

Topic 5: Screening of the neonate/infant with prenatal hydronephrosis

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Index patient

The healthy neonate with unilateral mild (Society for Fetal Urology [SFU] grade 1) to moderate (SFU grades 2–3) hydronephrosis identified on a screening prenatal ultrasound at 30 weeks gestation.

Introduction

Postnatal evaluation of prenatal hydronephrosis (PNH) offers the opportunity to diagnose and manage vesicoureteral reflux (VUR) before secondary damage occurs from urinary tract infection (UTI). Prior studies in patients with ipsilateral renal function loss but no history of infection have already led to the recognition that maldevelopment in the absence of infection can contribute to the clinical picture of “reflux nephropathy”. Evaluation of affected infants could additionally provide insights into the benefits, if any, of early identification of VUR and institution of continuous antibiotic prophylaxis to prevent UTI, pyelonephritis and renal scarring.

Methodology

Literature Search, Data Extraction, and Evidence Combination

A meta-analysis of the existing literature was performed to determine the impact of postnatal management of neonates/infants with PNH in prevention of UTI, pyelonephritis, and new renal scarring, and to develop recommendations for screening to detect VUR. Outcomes included the incidence of VUR (stratified by sex, laterality, and postnatal diagnosis of reflux), incidence of UTI, and incidence of renal cortical abnormalities. Of the 43 studies selected for meta-analysis involving at least 6,579 infants with PNH (who were evaluated postnatally), there were 34 studies reporting VUR incidence among 4,756 infants with PNH, 12 studies providing information on renal abnormalities in 530 infants, and eight studies reporting UTI in 616 infants. There was large variability across these studies regarding the definition of PNH, indications and timing of postnatal evaluation; therefore the percentage of patients undergoing renal ultrasonography,

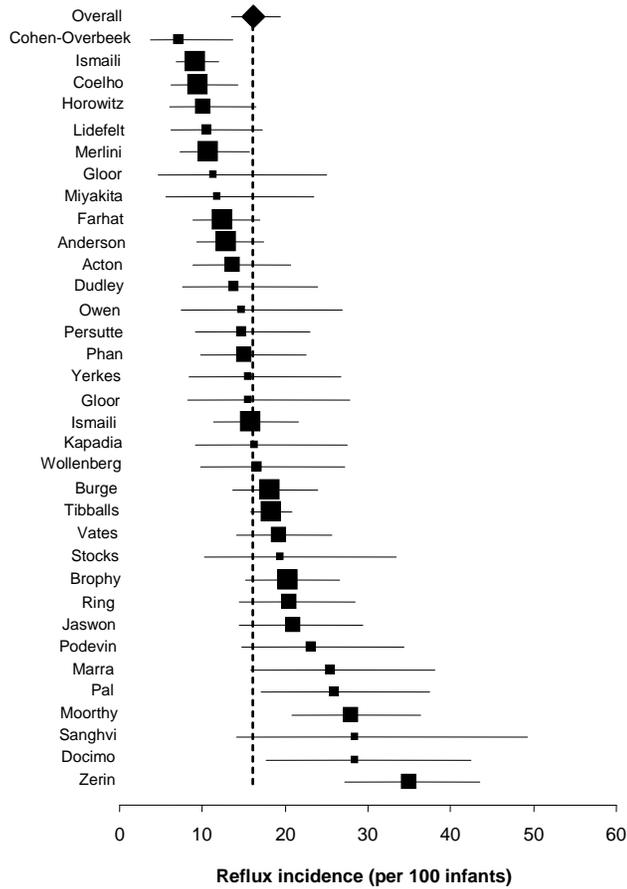
cystography, or other investigations also varied. Articles that included other diagnoses, (such as posterior urethral valves, ureterocele, etc.) that could not be separated were excluded from analysis.

Outcomes Analysis

Incidence of Vesicoureteral Reflux

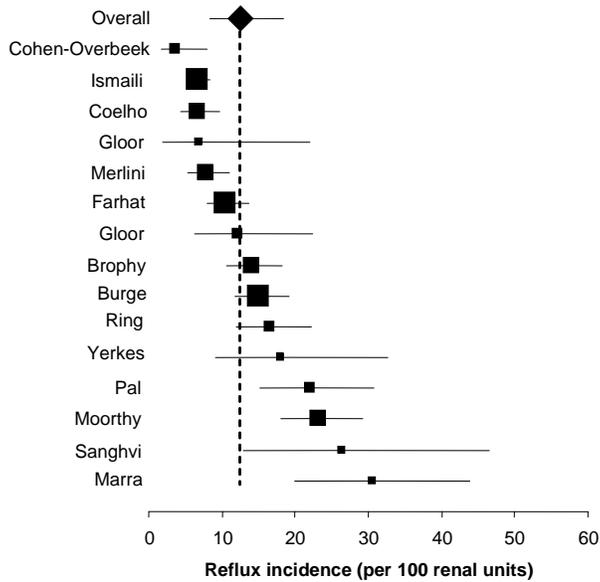
The incidence of VUR in patients with PNH was reported by 34 studies. Of these, the mean percentage of neonates/infants screened by cystography was 78% (range, 11% to 100%). Reflux was detected in 7% to 35% of patients undergoing cystography, averaging 16.2% (Figure 1).

Figure 1. Forest plot of VUR incidence rate among infants with PNH



Reflux per renal unit with PNH was determined from 15 studies, yielding a mean of 12.6% (95% CI: 8, 18%) as shown in Figure 2.

Figure 2. Forest plot of reflux incidence rate among renal units with PNH



Some studies did not perform cystography if postnatal renal ultrasonography was normal, potentially leading to an erroneous estimate of VUR incidence. Considering the 16 studies in which 100% of neonates/infants with PNH and hydronephrosis confirmed postnatally underwent cystography, the mean percentage of patients with VUR was 15.2% (95% CI: 10.9, 20.7).

Considering only those studies in which 100% of patients with PNH underwent cystography (even if no hydronephrosis is detected postnatally), the incidence of reflux was 18.2 (95% CI: 13.0, 24.8) per 100 infants.

In eight studies, information was provided regarding VUR into a contralateral normal kidney. VUR into the nondilated kidney accounted for a mean of 25.2% (95% CI: 17.6, 34.7) of detected reflux. Considering the total of 3,082 renal units screened, there was a mean incidence of 4.1% VUR (95% CI: 2.3, 7.4) into a nondilated kidney.

Table 1 provides estimates for VUR incidence stratified by sex, laterality, and postnatal diagnosis of reflux. The distribution of VUR grade was approximately one-third grades I–II, one-third grade III and one-third grades IV–V based upon maximum grade in both patients and renal units. Approximately one-half of the patients had bilateral VUR.

Females with a prenatal diagnosis of PNH had a significantly higher ($p = 0.022$), incidence of VUR compared to male infants. In nine studies the mean incidence of reflux was 17.0% (95% CI: 10.7, 25.8) (17.0% vs. 15.6%, $p = 0.59$), in children with PNH having a normal postnatal ultrasound. Therefore the incidence of VUR in neonates/infants with a history of PNH was the same regardless of postnatal renal ultrasonography findings (Table 1).

Table 1. VUR incidence rate per 100 infants screened

Sex	<u>Overall</u>	<u>Male</u>	<u>Female</u>
	18.2 (11.6, 27.4)	16.1 (9.9, 25.1)	23.0 (14.2, 35.0)
N	1,300	911	389
Laterality	<u>Overall</u>	<u>Unilateral</u>	<u>Bilateral:</u>
	16.2 (11.5, 22.3)	7.7 (5.4, 10.7)	8.0 (5.4, 11.5)
N	2,379		
By postnatal US	<u>Overall</u>	<u>Normal or RPD <5mm</u>	<u>Abnormal or RPD ≥5mm</u>
	16.2 (10.7, 23.7)	17.0 (10.7, 25.8)	15.6 (10.0, 23.6)
N	1,337	835	502
By postnatal US*	<u>Overall</u>	<u>Normal or RPD <5mm</u>	<u>Abnormal or RPD ≥5mm</u>
	16.1 (8.9, 27.3)	13.3 (7.0, 24.0)	18.6 (10.3, 31.4)
N	909		

*Includes only studies in which VCUG was performed.

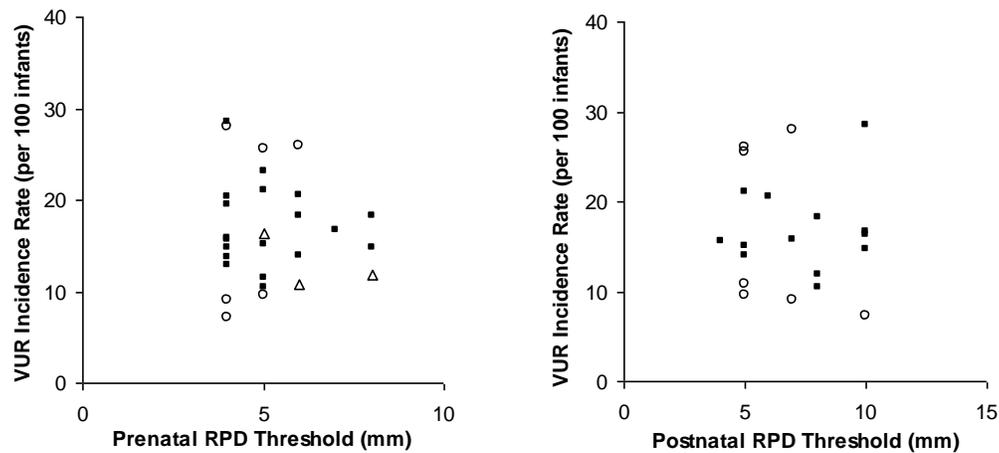
RPD, renal pelvic diameter; US, ultrasound; VCUG, voiding cystourethrogram

Note: N corresponds to the number of neonates/infants screened. Numbers within parenthesis correspond to the 95% confidence interval.

PNH is determined by the anterior-posterior renal pelvic diameter (RPD) measured in transverse section. However, no universally accepted threshold defines patients who are most likely to

benefit from postnatal evaluations. Figure 3 shows the incidence of VUR based upon the minimum prenatal and postnatal RPD used to prompt screening cystography. Increasing RPD did not predict an increased likelihood of VUR, with RPD of only 4 mm associated with reflux in approximately 10% to 20% of neonates/infants screened.

Figure 3. VUR incidence by prenatal and postnatal RPD thresholds (Open triangles=3rd trimester as first evaluation; Open circles=outliers; Filled squares=all other



Other factors that might influence the incidence of VUR were investigated, including trimester of PNH assessment, timing of postnatal evaluation (from 1 to 3 months), and percentage of patients screened. None of these factors had a correlation with findings of reflux.

Incidence of Urinary Tract Infections during Screening Period

Eight studies reported data on the occurrence of UTI 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 found to have VUR

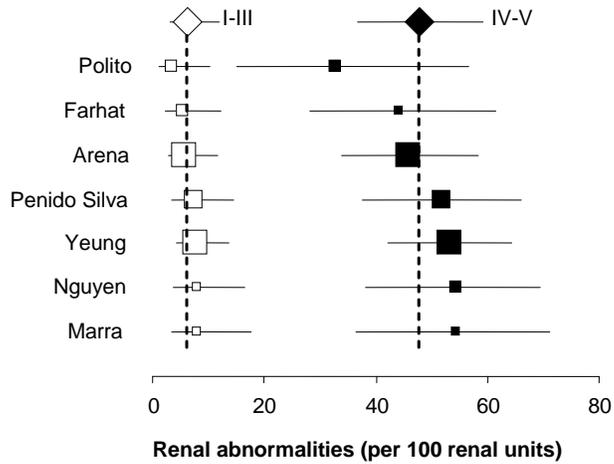
and/or PNH. Agents used were not uniformly reported. Consequently the risk of UTI in patients with PNH with and without VUR cannot be determined, nor can the possible impact of antibiotic prophylaxis. Within the variable conditions mentioned above, the incidence of reported UTI ranged from 0.5–21.3 cases per 100 infants under surveillance, averaging 4.2%; most of these cases were in patients with VUR.

Renal Cortical Abnormalities

Of 43 extracted publications, five reported DMSA screening in a mean of 60 (range 23–155) patients, while nine reported a mean of 79 (range 24–236) renal units screened with DMSA nuclear scintigraphy. There was heterogeneity in descriptions of these renal abnormalities, variously categorized as focal or diffuse renal cortical scars and/or decreased global uptake. Of studies reviewed, 94% of patients and 98% of renal units with VUR underwent DMSA screening in the early postnatal period. The incidence of any renal abnormality before UTI in patients with VUR ranged from 2–63% of patients with a mean of 21.8%. The incidence of abnormalities per renal unit ranged from 26% to 42%, with a mean of 32.3%.

In seven of nine studies reporting abnormalities by renal unit, reflux grade was also available. For this meta-analysis, VUR severity was categorized as low-moderate (grades I–III) and severe (grades IV–V). The overall prevalence of renal abnormalities was 29.4 per renal unit (Figure 4). In the low-moderate group (grades I–III) the prevalence was 6.2% versus 47.9% in those with severe reflux (grade IV–V) ($p < 0.0001$).

Figure 4. Forest plots of renal cortical abnormality rates by reflux grade



Recommendation: Voiding cystourethrogram is recommended for children with high-grade (Society of Fetal Urology grade 3 and 4) hydronephrosis, hydroureter or an abnormal bladder on ultrasound (late term prenatal or postnatal), or who develop a urinary tract infection on observation.

[Based on review of the data and Panel consensus]

Option: An observational approach without screening for VUR, with prompt treatment of any urinary tract infection, may be taken for children with prenatally detected hydronephrosis (SFU grade 1 or 2), given the unproven value of identifying and treating VUR. It is also considered an option to perform a voiding cystourethrogram in these patients to screen for VUR.

[Based on Panel consensus]

Summary

Within the limitations mentioned above, this meta-analysis found that approximately 16% of neonates and infants with PNH have reflux. This incidence was independent of prenatal RPD, with reflux also detected in non-dilated renal units. The incidence of VUR was similar when postnatal urinary tract ultrasonography was normal. Reflux grade was III or greater in two-thirds of patients, with renal abnormalities occurring in nearly 50% of those with grades IV–V.

Given the widely accepted view that VUR occurs in only approximately 1% of otherwise normal infants,¹ those with PNH represent a group at increased risk for reflux. Furthermore, the reflux grade was more severe than expected in older children presenting with UTI. The finding that renal abnormalities are already present in a significant percentage of renal units with higher grades of reflux raises concern for the additional negative impact even a single UTI might impart. Together these considerations potentially support postnatal cystography in all neonates with PNH, an age group in which cystography also may be better accepted by families. However, the lack of a prospective study demonstrating benefit of reflux detection in asymptomatic neonates and recent data from prospective studies that question efficacy of antibiotic prophylaxis to prevent UTI make screening cystography an option, rather than a recommendation.

References

1. Arant, B. S., Jr.: Vesicoureteric reflux and renal injury. *Am J Kidney Dis* 1991; **17**: 491.