Title:
Antibiotic Use Following Distal and Mid-shaft Hypospadias Repair

NCT number: NCT02593903

Date: 12/16/2013

Children's Hospital and Health System™

INSTITUTIONAL REVIEW BOARD SUMMARY

PRINCIPAL INVESTIGATOR: Travis Groth, MD

STUDY TITLE: Prophylactic Antibiotics Following Distal/Mid shaft Hypospadias Repair: Are they necessary?

A. PURPOSE OF THE STUDY

The purpose of this study is to evaluate the efficacy of prophylactic antibiotics following distal/mid-shaft hypospadias repair in influencing the rate of postoperative urinary tract infection and complications.

B. HYPOTHESIS / SPECIFIC AIMS

We hypothesize that the use of prophylactic antibiotics following distal/mid-hypospadias repair will reduce the rate of post-operative urinary tract infection (UTI) when compared to patients not treated with prophylactic antibiotics.

C. BACKGROUND, SIGNIFICANCE, AND RATIONALE

Hypospadias is a congenital abnormality involving the glans, meatus and the penis, and is a common diagnosis encountered by pediatric urologists. Most often hypospadias involves the distal/mid-shaft portion of the urethra, and the only corrective treatment is surgical.

There is no consensus among pediatric urologist regarding the use of postoperative antibiotics.

The rationale for using prophylactic antibiotics is to decrease the occurrence of UTIs and complications. However, even though prophylactic antibiotics are used by some pediatric urologists, to date there has been no evidence supporting the role of prophylactic antibiotics in decreasing UTIs or complications.

Upon reviewing the literature, only one similar study was found by David Ben Meir et al. in 2004, which was a prospective study with 2 groups with and without antibiotic prophylaxis. That study included proximal hypospadias patients, which is much different than distal hypospadias in terms of outcome and complications rate. The study was also underpowered to detect a difference. They concluded that prophylactic antibiotics appeared to decrease complications and urinary tract infections but did not achieve a statistically significant difference.

D. DESIGN AND METHODS

This is a prospective, randomized trial involving children undergoing distal/mid-shaft hypospadias repair, age between 6 months and 2 years. Patients will be randomly assigned to two groups using a randomization method designed by CHW pharmacy; sample size of 80 patients in each group, for a total of 160 participants. Group 1 will receive prophylactic oral antibiotics following the surgery and catheter placement (Septra, 3 mg/kg), and

will continue the medication for 24-hours following catheter removal (4-8 days postoperatively). Group 2 will receive regular clinical care without prophylactic antibiotics, also including catheter placement/removal as above.

The surgical techniques used for repair of mid/distal hypospadias will be based upon individual surgeon's preference. The most frequent repairs are TIP (tabularized incised urethral plate) urethroplasty, Mathieu flip-flap and preputial flap; all of which are all well validated surgical techniques in managing such patients.

Inclusion Criteria:

- all children between ages 6 months to 2 years under going distal/mid shaft hypospadias repair
- children of parents who give informed consent
- English speaking
- participant must be available for follow-up 3 and 12 months post-surgery

Exclusion criteria:

- all proximal hypospadias and redo hypospadias repairs
- children who are allergic to sulfa medications, or are contraindicated for Septra use based on concomitant medications or G6PD deficiency based on pre-operative H&P assessment by surgeon
- patients who have UTI at time of surgery (proven by culture)

Measurements:

Information from patients' medical records will also be collected for this study. This information will be about the hypospadias diagnosis, surgery, and follow-up. Data elements include: weight, age, glanular size at time of surgery, type of repair, location of hypospadias, chordee repair, days to catheter removal, urine analysis and culture results, urinary tract infection symptoms. Data will be collected into a secure RedCap™ database.

We will collect data from two urine samples for urine analysis and culture: one at time of surgery and one at time of catheter removal. These tests are standard of care for all surgical hypospadias patients. Testing will evaluate for bacteruria, pyuria, UTI and complication (fistula, wound infection, meatal stenosis) rates in both groups.

UTI will be diagnosed based on urine culture positive at 50,000CFUs per mL with one or both of the following: fever >38^{o}C, or significant fussiness and irritability with voiding per parent report. Assymptomatic bacteriuria is known and expected in this population; therefore culture positive results alone will not be sufficient to meet the definition of UTI.

Patients in both groups will be followed up for one year following surgery to report and evaluate for postoperative complications via clinic visits already attended for regular standard of care in hypospadias patients.

E. TOTAL NUMBER OF HUMAN RESEARCH PARTICIPANTS PROPOSED FOR THIS STUDY AT THIS SITE AND GLOBALLY. WHAT ARE THESE NUMBERS BASED ON?

This study will include 160 participants; 80 patients in each of two groups. This number is based on current hypospadias rates available in the literature; sample size calculation, power of 0.80, p value of 0.05.

F. DRUGS OR PROCEDURES

Patients will be randomly assigned to two groups: **Group 1** will receive prophylactic oral antibiotics following the surgery and catheter placement (Septra, 3 mg/kg/dose once daily), and will continue the medication for 24-hours following catheter removal (4-8 days postoperatively), and **Group 2** will receive regular clinical care without prophylactic antibiotics, including catheter placement/removal.

Group 1 Study Table

	Visit 1 Screening/ Surgery	Visit 2 4-8 Days Post Surgery	Visit 3 3 months Post Surgery	Visit 4 12 months Post Surgery
Study Explained/Consent	X			
Collect Urine Sample	X	X		
Administer Antibiotic	X	X		
Monitor for Adverse Events at Follow-up Clinic Visit		X	X	X

Group 2 Study Table

	Visit 1 Screening/ Surgery	Visit 2 4-8 Days Post Surgery	Visit 3 3 months Post Surgery	Visit 4 12 months Post Surgery
Study Explained/Consent	X			
Collect Urine Sample	X	X		
Monitor for Adverse Events at Follow-up Clinic Visit		X	X	X

Study drug will be provided through Children's Hospital of Wisconsin research pharmacy.

G. RISK CATEGORY:

(2) 45 CFR 46.405 - Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual child subjects involved in the research.

H. RISKS AND THE PRECAUTIONS WHICH WILL BE TAKEN TO MINIMIZE RISK EXPOSURE

There is always a risk when taking any medication, including Septra, of developing adverse reactions. The adverse reaction incidence is low and usually minor, and may vary from one individual to another. Side effects that may be caused from antibiotics include:

-allergic reaction
-fever
-sore throat
-headache

-skin rash
-easy bruising or bleeding
-cough
-shortness of breath
-diarrhea
-nausea
-vomiting
-photosensitivity

Antibiotics do not guarantee that a child will not develop an infection or complication from this procedure. We will exclude all patients in which use of Septra (Sulfa medication) is contraindicated.

In the event a child needs antibiotics to treat a UTI, he will be given the appropriate treatment regardless which group he is assigned to.

The families are encouraged to report any adverse reaction, regardless of treatment arm. Contact information will be provided at time of informed consent.

I. PROVISION FOR THE PROTECTION OF PRIVACY OF SUBJECTS AND TO MAINTAIN THE CONFIDENTIALITY OF DATA

All research projects that collect electronic data must use appropriate security measures to ensure that data is protected from theft or loss in order to prevent breaches of confidentiality. You must indicate what encryption tools (or why they are not necessary) from the options below. The IRB will not review this protocol unless you indicate the encryption tools being used to secure your research data. If you do not have encryption in place on your systems, please contact your Information Systems support to arrange for one of the encryptions options listed below.

The following encryption products employ cryptographic modules that the National Institute of Standards and Technology has certified as meeting FIPS 140-2 requirements. Children's Hospital and Health System endorsed the use of these products made to encrypt hard drives and removable media. All electronic research data must be encrypted using one or more of these products.

Please indicate which encryption tools you are using to secure your research data.

___Credent Mobile Guardian (RS, PD)
_X_GuardianEdge Hard Disk and GuardianEdge Removable Storage Encryption (HD, RS, PD)
___IronKey encrypted flash drives (RS)
___McAfee Endpoint Encryption (HD, RS)
___Microsoft Bitlocker (HD, RS when used with Windows 7 and FIPS compliant algorithms are enabled)
___PGP Whole Disk Encryption and PGP Portable (HD, RS)
___SafeNet Protect Disk and SafeNet Protect File (HD, RS)
___Seagate Secure Self-Encrypting Drives (HD when encryption option is enabled)
___Symantec Endpoint Encryption (HD, RS, PD)

Does not apply because:
___ Data is de-identified – no PHI collected (please provide detailed information on data elements in your protocol application)
___ Data is stored on paper only
_X_ Data is stored on CHW secured shared drives only.

Key
HD = Hard Drive
RS = Removable Storage (USB flash drive, CD, etc.)
PD = Portable Device (iPod; iPhone; PDA, etc.)

J. PROVISIONS FOR MONITORING DATA TO ENSURE THE SAFETY OF SUBJECTS; AND ADDITIONAL SAFEGUARDS TO PROTECT THE RIGHTS AND WELFARE OF SUBJECTS WHO ARE LIKELY TO BE VULNERABLE

Urine analysis, as part of standard clinical treatment in these patients, will provide the necessary monitoring of patient health during the study. Patients who develop a UTI will be treated with culture based antibiotics. As the use of prophylactic antibiotics varies widely between providers, patients in this study will be exposed to no more or less risk than patients receiving standard medical care.

Weekly study team meetings will take place to review patients' lab values and any other adverse events.

K. ANTICIPATED BENEFITS ASSOCIATED WITH THE PROTOCOL TO HUMAN RESEARCH PARTICIPANTS AND SOCIETY

We expect this study to provide us with answers to the question of whether prophylactic antibiotics will influence outcomes following distal/mid hypospadias repair in children, which is an extremely important issue touching the lives of these children and their families. These results are also immediately applicable to the medical and financial costs associated with postoperative infections and complications.

The information obtained from this study may be useful scientifically and possibly helpful to patients undergoing hypospadias repair in the future. The benefits that may be expected from participating in this study for Group 1 patients are: possible prevention of urinary tract infections and complications following surgery. The possible benefits for Group 2 are: avoiding the use of unnecessary antibiotics and thus the potential risk of exposure to medication which could cause adverse or allergic reactions.

L. STOPPING POINTS THAT WOULD NOT ALLOW THE STUDY TO CONTINUE AS PROPOSED

Participants may be terminated from the study at any point if the PI or regular physician determine that it is unsafe for any reason for that participant to continue. Participants are also free to stop participating at any point during the study.

M. IS THERE A DATA SAFETY MONITORING BOARD IN PLACE? WHO ARE ITS MEMBERS? HOW OFTEN DO THEY MEET?

This study is investigating the efficacy of two standard of care treatments in a randomized fashion. As such, a DSMB is not necessary. Please see Section J for information on data safety monitoring.

N. DESCRIBE HOW THE CONSENT PROCESS WILL TAKE PLACE. INCLUDE A LIST OF APPROPRIATELY TRAINED PERSONNEL WHO WILL BE INVOLVED

The consenting process will be conducted by Dr. Travis Groth or one of the trained research coordinators on the study team. Informed consent will be documented in the patient chart, and all applicable signed documents will be copied and given to the family for their records.

As the population being studied is under 2 years of age, no assent documents will be used for this project.

O. PROCEDURES TO BE EMPLOYED IN ANALYZING DATA AND THE ANTICIPATED SIGNIFICANCE OF THE PROPOSED STUDY

Data will be entered into a RedCap™ database, allowing for menu driven options, built-in checks and generation of reports. Missing data patterns will be examined and where data are missing at random, imputation will be used. We will examine the effect of covariates using logistic regression.

Statistical software employed for data analysis will be: Cytel StatXact, SAS version 9.2, and SPSS Version 19.0. The power calculation was made using PASS 2008.

P. FINANCIAL RELATIONSHIPS

The prophylactic antibiotics for this study are being paid for with money from an internal pediatric urology research fund. The study team is not being reimbursed for their time/effort to run this project. All costs related to regular medical treatment associated with standard of care hypospadias treatment are the sole responsibility of the patient and their family.

Q. ADVERTISEMENTS / FLIERS

NONE

R. BIBLIOGRAPHY

David Ben Meir and Pinhas M. Livne: Is Prophylactic Antimicrobial Treatment Necessary after Hypospadias Repair? J Urol, 171:2621-2622, 2004.