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The association between continuous antibiotic prophylaxis and UTI from birth until initial postnatal imaging evaluation among newborns with antenatal hydronephrosis

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Summary

Introduction—There is a lack of consensus regarding the use of continuous antibiotic prophylaxis (CAP) during the interval between birth and initial postnatal imaging in infants with a history of antenatal urinary tract dilation (AUTD).

Objective—To determine the incidence of urinary tract infection (UTI), and the association between CAP use and UTI during the interval between birth and the first postnatal renal ultrasound (RUS) in infants with AUTD.

Study Design—A single-institution, retrospective cohort study of newborns with a history of AUTD. Infants undergoing RUS within 3 months of birth for an indication of 'hydronephrosis' between 2012 and 2014 were identified. A random sample of 500 infants was selected; six were excluded for concomitant congenital anomalies. Baseline patient (sex, race, insurance) and clinical characteristics (circumcision status, UTD risk score, receipt of CAP, UTI prior to RUS, age at UTI, and age at RUS) were collected via retrospective chart review. Descriptive statistics were calculated. To adjust for receipt of CAP, propensity score adjusted univariate logistic regression for UTI based on CAP status was performed.

Results—Among the 494 infants with AUTD, 157 (32%) received CAP. Infants with normal/low-risk UTD scores were less likely to receive CAP than those with medium/high-risk UTD (23% vs 77%; $P<0.001$). There was no difference in CAP based on sex, insurance, or circumcision status (among 260/365 males with known circumcision status). Overall, seven infants (1.4%) developed UTI prior to imaging: six (1.8%) without CAP vs one (0.64%) with CAP ($P=0.44$). The median age at UTI was 59 days (range 2–84); among those with UTI, initial imaging occurred significantly later (66 vs 28 days; $P=0.001$). The propensity score adjusted odds of developing UTI with CAP (vs without) was 0.93 (95% CI 0.10–8.32; $P=0.95$). The Summary Table describes the infants with UTI.

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Conclusion—The incidence of UTI prior to initial neonatal imaging in newborns with AUTD was low. Use of CAP was not associated with UTI incidence after adjusting for UTD severity. Routine use of CAP in newborns with AUTD prior to initial imaging may be of limited benefit in most patients.

Keywords

Continuous antibiotic prophylaxis; Antenatal hydronephrosis; Newborn UTI

Introduction

Antenatal urinary tract dilation (AUTD) is one of the most common anomalies identified on antenatal sonographic screening [1]. Although most cases will resolve spontaneously, some may be associated with significant pathology, and almost all will undergo postnatal imaging to definitively diagnose the underlying etiology. As these newborns may be at increased risk of UTI, it has been common historically to start such neonates on continuous antibiotic prophylaxis (CAP) from birth until initial postnatal imaging has been completed. At that time, based on the findings, a determination is made regarding the need to continue CAP [1,2].

However, contemporary practice patterns surrounding the use of CAP in AUTD patients vary greatly [3,4]. Close to 50% of providers do not use CAP at all, even in patients with a history of Grade 3 or 4 AUTD [3]. This may reflect increasing awareness among medical professionals of the potential downsides of CAP, including the: development of antimicrobial resistance [5–7], difficulty in giving daily medication to an infant, risk of adverse events, and medication costs.

There are very limited data on the efficacy of CAP in preventing UTI among newborns with AUTD. In general, febrile infections are relatively rare at this age, with a small proportion of those infections related to UTI [8–10]. The low incidence may relate, in part, to passive maternal immunity [11–14]. Among infants and young children with AUTD pooled infection rates are between 8–10%, regardless of CAP use, though this reflects UTI occurring between birth and 1–2 years of life [15]. No studies have specifically focused on the interval between birth and initial postnatal imaging. If neonatal UTI among infants with a history of AUTD is indeed rare, then using CAP in all infants with AUTD may be of limited benefit, even if CAP is effective in reducing UTI risk.

The current study aimed to assess the incidence of UTI, and the association between CAP and UTI between birth and initial postnatal imaging among newborns with a history of AUTD.

Methods

Design

A single-institution retrospective cohort study of newborns with a history of AUTD was performed. Incidence of early UTI among infants who did or did not receive postnatal antibiotic prophylaxis was compared. The primary outcome of interest was the incidence of UTI between birth and the child's first postnatal renal ultrasound evaluation.

Radiology records from 2012–2014 were reviewed to identify all children who underwent RUS within the first 3 months of life for the indication of 'hydronephrosis', and who had at least 3 months of follow-up at the current institution after initial imaging. Additional exclusion criteria included: infants with severe congenital genitourinary anomalies (e.g. bilateral renal agenesis, horseshoe kidney, crossed-fused ectopia, bilateral multicystic dysplastic kidney, bladder exstrophy, and cloacal exstrophy); no clinical follow-up at the current institution; a history of prenatal intervention; or postnatal surgery prior to their initial ultrasound. Of the 915 infants who met inclusion criteria, 500 were randomly selected based on the research plan for a separate institutional study of the urinary tract dilation (UTD) classification system. Retrospectively collected data for this sample were then leveraged to answer the current study question.

Exposure and Outcome

Use of CAP was based on a review of clinic notes, medication histories, and scanned outside hospital records. Any infant starting antibiotic prophylaxis within 7 days of life and continuing it through initial imaging evaluation was allocated to the CAP cohort. These infants were compared to the remaining cohort who did not receive CAP prior to imaging (or first UTI). Febrile UTI episodes were initially identified based on mention in either clinic notes and/or radiologic reports. Further chart review, including scanned outside hospital records, emergency room records and microbiology results, were then used to verify the infection and the date it occurred. The American Academy of Pediatrics definition of febrile UTI was used when all data were available [35]. In the cases where microbiology and/or temperature data were unavailable, a clinical note clearly describing a febrile UTI was required. The timing of RUS and the use of CAP were at the discretion of the treating clinician.

Covariates

Baseline patient (sex, race, insurance) and clinical characteristics (circumcision status, UTD risk score, receipt of CAP, UTI prior to renal ultrasound (RUS), age at UTI and age at RUS) were collected. To lend detail to the analysis, the circumstances surrounding each UTI were reviewed in depth. This included what type of evaluation was performed when the infant presented (including lumbar puncture and chest x-ray), and whether or not the infant required hospitalization [16]. VCUG results (if performed) were also reviewed to identify infants with associated VUR (and VUR grade if present). Any other salient clinical information that would explain the etiology or characterize the severity of the infection was recorded. Severity of UTD was based on the UTD risk category from each infant's first postnatal RUS (as detailed obstetric ultrasound results were not routinely available) [17]. A low-risk UTD designation included an anterior-posterior renal pelvis diameter (APRPD) of 10–15 mm, limited to central calyceal dilation without parenchymal, ureteral or bladder abnormalities. A medium-risk UTD score included an APRPD >15 mm with peripheral calcyeal dilation and/or ureteral abnormalities (i.e. hydroureter). A high-risk score included an APRPD >15 mm with peripheral calyceal dilation and/or parenchymal, ureteral or bladder abnormalities. The UTD risk scores were based on independent readings by a pediatric urologist and pediatric radiologist; disagreements in UTD score were directly adjudicated by the two readers. The UTD risk was further dichotomized into ‘normal/low risk’ (P0/P1) and ‘medium/high risk’ (P2/P3).

Analysis

Descriptive statistics were calculated using nonparametric or Chi-squared tests. To adjust for use of CAP, a propensity score based on salient patient and clinical factors was designed *a priori* to include sex, race, insurance type, circumcision status, and UTD risk score. However, a large proportion of infants were missing chart data on race (26%) and circumcision status (28%), so these variables could not be included. Using the remaining variables, propensity score adjusted logistic regression was performed to evaluate the association between CAP use and newborn UTI. Multivariable analysis was not utilized due to a low event rate. All analyses were performed using SAS 9.4. The study was approved by the Institutional Review Board.

Results

A total of 500 infants were randomly sampled and included in the initial cohort; six of them were subsequently excluded after postnatal ultrasound review, due to imaging findings meeting exclusion criteria that were not initially identified (primarily multicystic dysplastic kidney).

The characteristics of the cohort are presented in Table 1, stratified by CAP status. Among the 494 included infants, 74% were male, 63% white (among the 74% of infants with known race), 72% had private insurance, and 32% received CAP. There was no difference in sex or insurance status between newborns with or without CAP (P=0.322 and P=0.744, respectively). Among the 72% of males (262/365) for whom circumcision status was known, approximately 70% were circumcised. Circumcision status was similar among newborns with CAP (22% uncircumcised, 26/121) and without CAP (23% uncircumcised, 51/244); however, more infants in the group without CAP were missing circumcision data (39% vs 6.6%). Among all infants, 51% were categorized as having normal/low-risk UTD and 49% as medium/high-risk UTD. When stratified by CAP use, infants with CAP were significantly more likely to have a medium/high-risk UTD classification (77% P2/P3, 121/157) compared to those without CAP (35% P2/P3, 119/337; P<0.001). Median time between birth and initial imaging was 28 days (IQR: 19, 40 days). Compared to those infants without UTI, those who had a UTI prior to imaging were significantly older at the time of initial imaging (66 vs 28 days; P=0.001). UTI prior to initial imaging occurred in seven infants (1.4%): six (1.8%) without CAP versus one (0.6%) with CAP (P=0.44). The propensity score-adjusted odds of developing a UTI among infants with CAP compared to those without was 0.95 (95% CI 0.10–8.32; P=0.95). Table 2 compares infant and clinical characteristic based on the occurrence of UTI.

Among the seven infants with UTI, four had positive urine cultures (>100,000 *Escherichia coli*) and documented fevers (>38 ºC). Three infants were treated at another hospital and lacked diagnostic data; however, chart review indicated that two were admitted for ‘septic work-up' with UTI as a discharge diagnosis, and one was described as having had 'pyelonephritis' and a 'febrile UTI' in two separate clinical documents. The median age at UTI was 59 days (range 2–84). Out of the entire sample, two infants developed UTI at <4 weeks of age (0.4%). Five of the seven had normal/low-risk UTD on postnatal imaging. Four UTIs occurred in females, of whom three underwent VCUG and were diagnosed with VUR. One girl with bilateral Grade 1 VUR had no associated hydronephrosis. Among the boys, two were uncircumcised and one was missing circumcision information. One of the uncircumcised boys had recurrent UTIs and after urologic evaluation was found to have a tight phimosis causing pooling of urine in his foreskin. His phimosis was managed with topical betamethasone and his infections resolved. The remaining two boys had no clear anatomic risk factor for UTI. All seven infants were hospitalized for their infection, and four had chest x-rays and lumbar punctures as part of a newborn fever work-up. Table 3 summarizes the clinical details of the seven infants with UTI.

Discussion

It is a difficult decision to use CAP starting at birth in infants with a history of AUTD. It is likely that the majority of these infants are at very low risk of neonatal UTI, as many will have spontaneous resolution of their hydronephrosis and not have high-grade VUR [1]. Such infants are presumably less likely to benefit from CAP. A low risk of UTI might be expected because of the short time frame and the presence of passive maternal immunity [14]. The current results support these suppositions: among infants with a history of AUTD, the rate of UTI was extremely low during the period between birth and initial imaging (especially when the imaging was performed within 8 weeks of birth). Furthermore, CAP was not associated with decreased risk of UTI in this particular sub-population, even when adjusting for gender and severity of UTD. This is the only study specifically focusing on this sub-population and time frame, and to address a practical question routinely faced by pediatric urologists.

The existing literature evaluating CAP for patients with AUTD is conflicting. Braga et al. published a meta-analysis of 21 studies of infants with AUTD and found that the UTI rate was similar, regardless of CAP (9.9% vs 8.3%); although, when they stratified by the severity of hydronephrosis, CAP was associated with a reduced risk of UTI in patients with high-grade dilatation [15]. While the current study saw no difference in UTI incidence based on CAP use, even after adjusting for UTD risk classification, it is important to recognize that nearly all prior studies followed AUTD patients well beyond the newborn period [18–25]. Such longer follow-up times would presumably increase the observed cumulative UTI incidence. In studies that explicitly identified age at UTI among infants with AUTD, neonatal UTI appeared to be relatively rare, with the reported average age of first UTI ranging from 2–14 months [19–21,23–27]. In the current cohort, two infants developed UTI prior to 8 weeks of age. Combining the literature reports with the current data, three patients (among a combined 2831) had UTI prior to 4 weeks [19,21,24–27]. This amounted to an effective UTI incidence of 0.1% prior to 4 weeks of age. In comparison, it is estimated that the risk of febrile UTI among a general population of newborns (0–3 months) is 0.07–0.14% [9,28]. From a population perspective, the use of CAP is illogical if the risk of UTI in newborns with AUTD is similar to the general population.

Timing of postnatal imaging evaluation may be a factor in neonatal UTI risk. The current study found that infants with UTI were significantly older at the time of initial imaging (median 9.4 weeks) compared to those without a UTI. The 2010 Society of Fetal Urology consensus statement on AUTD recommends imaging at ≤2–4 weeks of age, depending on UTD severity [2]. This aligns with the current results, which suggest that if imaging is performed early in the neonatal period, starting CAP from birth may not be necessary.

While these findings indicate that CAP is not associated with reduced neonatal UTI risk, important factors should be considered before neonatal CAP is abandoned. First and foremost is the significance of developing a serious bacterial infection during the newborn period. Infants are unable to communicate when they are ill and it is often difficult to distinguish minor febrile illnesses from life-threatening conditions [29]. Diagnostic uncertainty means that febrile or ill neonates are subjected to extensive testing, including lumbar puncture, radiation-associated imaging, and, typically, hospitalization [16,29]. In the current sample, for example, all UTI infants were hospitalized and four had lumbar punctures and chest x-rays. In light of the morbidity associated with serious bacterial infection in the newborn, it would be useful to identify high-risk groups where CAP is more likely to be beneficial. Examples may include premature and low birth weight infants, newborns with suspected bladder outlet obstruction, or significant UTD with ureteral dilation [8,28,34]. .

The results of this study must be interpreted in the context of its limitations. Given the low incidence of UTI, the study may have been underpowered to detect the risk reduction associated with CAP. This low event rate also made it difficult to adjust for potential confounders, though it was able to use propensity scoring to adjust for key covariates, including severity of hydronephrosis and sex. Similarly, it was limited by the amount of missing data for circumcision status, given that there may be an association between circumcision status and UTI [9]. It is important to note, however, that studies focused only on antenatal UTD patients have had mixed results regarding a relationship between circumcision and UTI [18,24,26,27]. Another limitation was the fact that it lacked detailed antenatal imaging results, upon which the decision to start CAP at birth was based; this was addressed by using the postnatal UTD scores to approximate the antenatal findings, albeit imperfectly. In addition, the cohort was restricted to infants with an initial ultrasound within 3 months of life, to best identify AUTD infants, but this meant excluding those with delayed postnatal imaging (or no imaging); UTI incidence among such patients may be different from that of the current cohort. Finally, the retrospective nature of this study meant that it relied on the accuracy of chart data.

Conclusion

The incidence of UTI prior to initial neonatal imaging in newborns with AUTD was low. Use of CAP was not associated with UTI incidence after adjusting for UTD severity. Routine use of CAP in newborns with AUTD prior to initial imaging may be of limited benefit in most patients.

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Table 1

Baseline characteristics for infants with a history of antenatal hydronephrosis stratified by receipt of early antibiotic prophylaxis.

	No prophylaxis (*n*=337)	**Prophylaxis (*n*=157)**	**Overall (*n*=494)**	***P*-value**
Sex				0.322
Male	244 (72%)	121 (77%)	365 (74%)	.
Female	93 (28%)	36 (23%)	129 (26%)	.
Race				
White	154 (46%)	75 (48%)	229 (46%)	--
Black	26 (7.7%)	5 (3.2%)	31 (6.3%)	
Other	73 (22%)	33 (21%)	106 (21%)	
Unknown	84 (25%)	44 (28%)	128 (26%)	
Insurance				0.744
Private	244 (73.3%)	112 (71.8%)	356 (72.8%)	.
Public	89 (26.7%)	44 (28.2%)	133 (27.2%)	.
Unknown	4 (1.2%)	1 (0.64%)	5 (1.0%)	
Circumcision status(*n*=365 males)				
Uncircumcised	51/244 (23%)	26/121 (22%)	77 (21%)	--
Circumcised	98/244 (40%)	87/121 (72%)	185 (51%)	
Unknown	95/244 (39%)	8/121 (6.6%)	103 (28%)	
UTD risk				<0.001
Normal/low risk	218 (65%)	36 (23%)	254 (51%)	
Medium/high risk	119 (35%)	121 (77%)	240 (49%)	

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Table 2

Baseline characteristics and receipt of antibiotic prophylaxis among infants with a history of antenatal hydronephrosis stratified by UTI prior to initial radiologic imaging evaluation.

	No UTI (*n*=487)	UTI (*n*=7)	Overall (*n*=494)	*P*-value
Prophylaxis				0.440
Yes	156 (32%)	1 (14%)	157 (32%)	
No	331 (68%)	6 (86%)	337 (68%)	
Median age at imaging (IQR)	28 days (18, 39)	66 days (43, 74)	28 (19, 40)	0.001
Sex				0.080
Male	362 (74%)	3 (43%)	365 (74%)	
Female	125 (26%)	4 (57%)	129 (26%)	
Race				
White	224 (46%)	5 (71%)	229 (46%)	--
Black	31 (6.4%)	0 (0%)	31 (6.3%)	
Other	106 (22%)	0 (0%)	106 (22%)	
Unknown	126 (26%)	2 (29%)	128 (26%)	
Insurance				0.680
Public	350 (73%)	6 (86%)	356 (73%)	
Private	132 (27%)	1 (14%)	133 (27%)	
Unknown				
Circumcision status (*n*=365)				--
Uncircumcised	75/362 (21%)	2/3 (67%)	77 (21%)	
Circumcised	185/362 (51%)	0/3 (0%)	185 (51%)	
Unknown	102/362 (28%)	1/3 (33%)	103 (28%)	
UTD risk				0.451
Normal/low risk	249 (51%)	5 (71%)	254 (51%)	
Medium/high risk	238 (49%)	2 (29%)	240 (49%)	

Table 3

Characteristics of infants with a history of antenatal hydronephrosis and a UTI prior to initial postnatal imaging.

Sex	Age UTI* (days)	Age Imaging (days)	CAP	Circumcision Status	UTD Risk	Ureteral Dilation	Race	Insurance	Comments
M	70	72	No	Uncircumcised	Normal/Low Risk	No	White	Private	Urine pooling in foreskin
M	73	74	No	Unknown	Normal/Low Risk	No	White	Private	No VUR
M	2	34	No	Uncircumcised	Normal/Low Risk	No	Missing	Private	No VCUG
F	84	85	No	NA	Normal/Low Risk	No	White	Private	No VCUG
F	57	59	No	NA	Medium/High Risk	Yes	Missing	Private	Grade 2 VUR
F	59	66	Ye	NA	Medium/High Risk	No	White	Public	Grade 4 & 5 VUR
F	14	43	No	NA	Normal/Low Risk	No	White	Private	Grade 1 & 1 VUR

*All infants were hospitalized for their UTIs and 4/7 had chest x-rays and lumbar punctures as part of the standard evaluation of a fever in a neonate

M = male, F = female, LP = lumbar puncture, CAP = continuous antibiotic prophylaxis, UTD risk = urinary tract dilation classification system risk

Summary Table

Characteristics of 7/494 infants with a history of antenatal hydronephrosis and UTI prior to initial postnatal imaging.

Sex	Age UTI* (days)	Age Imaging (days)	CAP	Circumcision Status	UTD Risk	Ureteral dilation	Race	Insurance	Comments
M	70	72	No	Uncircumcised	Normal/Low Risk	No	White	Private	Urine pooling in foreskin
M	73	74	No	Unknown	Normal/Low Risk	No	White	Private	No VUR
M	2	34	No	Uncircumcised	Normal/Low Risk	No	Missing	Private	No VCUG
F	84	85	No	NA	Normal/Low Risk	No	White	Private	No VCUG
F	57	59	No	NA	Medium/High Risk	Yes	Missing	Private	Grade 2 VUR
F	59	66	Ye	NA	Medium/High Risk	No	White	Public	Grade 4 & 5 VUR
F	14	43	No	NA	Normal/Low Risk	No	White	Private	Grade 1 & 1 VUR

* All infants were hospitalized for their UTIs and 4/7 had chest x-rays and lumbar punctures as part of the standard evaluation of a fever in a neonate M = male, F = female, LP = lumbar puncture, CAP = continuous antibiotic prophylaxis, UTD risk = urinary tract dilation classification system risk