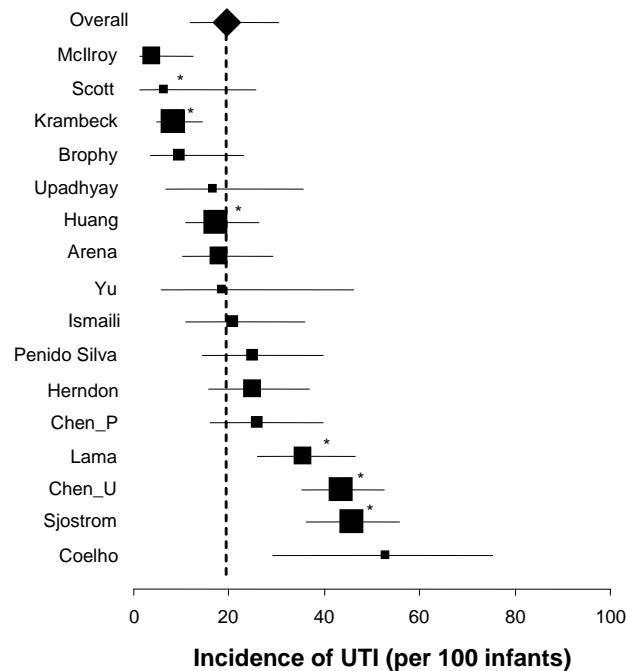


When stratified by sex, the resolution rates were 46.8 for males and 51.6 for females per 100 renal units (a nonsignificant difference). Renal units with severe grade (IV–V) VUR were 85% less likely to resolve than those with mild-moderate grade VUR (71/100 units with grades I–III VUR vs. 28/100 units with grades IV–V VUR; p-value<0.0001).

Incidence of Urinary Tract Infection

The incidence of UTI in infants diagnosed with PNH or UTI who were managed with CAP was 19.5 cases per 100 infants, with a mean follow-up of 24 months (Figure 2); the incidence of UTI for infants with PNH and no prior UTI was 17.5 per 100. The effect of gender, VUR grade or circumcision status could not be analyzed due to the insufficient data. Similarly, there was a lack of data clearly separating patients with proven pyelonephritis.

Figure 2. Forest plot of UTI incidence in infants with VUR managed with continuous antibiotic prophylaxis.



*Indicates studies with some children with prior history

Among infants initially receiving CAP, 17.7% had subsequent surgical treatment, usually with an open procedure. Criteria used to determine the need for surgery included persistent grade III-V VUR, development of a breakthrough UTI (BT-UTI), treatment noncompliance and deterioration of renal function. The distribution of VUR severity across children in the individual samples did not explain the rate of surgery, indicating that other factors were involved in the choice to proceed to surgical repair.

Renal Cortical Abnormalities

The overall incidence of renal cortical abnormalities (scarring or decreased uptake on scintigraphy) was 8.2 per 100 infants with VUR. It is not clear how many of these defects were present since birth (or without prior pyelonephritis), thereby representing congenital changes rather than scarring secondary to UTI. Due to the relatively small sample size, the potential effect of persistent VUR, high-grade VUR or UTI on renal outcomes could not be analyzed. Paucity of data on renal cortical abnormalities, as detected by scintigraphy, limits the analysis of heterogeneity and the conclusions that can be reached on this important outcome.

Recommendation: Continuous antibiotic prophylaxis is recommended for the child less than one year of age with VUR with a history of a febrile urinary tract infection. This approach is based on the greater morbidity from recurrent urinary tract infection found in this population.

[Based on review of the data and Panel consensus]

Recommendation: In the absence of a history of febrile urinary tract infection, continuous antibiotic prophylaxis is recommended for the child less than one year of age with VUR grades III–V who is identified through screening.

[Based on review of the data and Panel consensus]

Option: In the absence of a history of febrile urinary tract infection, the child less than one year of age with VUR grades I–II who is identified through screening may be offered continuous antibiotic prophylaxis.

[Based on review of the data and Panel consensus]

Option: Circumcision of the male child with VUR may be considered based on an increased risk of urinary tract infection in boys who are not circumcised compared

to those who are circumcised. Although there are insufficient data to evaluate the degree of this increased risk and its duration, parents need to be made aware of this association to permit informed decision-making.

[Based on review of the data and Panel consensus]

Summary

Primary VUR that is diagnosed during infancy and managed nonoperatively with CAP is likely to resolve within 12–48 months in approximately half of all children. This is an aggregate percentage that includes patients with a diagnosis of PNH as well as those diagnosed with a UTI. The probability of resolution was influenced by the initial VUR grade (a lower VUR grade had a higher resolution rate), a finding that supports the value of considering VUR grade when counseling parents. The reported UTI incidence data appeared to reflect the era in which they were published, with earlier studies (before the 1990s) tending to report lower incidences than those more recently published. These differences may reflect, among many things, better reporting, a heightened level of suspicion (and subsequent evaluation), and/or changes in the pattern of drug resistance. Not surprisingly, many outliers with a low reported incidence of UTI had an average follow-up of less than 18 months. This highlights the need for longer follow-up of events for which increased occurrence is likely to be detected with longer observation

The infant with VUR may have presented with prenatally detected hydronephrosis that prompted performance of the voiding cystourethrogram, or they may have presented with a UTI. It is widely presumed, without evidence, that these different patients may be distinct in terms of natural history and further risk of UTI and renal injury. The Panel attempted to assess this using the available data, but could not identify sufficient numbers of studies in which patient outcomes were stratified by presentation. The incidence of UTI is slightly different between those presenting after prenatal detection and after UTI (Fig. 2). However, we could only separate out a

subset of children with just PNH from the group, including both UTI and PNH presentation. We were not able to compare those presenting as UTI with those presenting with PNH. Therefore the data are presented as an aggregate group. No evidence is available that either supports or refutes the idea that infants with VUR presenting after UTI are distinct from those presenting with PNH in terms of risk of renal injury. A cautious approach would be to consider both groups as being at risk for further UTI until proven otherwise.

There are limited data to assess the efficacy of CAP in this subgroup of children. In the prospective trials, Roussey-Kesler, et al.¹ reported a benefit for boys with grade III VUR, while Pennesi, et al.² found no benefit for infants; however, both of these trials had very limited numbers of patients in these groups, suggesting that generalizing these findings to infants is risky. Most of the reviewed studies were conducted in an era when CAP was the standard of care; in the absence of a control group not receiving CAP, the role of CAP in VUR management cannot be accurately assessed. Although these recent studies of varying methodological quality raise questions as to its benefit, until its efficacy is specifically assessed in this population, CAP is recommended to protect infants while awaiting spontaneous resolution.

The role of circumcision in male patients, a potentially important variable in terms of UTI risk, could not be determined from the reviewed literature. While circumcision may have an important impact on the risk of UTI in boys³, its specific effect in the context of VUR could not be adequately assessed due to the lack of available data regarding circumcision status in the evaluated populations. The established reduction in UTI, however, coupled with the risk of UTI in infants with VUR, prompted the panel to consider circumcision an option in the management of the infant boy with VUR.

In this meta-analysis, upper urinary tract evaluation showed renal cortical abnormalities in approximately 14% of patients, including those without prior UTIs; it was not possible to

distinguish new abnormalities (renal scarring) from defects present since birth (congenital renal abnormality). With longer term follow-up, patients at risk for further damage may be detected.

References

1. Roussey-Kesler, G., Gadjos, V., Idres, N. et al.: Antibiotic prophylaxis for the prevention of recurrent urinary tract infection in children with low grade vesicoureteral reflux: results from a prospective randomized study. *J Urol* 2008; **179**: 674.
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3. Singh-Grewal, D., Macdcessi, J., Craig, J.: Circumcision for the prevention of urinary tract infection in boys: a systematic review of randomised trials and observational studies. *Arch Dis Child* 2005; **90**: 853.