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Is parenteral antibiotic prophylaxis associated with fewer infectious complications in stented, distal hypospadias repair?

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Hypospadias; Antibiotic stewardship; Antibiotic prophylaxis; Tubularized incised plate

Abbreviations
BCH, Boston Children's Hospital; IRB, Institutional Review Board; MAGPI, meatal advancement and glanuloplasty; PO, Per Os; SSI, Surgical Site Infection; TIP, Tubularized Incised Plate; UTI, Urinary Tract Infection

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Summary

Introduction
Judicious use of antibiotics for surgical prophylaxis is important for reducing antimicrobial resistance while preventing infectious surgical complications. In the setting of pediatric distal hypospadias repairs, it is unclear if antibiotic surgical prophylaxis is beneficial.

Objective
The purpose of this study was to compare rates of infectious complications in pediatric subjects undergoing distal hypospadias repair who received any peri-operative antibiotics to those who did not.

Study design
This was a review of a retrospective cohort from a database of individuals undergoing hypospadias repairs evaluating whether they received peri-operative or post-operative antibiotic prophylaxis and determining the rate of infectious complications in those who did compared to those who did not receive antibiotic prophylaxis. Infectious complications were defined as surgical site infection (SSI) or urinary tract infection (UTI).

Results
There was no significant difference in infectious complication rates between individuals who received peri-operative parenteral antibiotic prophylaxis and those who did not. All subjects with infectious complications received post-operative oral antibiotic prophylaxis. There was one instance of *C. difficile* infection in a subject who received peri-operative parenteral antibiotics.

Discussion
Reducing antibiotic utilization without increasing infectious surgical complications is important in safely reducing antimicrobial resistance. In this study of pediatric distal hypospadias repair, peri-operative antibiotics did not demonstrate a clear benefit and post-operative oral antibiotics demonstrated no benefit in preventing infectious complications. Other studies evaluating peri- and post-operative antibiotics for pediatric hypospadias repair have also failed to demonstrate a benefit for antibiotics in preventing infections. Practitioners should reconsider the use of antibiotics in this setting.

Conclusion
Routine antibiotic prophylaxis does not appear beneficial for preventing infectious complications following uncomplicated, stented pediatric distal hypospadias repairs.

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Introduction

Antimicrobial resistance is a growing concern that could reduce the availability of effective antibiotics for the treatment and prevention of infections [1]. Antimicrobial resistance in pathogens is driven by a variety of factors, including inappropriate use of antibiotics [1]. Because of growing concerns about antimicrobial resistance, many hospital systems have implemented antibiotic stewardship programs to reduce unnecessary antibiotic use [1]. However, many medical scenarios remain in which it is unknown whether antibiotics are beneficial.

Prophylactic peri-operative antibiotics are commonly used for a variety of urologic procedures, especially those involving entry into the genitourinary tract, which are classified as clean-contaminated wounds [2]. However, pediatric surgeries have often been excluded from studies and best-practice statements, resulting in a lack of guidance for pediatric surgeons regarding peri-operative and post-operative antibiotic use [2,3].

Antibiotics are frequently given peri-operatively and post-operatively after hypospadias repair. Justification for peri-operative antibiotics often relate to the entry into the urinary tract during the case. Post-operative antibiotics are also often given due to the presence of a urethral stent, both because of the continuous passage of urine in proximity to the surgical site and the stenting open of the urethral sphincter, theoretically allowing passage of bacteria into the bladder. However, several studies have questioned the benefit of antibiotics in the setting of surgery for hypospadias [3—5]. Thus, these procedures may represent an opportunity to avoid unnecessary antibiotic use.

The primary purpose of this study was to evaluate the impact of peri-operative antibiotic use in the setting of distal hypospadias repairs in the pediatric population. Secondarily, as a means of eliminating confounding variables, we evaluated the benefit of post-operative oral antibiotic prophylaxis on infectious complications in this population. To our knowledge, this represents the largest retrospective study of antibiotic prophylaxis in distal hypospadias procedures.

Materials and methods

Regulatory approval

The Boston Children's Hospital (BCH) institutional review board (IRB) approved all protocols prior to any data review or analysis. IRB protocol #: IRB-P00037330.

Study design

A single-center retrospective review was performed of a database of pediatric hypospadias repairs performed at BCH between January 2008 and December 2019.

Inclusion and exclusion criteria

Inclusion criteria were any distal hypospadias repairs in subjects up to 23 years of age. Exclusion criteria were: age older than 23 years, any cases involving mid-shaft or proximal repairs, or repairs performed without a urethral stent. Mid-shaft and proximal repairs were excluded to limit heterogeneity within our dataset given that they involve more complex operations and that individuals undergoing proximal repairs more often have other comorbidities [6].

Procedures

Cases performed by 13 surgeons at BCH were included in this study. Most study subjects underwent a tubularized incised plate (TIP) procedure with a stent in place for 3—7 days, per protocol, although, for logistical reasons, some had their stents for a longer duration [6]. Other subjects were managed with a Thiersch-Duplay repair, meatal advancement and glanuloplasty (MAGPI), Mathieu repair, or their repair type was not listed.

Antibiotic use

Information was collected retrospectively regarding whether any antibiotics, either parenteral or oral (PO), were administered. Antibiotics were chosen by the treating surgeon as part of a subject's treatment plan. Antibiotics may reflect physician preference, subject allergies, subject tolerance, or urine culture information. Peri-operative parenteral antibiotics were defined as antibiotics administered either immediately preoperatively or intra-operatively as surgical prophylaxis. Peri-operative parenteral antibiotics were not continued post-operatively; however, subjects may or may not have received prophylactic PO antibiotics during the period of urethral stenting. Antibiotics were chosen by the treating surgeon as part of a subject's treatment plan. Parenteral peri-operative antibiotics included cefazolin and clindamycin. Subjects receiving clindamycin were those with penicillin allergy in whom antibiotics were utilized with the aim of preventing SSI.

Definition of complications

Infectious complications were defined as either surgical site infection (SSI) or urinary tract infection (UTI). SSI was defined as cellulitis or tissue infection diagnosed by one of the treating urologists as requiring prescription of antibiotics following a physical exam. UTI was defined as $>$50,000 organisms on culture or clinical suspicion warranting antibiotic prescription by their treating pediatric urologist. Other medical records, such as those of subjects' primary care physicians, were not reviewed. We chose these infectious complications to focus our study of the effectiveness of antibiotic prophylaxis on the immediate post-

Table 1 Subject characteristics.

	No antibiotics		Parenteral only		Oral only		Parenteral + Oral	
Total	67		80		34		647	
Median age at procedure (Years)	0.95		0.99		0.85		0.76	
Median age at follow-up (Years)	9.59		9.24		6.57		8.32	
Antibiotic type								
Parenteral	N	%	N	%	N	%	N[a]	%
Ampicillin	—	—	0	0.00	—	—	3	0.00
Cefazolin	—	—	76	95.00	—	—	634	97.99
Cefoxitin	—	—	0	0.00	—	—	1	0.15
Ceftriaxone	—	—	0	0.00	—	—	1	0.15
Clindamycin	—	—	4	5.00	—	—	11	1.70
Gentamicin	—	—	0	0.00	—	—	3	0.46
Vancomycin	—	—	0	0.00	—	—	1	0.15
Oral								
Amoxicillin	—	—	—	—	3	8.82	12	1.85
Amoxicillin-Clavulanic acid	—	—	—	—	1	2.94	2	0.31
Cephalexin	—	—	—	—	0	0.00	276	42.66
Ciprofloxacin	—	—	—	—	0	0.00	1	0.15
Clindamycin	—	—	—	—	4	11.76	1	0.15
Nitrofurantoin	—	—	—	—	0	0.00	2	0.31
Trimethoprim	—	—	—	—	0	0.00	3	0.46
Trimethoprim-Sulfamethoxazole					25	73.53	350	54.10
Procedure type	N	%	N	%	N	%	N	%
Duplay	10	14.93	64	80.00	20	58.82	75	11.59
MAGPI	8	11.94	9	11.25	13	38.24	17	2.63
Mathieu	0	0.00	5	6.25	1	2.94	5	0.77
Other	0	0.00	2	2.50	0	0.00	6	0.93
TIP/Snodgrass	49	73.13	0	0.00	0	0.00	544	84.08
Re-Op	2	2.99	2	2.50	3	8.82	33	5.10

[a] Note: 6 out of 647 patients in this cohort received more than 1 parenteral antibiotic and have been accounted for within each type of antibiotic they received.

Table 2 Characteristics of individuals with infectious complications.

Characteristic	Number (n = 12)
Stent duration (Days)	5 (n = 2), 6 (n = 1), 7 (n = 6), 8 (n = 1), 9 (n = 1), Accidentally removed at 2 days (n = 1)
Procedure type	TIP (n = 11), MAGPI (n = 1)
Parenteral antibiotic prophylaxis	Cefazolin (n = 11), No antibiotic (n = 1)
Post-operative antibiotic type	Cephalexin (n = 6), Trimethoprim-Sulfamethoxazole (n = 6)
Hypospadias type	Coronal (n = 7), Subcoronal (n = 2), Distal (n = 3)
Infectious complication	UTI (n = 7), SSI (n = 5)
Time to complication (Days)	2–42 (n = 11)

operative complications that antibiotics are prescribed to prevent.

Statistical analysis

Logistic regression was used to compare the effect of antibiotic use on infectious complications. Propensity scores for antibiotic use by surgeon were constructed and accounted for in the main analysis. Statistical analysis was performed using R statistical software [7].

Results

Subject characteristics

A total of 828 cases by 13 attending surgeons were included in this analysis with a median follow-up of 7.18 years (Table 1). Median age of subjects was 9.8 months (IQR: 7.1–14.9). Subject ages ranged from 2 months to 23 years. 728 (88%) of subjects received parenteral antibiotics, which included cefazolin and clindamycin, while 100 (11%) of subjects did not. 828 (82%) of subjects underwent at TIP repair, 107 (13%) a Thiersch-Duplay repair. 31 (4%) a MAGPI, and 5 (1%) the Mathieu; the remaining 8 (1%) did not have their procedure type listed. 48 of the cases included represented reoperative repairs.

Complication rates

A total of 12 infectious complications were noted in the study (1.45%) with 11 (1.5%) occurring in patients who had received preoperative parenteral antibiotics compared with 1 (1%) in the group that had surgery with no parenteral antibiotics (Table 2). There was no significant difference in terms of infectious complications between those who received preoperative parenteral antibiotics (OR = 0.65, 95% CI 0.08–15.5, p = 0.73). Complications in the parenteral antibiotic group included 6 instances of UTI, 3 instances of cellulitis, 1 infected inclusion cyst and 1 wound infection with glans dehiscence. All subjects with infectious complication had received peri-operative cefazolin. The infectious complication in the group with no parenteral antibiotics was 1 UTI. All subjects experiencing SSI underwent a TIP procedure and, among individuals experiencing a UTI, 5 of 6 had a TIP procedure and 1 underwent a MAGPI. None of the infectious complications occurred following reoperative cases.

Complications of parenteral antibiotics

One patient in the parenteral antibiotic group, who received 1 dose of cefazolin preoperatively, had a recurrent *C. difficile* infection, requiring further treatment. No other antibiotic-related complications were noted.

Post-operative oral antibiotic use

681 subjects (82%), which included individuals from both the parenteral antibiotic group and the group that did not receive antibiotics, received oral antibiotics for post-operative prophylaxis. Antibiotics were administered until stent removal, which occurred between 3 and 7 days post-operatively. Antibiotics administered included cephalexin, trimethoprim-sulfamethoxazole, clindamycin, and ciprofloxacin (Table 1).

All 12 patients who experienced a complication received oral antibiotics to be taken at home following surgery. In the group of patients who did not receive oral antibiotic prophylaxis, there were no infectious complications.

Discussion

Antibiotic stewardship to reduce bacterial antibiotic resistance is an area of substantial interest. Antibiotic exposure induces selective pressures on bacterial populations, rendering future generations of bacteria less susceptible to both antibiotics they are exposed to and, possibly, other antibiotics with similar chemical structures [8]. Thus, safely reducing antibiotic use is an important goal in preventing antimicrobial resistance. Antibiotic use also carries risks to patients, as demonstrated by the instance of *C. difficile* in this study. Furthermore, diarrhea resulting from antibiotic exposure may contaminate penile surgical dressings and wounds which could, theoretically, increase the risk of wound complications and UTIs. Additionally, UTIs and SSIs are uncommon after distal hypospadias repair and their prevention likely does not warrant antibiotic use.

To our knowledge this study is the largest retrospective analysis of peri-operative and post-operative antibiotic use in distal hypospadias repair. Our results demonstrate no

advantage of antibiotic use in preventing infectious complications in the setting of distal hypospadias repair. Strengths of this study include the large cohort and the inclusion of cases performed by multiple surgeons. Weaknesses include the retrospective nature of the study and the inconsistent antibiotic prescribing practices with some subjects receiving both peri-operative parenteral and post-operative oral antibiotics, some receiving one of these, and some receiving none. One alternative explanation for the findings is that the treating physician may have had a high clinical suspicion for infectious complications, leading to the utilization of antibiotics given in this study. However, given the high rate of antibiotic utilization, coupled with the routine nature of the cases included in this study, this seems less likely. Another weakness of this study is that records other than subjects' urologic records, such as those of the subjects' primary care physicians, were not reviewed. Thus, UTIs and SSIs diagnosed outside subjects' follow-up visits may have been missed.

Despite extensive study, the use of antibiotics in the setting of pediatric hypospadias repair does not provide a clear benefit. A systematic review and metanalysis concerning 7 studies of 4 cohorts of patients undergoing pediatric distal hypospadias repairs demonstrated no difference in complications in the group receiving post-operative antibiotics compared to those who did not [9]. In this review, there was a higher incidence of asymptomatic bacteriuria when antibiotics were not used, however, this finding may not be clinically significant [9]. A randomized trial demonstrated an equivalent rate of infectious complications in subjects following hypospadias repair whether or not they received antibiotics post-operatively [5]. However, this study was underpowered to detect a difference between the groups and thus its results do not rule out efficacy for prophylaxis in this setting. Another randomized trial comparing PO trimethoprim-sulfamethoxazole prophylaxis following hypospadias repair to no antibiotics in children 6 months to 2 years of age demonstrated no clinically significant UTIs in either group, and no difference in complications between the two groups [10].

The benefit of peri-operative parenteral antibiotics, so common in reconstructive surgery, has rarely been questioned. One retrospective review comparing subjects who received peri-operative antibiotics to those who did not demonstrated no difference in SSI between the groups [4]. Another analysis by the same research group compared subjects who had received either peri-operative antibiotics, post-operative antibiotics, peri- and post-operative antibiotics or neither and found no difference in complications between any of the groups [3]. Additionally, there were no infectious complications in the group of subjects who had neither peri-operative parenteral antibiotics or post-operative oral antibiotic prophylaxis. Thus, parenteral peri-operative and PO post-operative antibiotics may not be beneficial in this population.

Conclusions

The utilization of parenteral peri-operative or post-operative oral antibiotics is not associated with reduced infectious complications following distal hypospadias repair. Thus, antibiotics should be used with caution in this setting, driven by clinical concern for infections, rather than as routine practice.

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Conflicts of interest

KMD owns stock in Merck and Organon&Co. Otherwise we have no conflicts of interest to disclose.

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