

Neonatal Circumcision and Urinary Tract Infections in Infants With Hydronephrosis

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abstract

BACKGROUND: Boys with urinary tract abnormalities may derive a greater benefit from newborn circumcision for prevention of urinary tract infection (UTI) than the general population. However, the effect of newborn circumcision on UTI is not well characterized across the etiological spectrum of hydronephrosis. We hypothesized that boys with an early diagnosis of hydronephrosis who undergo newborn circumcision will have reduced rates of UTI.

METHODS: The MarketScan data set, an employer-based claims database, was used to identify boys with hydronephrosis or hydronephrosis-related diagnoses within the first 30 days of life. The primary outcome was the rate of UTIs within the first year of life, comparing circumcised boys with uncircumcised boys and adjusting for region, insurance type, year of birth, and infant comorbidity.

RESULTS: A total of 5561 boys met inclusion criteria, including 2386 (42.9%) undergoing newborn circumcision and 3175 (57.1%) uncircumcised boys. On multivariate analysis, circumcision was associated with a decreased risk of UTI in both boys with hydronephrosis and healthy cohorts: odds ratio (OR) 0.36 [95% confidence interval [CI] 0.29–0.44] and OR 0.32 [95% CI 0.21–0.48], respectively. To prevent 1 UTI, 10 patients with hydronephrosis would have to undergo circumcision compared with 83 healthy boys. Among specific hydronephrosis diagnoses, circumcision was associated with a reduced risk of UTI for those with isolated hydronephrosis (OR 0.35 [95% CI 0.26–0.46]), vesicoureteral reflux (OR 0.35 [95% CI 0.23–0.54]), and ureteropelvic junction obstruction (OR 0.35 [95% CI 0.20–0.61]).

CONCLUSIONS: Newborn circumcision is associated with a significantly lower rate of UTI among infant boys with hydronephrosis.



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WHAT'S KNOWN ON THIS SUBJECT: Boys with hydronephrosis are at an increased risk for urinary tract infections. Although circumcision confers a small benefit in healthy boys, this benefit appears to be greater in severe urological diseases, such as posterior urethral valves and high-grade vesicoureteral reflux.

WHAT THIS STUDY ADDS: In this study, we use a nationwide database to show a reduced rate of urinary tract infections in circumcised boys with hydronephrosis. Boys with underlying diagnoses of ureteropelvic junction obstruction and vesicoureteral reflux appear to have a similar benefit with regard to risk reduction.

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Hydronephrosis, often discovered antenatally, is a common newborn diagnosis that impacts 1% to 3% of all live births.¹ Boys with hydronephrosis are at an increased risk of urinary tract infections (UTIs), especially early in life.^{2,3} Circumcision is known to provide a small yet significant risk reduction of early UTIs in healthy boys.^{4,5} Populations with a higher innate prevalence of UTIs may realize a greater benefit of circumcision.⁶ Indeed, the American Academy of Pediatrics' consensus statement on male circumcision suggests boys with urological abnormalities may receive additional benefit from circumcision with regard to UTI risk reduction.⁵

Our understanding of the relationship of circumcision on UTIs in boys with hydronephrosis or hydronephrosis-related diagnoses is limited by the lack of stratification across diagnoses or the inclusion of only higher-risk pathologies, such as posterior urethral valves (PUVs) or high-grade vesicoureteral reflux (VUR). Uncircumcised status has been shown to be a risk factor for UTIs in boys with hydronephrosis. However, hydronephrosis encompasses a spectrum of underlying diagnoses with varying degrees of severity and resultant health outcomes.^{7,8} Without stratification by these underlying diagnoses, the demonstrated benefit for circumcision may be driven by higher-risk diagnoses, such as PUVs.

We examined the association of circumcision across a broad population of boys with hydronephrosis using a nationwide data set of insured children. We had 2 primary aims for this study. First, we sought to define the risk of UTI for healthy boys and those with hydronephrosis or associated diagnoses. Second, we sought to clarify the association of circumcision with UTIs within the first year of life across multiple diagnoses of hydronephrosis. We hypothesized that circumcision

would be associated with a reduced risk of UTI irrespective of underlying hydronephrosis diagnosis, with a disproportionate benefit compared with healthy boys.

METHODS

Data Source

We accessed the Thomson Reuters MarketScan Commercial Claims and Encounters database from 2007 to 2013. The MarketScan claims databases comprise 143 million unique patients (including 50 million covered lives) in the most recent full data year. MarketScan includes Americans with employer-provided health insurance and Medicaid, although the majority of MarketScan data are sourced from large employers. All employee beneficiary data are included, which allows for the assessment of health care use of pediatric beneficiaries. The data set captures longitudinal billing and claims data on inpatient admissions, emergency department evaluations, and outpatient visits. Employer-provided data allows longitudinal inclusion of patients across health plans, enabling ascertainment of patients who would be otherwise lost in plan-based data sources.⁹ Because data are captured in MarketScan only while patients are insured, we included only boys with 12 months of continuous coverage starting at birth to ensure adequate follow-up.

Study Patients

We included boys with hydronephrosis or a hydronephrosis-related diagnosis (ie, ureteropelvic junction obstruction [UPJO], VUR, ureterovesical junction obstruction, PUVs, and ureterocele) within the first month of life. Patients with severe urologic comorbidities of the bladder or cloacal exstrophy, myelomeningocele, omphalocele, sacrococcygeal teratoma, cloacal anomaly, sacral agenesis, and prune belly syndrome were excluded.

Because additional diagnostic evaluations may yield specific hydronephrosis diagnoses, the assigned diagnosis incorporated the most recent hydronephrosis-related diagnosis at 12 months of life.

Control Patients

A random sample of boys <1 year of age was selected and matched by year of birth in a 2:1 ratio to boys with hydronephrosis, excluding boys with a urological diagnosis as outlined above (see Supplemental Tables 3 and 4 for codes).

Variables Collected

In addition to diagnosis and circumcision status, patient demographic and clinical information ascertained included year of birth, nonurological comorbidity (defined by Elixhauser et al¹⁰) index at 2 months, insurance type, exposure to prophylactic antibiotics, and geographic region of care. Prophylactic antibiotic exposure was defined as a single prescription or a cumulative prescription for antibiotics >30 days in length for sulfamethoxazole-trimethoprim, trimethoprim, cephalexin, nitrofurantoin, or amoxicillin.

Intervention

Circumcision within the first 28 days of life was defined by using *Current Procedural Terminology* (CPT) codes 54150, 54160, and 54161 as well as visit code v 50.2. To exclude early UTI from biasing the intervention (ie, excluding patients who underwent circumcision for cause), we excluded patients with a diagnosis of UTI within the first 30 days of life.

Outcome

Our outcome of interest was the diagnosis of UTI within the first year of life. As a sensitivity analysis, we used a definition of UTI as described by Copp et al¹¹ to include a primary diagnosis of UTI or secondary codes for UTI (as above), plus codes for

TABLE 1 Characteristics Based on Circumcision Status and Diagnosis

	Hydronephrosis			<i>P</i>	Normal Cohort			<i>P</i>
	All, <i>N</i> (%)	Circumcision, <i>n</i> (%)	No Circumcision, <i>n</i> (%)		All, <i>N</i> (%)	Circumcision, <i>n</i> (%)	No Circumcision, <i>n</i> (%)	
Total	5560 (100)	2386 (42.9)	3174 (57.1)		11 120 (100)	5769 (51.9)	5351 (48.1)	
Birth y				.02				<.001
2007	386 (6.9)	173 (7.2)	213 (6.7)		772 (6.9)	415 (7.2)	357 (6.7)	
2008	938 (16.9)	408 (17.1)	530 (16.7)		1876 (16.9)	915 (15.9)	961 (18.0)	
2009	917 (16.5)	362 (15.2)	555 (17.5)		1834 (16.5)	879 (15.3)	955 (17.8)	
2010	968 (17.4)	387 (16.2)	581 (18.3)		1936 (17.4)	1064 (18.4)	872 (16.3)	
2011	1270 (22.8)	562 (23.6)	708 (22.3)		2540 (22.8)	1335 (23.1)	1205 (22.5)	
2012	1081 (19.5)	494 (20.7)	587 (18.5)		2162 (19.5)	1161 (20.1)	1001 (18.7)	
Geographic region				<.001				<.001
Northeast	1026 (18.5)	397 (16.6)	629 (19.8)		1748 (15.7)	777 (13.5)	971 (18.2)	
North Central	1432 (25.8)	708 (29.7)	724 (22.8)		2830 (25.5)	1705 (29.6)	1125 (21.0)	
South	2024 (36.4)	885 (37.1)	1139 (35.9)		4140 (37.2)	2295 (39.8)	1845 (34.5)	
West	925 (16.6)	345 (14.5)	580 (18.3)		1997 (18.0)	857 (14.8)	1140(21.3)	
Unknown	153 (2.7)	51 (2.1)	102 (3.2)		405 (3.6)	135 (2.3)	270 (5.0)	
Infant comorbidities				<.001				.50
0–1	5308 (95.5)	2327 (97.5)	2981 (93.9)		11 055 (99.4)	5738 (99.5)	5317 (99.4)	
≥2	252 (4.5)	59 (2.5)	193 (6.1)		65 (0.6)	31 (0.5)	34 (0.6)	
Final diagnosis				.003				
Hydronephrosis	3996 (71.9)	1756 (73.6)	2240 (70.6)		—	—	—	—
PUV	120 (2.1)	39 (1.6)	81 (2.5)		—	—	—	—
UPJO	581 (10.4)	260 (10.9)	321 (10.1)		—	—	—	—
Ureterocele	70 (1.3)	32 (1.3)	38 (1.2)		—	—	—	—
VUR	688 (12.4)	254 (10.7)	434 (13.7)		—	—	—	—
Other	105 (1.9)	45 (1.9)	60 (1.9)		—	—	—	—

—, not applicable.

780.6 (fever) or 788.1 (dysuria), plus antibiotic prescription within 3 days before and 5 days after UTI visit. To ensure no confounding with concomitant surgical procedures for correction of hydronephrosis, we assessed rates of surgical correction at the same time as circumcision as well, by using CPT codes as previously reported (Dy et al⁷).

Statistical Analysis

Patient characteristics of circumcised and uncircumcised boys were compared by using χ^2 tests. Logistic regression was used to identify the association between circumcision status and the occurrence of UTIs independent of other patient demographic and clinical characteristics. The adjusted model included year of birth, geographic region, insurance plan type, and Elixhauser et al¹⁰ comorbidity index. For the comorbidity index, Elixhauser et al¹⁰ conditions were enumerated, and we categorized the burden of

comorbid health problems as 0 to 1 or ≥ 2 comorbidities. The number needed to treat (NNT) was calculated as the inverse of the risk difference between uncircumcised and circumcised boys. Among boys with hydronephrosis, odds ratios (ORs) and NNT were calculated for the group overall as well as for specific hydronephrosis diagnoses. Statistical analysis was performed by using SAS version 9.4 (SAS Institute, Inc, Cary, NC).

RESULTS

We identified 5560 boys with hydronephrosis and 11 120 healthy boys in the study. Circumcision within 28 days was performed in 43% of boys with hydronephrosis and 52% of healthy controls ($P < .001$). Demographic information stratified by circumcision status is displayed in Table 1. Among healthy boys, 3098 (54%) underwent circumcision within 2 days of

life compared with 34% of those with hydronephrosis. The median age for healthy boys and boys with hydronephrosis undergoing circumcision was 2 and 9 days of life, respectively ($P < .01$). Only 0.8% of boys with hydronephrosis underwent circumcision at the time of surgery to correct hydronephrosis. Antibiotic prophylaxis was noted in 3.7% of boys with hydronephrosis, distributed equally among circumcised (89, 3.7%) and uncircumcised (119, 3.7%) boys ($P = .99$).

UTIs occurred in 12% of boys with hydronephrosis and 1% of healthy boys. UTIs were significantly less common among circumcised boys with hydronephrosis compared with healthy cohorts (Fig 1). On multivariate analysis, circumcision was associated with a significantly decreased risk of UTI (OR 0.36 [95% confidence interval (CI) 0.29–0.44] for boys with hydronephrosis; OR 0.32 [95% CI 0.21–0.48] for

healthy patients). Among boys with hydronephrosis, 10 would need to undergo circumcision to prevent 1 UTI compared with 83 healthy boys needing to undergo circumcision to prevent 1 UTI.

Stratified by hydronephrosis diagnosis, circumcision was associated with lower odds of UTI among those with isolated hydronephrosis, UPJO, and VUR (Table 2). The NNTs for specific hydronephrosis diagnoses and the healthy cohort to prevent 1 UTI are displayed in Fig 2. We conducted a sensitivity analysis in which we used a more specific definition of UTI. This demonstrated a decreased prevalence of UTIs in the 12-month study period with a preserved benefit of circumcision on the occurrence of UTIs among boys with hydronephrosis and healthy boys (Supplemental Table 5). On the basis of the incidence of UTI

on the sensitivity analysis, 38 boys with hydronephrosis would need to undergo circumcision to prevent 1 UTI compared with 370 healthy boys who would need to undergo circumcision to prevent 1 UTI.

DISCUSSION

In this nationally representative sample of insured children, circumcision was associated with a significantly decreased risk of UTI among both healthy boys and those with a diagnosis of hydronephrosis in infancy. Although the absolute risk reduction in these populations is similar, the increased prevalence of UTI in boys with hydronephrosis resulted in a substantially lower NNT than that for healthy controls. The benefit of circumcision on reducing UTI risk held for boys with isolated hydronephrosis as well as the most common underlying diagnoses,

UPJO and VUR. That the benefit was not seen in boys with less common diagnoses of PUV and ureterocele (although circumcision trended toward benefit) may relate to lower prevalence of these diagnoses in our study sample. The NNTs were similar across all diagnoses of hydronephrosis, suggesting that this benefit may extend beyond higher risk urinary tract pathology.

Our results support previous studies whose authors suggest circumcision status is protective against UTIs in boys with hydronephrosis. Because the authors of these studies did not usually stratify hydronephrosis by its underlying diagnosis, the clinical implementation of these findings to individual patients was challenging.^{3,12} With respect to specific patient populations, circumcision has consistently demonstrated risk reduction for UTIs among children with PUV and high-grade VUR.¹³ We found that this benefit extends beyond these high-risk diagnoses to boys with UPJO and isolated hydronephrosis.

We limited the scope of our study to the first year of life on the basis of previous data that suggest that the risk of UTI and the potential benefit of circumcision decreases substantially beyond infancy.⁶ Bacterial colonization of the foreskin appears to change during the first year of life, which may explain lower UTI risks in older uncircumcised boys.¹⁴ However, the risk of UTIs in boys with urological abnormalities may persist after the first year of life.³ As such, the benefits of circumcision seen in our study may also impact older boys. At minimum,

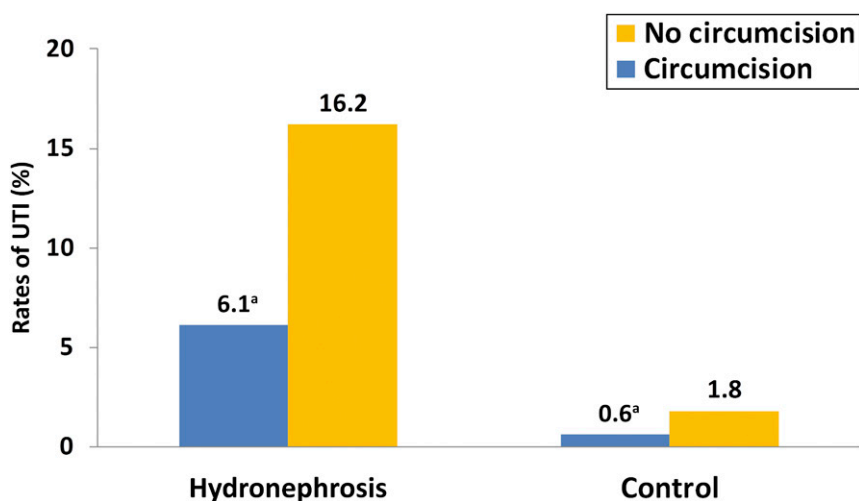


FIGURE 1 Rates of UTI in healthy boys and those with hydronephrosis, stratified by circumcised status. ^a Significant difference in UTI rates compared with uncircumcised group ($P < .0001$).

TABLE 2 OR of UTIs by Hydronephrosis Group (Compared With Uncircumcised Boys)

	OR Unadjusted (95% CI)	OR Adjusted (95% CI)	UTI, %
Hydronephrosis	0.32 (0.24–0.42)	0.34 (0.26–0.45)	8.1
PUV	0.46 (0.19–1.09)	0.41 (0.14–1.19)	34.2
UPJO	0.38 (0.22–0.63)	0.35 (0.20–0.62)	14.1
Ureterocele	0.54 (0.15–1.98)	0.36 (0.05–2.52)	17.1
VUR	0.34 (0.23–0.51)	0.35 (0.23–0.54)	26.5
Other	0.14 (0.14–1.24)	0.34 (0.1–1.17)	18.1

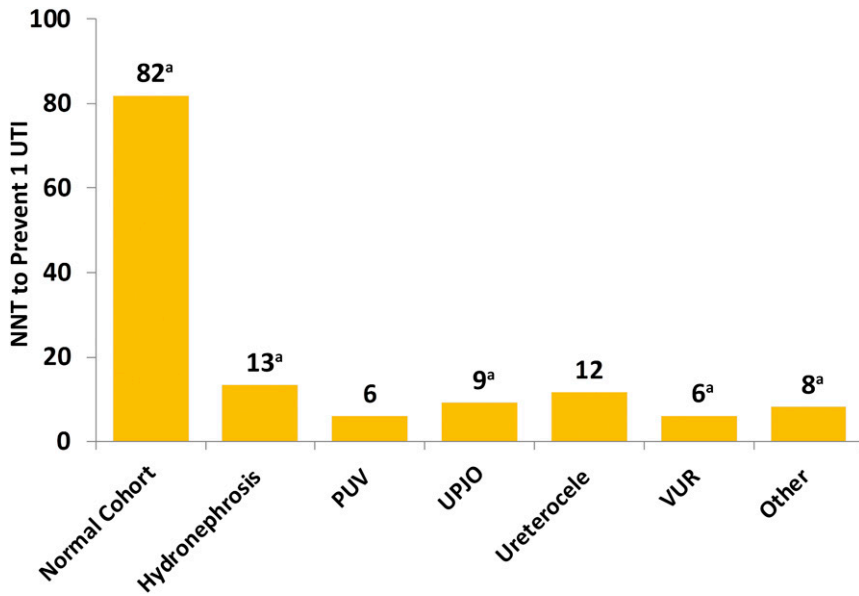


FIGURE 2

NNT to prevent 1 UTI in the healthy population and across individual diagnoses of boys with hydronephrosis. ^a Significantly reduced OR for UTI on multivariate analysis.

our data support a greater benefit of circumcision among patients with a higher innate risk for UTIs, although circumcision may also be considered for older boys who present with hydronephrosis.

Our study was limited to boys with a diagnosis of hydronephrosis in infancy. We sought to inform clinical decision-making regarding circumcision in the newborn period. Because we excluded boys with previous UTI diagnoses, the majority of boys in this study were likely diagnosed antenatally or were found to have hydronephrosis incidentally on postnatal imaging. By excluding boys with previous UTI diagnoses, we attempted to eliminate bias in circumcision counseling that may be driven by a history of infection. Interestingly, hydronephrosis alone did not appear to impact circumcision counseling because a greater proportion of healthy boys were circumcised. Only 0.8% of boys underwent circumcision and corrective surgery for hydronephrosis concomitantly; thus, it is unlikely that concomitant correction of hydronephrosis biased the results in any way. Boys

diagnosed with UTI later in the first year of life may also benefit from circumcision, although because the feasibility of office-based circumcision decreases, providers must weigh the potential need for general anesthesia.

Our study has several notable limitations. First, we accessed an administrative billing data set, which is subject to appropriate scrutiny. A diagnosis of UTI is prone to miscoding and suboptimal collection techniques. We attempted to address this by conducting a sensitivity analysis using a more rigid definition of UTI, as has been previously described for this data set.⁷ The sensitivity analysis demonstrated consistent results with preserved statistical significance, supporting the validity of our main results. Second, an administrative data set lacks the clinical granularity that allows for inference of disease severity of an individual diagnosis. Thus, hydronephrosis and VUR grading, defined by imaging results, could not be assessed in this study. However, given our broad inclusion criteria and large study sample, we believe our findings are representative

of a typical hydronephrosis population. Because severe grades of hydronephrosis and VUR are less prevalent, it is unlikely that the boys with severe hydronephrosis would be driving our findings. We do believe our results would be best supported with granular clinical data capable of examining nuances in hydronephrosis care, such as through a registry. Furthermore, such administrative data sets are reliant on accurate coding both for procedures and diagnoses. Thus, it is possible that circumcisions may not be captured either because of bundled charges into newborn care or lack of insurance coverage for this procedure. However, we did find a large proportion of boys undergoing circumcision within the first 2 days of life, consistent with an accurate ascertainment of the procedure in the early newborn period. However, this specific limitation would bias toward the null hypothesis by grouping some circumcised boys in the uncircumcised cohort. Thus, we do not believe misclassification of circumcision would invalidate our results. Likewise, hydronephrosis could be misclassified as well. To our knowledge, use of hydronephrosis-related CPT codes have not been validated in other administrative data sets, and because MarketScan includes only deidentified data, it would be impossible to do so through this data set. Finally, UTI itself could be misclassified, which would likely have the greatest impact on our study conclusions. To that end, we performed a sensitivity analysis, as other authors have used,¹¹ to investigate these associations in a more specific patient population. Not surprisingly, the incidence of UTI was substantially lower in the sensitivity analysis (2.6% in boys with hydronephrosis and 0.2% in healthy controls), with resultant lower NNTs for both groups as well. Because the proportional decrease in incidence was similar in both cohorts, the relationships

between decreased UTI rates and circumcision were maintained within the sensitivity analysis. Notably, the incidence of UTI in the primary analysis as well as the potential benefit within the healthy population is more similar to previous reports on UTI risk and circumcision in healthy boys.¹⁴ Although relying primarily on UTI codes alone may overestimate the risk of UTI, the more stringent sensitivity analysis likely underestimates this risk; therefore, the actual reality likely resides somewhere between these 2 analyses.

These limitations notwithstanding, we identified an association between newborn circumcision and reduced UTI risk over the first year of life for infant boys with hydronephrosis. Importantly, this association was consistent across hydronephrosis

diagnoses, distinguishing our findings from previous studies that revealed a benefit for higher risk diagnoses. Our results may aid pre- and postnatal counseling regarding the patient-centered risks and benefits of circumcision. Further work is needed to define the association between circumcision and UTI stratified for hydronephrosis severity because recommendations regarding newborn circumcision in the setting of urinary tract pathology are confounded by a dearth of high-quality data.⁵

CONCLUSIONS

Among infant boys with hydronephrosis, newborn circumcision was associated with a reduced risk of UTI. The associated benefit of newborn

circumcision was greater for boys with hydronephrosis than healthy controls. Importantly, this associative benefit was consistent across different underlying hydronephrosis diagnoses. These results are hypothesis generating and may guide future prospective studies for this population.

ABBREVIATIONS

CI: confidence interval
CPT: *Current Procedural Terminology*
NNT: number needed to treat
OR: odds ratio
PUV: posterior urethral valve
UPJO: ureteropelvic junction obstruction
UTI: urinary tract infection
VUR: vesicoureteral reflux

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