Melissa Laudano
Protocol Submission, ICCR Rotation
August 6, 2007

Antibacterial perineal wash as prophylaxis for recurrent urinary tract infections in a female pediatric population

A. Study Purpose and Rationale

Urinary tract infection is a common problem in the pediatric population affecting up to 7% of girls and 2% of boys by the age of 6 years[1]. For many children, it is not an isolated problem. Prior studies have estimated 6- to 12-month recurrence rates of between 20 to 48%. However, this may overestimate the true rate because the study population included referral populations with multiple previous UTIs or patients from trials in which asymptomatic children were catheterized, which identified some patients who were otherwise asymptomatic[1, 2]. A UTI is defined as bacteriuria in the presence of inflammation. In adults, a culture confirmed UTI is defined as ≥100,000 cfu/mL of uropathogenic bacteria on clean catch specimen. This cutoff has also been used in children and will be the definition of a UTI for the purposes of this study. Although a well-designed prospective study of children with urine samples obtained by catheterization defined lower cutoffs (50,000 cfu/mL),[3] specimens in this study will be clean catch and this cutoff will be ≥100,000 cfu/mL.

Most UTIs in children are monomicrobic and approximately 80% of the cases are caused by *Escherichia coli*. Other bacteria include *Klebsiella, Proteus, Enterobacter, Citrobacter, Staphylococcus saprophyticus, Enterococcus*, and rarely *Staph Aureus*. The vast majority of these infections are spread via an ascending route, traveling up the urethra to the bladder and possibly continuing to the ureters and kidneys. Bacteria attach to the uroepithelial cells in a process mediated by specific bacterial adhesins and epithelial receptors. The pathogenesis of *E.coli*, the most common pathogen has been well defined. *E. coli* have P fimbriae, hair-like appendages on the cell surface which bind to human digalactoside P blood group determinants, which are found on erythrocytes and uroepithelial cells[4]. Fecal matter is one source of *E.coli* found in the perineal region. Contamination of the urinary system with fecal bacteria, such as E.coli, is more common in women given the close proximity of the anus and urethral meatus. Sterilization of the perineal region will eliminate a substantial source of bacteria that go on to cause infection via the ascending pathway.

There are several factors that increase a child's risk of experiencing UTIs, including age, gender, race, familial predisposition, being uncircumcised, dysfunctional elimination, vesicoureteral reflux (VUR), obstruction and sexual activity. The highest prevalence rates of childhood UTI occur in males under the age of one and females under the age of four. Females have a 2 to 4-fold higher prevalence of UTIs than males. For reasons that are not understood, Caucasian children also have a 2 to 4-fold higher prevalence of UTIs when compared to African American children. One controlled trial involving 90 Swiss

girls, found that family history and behavioral abnormalities such as infrequent voiding, poor fluid intake, and functional stool retention was associated with an increased risk of recurrent urinary tract infections[5]. As mentioned above certain receptors on uroepithelial cells make them prone to bacterial adherence may explain part of the genetic component. Additionally, hygiene practices may similarly be a behavior taught by parents. Another risk factor implicated in this study was infrequent voiding, defined as urinating less than 4 times per day, which promotes urine stasis and infection. Several studies have also identified a relationship between UTIs and chronic constipation. One study evaluated the frequency of urinary tract infections in 234 chronic constipated and encopretic children and found UTIs were experienced by 33% of girls and 3% of boys[6]. One final risk factor in the development of childhood UTIs is vesicouretal reflux. In the Swiss study, vesicoureteral reflux was detected in approximately 25% of the 90 Swiss girls with recurrent urinary tract infections[5].

In the past, recurrent UTIs have been treated prophylactically with oral antibiotics. Unfortunately, there are problems with this intervention. First and foremost, there is only weak evidence to support that they prevent UTIs. One review article examined 8 randomized comparisons of different antibiotics, placebo, or no treatment to prevent recurrent UTI. This review found that nitrofurantoin was more effective than trimethoprim for prevention of recurrent UTI, however it was associated with a greater number of side effects whose harmful effects outweigh the prophylactic effects[7]. A recent study in JAMA found that in a large cohort of children aged 6 and younger, there was no association between antimicrobial prophylaxis and risk of recurrent UTI[2]. This study found that exposure to antimicrobial prophylaxis was associated with significantly increased risk of resistant infections[2]. These studies validated previously noted concerns for both parents and physicians that prophylactic oral antibiotics are associated with adverse side effects and increased resistance. Administering antimicrobials topically to the source of infection has promise to provide antibiotic treatment without causing systemic side effects and resistance.

There have been several studies evaluating the use topical antibacterial agents for UTI prophylaxis. One study applied antibacterial ointment to the urethral meatus in females with recurrent UTI, and found that it was not effective in prevention[8]. However this study was conducted in adults who have different risk factors for UTIs, including sexual activity. Additionally, the active agent was hexachlorophene, a bacteriostatic agent with primarily gram-positive action. It is not surprising that this was unsuccessful given that 80% of UTIs are caused by E. coli, which are gram-negative bacteria. The product that we have selected to use in this trial is Provon antibacterial perineal wash, which contains triclosan 0.15% as the active antimicrobial agent. It is a broad-spectrum antimicrobial, acting against bacterial and fungal infections. Its primary mechanism of action is inhibiting bacterial fatty acid synthesis(ref). Triclosan has been used to treat urinary tract pathogens in the literature. One study examined the effect of triclosan on the formation of catheter biofilms and found that it prevented catheter biofilm formation by *Escherichia coli, Klebsiella pneumoniae, Staphylococcus aureus* and *Proteus mirabilis*[9]

B. Study Design and Statistical Analysis

This is a randomized controlled trial designed to assess the efficacy of using an antibacterial perineal wash to significantly reduce the recurrence rate of UTIs in a pediatric population of females who have a history of recurrent urinary tract infections (≥3 culture proven urinary tract infection in one year.) Unfortunately, there is no definition of recurrent UTI confirmed in the literature, but this value was chosen based on the clinical experience of pediatric urology faculty at CPMC. The primary endpoint will be number of culture proven UTIs defined as ≥100,000 cfu/mL of uropathogenic bacteria on a clean catch specimen over a 12-month period. The secondary endpoint will be time (in days) to first recurrence. Other outcomes will include: hospitalizations associated with recurrent UTIs, side effects, and non-adherence to therapy.

Pediatric patients with a history of recurrent UTIs will be randomized to the treatment or control group. Enrolled patients must have had 3 documented, culture proven UTIs in a one-year period. If a patient is symptomatic on presentation, they will receive a urine culture, and if it is positive the patient will be treated with an adequate treatment dose of oral antibiotics. All symptoms must resolve prior to enrollment in either arm of the study. Patients assigned to the treatment group will be instructed to clean (done by participant or guardian depending on participant's age) their perineal area with the antibiotic perineal wash twice daily as instructed in package details. Patients assigned to the treatment and control groups will receive the current standard of care for prevention of UTIs, which consists of patient and parent education about proper wiping and cleansing of the perineal region.

The sample size will be 30 participants in each arm of the trial for an n = 60. This sample size was calculated with a power of 80% and $\alpha = 0.05$. The number of recurrent UTIs experienced over a year period will be documented for each patient. This value will be compared to their prior history of documented UTIs, which must have been obtained in order for them to be enrolled in this study. The difference of these two values will be calculated for each participant and then the mean difference for the treatment and control group will be compared using an unpaired t-test. The sample size was calculated with an estimated standard deviation of 5/4 based on the estimated range of UTI recurrences in one year of 5 included within a 95% confidence interval. The estimated effect of interest would be a difference of 1 UTI. The calculated N=26 in each group, however in planning for a 10-20% dropout rate we plan to enroll 30 patients in each group.

$$N = 1 + 16\,((5/4) / 1)^2 = 26 \quad SD=5/4 \text{ error}=1$$

The control and treatment groups will be stratified by age and prior number of UTIs in a year. There will be two age strata, 3-6 and 7-10. The prior number strata will be divided into a 3-4 recurrence strata and a 5 or greater strata. Patients will be assigned to treatment or control using stratified randomization.

C. Study Procedure

Participants enrolled in the study will be instructed to return to the Pediatric Urology group at Columbia Presbyterian Hospital for evaluation if they experience any symptoms of UTI, such as dysuria, urinary frequency, or hematuria. A clean catch urine sample will be obtained with a value of ≥100,000 cfu/mL defining a positive result. Patients will be instructed not to seek medical care at other centers and follow-up exclusively with our team. However, if this is unavoidable they will be instructed to call the research team and report or send urine culture results, so that the team will be able to document all UTIs experienced by patients in either group.

Confirmed UTIs for any patient enrolled in either arm will be treated with the appropriate course of oral antibiotics. Patients enrolled in the treatment group who experience a UTI will continue twice daily perineal washes in addition to receiving a course of oral antibiotics to treat their culture confirmed UTI. Any culture confirmed UTI that is experienced subsequent to enrollment will be recorded as a recurrence. However, if a child fails treatment and requires a second course of antibiotics this entire incident will be recorded as one recurrence.

The principal investigator or research assistant will contact each participant to for follow-up at 3-month intervals following enrollment. At that time they will be questioned about UTIs diagnosed and treated at outside sites and adverse affects. All enrolled patients will be followed for one year and data will be analyzed at 6 months and 1 year.

If any patients in the treatment arm experience any side effects secondary to the treatment they will be instructed to discontinue use of the product, however the research team will continue to follow them for the duration of the study in an intention to treat analysis.

D. Study Drugs

The product that we have selected to use in this trial is Provon antibacterial perineal wash, which contains triclosan 0.15% as the active antimicrobial agent. It was evaluated by the company for the potential irritation in humans through a 21-day human irritancy assay with delayed challenge. It received an average score of 0.00 (scale 0-4), which indicated a low potential for skin irritation and allergic contact dermatitis. The product was also tested for evaluation of the antimicrobial effectiveness in vitro with a thirty-second exposure kill study. This study results showed that the product achieved >99.999 reduction in a broad range of organisms, including Escherichia coli. Potential health effects listed on the Material Safety Data Sheet by GOJO Industries of the perineal wash include: eye irritation if applied to eyes and upset stomach and nausea (from abnormal entry route).

Triclosan has been used to treat urinary tract pathogens in the literature. One such study examined the effect of triclosan on the formation of catheter biofilms and found that it prevented catheter biofilm formation by Escherichia coli, Klebsiella pneumoniae, Staphylococcus aureus and Proteus mirabilis[9].

E. Study Subjects

Inclusion criteria:

1. Female patients with a documented history of recurrent UTIs (≥3 culture proven urinary tract infection in one year.)
2. Must be asymptomatic (dysuria, hematuria, increased urinary frequency) at the time of enrollment.
3. Age ≥3 and ≤10 years.
4. Must be toilet trained.
5. Must be premenstrual.
6. Must be willing to adhere to the treatment algorithm and follow-up all subsequent urological issues with the study group.

Exclusion criteria:

1. Patients cannot have had an abnormal renal ultrasound or abnormal VCUG study.
2. Patients cannot have been successful treated for recurrent UTIs with timed voiding trials or a bowel regimen.
3. Patients cannot be taking oral antibiotics on a consistent basis.
4. Patients cannot be sexually active.

This study is designed to investigate a possible alternative to the standard of care for treatment of recurrent urinary tract infections in female children, which necessitates the inclusion of minors. In order to protect the children, parents will be taught how to apply the treatment and will be encouraged to do so at their discretion if they feel that their child is not capable of applying it adequately themselves. Both parents and participants in the treatment will be counseled to report any adverse reactions and discontinue use immediately. Only females will be included in this study because they have a higher prevalence of this condition.

F. Recruitment of Subjects

All eligible subjects referred to or being treated at the Department of Pediatric Urology at Columbia University Medical Center who meet the inclusion and exclusion criteria will be offered study participation.

G. Confidentiality of Study Data

Any information obtained during this study will remain confidential. A record of study data will be kept at the CUMC Department of Urology. Personal identifiers will not be listed on study data collected, and instead numerical identifiers will be used. Information obtained from this study and from subjects' medical records may be used for research purposes and published. No patient identification will be released without separate consent, except as specifically required by law.

H. Potential Conflict of Interest

None

I Location of the Study

The study will be conducted in the Department of Pediatric Urology at CPMC.

J. Potential Risks

Potential health effects listed on the Material Safety Data Sheet by GOJO Industries of the perineal wash include: eye irritation if applied to eyes and upset stomach nausea (from abnormal entry route).

K. Potential Benefits

It is possible that patients will benefit directly from this study. All patients will be followed for any recurrence of UTIs and will receive counseling about proper wiping and cleansing practices for the perineal region.

L. Alternative Therapies

An alternative is prophylactic treatment with oral antibiotics, however there is little evidence to support this[7] as described in section A. This alternative has also been associated with increased risk of resistant infections[2]. Alternatives to this study include follow-up and treatment not based on the treatment protocol outlined in this study.

M. Compensation to Subjects

There will be no compensation provided to patients who enroll in this study.
The treatment products in this study will be provided by GOJO Industries. Patients in the control arm will receive standard-of-care treatment that is regularly covered by insurance.

N. Costs to Subjects

The subjects will not incur any additional costs as a result of participating in the study.

O. Minors as Research Subjects

Given the intervention involved in this study, risk can be classified as greater than minimal risk. There is potential benefit to subjects enrolled in this study making this a category 405.

References

1. Winberg, J., Andersen, H. J., Bergstrom, T. et al.: Epidemiology of symptomatic urinary tract infection in childhood. Acta Paediatr Scand Suppl: 1, 1974

2. Conway, P. H., Cnaan, A., Zaoutis, T. et al.: Recurrent urinary tract infections in children: risk factors and association with prophylactic antimicrobials. Jama, 298: 179, 2007

3. Hoberman, A., Wald, E. R., Reynolds, E. A. et al.: Pyuria and bacteriuria in urine specimens obtained by catheter from young children with fever. J Pediatr, 124: 513, 1994

4. Servin, A. L.: Pathogenesis of Afa/Dr diffusely adhering Escherichia coli. Clin Microbiol Rev, 18: 264, 2005

5. Stauffer, C. M., van der Weg, B., Donadini, R. et al.: Family history and behavioral abnormalities in girls with recurrent urinary tract infections: a controlled study. J Urol, 171: 1663, 2004

6. Loening-Baucke, V.: Urinary incontinence and urinary tract infection and their resolution with treatment of chronic constipation of childhood. Pediatrics, 100: 228, 1997

7. Williams, G. J., Wei, L., Lee, A. et al.: Long-term antibiotics for preventing recurrent urinary tract infection in children. Cochrane Database Syst Rev, 3: CD001534, 2006

8. Cass, A. S., Ireland, G. W.: Antibacterial perineal washing for prevention of recurrent urinary tract infections. Urology, 25: 492, 1985

9. Jones, G. L., Muller, C. T., O'Reilly, M. et al.: Effect of triclosan on the development of bacterial biofilms by urinary tract pathogens on urinary catheters. J Antimicrob Chemother, 57: 266, 2006