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Incidence of Breakthrough Urinary Tract Infection in Hospitalized Infants Receiving Antibiotic Prophylaxis

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Abstract

Breakthrough urinary tract infections (BUTIs) are a source of great morbidity in children on urinary prophylactic antibiotics. The incidence of BUTI in critically ill infants is not known. We investigated the incidence of BUTI in a cohort of infants hospitalized on prophylactic antibiotics in neonatal intensive care units. Predictors of BUTI were evaluated using multivariable Cox regression. Out of 716,787 infants, 631 (0.09%) were prescribed 821 courses of antibiotic prophylaxis. Among this cohort, 60 infants (9.5%) suffered a total of 65 BUTIs. Of all prophylactic antibiotic courses, 65/821 (7.9%) were complicated by BUTI. *Klebsiella, Enterobacter*, and *Escherichia coli* species were the most common causes of BUTI. There was no statistically significant difference in BUTI incidence among the four antibiotics assessed (amoxicillin, cephalexin, nitrofurantoin, or trimethoprim-sulfamethoxazole) (p=0.78).

Keywords

breakthrough urinary tract infection; antimicrobial prophylaxis; infants; antibiotics; neonatal intensive care units

Introduction

Urinary tract infections (UTI) are a substantial source of morbidity in the neonatal intensive care unit (NICU). UTIs in newborns frequently are associated with bacteremia and may result in long-term complications.[1,2] The incidence of UTIs is as high as 8–10% in premature infants.[3,4]

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Declaration of Conflicting Interests

The remaining authors have no conflicts to disclose.

UTIs recur in roughly 75% of children who have their initial infection during infancy, compared with 40% of females and 30% of males with a first UTI after one year of age.[5] Given that UTIs are a source of significant patient discomfort and that the risk of renal damage increases with each successive UTI, the avoidance of future UTIs is an important goal.[6]

There are no clear guidelines for the use of prophylactic antibiotics for UTI prevention in the NICU. Indeed, the most recent American Academy of Pediatrics (AAP) guidelines for the treatment of initial febrile UTIs in children specifically excludes infants <2 months of age. It is unknown whether and to what extent providers are applying the AAP or other guidelines to the NICU population. Anecdotally, it is not unusual for NICU patients to be placed on antibiotic prophylaxis for the prevention of UTIs. To our knowledge, frequency of antibiotic prophylaxis use in the NICU setting has not been investigated previously, nor is the likelihood of BUTI known for this cohort of patients.

Given that the prevailing patterns of prophylactic antibiotic use in the NICU setting are unclear, as is the likelihood of breakthrough UTI in this population, we investigated the use of antibiotic prophylaxis in this group.

Patients and methods

Data source

We examined a cohort of all infants discharged from 322 NICUs managed by the Pediatrix Medical Group from 1997–2010 treated with a course of prophylactic antibiotics. Details of the database and data collection have been previously described.[7–9] Clinical data for these infants were recorded prospectively for the database and analyzed retrospectively for the purposes of this article.

Definitions

Infants were included if they were treated with a course of prophylactic antibiotics. Antibiotics considered as potential agents for prophylaxis included amoxicillin, cephalexin, nitrofurantoin, or trimethoprim-sulfamethoxazole. We selected these antibiotics based on a review of the literature and the clinical experience of practicing pediatric urologists and neonatologists. We considered a course of antibiotic treatment as prophylaxis if the following criteria were met: 1) the course was preceded by a positive urine culture during the hospitalization; 2) the course started or extended at least 10 days after the last positive blood, cerebrospinal fluid (CSF), or urine culture; and 3) the course was composed of a single antibiotic.

When defining prophylactic courses, we recognized that intravenous (IV) formulations existed for some of the per os (PO) antibiotics studied, specifically ampicillin for amoxicillin and cefazolin for cephalexin. In cases where ampicillin or cefazolin were used in isolation, they were not considered as candidates for antibiotic prophylaxis. However, in cases where ampicillin immediately preceded, followed, or was interspersed with amoxicillin administration (or cefazolin with cephalexin), the IV medications were treated as if they were the PO preparations, given the similarity in pharmacologic mechanisms and indications

for use of these drugs. In these mixed IV/PO courses, the same criteria listed above for definition of a course of prophylaxis had to be met for the mixed course to meet the standard for prophylaxis. We excluded courses without an end-date captured in the database.

We defined a UTI as bacterial growth in a urine culture specimen obtained via in-and-out catheterization, supra-pubic aspiration, or capture of a voided sample in a urinary collection bag. We excluded fungal UTIs from our analysis. We defined breakthrough urinary tract infection (BUTI) as a UTI that occurred during a course of antibiotic prophylaxis.

In our assessment of positive cultures (urine, blood, and CSF), those that grew coagulase-negative *Staphylococcus* (CoNS) species were included if there were 2 positive cultures within 4 days, 3 positive cultures within 7 days, or 4 within 10 days.

Statistical analysis

We used median and interquartile ranges (IQR) to describe continuous variables and counts and percentages to describe categorical variables. We compared clinical characteristics between infants with and without BUTIs using the chi-square test for categorical variables. We described the frequency of prophylactic antibiotic courses by type of antibiotic and the proportion of prophylactic antibiotic courses during which a BUTI occurred. A multivariable Cox proportional hazards model was used to determine the risk of BUTI with each antibiotic course, controlling for sex, gestational age, race/ethnicity, birth weight, postnatal age, and type of admission. We compared organisms between BUTIs and first-documented UTIs using the chi-square test to assess for overall difference and univariable logistic regression to assess for difference by infectious organism. We conducted all analyses using Stata 12 (College Station, TX) and considered a p-value <0.05 statistically significant.

We used data on subject sex, gestational age, birth weight, day of life, race/ethnicity, type of admission, urine culture results, and antibiotic prescriptions. Medication dosing quantities were not recorded. The study was approved by the Duke University Institutional Review Board without the need for written informed consent because the data were collected without identifiers.

Results

Infant clinical characteristics

During the study period, 631/716,787 (0.09%) infants were prescribed at least one course of prophylactic antibiotics. Of these, BUTI was documented in 60/631 (9.5%) infants (Table 1). In our cohort, infants prescribed antibiotic prophylaxis who were never diagnosed with a BUTI were 70% male and 46% white, with a median gestational age of 27 weeks (IQR 25–30). Median birth weight of infants without BUTI was 918 g (710–1333). Infants diagnosed with BUTI were 80% male and 29% white, with a median gestational age of 27 weeks (IQR 25–32). Median birth weight of infants with BUTI was 765 g (910–1659). Sex, race/ethnicity, birth weight, and admission type were not significantly different between those who did and did not have a BUTI. The most common pathogens observed in BUTIs were *Klebsiella* spp. (20%), *Enterobacter* spp. (19%), *Escherichia coli* (16%), and *Pseudomonas* spp. (14%) (Table 2).

Antibiotic usage patterns and likelihood of BUTI

A total of 821 courses of antibiotic prophylaxis were administered. The majority of antibiotic courses were prescribed to infants >60 days of age (58%). The median duration of all prophylactic courses was 10 days (5–20). Amoxicillin was the most commonly used prophylactic antibiotic (549/821, 67%), followed by trimethoprim/sulfamethoxazole (170/821, 21%), cephalexin (89/821, 11%), and nitrofurantoin (13/821, 2%). Median duration of use by drug was 11 days (5–23) for amoxicillin, 8 days (4–15) for cephalexin, 12 days (9–14) for nitrofurantoin, and 8 days (4–12) for trimethoprim/sulfamethoxazole. Of these prophylactic courses, 65 were complicated by a BUTI (7.9%). The median duration for prophylactic courses complicated by BUTI was 26 days (16–39).

Trimethoprim/sulfamethoxazole was associated with the lowest incidence of BUTI (5.9%, 10/170). The incidence of BUTI was 7.7% for nitrofurantoin (1/13), 8.0% for amoxicillin (44/549), and 11.2% for cephalexin (10/89). However, these differences did not reach statistical significance by chi-square test (p=0.78), nor was any single antibiotic seen to be more effective in preventing BUTI than any other when examined in a multivariable time-to-event analysis based on days of antibiotic given (Table 3). On multivariate Cox regression, black race (hazard ratio [HR] 2.14, p=0.02) and gestational age 29–32 weeks (HR 3.02, p=0.04) were the only statistically significant predictors of BUTI (Table 3).

Discussion

BUTIs are a concern when caring for children on urinary prophylactic antibiotics. However, the incidence of BUTI in critically ill infants is poorly characterized. We systematically investigated the incidence of BUTI within a large cohort of critically ill infants. We documented BUTI in 60/631 (9.5%) of infants and a higher incidence among black infants. In our analysis, amoxicillin was the most commonly prescribed prophylactic antibiotic. Numerically, the lowest incidence of breakthrough UTI was seen with trimethoprim/sulfamethoxazole (5.9%) prophylaxis, though differences between antibiotics did not reach statistical significance.

Previous studies have demonstrated an incidence of BUTI in 25–38% of older children.[5] This differs substantially from the 9.5% BUTI incidence we found in critically ill infants. Several plausible explanations may account for this discrepancy. First, the prophylactic antibiotics administered to the infants in this study were given in a highly controlled intensive care unit setting, whereas antibiotics administered to older children in prior studies were given at home by parents. The infants in our study were likely receiving antibiotics more consistently and on a more routine schedule. Additionally, BUTI criteria were stringent in this study: a positive urine culture documented in the medical record. If BUTI criteria were less strict in prior studies, for example, including “infections” that were diagnosed by irritative voiding symptoms or parental concerns for malodorous urine only, the likelihood of BUTI would appear falsely elevated. Finally, prophylactic antibiotic courses in our study did not have to meet a minimum duration; rather they only needed to meet our criteria of occurring at least 10 days after the last positive culture and including only a single antibiotic of the four we studied. It is plausible that if the mean duration of therapy were longer, we may have seen more BUTIs, as bacterial resistance patterns shifted to surmount the

antimicrobial mechanisms of the prophylactic antibiotics. This scenario may have been borne out in the previous studies conducted on older children.

Prior studies have shown UTIs to be four times more common in males than in females during the neonatal period.[10] Levy and colleagues found similar results in their cohort of premature Israeli infants, in which male sex was an independent predictor of UTI.[11] However, there was no statistically significant difference in BUTI incidence between male and female infants on prophylaxis in our cohort. This initially seems counterintuitive because the aforementioned data would seem to suggest that BUTIs should also be more likely in males, for the same reasons that non-BUTIs occur with greater frequency. However, it seems plausible that whatever anatomical or physiological abnormalities initially predisposed the female infants to their first UTI produced an equivalent risk in these females to the male infants in the prophylactic antibiotic cohort. A competing, but perhaps less plausible, explanation would be that continuous antibiotic prophylaxis simply works “better” in males, though there is no clear mechanistic underpinning to this line of reasoning. Finally, we cannot rule out that this is an issue of our small sample lacking power to detect a difference between the groups.

E. coli is the most-commonly observed infectious organism in infants with UTI, a finding that was borne out in the initial UTIs captured in our study data, prior to the initiation of antibiotic prophylaxis.[12] Notably, in this investigation, infectious organisms observed on urine culture varied significantly between first UTIs and BUTIs (p=0.02). We specifically examined infants’ first-documented UTIs relative to BUTIs because first UTIs—versus all non-BUTIs occurring at any time during the hospital course—were believed to be most indicative of the innate pathogenicity of the local flora, independent of the effects of previous antibiotic treatment, which may predispose to certain types of subsequent infections. In BUTIs, *Klebsiella, Enterobacter* spp., coagulase-negative *Staphylococcus* spp., and *Pseudomonas* spp. infections were observed more frequently than in non-BUTIs, with similar likelihood of *Staphylococcus aureus* infections. *E. coli* and *Enterococcus* infections were observed less frequently in BUTIs.

The most common prophylactic antibiotic was amoxicillin, used in 67% of all episodes of prophylaxis. This antibiotic offers less protection against resistant gram-negative rods. This may account for the increased rates of *Enterobacter, Klebsiella*, and *Pseudomonas* infections seen in the BUTI cohort, relative to the first UTI causative organisms. This may speak to greater pathogenicity of these gram-negative organisms or reduced antibiotic efficacy against them. In their 2008 study, Prelog et al. found recurrent UTIs (any UTI other than the child’s first UTI) to have higher *E. coli* resistance rates against trimethoprim-sulfamethoxazole and ampicillin, when compared with first UTIs.[13] Our work confirms that recurrent infections are characterized by different bacterial pathogenicity profiles than those found in first infections. Similar studies have shown increasing resistance in *E. coli* to trimethoprim-sulfamethoxazole and amoxicillin over time.[14] Ultimately, knowledge of pathogens causing UTIs and their antibiotic susceptibility is mandatory to ensure appropriate treatment, whether prophylactic or therapeutic.

This analysis is not without limitations. The data were collected for clinical documentation and analyzed retrospectively, rather than being collected prospectively to answer our specific study question. Further, we were limited by the urine culture data available to us. The majority of urine cultures in the database resulted from voided specimens collected in a urine bag that was adhered to the infant's peri-genital region after this area was sterilized with topical cleansing agents. The likelihood of contamination is greater with bag-collected specimens than catheterization or suprapubic aspiration. However, treatment decisions are made based on all three types of urine culture. Hence, we felt it inappropriate to discard a large proportion of the urine cultures based on the collection mechanism.

Finally, courses of antibiotic prophylaxis were not defined explicitly as such in this administrative database. We thus had to use clinical inference to differentiate between prophylactic and therapeutic courses of antibiotics. However, our methods were robust: first, the antibiotic course must have been preceded by a positive urine culture at some point in the hospitalization; second, the course must have started at least 10 days after the last positive blood, CSF, or urine culture; and third, the course had to be composed of a single antibiotic. We required a previous positive urine culture to guarantee a history of UTI and a reason for prophylaxis. Because nearly all treatment courses of antibiotics last 10 or fewer days, we required that the prophylactic course start at least 10 days after the last positive culture. We also required that the prophylactic course be composed of a single antibiotic so as not to spuriously capture ampicillin courses in which ampicillin was combined with another antibiotic for treatment of an infectious process, as is common clinical practice. Indeed, we believe our rigorous definition is more likely to artificially exclude prophylactic courses than to over-generously include courses that were not meant as prophylaxis.

Conclusion

In critically ill infants prescribed prophylactic antibiotics, BUTIs were observed in 60/631 (9.5%) of patients. Infectious organisms differed significantly between first documented UTIs and BUTIs. There was no statistical difference in BUTI incidence among the four antibiotics assessed (amoxicillin, cephalexin, nitrofurantoin, and trimethoprim-sulfamethoxazole).

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Table 1

Population Characteristics of Infants Receiving Antibiotic Prophylaxis.[a]

	No BUTI (n=571)	BUTI (n=60)	p
Female	169 (30)	12 (20)	0.13
Gestational age, weeks			
≤25	181 (32)	16 (27)	0.69
26–28	201 (37)	20 (33)	
29–32	101 (18)	12 (20)	
33–36	44 (8)	7 (12)	
≥37	35 (6)	5 (8)	
Birth weight, g			
<1000	330 (58)	36 (60)	0.12
1000–1499	134 (23)	7 (12)	
1500–2499	70 (12)	10 (17)	
2500–3499	31 (5)	5 (8)	
≥3500	6 (1)	2 (3)	
Race/ethnicity			
White	258 (46)	17 (29)	0.07
Black	117 (21)	18 (31)	
Hispanic	152 (27)	21 (36)	
Other	30 (5)	3 (5)	
Admission type			
Inborn	413 (74)	45 (78)	0.57
Postnatal age at initiation of prophylaxis, days			
0–30	151 (13)	11 (7)	0.002
31–60	375 (32)	32 (22)	
>60	652 (55)	104 (71)	

[a]Data are presented as n(%).

BUTI: breakthrough urinary tract infection.

Table 2

Urine Culture Data for First and Breakthrough Urinary Tract Infections.

	First UTI prior to prophylaxis, n (%)	Breakthrough UTIs, n (%)
Number of positive urine cultures	**634**	**65**
Gram-positive organisms	**135 (21)**	**16 (25)**
Coagulase-negative *Staphylococcus*	20 (3)	7 (11)
Enterococcus spp.	91 (14)	7 (11)
Gram-positive cocci, not otherwise specified	5 (1)	1 (2)
Group B *Streptococcus*	12 (2)	-
Staphylococcus aureus	7 (1)	1 (2)
Gram-negative organisms	**471 (74)**	**47 (72)**
Citrobacter spp.	16 (3)	1 (2)
Enterobacter spp.	99 (16)	12 (19)
Escherichia coli	153 (24)	10 (16)
Gram-negative rod, not otherwise specified	15 (2)	1 (2)
Klebsiella spp.	123 (19)	13 (20)
Proteus spp.	16 (3)	1 (2)
Pseudomonas spp.	30 (5)	9 (14)
Serratia spp	19 (3)	-
Other bacterial species	**28 (4)**	**2 (3)**

UTI: urinary tract infection.

Table 3

Cox Proportional Hazards Model of BUTI by Antibiotic.

Antibiotic	Hazard ratio	95% Confidence interval	p
Amoxicillin	reference	-	-
Cephalexin	1.26	0.64–2.51	0.50
Nitrofurantoin	0.52	0.05–5.63	0.59
Trimethoprim-sulfamethoxazole	0.86	0.41–1.81	0.69
Sex			
Female	reference	-	-
Male	1.57	0.77–3.21	0.22
Gestational age, weeks			
≤25	reference	-	-
26–28	1.77	0.92–3.40	0.09
29–32	3.02	1.06–8.58	0.04
33–36	1.69	0.36–7.93	0.50
≥37	1.02	0.15–6.83	0.98
Race/ethnicity			
White	reference	-	-
Black	2.14	1.15–3.98	0.02
Hispanic	1.56	0.77–3.20	0.22
Other	2.49	0.86–6.83	0.09
Birth weight, g			
<1000	reference	-	-
1000–1499	0.47	0.21–1.05	0.07
1500–2499	1.26	0.42–3.19	0.68
2500–3499	2.11	0.39–11.31	0.38
≥3500	3.71	0.55–25.81	0.19
Admission type			
Inborn	reference	-	-
Outborn	1.37	0.75–2.87	0.26
Postnatal age, days			
0–30	reference	-	-
30–60	1.12	0.37–3.39	0.84
>60	1.41	0.48–4.15	0.53

BUTI: breakthrough urinary tract infection.