

The Fate of Primary Nonrefluxing Megaureter: A Prospective Outcome Analysis of the Rate of Urinary Tract Infections, Surgical Indications and Time to Resolution

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Abbreviations and Acronyms

CAP = continuous antibiotic prophylaxis
DRF = differential renal function
fUTI = febrile UTI
HN = hydronephrosis
HUN = hydronephrosis
NNT = number needed to treat
UTI = urinary tract infection
VUR = vesicoureteral reflux

Accepted for publication November 20, 2015.
No direct or indirect commercial incentive associated with publishing this article.

The corresponding author certifies that, when applicable, a statement(s) has been included in the manuscript documenting institutional review board, ethics committee or ethical review board study approval; principles of Helsinki Declaration were followed in lieu of formal ethics committee approval; institutional animal care and use committee approval; all human subjects provided written informed consent with guarantees of confidentiality; IRB approved protocol number; animal approved project number.

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Purpose: We examined data on a cohort of patients with primary nonrefluxing megaureter to determine risk factors for febrile urinary tract infection, indications for surgery and time to resolution.

Materials and Methods: The records of patients younger than 24 months with primary nonrefluxing megaureter were prospectively captured from 2008 to 2015. Six a priori defined variables were studied, including gender, circumcision status, hydronephrosis SFU (Society for Fetal Urology) grade (low—1 and 2 vs high—3 and 4), continuous antibiotic prophylaxis use, ureteral dilatation (greater than 11 mm) and tortuosity. Univariate analyses and Cox hazard regression were done for febrile urinary tract infection risk factors. Resolution trends were analyzed using Kaplan-Meier curves.

Results: Mean \pm SD age at the first clinic visit was 3.7 ± 4 months and mean followup was 26.3 ± 16.6 months. Of 80 patients with primary megaureter 66 (83%) had high grade hydronephrosis, 72 (90%) were male, 21 (26%) were circumcised and 40 (50%) had ureteral dilatation greater than 11 mm at baseline. Overall continuous antibiotic prophylaxis was prescribed to 34 patients (43%) and febrile urinary tract developed infection in 27 (34%) at a mean age of 5.8 months (median 3, range 1 to 24). Cox regression identified uncircumcised male gender (HR 3.4, 95% CI 1.1–10.7, $p = 0.04$) and lack of continuous antibiotic prophylaxis (HR 4.1, 95% CI 1.3–12.7, $p = 0.01$) as independent risk factors for febrile urinary tract infection. The 19 surgical patients (24%) had a larger mean ureteral diameter immediately preoperatively than those who did not require surgery (17 ± 5 vs 12 ± 4 mm, $p < 0.01$). Kaplan-Meier curves showed that 85% of primary nonrefluxing megaureters that did not require surgery resolved in a median of 17 months.

Conclusions: Febrile urinary tract infection developed in 34% of patients with primary nonrefluxing megaureter within the first 6 months of life. Circumcision and continuous antibiotic prophylaxis significantly decreased febrile urinary tract infection rates in those infants. Ureteral diameter 17 mm or greater was significantly associated with a higher rate of surgical intervention. Overall 76% of megaureters resolved during a median followup of 19 months.

Key Words: ureter, urinary tract infections, hydronephrosis, prenatal diagnosis, antibiotic prophylaxis

PRIMARY nonrefluxing megaureter is a congenital dilatation of the ureter not associated with VUR, bladder outlet obstruction or another structural anomaly such as ureterocele or ectopic ureter.^{1,2} Primary nonrefluxing megaureter comprises 5% to 10% of all prenatal HN cases and it is substantially more common in males.^{3,4}

Previous studies have assessed outcomes of children with varying etiologies of HN.⁵ However, prospective information on the risk of fUTI and on the natural history of patients with primary nonrefluxing megaureter specifically has been scarcely reported.^{6,7} To address this gap in the literature we designed a prospective longitudinal study with the primary objective of determining risk factors for fUTI in pediatric patients with primary nonrefluxing megaureter. In addition, we examined indications for surgical intervention and time to HUN resolution. We hypothesized that patients with higher HN grades, tortuous and dilated ureters, and not receiving CAP would have higher fUTI rates. We also postulated that primary nonrefluxing megaureters with a larger ureteral diameter would be less likely to resolve spontaneously and be more prone to requiring surgical intervention.

METHODS

Setting, Population, and Study Inclusion and Exclusion Criteria

After receiving approval from our ethics board we prospectively screened the records of 850 consecutive patients referred to a tertiary pediatric hospital for prenatal HN assessment between 2008 and 2015. First we excluded patients without HN and those older than 24 months at the baseline visit. After further excluding patients with simple duplex kidneys, ectopic ureter, ureterocele, posterior urethral valves, multicystic dysplastic kidney, horseshoe kidney, neurogenic bladder and prune belly syndrome as well as those with isolated renal pelvic dilatation (or ureteropelvic junction obstruction-like) and VUR a total of 80 infants with primary nonrefluxing megaureter formed our study population and were included in analysis.

Primary nonrefluxing megaureter was defined as HUN with ureteral dilatation 7 mm or greater and absent VUR as documented by voiding cystourethrogram. The voiding cystourethrogram indications for prenatal HN cases were based on physician discretion and included high grade HN, ureteral dilatation and bladder abnormalities on ultrasound (large capacity and thickening of the wall).

Primary Outcome of Interest and Independent Variables

The primary outcome was the development of fUTI, strictly defined by documented fever (38C or greater), pyuria (urinalysis with positive leukocyte esterase and greater than 10 white blood cells per high power field), bacteria on Gram stain and urine culture yielding greater

than 100,000 cfu/ml of a single microorganism from a catheterized specimen.

Six potential risk factors for fUTI were chosen a priori, including gender, circumcision status, HN grade (low vs high), CAP use, ureteral dilatation (7 to 11 vs greater than 11 mm) and presence of ureteral tortuosity. Low grade HN was defined as grade 1 or 2 and high grade was defined as 3 or 4 according to the SFU grading system.⁸ CAP was prescribed according to pediatric urologist discretion. CAP status in 27 patients (33%) enrolled in a concurrent randomized, controlled trial could not be determined due to blinding. These patients were considered separately in the analysis of CAP as a risk factor.

We used the 11 mm ureteral diameter cutoff based on previous data, which suggested that ureters greater than 10 mm were unlikely to resolve spontaneously and required surgery.⁹ Ureteral tortuosity was defined as tortuosity of the entire ureter (proximal, mid and distal thirds). The largest ureteral caliber measured at its most distal part on a transverse ultrasound view of the bladder served as our measurement criterion as reported by the radiologist.

Secondary Outcomes

Surgical indications included development of fUTI or renal stones, half-time time greater than 40 minutes (plateau curves) on renogram associated or not associated with a decrease in DRF greater than 5% on serial renal scintigraphy and worsening HUN on repeat ultrasounds. Patients who had 10 mm or less anteroposterior diameter of the renal pelvis, less than 8 mm ureteral dilatation and/or SFU HN grade 2 or less at the last followup clinic visit were considered to have achieved HUN resolution for study purposes.

All data, including renal ultrasound images, were prospectively collected at the time of the patient clinic visit. Patients were followed until HUN resolution or were censored at the last followup visit, at surgery or at development of the outcome of interest (fUTI). Minimum acceptable monitoring time was 6 months.

Statistical Analyses

Univariate analyses on the 6 a priori decided risk factors for fUTI were performed using the chi-square test. We also created a Cox proportional hazard regression model, introducing adjustment for time dependent variables that could affect resolution rates, to determine whether they were independent risk factors for fUTI. HRs with the 95% CI were calculated for each predictor variable. Indications for surgery were summarized using descriptive statistics, including frequency and proportions. Kaplan-Meier curves were drawn to illustrate the cumulative rate of unresolved HN according to the number of ureteral units. All statistical analyses were done with SPSS®, version 22 with $p < 0.05$ considered statistically significant.

RESULTS

The study population consisted of 80 patients with primary nonrefluxing megaureter, including 72 males (90%) of whom 21 (26%) had undergone circumcision. Mean age at the first clinic visit was

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