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Incidence of Urinary Tract Infections in Newborns with Spina Bifida: Is Antibiotic Prophylaxis Necessary?

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Abstract

PURPOSE: Urinary tract infections (UTI) commonly occur in patients with spina bifida (SB) and pose a risk for renal scarring. Routine antibiotic prophylaxis has been utilized in newborns with SB to prevent UTI. We hypothesized that prophylaxis can safely be withheld in newborns with SB until clinical assessment allows for risk stratification.

MATERIALS AND METHODS: Newborns with myelomeningocele at nine institutions were prospectively enrolled in the UMPIRE study and managed by a standardized protocol with a strict definition for UTI. Patient data were collected regarding details of reported UTI, baseline renal ultrasound findings, vesicoureteral reflux, use of clean intermittent catheterization (CIC), and circumcision status in boys. Risk Ratios (RRs) and corresponding 95% confidence intervals (CIs) were calculated using log-binomial models.

RESULTS: From 2/2015 through 8/2019, data were available on 299 newborns (50.5% male). During the first four months of life, 48 (16.1%) newborns were treated for UTI with 23 (7.7%) having positive cultures; however, only 12 (4.0%) met the strict UTI definition. Infants with grade

Conflict of Interest: None relevant to this research.

3–4 hydronephrosis had an increased risk of UTI compared to infants with no hydronephrosis (RR=10.1; 95%CI=2.8, 36.3). Infants on CIC also had an increased risk of UTI (RR=3.3; 95%CI=1.0, 10.5).

CONCLUSIONS: The incidence of a culture-positive, symptomatic UTI among newborns with SB in the first 4 months of life was low. Patients with high grades of hydronephrosis or those on CIC had a significantly greater incidence of UTI. Our findings suggest that routine antibiotic prophylaxis may not be necessary for most newborns with SB.

Keywords

spina bifida; urinary tract infection; newborn

INTRODUCTION

Urinary tract infections (UTI) are a common source of morbidity among infants with spina bifida (SB) and may lead to renal scarring. The incidence of UTI among patients with SB has been shown to be 50% by 15 months of age; however, definitions of UTI vary widely throughout the literature.[1, 2] Strategies aimed at preventing UTI include antibiotic prophylaxis, management of constipation, and anticipatory bladder management, including CIC.

Risk stratification to determine which patients benefit most from antibiotic prophylaxis includes vesicoureteral reflux (VUR) status and bladder characteristics based on cystography and urodynamic studies. This information is not typically available at the time of neonatal hospitalization discharge but should be obtained by 3 months of life.[3, 4] Some centers routinely place all newborns with SB on antibiotic prophylaxis until these studies are obtained.

Patients enrolled in the Urologic Management to Preserve Initial Renal Function Protocol for Young Children with Spina Bifida (UMPIRE) are followed on a clearly outlined protocol with a strict definition for UTI.[5] We hypothesized that withholding antibiotic prophylaxis in newborns with SB until clinical assessment is completed to allow for risk stratification does not result in a greater incidence of UTI.

MATERIALS AND METHODS

Newborns with myelomeningocele at nine institutions were prospectively enrolled in the UMPIRE study and managed by a standardized protocol.[5] This iterative protocol is based on standard-of-care and specifies when the timing of urologic clinic visits, tests, and procedures should occur. A treating physician can deviate from the protocol for any reason and deviations are documented. The institutional review board at each site approved the study. The protocol specifies that infants are not placed on prophylactic antibiotics at birth. Perioperative antibiotics are stopped after back closure or never started if closure was performed prenatally. If infants were not born at a study institution and it was unknown if antibiotics were stopped, they were grouped with the infants who were still on antibiotics after back closure.

We used the first renal bladder ultrasound (RBUS) performed within the first 59 days of life. Hydronephrosis was graded (0–4) using the Society of Fetal Urology classification.[6] Reflux status was assessed from a voiding cystourethrogram or during video urodynamics within the first 179 days of life. The International Reflux Study grading system was used to grade the results.[7] CIC was initiated on all newborns every 6 hours and parents were instructed on the technique. If catheterized urine volumes remained <30ml for 24 hours, CIC frequency was decreased daily to every 8 hours, then every 12 hours and finally discontinued. Infants with regular catheterized volumes >30ml were discharged from their newborn admission on CIC. Infants who remained on CIC at the three-month clinic visit were identified.

The protocol tracks UTIs throughout follow-up. Caregivers report if the infant has been treated for a UTI to the SB clinic staff who obtain detailed information including the location of diagnosis, laboratory report, and symptoms. An education tool was created and provided to families and shared with their primary care physicians.[8] This tool included information on the signs and symptoms of UTI, actions a family should take if a UTI is suspected, the importance of obtaining a catheterized urine specimen and instructions to contact their SB clinic when their child is diagnosed with a UTI.

We examined 2 definitions of UTIs. The first was a treated UTI regardless of laboratory results or symptoms. The second definition is a subset of the first definition that meets the strict criteria of a true UTI in the protocol. These infections must be laboratory positive defined as positive both on urinalysis (> 10 WBC/HPF on urine microscopy and/or leukocyte esterase ≥ 2+ on dipstick) and urine culture (≥100,000 CFU/ml of 1 or 2 speciated organisms). Patients must also exhibit at least 2 symptoms of UTI. As the protocol was designed to follow patients up to 5 years of life, symptoms may include: fever > 100.4° F (38° C), gross hematuria (defined as pink or red urine), abdominal, suprapubic, or flank pain or tenderness, new or worsening incontinence, new or worsening urinary urgency, frequency, or hesitancy, pain with catheterization or urination, and malodorous/cloudy urine. Infants less than 1 year of age, which includes all patients in this study, can have the following additional symptoms: failure to thrive, dehydration, hypothermia, increasing spasticity, febrile seizures, fussiness/irritability, or other. For each definition, we used the first UTI that occurred within the first 119 days (<4 months of age) for our analysis.

Eligibility for enrollment included age 3 months or less when born at a study institution or up to age 6 months if transferred into a study institution and newborn care followed the protocol with only minimal deviations prior to transfer. Written informed consent was obtained from a patient’s parent or guardian. Infants enrolled were born from the start of the study on February 1, 2015 through May 31, 2019, and had their three-month visit by August 31, 2019. Frequencies and percentages were calculated for baseline demographics, each type of UTI, and UTI characteristics. Unadjusted risk ratios and corresponding 95% confidence intervals (CI) for the association between selected characteristics and UTI were calculated using log-binomial models. Multivariable models were not constructed because of small numbers. Results were replicated and all analyses were conducted using SAS 9.4 (Cary, NC).

RESULTS

A total of 351 infants were enrolled in the UMPIRE study and 299 infants (85.2%) were eligible for analysis. Baseline demographics are displayed in Table 1. Forty-eight infants (16.1%) were treated for a UTI before 4 months of age, with 12 (4.0%) having a UTI that met the protocol's strict definition of UTI. Of the 48 infants treated for UTI, 8 (16.7%) had 2 or more UTIs during the time period. We identified 23/48 infants treated for laboratory positive UTI with at least one symptom. Sixteen (69.6%) of these 23 infants demonstrated fever. For the 12 infants with laboratory positive UTI and at least 2 symptoms, 9 (75%) reported fever.

Among the 48 treated for a UTI, laboratory results were confirmed in 45 infants (93.8%). Clinical information about treated UTI and laboratory positive UTI with at least 2 symptoms is displayed in Table 2. For both treated UTI and laboratory positive UTI with at least 2 symptoms, the emergency department was the most common site of diagnosis (37.5% and 58.3%, respectively), and catheterization (87.5% and 100%) was the most common urine collection method.

The risk of treated UTI and laboratory positive UTI with at least 2 symptoms by selected characteristics is displayed in Table 3. Antibiotics were used beyond the perioperative period in 26 (8.7%) of the 299 infants.(Table 4) Infants whose antibiotics were discontinued postoperatively had a lower incidence of UTI than infants who remained on antibiotics (15% vs. 26.9% respectively), but the difference was not statistically significant. For treated UTI and laboratory positive UTI with at least 2 symptoms, respectively, the risks among those who received no antibiotic prophylaxis beyond the perioperative period were 0.6 (95% CI= 0.3, 1.1) and 0.5 (95% CI= 0.1, 2.1) times the risk compared with those in whom antibiotic use was continued or was unknown.

Regarding treated UTI, the risk among infants who were managed with CIC was 2.7 times (95%CI=1.6, 4.5) the risk of those who were not using CIC; the risk among infants who had grade 3 or 4 hydronephrosis was 4.0 times (95%CI= 2.2, 7.5) the risk of those without hydronephrosis; and the risk among infants with VUR grade 3–5 was 2.4 times (95%CI= 1.3, 4.3) the risk of those without VUR. Regarding laboratory positive UTIs with at least two symptoms, the risk among infants who were using CIC was 3.3 times (95%CI=1.0, 10.5) the risk of those who were not on CIC; and the risk among those who had grade 3 or 4 hydronephrosis was 10.1 times (95%CI=2.8, 36.3) the risk of those without hydronephrosis. The relative risk for patients with grades 3–5 VUR was 3.1; however, this did not reach statistical significance.

DISCUSSION

Our series of infants with SB demonstrated a low risk of treated UTI and an even lower risk of UTI that met strict criteria based on laboratory findings and at least two symptoms. Patients who were on CIC or had higher grade hydronephrosis were at higher risk. Presence of VUR increased the likelihood of being treated for UTI but did not increase the likelihood of having a laboratory positive UTI with at least two symptoms.

Based on this analysis of newborns with myelomeningocele managed prospectively by a strict protocol, we believe that routine prophylactic antibiotics for UTI can be withheld until evaluative procedures are completed during the first four months of life. The increased risk of UTI in infants with higher grade hydronephrosis and on CIC suggest that risk stratification may be employed, but given the small numbers of infants with SB developing UTIs, the UMPIRE protocol will continue to withhold antibiotic prophylaxis in the neonatal period.

Baseline imaging characteristics of newborns in our study group have been previously reported and demonstrated that infant VUR rates were low (15%), most patients had either normal kidneys (56%) or only mild hydronephrosis (40%), and less than 10% had cortical defects on initial renal scan.[9] The small proportion of obvious congenital upper tract anomalies lend further support to the UMPIRE protocol for withholding antibiotic prophylaxis.

Although UTI is the most common bacterial infection in infants under 3 months of age, the true incidence of UTI in the general population is difficult to determine due to varying definitions of UTI. A Swedish study of 26 pediatric departments involving over 140,000 children found that the mean incidence of UTI in children under 2 years of age was 1% for both boys and girls.[10] Their criteria for UTI included a positive culture (>100,000 CFU) and positive nitrites on urinalysis. Specimens were obtained by suprapubic aspiration, catheterization, mid-stream, or bagged specimens. Freedman reported data from the Urologic Diseases in America Project, which showed an incidence of UTIs of 2.4% to 2.8% among all American children (ages 0 to 18 years) with higher rates among children under 3 years of age.[11] UTI in that study was determined by diagnostic coding, which has significant limitations. Previous studies have not reported the incidence of UTI among patients with SB using a standard definition.[2]

We identified an increased risk of receiving treatment for UTI and laboratory positive UTI with at least 2 symptoms in patients who were on CIC. While this intervention may be necessary due to high residual urine volumes in the newborn period, CIC can introduce bacteria into the bladder.[12] Patients enrolled in the UMPIRE study are initially managed with CIC during the postnatal hospitalization, but CIC is stopped if bladder residual volumes remain low.[5]

While the number of patients on CIC after hospital discharge was low (20%), the incidence of receiving treatment for UTI was over twice that of patients who were not being catheterized. These findings are consistent with a recent single-institution retrospective review of children with SB from birth to 3 years of age.[13] The authors found UTI rates among patients on CIC to be twice that of those infants managed without CIC. It is not clear if the higher UTI rate is due to the introduction of bacteria into the bladder by CIC or if there are co-existing urinary tract abnormalities contributing to the increased risk. It may also be that more asymptomatic bacteriuria is being identified and treated as a UTI in patients on CIC.

We also identified an increased risk of UTI among the infants with high grade hydronephrosis. A recent systematic review of the literature demonstrated higher rates of UTI among healthy infants with antenatal hydronephrosis; however, the authors were unable to establish any benefit for antibiotic prophylaxis over observation alone.[14] It may be that high-grade hydronephrosis in patients with SB is a marker for anatomic abnormalities or alterations in bladder physiology that put patients at increased risk. In one study of 128 patients with neurogenic bladders managed with CIC, no specific urodynamic parameters were associated with more frequent UTI.[15]

The use of prophylactic antibiotics in patients with VUR remains controversial. A recent meta-analysis examining the efficacy of prophylaxis in patients with VUR showed variable results.[16] The same meta-analysis was also unable to clearly show that patients with dilating or high-grade VUR were at increased risk of UTI. Our series does demonstrate that patients with higher grades of VUR were more likely to be treated for a UTI, but there was no significant difference noted in patients who met the protocol criteria for UTI. It is important to note that VUR status in our patient population was not identified in the neonatal period as cystography or video urodynamics was typically performed at the 3-month visit.

These findings have several limitations. While patient data are collected from tertiary care centers with established, multidisciplinary SB clinics, UTI diagnosis may not be entirely accurate because patients may have been diagnosed and treated for UTI by primary care providers and urgent care centers closer to home and method of specimen collection was not uniform. The current study only analyzed patient UTI data during the first 4 months of life. We did not include urodynamic data in this analysis because of variability in performance and interpretation of urodynamic studies in infants among the nine sites and multiple urologists.[17] We are actively taking steps to standardize performance and interpretation.

Despite the relatively large number of newborns with SB, the number of patients with UTI remains low. The analysis was underpowered to test for some statistically significant differences and unable to adjust for multiple factors. While this study focused on the risk of UTI in newborns until 4 months of age, future directions for looking at UTI rates in our study population include identifying additional risk factors, such as urodynamic findings, that may predict increased risk of UTI.

CONCLUSION

The incidence of UTI among newborns with SB in the first 4 months of life was low although more were treated for UTI without meeting strict criteria of laboratory positive with at least two symptoms. We identified patients with higher grade hydronephrosis, those on CIC, or patients with higher grade VUR as being at greater risk for treatment of UTI, but only patients with higher grade hydronephrosis or those on CIC had an increased risk of laboratory positive UTI with at least two symptoms. Our findings suggest that prophylactic antibiotics may not be necessary for a majority of newborns with SB who do not require CIC and have low-grade or no hydronephrosis. Further imaging, urodynamic testing and longer follow-up may provide additional data for better stratification of risk.

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Table 1.

Baseline demographics for 299 infants with spina bifida enrolled in the UMPIRE study, 2015–2019

Demographics	n	%
Sex		
Male	151	50.5
Female	148	49.5
Race/Ethnicity		
Non-Hispanic White	183	61.2
Non-Hispanic Black	25	8.4
Hispanic	80	26.8
Other	10	3.3
Unknown	1	0.3
Health insurance		
Any private	153	51.2
Public only	130	43.5
Public and supplementary	11	3.7
Uninsured	3	1.0
Unknown	2	0.7
Prenatal back closure		
Yes	58	19.4
No	240	80.3
Unknown	1	0.3

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Table 2.

Description of UTIs among infants with spina bifida enrolled in the UMPIRE study, 2015–2019

	Treated UTI N=48 n (%)	Lab positive and 2+ symptoms* N=12 n (%)
UTI diagnosis location		
Emergency Department	18 (37.5)	7 (58.3)
Inpatient Hospital	14 (29.2)	1 (8.3)
Pediatrician/Primary Care	6 (12.5)	3 (25.0)
Spina Bifida Clinic	4 (8.3)	
Other	6 (12.5)	1 (8.3)
Urodynamics lab	5	1
Nephrology clinic	1	
Urine collection method		
Catheterization	42 (87.5)	12 (100)
Clean catch	1 (2.1)	
Unknown	5 (10.4)	
Use of oxybutynin at time of the diagnosed UTI	4 (8.3)	3 (25.0)
Use of prophylactic antibiotic at the time of the diagnosed UTI	5 (10.4)	1 (8.3)
Patient catheterizing as prescribed at the time of the diagnosed UTI	23 (45.8)	7 (58.3)

* fever > 100.4 degrees Fahrenheit, gross hematuria (defined as pink or red urine), abdominal, suprapubic, or flank pain or tenderness, new or worsening incontinence, new or worsening urinary urgency, frequency, or hesitancy, pain with catheterization or urination, and malodorous/cloudy urine. Infants less than 1 year of age can have the following additional symptoms: failure to thrive, dehydration, hypothermia, increasing spasticity, febrile seizures, fussiness/irritability, or other.

UTI – urinary tract infection

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Table 3.

Risk of UTI among infants with spina bifida by selected characteristics, UMPIRE 2015–2019

		Treated UTI			Lab Positive and 2+Symptoms		
	Total N=299	**Yes N=48 n (%)**	**No N=251 n (%)**	**Risk Ratio[1] (95% Confidence Interval)**	**Yes N=12 n (%)**	**No N=287 n (%)**	**Risk Ratio[1] (95% Confidence Interval)**
Sex							
Female	148	29 (19.6)	119 (80.4)	1.6 (0.9,2.7)	6 (4.0)	142 (96.0)	1.0 (0.3,3.1)
Male	151	19 (12.6)	132 (87.4)	referent	6 (4.0)	145 (96.0)	referent
Circumcision among males							
Yes	61	9 (14.8)	52 (85.3)	1.3 (0.6,3.1)	2 (3.3)	59 (96.7)	0.7 (0.1,3.9)
No	90	10 (11.1)	80 (88.9)	referent	4 (4.4)	86 (95.6)	referent
Discontinued antibiotic after perioperative period							
Yes/Never Started	273	41 (15.0)	232 (85.0)	0.6 (0.3,1.1)	10 (3.7)	263 (96.3)	0.5 (0.1,2.1)
No/Unknown	26	7 (26.9)	19 (73.1)	referent	2 (7.7)	24 (92.3)	referent
Use of CIC at 3, month visit[2]							
Yes	60	19 (31.7)	41 (68.3)	2.7 (1.6,4.5)	5 (8.3)	55 (91.7)	3.3 (1.0,10.5)
No	238	28 (11.8)	210 (88.2)	referent	6 (2.5)	232 (97.5)	referent
Neonatal RBUS results[3]							
Grade 3,4	10	6 (60.0)	4 (40.0)	4.0 (2.2,7.5)	3 (30.0)	7 (70.0)	10.1 (2.8,36.3)
Grade 1,2	109	16 (14.7)	93 (85.3)	1.0 (0.9,1.1)	4 (3.7)	105 (96.3)	1.2 (0.3,4.5)
No hydronephrosis	168	25 (14.9)	143 (85.1)	referent	5 (3.0)	163 (97.0)	referent
Vesicoureteral Reflux[4]							
Grade 3,4,5	28	10 (35.7)	18 (64.3)	2.4 (1.3,4.3)	3 (10.7)	25 (89.3)	3.1 (0.9,10.9)
Grade 1 and 2	15	0 (0)	15 (100)	n/a	0 (0)	15 (100)	n/a
No reflux	229	34 (14.9)	195 (85.2)	referent	8 (3.5)	221 (96.5)	referent

[1] Risk ratios are not adjusted for other characteristics

[2] One newborn with treated UTI missing CIC information; one newborn with lab positive and 2+ symptoms missing CIC information

[3] One newborn with treated UTI and 11 newborns without treated UTI missing RBUS results; 12 newborns without lab positive and 2+symptoms UTI missing RBUS results

[4] Four newborns with treated UTI and 23 newborns without treated UTI missing RBUS results; 1 newborn with lab positive and 2+ symptoms and 26 newborns without lab positive and 2+ symptoms UTI missing RBUS results

UTI – urinary tract infection

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Table 4.

Reasons for not discontinuing antibiotics after back closure

Reason	N=26
Clinician forgot	4
Born at another hospital /non, study institution	5
Changes in ultrasound, VUDY, or VCUG	1
Hospitalized/ other surgeries	2
Started then stopped	1
Clinician disagreed with protocol	1
Continued as long as EVD was in place	1
Missing/unknown	11