Risk Factors for Febrile Urinary Tract Infection in Children with Prenatal Hydronephrosis: A Prospective Study

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Abbreviations and Acronyms

CAP = continuous antibiotic prophylaxis
fUTI = febrile UTI
HN = hydronephrosis
HUN = hydroureteronephrosis
PHN = postnatally confirmed prenatal hydronephrosis
SFU = Society for Fetal Urology
UPJO = ureteropelvic junction obstruction
UTI = urinary tract infection
VCUG = voiding cystourethrogram
VUR = vesicoureteral reflux

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Purpose: We prospectively investigated the impact of risk factors for febrile urinary tract infection in infants with postnatally confirmed prenatal hydronephrosis.

Materials and Methods: Patients seen for prenatal hydronephrosis from 2010 to 2013 were prospectively followed. Those with ectopic ureters and ureteroceles, posterior urethral valves and neuropathic bladders were excluded. The primary outcome was febrile catheter specimen urinary tract infection. We performed univariate analysis of 7 a priori risk factors, including age, hydronephrosis grade (low—I or II vs high—III or IV), type (isolated hydronephrosis vs hydroureteronephrosis), continuous antibiotic prophylaxis, vesicoureteral reflux grade, gender and circumcision status. Time to febrile urinary tract infection curves analyzed by Cox proportional regression were generated to adjust for confounders.

Results: We collected data on 334 patients, of whom 78% were male. A febrile urinary tract infection developed in 65 patients (19%) at a median of 4 months (range 1 to 31). High grade hydronephrosis was present in 192 infants (57%). Continuous antibiotic prophylaxis was prescribed in 96 cases (29%). Of patients on continuous antibiotic prophylaxis 69% had high grade hydronephrosis. Vesicoureteral reflux was identified in 57 of 238 patients in whom voiding cystourethrogram was done. Reflux was grade I to III in 14 cases and grade IV or V in 43. Two-thirds of the patients with reflux were on continuous antibiotic prophylaxis. Circumcision was performed in 95 males (36%). Cox proportional regression identified female gender (HR 3.3, $p = 0.02$), uncircumcised males (HR 3.2, $p = 0.02$), hydroureteronephrosis (HR 10.9, $p < 0.01$), vesicoureteral reflux (HR 20.8, $p < 0.01$) and lack of continuous antibiotic prophylaxis (HR 5.2, $p < 0.01$) as risk factors for febrile urinary tract infection. Subgroup analysis excluding vesicoureteral reflux showed that high grade prenatal hydronephrosis was also a significant risk factor (HR 3.0, $p = 0.04$).

Conclusions: After patients with vesicoureteral reflux were excluded from the study, females and uncircumcised males with high grade hydroureteronephrosis had significantly higher febrile urinary tract infection rates. Therefore, those patients may benefit from continuous antibiotic prophylaxis.

Key Words: kidney, hydronephrosis, urinary tract infections, antibiotic prophylaxis, risk

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PRENATAL hydronephrosis is one of the most common congenital urological anomalies, reported in up to 5% of all pregnancies.[1] Physiological (transient) HN, also called UPJO-like, and VUR are the most frequent etiologies of prenatal HN, followed by primary megaureter (HUN).[1] Infants with these conditions are thought to be at risk for fUTI, mainly in the first 2 years of life.[1,2] Evidence suggests that the fUTI rate increases with the severity of prenatal HN.[3] According to previous guidelines CAP is recommended in infants with PHN despite the lack of high quality studies to support this practice.[1,4]

Based on a recent systematic review of 21 articles high grade HN and lack of CAP emerged as key risk factors for fUTI. However, the strength of these findings was limited by poor quality data and the analysis failed to adjust for known confounding factors such as VUR, primary megaureter and gender.[3] To overcome some of those shortcomings we explored risk factors for fUTI in infants with PHN in a more controlled setting by reviewing the records of patients with PHN at our institution.[5] Those with high grade HN, females and uncircumcised males were at significantly higher risk for fUTI. Unfortunately limitations inherent to the retrospective nature of the study design prevented us from adjusting for confounders such as VUR and primary megaureter.

To further address those limitations we designed a prospective longitudinal study with the primary objective of verifying the effect of gender, circumcision status, HN grade, etiology (type) and CAP, considering time to fUTI in patients with PHN. We hypothesized that females and uncircumcised males with high grade HUN who were not prescribed CAP would have significantly higher fUTI rates than those without these characteristics.

METHODS

Setting, Population and Study Inclusion/Exclusion Criteria

We performed a prospective longitudinal study in patients diagnosed with PHN at a tertiary pediatric hospital after obtaining ethics board approval. To minimize selection bias we screened 502 consecutive patients diagnosed with PHN from June 2010 to October 2013. Of these patients 334 (67%) were included in study based on the criterion of a primary diagnosis of prenatal HN confirmed by postnatal renal bladder ultrasound. Excluded from the study were 168 patients (33%) with ectopic ureters and ureteroceles (76 or 45%), posterior urethral valves (31 or 18%) or neurogenic bladder (17 or 10%), or those in whom HN was diagnosed after 24 months (43 or 26% in whom it was discovered at that time).

Independent Risk Factors for fUTI and Outcome of Interest

According to the SFU grading system low grade HN was defined as grade I or II and high grade HN was defined as grade III or IV.[6] HN grade was determined by the radiologist who read the study at the time that it was performed. In patients with bilateral PHN the highest grade was used for analysis. VUR was categorized as none, low (I to III) or high grade (IV to V) into a single or duplicated system.

Based on ureteral dilation the type of PHN was considered UPJO-like (collecting system dilation only with no reflux), primary megaureter (collecting system and ureteral dilation 7 mm or greater with no reflux) or VUR (reflux with ureteral dilation or ureteral plus collecting system dilation). The indication for VCUG was based on physician discretion.

Seven potential risk factors for fUTI were chosen a priori, including patient age, gender, circumcision status, HN type (isolated HN or UPJO-like) or HUN (primary megaureter), HN grade (low vs high), CAP (yes vs no) and VUR grade (none, low and high). All data, including renal ultrasound, were prospectively collected at the time of the patient clinic visit.

CAP was prescribed according to pediatric urologist discretion. CAP status in 58 patients (17%) enrolled in a concurrent randomized, controlled trial could not be determined due to blinding. These patients were considered separately in analyses of CAP as a risk factor. All patients were followed until the outcome of interest (fUTI) developed or PHN resolved (SFU grade I or 0—no hydronephrosis), or they continued to be monitored until the study end point (last followup visit).

The outcome of interest was fUTI, which was prospectively ascertained weekly when possible in 244 cases, and by retrospective review of emergency department and inpatient records in 90. We defined fUTI as urine culture yielding 100,000 cfu/ml or greater of a single organism from a catheter specimen in a patient with pyuria (defined as greater than 10 white blood cells per high power field) associated with fever 38C or greater.

Statistical Analysis and Sample Size Calculation

Univariate analysis of risk factors was done with the chi-square or Fisher exact test based on data characteristics. A Cox proportional regression model was created to determine independent risk factors for fUTI, adjusting for known confounders (covariates) and considering time to event or followup duration. The HR and 95% CI were generated for each fUTI risk factor. Subsequently we performed a priori defined subgroup analysis of potential risk factors for fUTI, excluding patients with VUR, to adjust for the confounding effect of VUR on fUTI. The variable VCUG/VUR was excluded from multivariable analysis due to collinearity between HN type and VCUG/VUR. We estimated the overall UTI-free rate of each variable using Kaplan-Meier curves and compared rates between variables using the log rank test. Adjusted Kaplan-Meier curves of UTI-free rates in our Cox regression model were plotted to determine fUTI rates stratified by gender, circumcision and VUR status.

Based on expected UTI rates of 15% and 29% in patients with PHN who were and were not on CAP, respectively,[3] and assuming 80% power and an α error of 5% the required sample size to properly answer the research question was 302 patients, accounting for 10% loss to followup.