Trial of Randomized Antibiotic Administration in Percutaneous Nephrolithotomy

Bradley A. Morganstern, David Leavitt, Sammy E. Elsamra David Hoenig, Arthur D. Smith and Zeph Okeke

Smith Institute for Urology, Northwell

New Hyde Park, New York

INTRODUCTION

For large renal stone burdens and/or complex stones, Percutaneous Nephrolithotomy (PCNL) has become the mainstay for treatment, replacing open kidney stone surgery since it's introduction in 1976[1]. However, PCNL is not without its complications, specifically infectious. The procedure carries up to 25% incidence of infectious complications with approximately 1% rate of severe sepsis even with completely sterile conditions[2]. Therefore, the use of antibiotics becomes paramount, but to date there are no PNCL specific guidelines for the appropriate duration and class of antibiotics. This fact leaves the practicing urologists to their own subjective experiences to the guide them. In addition, in an age where there are increasing numbers of resistant microbes the judicious use of antibiotics is in even more paramount[3].

General guidelines by the AUA recommend 24 hours of perioperative antibiotics with the first choice of class being 1st/2nd generation cephalosporins or aminoglycoside + metronidazole or clindamycin and the alternative for allergies being aminoglycoside/ sulbactam or fluoroquinolone[4]. The guidelines also include a clause for extended use of antibiotics if external urinary catheters are in place. Of note, only a few studies have been conducted that help to guide these recommendations and these were carried out with relatively small sample sizes.

In 2002 Dogan et al reported, in a small prospective randomized study (n=81), no difference in infectious complications with the use of a single perioperative dose of ofloxacin versus continued use until the nephrostomy tube was removed[5]. A retrospective match control study in 2012 reported the importance of perioperative antibiotics in reducing the fevers postoperatively (1.9% vs 22.0%, p <0.0001) in patients

who received them versus patients who did not (all patients had negative preoperative urine cultures)[3]. Another randomized prospective study (n=191) concluded no difference in the use of ampicillin-sulbactam versus cefuroxime with a single administration being sufficient[6]. The most recent randomized prospective study (n=73) published this year found no difference in septic complications with a single perioperative dose of ceftriaxone compared to the addition of continued oral 3rd generation cephalosporins[2]. Whereas these studies support the notation that 24 hours of antibiotics may be sufficient in low risk patients undergoing PCNL further, larger studies are needed to establish firm guidelines.

We purpose a randomized intention to treat prospective study to explore the duration and type of antibiotics in a larger population then previously studied. We hypothesize that there will be no difference in complications between two groups: 1) 24 hours of perioperative antibiotics versus 2) Continued antibiotics until the removal of any external catheters. We will model the antibiotics choices and duration after the 2013 AUA Urologic Surgery Antimicrobial Prophylaxis recommendations, modified by our local antibiotogram as necessary. Our objective is to compare the clinical efficacy of a single-day protocol with a short-course protocol for PCNL. Our hope is to reduce the use of possibly unnecessary prolonged antibiotic administration, reduce hospital costs and prevent the further propagation of resistant microbes.

***Primary Objective**:*

To compare the clinical efficacy of a single-dose protocol (antibiotics for 24 hours) with a short-course protocol (antibiotics continued until external catheters are removed) for PCNL.

Patient Recruitment and Randomization

All patients meeting exclusion and inclusion criteria for the study, who require a PCNL for treatment of kidney stone disease will be approached for enrollment in the

study. After informed discussion of the study with potential participants, interested patients will be given a copy of the consent form. The consent form will be reviewed and explained with the potential study subject. All information about the study will be provided. Ample time will be given for individuals to ask questions regarding participation and to have questions answered prior to signing the consent form. If so desired, those interested will be given a copy of the consent form to take home so that they may have the opportunity to discuss participation further with family and/or advisors. If an individual chooses to enroll, the consent form will be signed before the procedure begins. Once an individual joins the study and informed consent is obtained, the subject will receive a signed copy of the consent form. Individuals may chose not to be enrolled in the study or may withdraw from the study at any time without repercussions to subsequent care.

All subjects of childbearing potential who are not surgically sterile will be given a urine pregnancy test during the screening exam.

Patients agreeing to participate in the study will be randomized on the day of surgery. Stratified randomization will be utilized to balance the number of patients between the two groups. Subjects will be randomly assigned by a 1:1 ratio to either:

1. Antibiotics for a period of 24 hours

2. Antibiotics for a period until external catheters are removed

The Biostatistics Unit will develop a randomization procedure using a permuted block design. Details of the procedure, including required record keeping, will be further developed upon approval of this protocol.

Inclusion criteria:

1. Patients $\geq$18 years old.
2. Negative urine culture within 1 month prior to procedure

3. Renal Calculi which would optimally require PCNL for treatment.

Exclusion criteria:

1. Patients <18 years old.
2. Patients who are not able to give consent for study
3. Patients currently on antibiotics immediately prior to the procedure
4. Previous history of sepsis or SIRS from stone manipulations
5. Foley catheter in place for greater than 1 week duration
6. Patients under going planned, multi-staged procedures
7. Immunosuppressed patients
8. Pregnant women (urine HCG obtained at PST)
9. Patients with more than one allergy to antibiotics
10. Patients who are breastfeeding

Intervention

Antibiotics Regiment/External Catheter Procedure

At our institution there has been no standardized utilization of administration of antibiotics and it has been at the discretion of the attending as to the duration. The typical low risk (as defined by inclusion and exclusion criteria) patient would start with perioperative antibiotics within 60 minutes prior to procedure and continued for a duration of 5-7 days. If no signs or symptoms of systemic inflammatory response syndrome (SIRS), as defined as two or more signs including temperature <36°C or >38°C, heart rate >90/min, respiratory rate >20min or PaCO2 <32mmHg, or white blood cell count <4000/mm^3 or >12000/mm^3, or sepsis occurred they may be continued longer.

The protocol would standardize the administration. In regards to the external catheters the usual routine would be continued with urethral foley catheter being removed post-operative day one and the nephrostomy tube being removed post-operative day two if no signs of infection or ureteral obstruction occur (based on clinical signs of flank pain with clamp trial, CT, or nephrostogram).

In accordance with AUA guidelines we use Ancef, a 1st generation cephalosporin, as the primary antibiotics. It would be started within 60 minutes of the procedure. Dosing would be 1 gram IV every 8 hours and would be adjusted for renal dosing as needed: creatinine clearance of 35-54 would be every 8hrs; 11-34 would give on time dose then decrease by 50% and administer every 12 hrs; <10 will give usual one time dose then decrease dose by 50% and administer every 24hrs; if on hemodialysis will supplement 1g at time of dialysis. If the patient has an allergy to penicillin or cephalosporin then Cipro would be used. It would started within 120 minutes of the procedure, as per AUA recommendations, at 400mg IV and would be continued every 12hrs if patient has a normal creatinine clearance. If the creatinine clearance is between 5-29 then the patient would receive 200mg IV every 18 hours and if on dialysis then the patient would get 200mg IV 12 hours after dialysis. Regardless of which antibiotic that is used they would either be discontinued after 24 hours or continued until both external catheters are removed (using the usual timing defined above). If the SIRS or sepsis occurs then the patient would be treated according the clinical indicated or based on the presence of positive blood, urine cultures and the sensitivities. The patient would remain in the study as it is an intention to treat design. With this regiment confounders should be minimal as the majority of patients will be treated with Ancef and the point of antibiotics is preventative since the patients are deemed not infected at the started per exclusion criteria.

Surgical procedure

For patients undergoing PCNL, a temporary retrograde ureteral catheter will be placed with the patient in dorsal lithotomy or prone position (according to surgeon preference). The distal end of the ureteral catheter will be connected to a syringe with

diluted contrast. The patient's initially approached in lithotomy are then repositioned into the prone position with all pressure points well padded, and then re-prepped and draped. The collecting system is then delineated with a retrograde pyelogram via contrast instillation through the previously placed ureteral catheter. The appropriate calyx of entry is the determined, targeted and punctured with an 18 or 21G diamond-tipped needle. Once access to the collecting system is obtained a guide wire is threaded antegrade down the ureter. The percutaneous tract is then dilated with Amplatz dilators or a radial balloon dilator. The working sheath is secured in place over the dilator, and rigid nephroscopy is then commenced. Stones are then removed if small enough, and are fragmented with a lithotripter and removed with a combination of suction and manual extraction. Once all stones are removed, a kidney drain is placed under fluoroscopic guidance. All PCNL procedures will be performed in the standard clinical manner by three fellowship-trained endourologists with high-volume stone practices (Zeph Okeke, David Hoenig and Arthur Smith).

Follow-up

All patients are seen in the office within 30 days post-operative or sooner if clinical indicated (signs of infection after discharge or needs removal of external catheter). Patients are instructed to contact the office if any symptoms of infection occur and will be treated either in an outpatient or inpatient setting as clinical warranted. The research team will carry periodic reviews of both inpatient and outpatient records to tract any complications that occur within 30 days of the procedure.

Outcomes

Primary Outcomes:

- **Postoperative infection**
- **Infection-related events:**
    - **Fever**
    - **Bacteriuria**
    - **Bacteremia**

Secondary Outcomes:

1. **ICU for hypotension postoperatively**
2. **Length of stay (LOS)**
3. **Need for additional lithotripter energy modalities**
4. **Intraoperative complications**
5. **Immediate postoperative complications**
6. **Postoperative complications within 30 days of the procedure**
7. **Stone cultures**
8. **Operative time (duration of the surgical procedure, beginning with percutaneous access and ending with closure of the surgical track)**
9. **Adverse and allergic reactions to antibiotics**
10. **Incidence of *clostridium difficile* infection**
11. **Evidence of Systemic Inflammatory Response Sydrome (SIRS)**

Sample Size Calculation

The proposed sample size for this study is **n=290 subjects** (**n=145 per group**).

As a non-inferiority trial, antibiotics for 24 hours will be considered non-inferior to antibiotics for continued antibiotics if the difference in the rate of fever is less than 5% (δ=margin of inferiority). More formally, let p24 and pC be the rate of fever for antibiotics for 24 hours and antibiotics continued until catheters are removed, respectively. The following are the null hypothesis and alternative hypothesis:

H_0: $d = p24 - pC \geq \delta$ vs.

H_A: $d = p24 - pC < \delta$

Based on estimates from Tuzel et al[2]., the rate of fever using 24 hours of antibiotics = 11% and the rate of fever using antibiotics until external catheters are removed = 16%, and assuming a non-inferiority margin of 5%, a target of 145 subjects

per group (n=290 in total) would yield 80% power to determine that 24 hours of antibiotics is not inferior to continued antibiotics, assuming a 1-sided α-level of 0.05.

Data Analysis

Intention to Treat (ITT):

The primary analyses will be based on the ITT population. The ITT population will be defined as any subject who is randomized, regardless of whether the subject completes the full course of antibiotics.

Statistical Methods:

Descriptive statistics (means ± standard deviations or medians and interquartile range [25th percentile, 75th percentile] for continuous data; frequencies and percentages for categorical data) will be calculated by group (antibiotics for 24 hours or antibiotics until external catheters are removed).

The two-sample t-test or Mann-Whitney test will be used to compare these two groups for continuous variables. The chi-square test or Fisher's exact test, as deemed appropriate, will be used to compare these two groups for categorical outcomes (i.e. fever, bacteriuria, bacteremia, etc.)

LOS and operative time will be analyzed by applying standard methods of survival analysis, i.e., computing the Kaplan-Meier product limit curves, where group will be the stratification variable. [No data will be considered censored.] The two groups will be compared using the log-rank test. The median LOS / operative time and corresponding 95% confidence intervals for each group will be obtained from the Kaplan-Meier Product-Limit Estimates.

A result will be considered statistically significant at the $p<0.05$ level of significance. All analyses will be performed using SAS version 9.3 (SAS Institute, Cary, NC).

Risks

All patients will have the surgery regardless of whether or not they are part of the study and face the same risks associated with the surgery. The AUA recommends using antibiotics and all patients undergoing this surgery will be put on an antibiotic as standard of care. This study is looking to compare the clinical efficacy of a single-day protocol with a short-course protocol for PCNL. Our hope is to reduce the use of possibly unnecessary prolonged antibiotic use, reduce hospital costs and prevent the further propagation of resistant microbes. All serious adverse events and unanticipated problems will be reported in compliance with the NSLIJHS IRB policy.

Some possible serious side effects from antibiotics may include:

- diarrhea that is watery or bloody;
- white patches or sores inside your mouth or on your lips;
- skin rash, bruising, severe tingling, numbness, pain, muscle weakness; fever, swollen glands, body aches, flu symptoms;
- unusual bleeding (nose, mouth, vagina, or rectum), purple or red pinpoint spots under your skin;
- urinating less than usual or not at all;
- seizure (black-out or convulsions);
- or severe skin reaction -- fever, sore throat, swelling in your face or tongue, burning in your eyes, skin pain, followed by a red or purple skin rash that spreads (especially in the face or upper body) and causes blistering and peeling.
- Another type of infection named Clostridium difficile

Less serious side effects may include:

- pain, swelling, or a hard lump where the injection was given;
- stomach pain, nausea, vomiting, loss of appetite;
- skin rash or itching;
- rectal itching; or vaginal itching or discharge.

These side effects are general for all patients who get antibiotics and are very rare. All patients will be monitored for potential side effects.

Data and Safety Monitoring Plans

The principal investigator, Dr Zeph Okeke, is responsible for overall oversight of the data, monitoring the data, assuring protocol compliance, and conducting the safety reviews during quarterly meetings or more frequently if needed. Dr ~~David Leavitt~~Bradley Morganstern will also be responsible for compiling the data sheets, day to day oversight of research and ensuring the integrity and privacy of the data. During the review process the principal investigator, along with the other investigators will evaluate whether the study should continue unchanged, require modification/amendment, or close to enrollment. The principal investigator or the Institutional Review Board (IRB) have the authority to stop or suspend the study or require modifications.

This protocol presents minimal additional risks to the subjects outside of those traditionally associated with PCNL. Adverse events or other problems are not anticipated. In the unlikely event that such events occur, serious and unanticipated and related adverse events or unanticipated problems involving risks to subjects or others will be reported in writing within 48 hours to the IRB and any appropriate funding and regulatory agencies. The investigator will apprise fellow investigators and study personnel of all adverse events that occur during the conduct of this research project via email as they are reviewed by the principal investigator and then discussed as a group during regular quarterly meetings. **Data and safety concerns will be reviewed after every 20 patients and will include the research team and surgeons. Outside of these scheduled meetings, safety concerns can be raised at anytime and by anyone. Serious adverse events will be reported to the IRB.**

The trial will not be registered at Clinicaltrials.gov as this is not an open trial, funded by a government agency, subject to FDA regulation (antibiotics are being used via approved guidelines), nor are the antibiotics being exported for research. This conclusion has been reached but exploring outline of FDAAA801 on provided by Clinicaltrials.gov.

References:

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