Journal of Pediatric Urology (2014) 10, 650—654

Journal of Pediatric urology

Continuous antibiotic prophylaxis reduces the risk of febrile UTI in children with asymptomatic antenatal hydronephrosis with either ureteral dilation, high-grade vesicoureteral reflux, or ureterovesical junction obstruction

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Received 14 February 2014; accepted 15 June 2014
Available online 22 July 2014

KEYWORDS
Antenatal hydronephrosis;
Antibiotic prophylaxis;
Febrile urinary tract infection

Abstract *Background:* The efficacy and utility of continuous antibiotic prophylaxis (CAP) in children with congenital antenatal hydronephrosis (ANH) is uncertain. The literature has both supportive and contradictory evidence. The growing trend not to place children with ANH on CAP has created varied clinical practice based on anecdotal individual case characteristics. Our goal was to compare individual infant characteristics between those children who were maintained on CAP to those that were not to try to determine predisposing risk factors to febrile.

Methods: All electronic medical records (EMRs) of children referred to our institution for congenital ANH over a period from 2001 to 2011 were examined. We excluded those referred for urinary tract infection (UTI) who had a history of congenital ANH. We also excluded those with incomplete records, or follow-up less than 2 years. Children were divided into two groups: those maintained on CAP (YCAP) and those not maintained on CAP (NCAP). Our primary

Abbreviations: UPJ, ureteropelvic junction; UVJ, ureterovesical junction; VUR, vesicoureteral reflux; ANH, antenatal hydronephrosis; CAP, continuous antibiotic prophyalxis; SFU, Society of Fetal Urology; VCUG, voiding cystourethrogram; YCAP, yes continuous antibiotic prophylaxis; NCAP, no continuous antibiotic prophylaxis.

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http://dx.doi.org/10.1016/j.jpurol.2014.06.009

endpoint was febrile UTI. Follow-up was at least 24 months. Demographic, perinatal and postnatal clinical data were recorded. Statistical analysis was performed using STATA Version 11.1.
Results: Of the 405 children fitting inclusion criteria, 278 (68.6%) children were maintained on CAP and 127 (31.4%) were not on CAP. The incidence of prematurity, oligohydramnios, perinatal respiratory complications, use of perinatal antibiotics, circumcision status, renal anomalies, associated medical diagnoses, and low birth weight did not differ between the two groups. Overall the incidence of febrile UTI during the follow-up period was 22.2%. The incidence of febrile UTI between the YCAP and NCAP groups was significant (YCAP = 7.9% and NCAP 18.7%, $p = 0.021$). Multivariate logistic regression using CAP as the dichotomous dependent variable revealed that ureteral dilation, high-grade vesicoureteral reflux (VUR), and ureterovesical junction (UVJ) obstruction were independent risk factors for febrile UTI. More specifically, children with ureteral dilation >11 mm NOT maintained on CAP had a 5.54 (OR = 5.54; CI = 3.15—7.42, $p = 0.001$) fold increased risk of febrile UTI compared to those maintained on CAP.
Conclusions: The presence of ureteral dilation, high grade VUR, and UVJ obstruction were independent risk factors for development of UTI in children with congenital ANH. Therefore CAP may have a significant role in reducing the risk of febrile UTI in children with ANH with those identifiable risk factors, but otherwise seems unnecessary.

Introduction

Antenatal hydronephrosis (ANH) is the most common fetal abnormality noted on prenatal ultrasound. It is detected in 1—5% of all pregnancies that have an ultrasound [1]. The collecting system dilation is transient in most, but in a smaller percentage it represents a significant anatomic and functional abnormality of the renal collecting system, such as vesicoureteral reflux or obstruction [1,2]. The dilemma for the practitioner is our ability to predict which will become clinically significant. Our ability to predict is based largely on information from invasive postnatal testing, and partly on anecdotal and biased data. We do know from prior studies that children with ANH are at increased risk of postnatal UTI [3], and that this risk increases with severity and persistence during the first year of life [2—4]. Unfortunately, to date there are no complete prospective randomized studies that determine the risk of functional abnormality, risk of UTI, or development of renal damage based on the degree or character of prenatally detected hydronephrosis. Because of this uncertainty, traditional practice has been to attempt to prevent UTI from birth with continuous antibiotic prophyalxis (CAP) and determine with postnatal radiographic studies if there is a functional abnormality of the urinary tract. In many cases, the initial work-up is inconclusive or creates a picture of potential functional abnormality by the presence of VUR or partial obstruction, and the child will then be followed with serial examinations and longer term CAP without ever having a febrile UTI or evidence of renal damage. Whether this is because of practitioner anxiety, parental anxiety, fear of medicolegal action for failure of diagnosis, many children, it is clear, undergo unnecessary testing and endure long-term CAP. In addition, despite initial enthusiasm and guidelines [5,6], many have questioned the efficacy of CAP citing numerous studies that show no benefit in children with UTI [5—8,12—14]. Although poorly documented and reported, in some cases, it is parental refusal, clinician preference, and/or physical intolerance that prevent the use of CAP. Indeed, all these factors can shape our ability to conduct immediate postnatal prospective randomized trials to determine the necessity, safety, and efficacy of CAP. Despite their limitations, observational studies can help us make these difficult decisions. We present the results of an observational study of children referred to our tertiary care medical center for antenatal hydronephrosis to determine the necessity of CAP.

Study methods

We performed a retrospective observational study of children referred for antenatal hydronephrosis. The EMR of children referred to our tertiary care center were screening for the ICD-9 diagnosis of prenatal, antenatal, or congenital hydronephrosis from 2001 to 2011. We excluded those children whose primary referral was for UTI and who had a history of ANH. We also excluded all those with incomplete medical records, and those with <2 years of follow-up data. We then divided the children included in the study into two groups. The first group was those children who had been maintained on CAP for a period no shorter than 3 months (YCAP), and the second group where those who were not maintained on CAP (NCAP). The primary outcome variable was febrile UTI. Statistical analysis of the two study groups and study variables was performed to determine the similarity between the two primary groups. Of the children that had a febrile UTI in the 2-year period of data collection, and using the YCAP and NCAP groups as the dichotomous outcome variable, we performed a univariate and multivariate logistical regression of study variables to determine if any of the variables were independent risk factors for febrile UTI (STATA Version 11.1).

UTI was defined as $>10^6$ CFU/mL of bacteria in a catheterized urine specimen or a bag specimen associated with

pyuria in a symptomatic child with fever. No catheter specimens obtained at the time of VCUG were used. UTI in the YCAP group was only considered a positive endpoint if this occurred while taking antibiotics. Demographic data including age at the time of referral, gender, vesicoureteral reflux status, circumcision status, gestational age and weight at birth, use of perinatal antibiotics for reasons other than UTI, other associated medical conditions, and ultrasound data from both postnatal and prenatal ultrasound. Pre-natal ultrasound data was recorded where available, but incomplete prenatal information was not an exclusion criteria. Vesicoureteral reflux status was recorded by results on VCUG and obstruction was recorded as well as differential function on renal scan. SFU grade of hydronephrosis was recorded in children <2 years of age, and the presence or absence of renal dysplasia/parenchymal abnormality and the degree and measurement of ureteral dilation in millimeters. Renal abnormality/dysplasia were judged by the character of the corticomedullary differentiation and the presence or absence of renal cortical parenchymal thinning. Ureteral obstruction was defined by anatomic position (UPJ vs. UVJ) using both MAG3 renal scan and ultrasound. Obstruction was further quantified by $T_{(1/2)} > 20$ min on Lasix MAG3 renal scan, in addition to a prolonged down slope, up slope, or flattened Lasix response curve.

Results

Five hundred and seven ($n = 507$) children fit initial criteria and had complete enough medical records for the analysis. We excluded 102 children due to a primary referral for UTI who had a history of ANH. Of the 405 children fitting inclusion criteria, 236 (58.3%) were male and 169 (41.7%) were female. Two hundred and thirteen (52.6%) were seen for prenatal counseling by a Pediatric Urology staff member. For the purposes of this study children were split into the YCAP ($n = 278$, 68.6%) and the NCAP ($n = 127$, 31.4%) groups. Overall, ages ranged from 2 days to 5.8 months at the time of referral with an average age of 3.8 weeks. The average age at referral in the YCAP group was 2.9 weeks, and 5.6 weeks in the NCAP group ($p = 0.032$). In the YCAP group 122 (43.9%) were female and in the NCAP group 49 (38.9%) were female ($p = 0.25$). Males were circumcised in 133 (85.3%) in the YCAP group and 64 (82%) in the NCAP group ($p = 0.12$). Premature birth and low birth weight were present in 39 (14%) and nine (3.2%) in the YCAP group, respectively, and 16 (12.6%) and three (2.5%) in the NCAP group, respectively. The percentage of prematurity, use of perinatal antibiotics, oligohydramnios, perinatal respiratory complications, circumcision status, renal anomalies, associated medical problems, and low birth weight did not differ significantly between the two groups. Vesicoureteral reflux was present in 62 (22.2%) children in the YCAP group and 22 (17.6%) children in the NCAP group ($p = 0.45$). Ureteral obstruction was present in 28 (10.3%) children in the YCAP group and 11 (8.8%) children in the NCAP group ($p = 0.065$). High-grade prenatal (SFU grades III and IV) hydronephrosis was present in 174 (62.6%) children in the YCAP group and 37 (29.1%) children in the NCAP group ($p = 0.007$). High-grade postnatal hydronephrosis was present in 145 (52.1%) children in the YCAP group and 35 (27.5%) children in the NCAP group ($p = 0.011$). Table 1 shows the comparison between the two study groups.

Overall the incidence of UTI was 37% ($n = 150$) with a febrile UTI rate of 22.2% ($n = 90$). This is shown in Table 2. Of the children with febrile UTI, a logistical regression revealed in univariate analysis that the presence of high grade VUR, ureteral dilation (defined as > 11 mm inner diameter on ultrasound), ureteral obstruction, high SFU grade hydronephrosis, and renal parenchymal abnormality were all independent risk factors for a higher risk of febrile UTI. This is shown in Table 3. Multivariate analysis found that only ureteral obstruction at the ureterovesical junction, ureteral dilation >11 mm, and high-grade VUR were independent risk factors for febrile UTI. This result is shown in Table 4. There was a five-fold increase risk of febrile UTI for those children with ureteral dilation with an odds ratio of 5.54 (3.15–7.42, $p < 0.001$). Age, gender, circumcision status, abnormal bladder, premature birth, low birth weight, ureteral obstruction (at the UPJ) and other associated or co-morbid conditions did not raise the risk of developing febrile UTI. Sub-stratification of ureteral obstruction into UPJ and UVJ revealed that UVJ obstruction was indeed an independent risk factor for febrile UTI. These results are shown in Table 4. Although renal parenchymal abnormality was significant in the univariate analysis it was not in the multivariate analysis possibly due to the link between parenchymal tinning and high grade VUR and UVJ obstruction.

Discussion

All clinicians understand that in controversial aspects of clinical medicine there will be a divide between what is recommended in medical texts and guidelines and what is "real-world" general knowledge and practice. This is often discussed in the current literature of the time, and prospective randomized blinded studies are often touted as

Table 1 Relationship of study groups to study variables.

Variable	YCAP ($n = 378$)	NCAP ($n = 129$)	*p value*
Age at referral (Weeks)	2.9	5.6	0.032
Gender (%Female)	43.8	38.9	0.25
Vesicoureteral Reflux (%Yes)	22.2	17.3	0.45
Ureteral dilation (%Yes)	12.2	14.1	0.35
Male circumcised (%Yes)	75.1	79.4	0.12
Urinary obstruction (%Yes)	10.1	8.8	0.65
Abnormal bladder (%Yes)	6.9	5.5	0.33
Premature birth (<37 weeks) (%Yes)	14.1	12.6	0.49
Low birth weight (%Yes)	3.1	2.7	0.68
Associated medical conditions (%Yes)	14.5	8.1	0.45
Renal abnormality/dysplasia (% Yes)	9.8	10.4	0.47
Grade III–IV hydronephrosis (%Yes)	62.4	28.9	0.007

Table 2 Rate of UTI and febrile UTI in study groups.

	Overall *n* (%)	YCAP *n* (%)	NCAP *n* (%)	*p-value*
All UTI	134 (33.1%)	68 (24.5%)	66 (51.9%)	*0.038*
Febrile UTI	86 (22.2%)	50 (17.9%)	36 (28.9%)	*0.017*

the solution to the clinical dilemma. However, these studies are often arduous, require a long time to produce meaningful data, and fraught with logistical problems of inter institutional communication and standardization as well as study participants breaking their allocation. In many cases, these studies take so long that they out-live the question they were designed to answer because of an overall shift in the tide of clinical practice. The RIVUR study is a prospective multicenter double-blind placebo-controlled trial designed to address the controversies of CAP in the management of children 2–72 months diagnosed with VUR after [1,2] febrile UTIs [9–11]. This study has concluded that there is a reduction in recurrent UTI in children who are given prophylactic antibiotics. However, in the case of ANH, currently there is insufficient data about CAP to inform risk stratification and solidify uniform clinical practice. In a meta-analysis published in 2010, eight of 34 studies analyzed included data about CAP in children with ANH. The general recommendation was that CAP was recommended in children with a history of UTI and an option for asymptomatic children. These studies were collectively underpowered and suffered from selection bias and a non-uniform definition of UTI and methods of urine collection for culture. In addition, no risk stratification for asymptomatic children was valid. However, in a recent systematic review involving 21 citations and 3876 asymptomatic children with ANH, there was an increased incidence of UTI in children with SFU grade III–IV hydronephrosis not maintained on CAP compared to those maintained on CAP, 28.9% versus 14.6%, respectively [6].

Table 3 Relationship of study variables to outcome based on CAP group.

Study variable	Febrile UTI ($n = 90$)			
	n	YCAP	NCAP	*p value*
SFU grade IV hydronephrosis	39	10.7	19.6	0.024
Gender (%Female)	122	64.1	65.9	0.43
VUR grade I–III (%Yes)	62	41.6	43.1	0.46
VUR grade IV–V (%Yes)	28	17.7	38.2	0.015
Ureteral dilation	34	18.5	39.6	<0.001
Renal parenchyma abnormality/dysplasia (%Yes)	27	16.4	31.8	0.004
Male circumcised (%Yes)	237	45.8	55.1	0.07
UPJ obstruction (%Yes)	28	15.4	19.6	0.08
UVJ obstruction (%Yes)	29	32.9	56.7	0.018
Abnormal bladder (%Yes)	19	6.1	8.2	0.12
Premature birth (<37 weeks) (%Yes)	39	6.5	7.1	0.76
Low birth weight (%Yes)	9	3.8	4.2	0.34
Associated med. conditions (%Yes)	35	15.8	14.5	0.61

Table 4 Multivariate odds ratio of febrile UTI and study risk factors.

Risk factor	OR (95% CI)	*p value*
UVJ obstruction	2.54 (1.12–3.75)	<0.001
Ureteral dilation		
< 11 mm	1.24 (0.65–1.89)	0.09
> 11 mm	5.54 (3.15–7.42)	<0.001
VUR		
Grade I–III	1.11 (0.045-1.73)	0.12
Grade IV–V	3.23 (1.7–4.78)	<0.001
Abnormal kidney		
Thin parenchyma	0.88 (0.39–1.23)	0.34
Hyper-echoic/ Poor CMD	1.98 (0.98–3.65)	0.08
Cortical cysts	0.39 (0.21–0.74)	0.67

Our observational study was designed as a retrospective analysis of all children referred for antenatal hydronephrosis at a tertiary care pediatric hospital in rural New England. Our context was to accept the current variation in clinical practice of the use of antibiotic prophylaxis in newborns with prenatally diagnosed hydronephrosis, and based on that variation to try to determine if there is benefit to using prophylactic antibiotics. Our goal was to look back over a 10-year period at all our referrals for antenatal hydronephrosis and to risk stratify based on the data available as a way to move forward to determine which children with ANH that might benefit from CAP, and possibly more important, which children do not need CAP.

Because at the outset we made an attempt to exclude those children with a history of ANH that were originally referred for UTI, we may have reduced selection bias at the time of referral, and therefore reduced the skew in the data. We did find that children with ureteral dilation, high grade VUR and ureterovesical junction obstruction were more prone to febrile UTI if they were maintained off antibiotics. We did not find that high SFU grade of hydronephrosis alone increased the risk of febrile UTI, likely because there was a large number of children with UPJ obstruction or transient hydronephrosis that do not have an increased risk of febrile UTI based on these risk factors alone.

Table 5 Etiology of study children with antenatal hydronephrosis ($n = 405$).

Etiology/Diagnosis	Number	Incidence
Transient	239	59.0%
UPJO	41	10.1%
VUR	84	20.7%
UVJO	43	10.6%
MCDK/Dysplasia	39	9.6%
PUV	7	1.7%
Ureterocele/Ectopic ureter	24	5.9%
Other	5	1.2%

Table 6 Propensity score match adjustment of risk of febrile UTI.

Model	Study covariate	OR (95%CI)	*p value*
Unadjusted multivariate	UVJ obstruction	2.54 (1.12–3.75)	*<0.001*
	Ureteral dilation (>11 mm)	5.54 (3.15–7.42)	*<0.001*
	VUR (high grade)	3.23 (1.7–4.78)	*<0.001*
PS adjusted multivariate	UVJ obstruction	1.84 (0.97–3.32)	0.059
	Ureteral DILATION (>11 mm)	4.89 (2.84–6.43)	*<0.001*
	VUR (high grade)	2.75 (1.13–4.04)	*0.004*

In any observational study there are inherent assumptions and bias. Prior to referral the parameters used to make the decision to use CAP were unknown and not standardized. In addition, we defined YCAP as those exposed to CAP for at least a 3 month period. This definition may not be valid. However, after referral, review of our data showed that the clinical allocation into the YCAP and NCAP groups prior to referral was only changed after referral in 8.8% ($n = 36$) of patients. Overall the incidence of UTI in our study population was 37% and the incidence of febrile UTI was 22.2%. This is higher than the normal cohort without ANH and consistent with the literature. One could also argue that all the children with ANH that are at low risk for UTI were not referred, and that we are studying a select high risk group of children referred to a tertiary center, and are not representative of the wide breadth of children born with ANH. However, if this were the case, this would show up in the demographics of our study population and skewed percentages of diagnoses. Table 5 shows that diagnoses in this cohort of 405 children followed for ANH, is consistent with the literature [1], thus making selection bias less likely.

To further measure the comparability of the two study groups and to try to compensate for the fact that the exposure to CAP was largely based on the discretion of the physician, and that the propensity for UTI (outcome) is related to the patient characteristics studied (covariates) we performed a stratified propensity match analysis which is illustrated in Table 6. What this shows is that hydroureteronephrosis due to ureteral dilation >11 mm, or high-grade VUR is an independent risk factor for febrile UTI; and in the absence of such CAP did not lower the risk of febrile UTI.

Conclusion

The presence of ureteral dilation, high-grade VUR, and UVJ obstruction were independent risk factors for development of UTI in children with congenital ANH. Therefore CAP may have a significant role in reducing the risk of febrile UTI in children with ANH with those identifiable risk factors, but otherwise seems unnecessary.

Conflict of interest

None.

Funding

None.

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