A Randomized Trial of Preoperative Prophylactic Antibiotics Prior to Percutaneous Nephrolithotomy: Part I Interval Update

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1. Specific Aims:

To determine the role of prophylactic pre-operative antibiotics prior to percutaneous nephrolithotomy (PCNL) in patients at low to moderate risk for post-surgical infectious complications. This report serves as an update for results of this study as this study is still in data collection stage.

2. Background and Significance:

Percutaneous Nephrolithotomy (PCNL) is a surgical procedure that is the standard of care for the removal of large kidney stones through a temporary tract placed through the patient's back during surgery. The procedure is extremely effective in certain populations, yielding high free stone rates. Although PCNL is less invasive than prior open procedure techniques for the removal of kidney stones, there is a significant risk of urinary tract infection (UTI) after PCNL, with complication rates ranging from 19-49%. Infectious complications are problematic, especially if discordance exists between preoperative bladder urine, renal pelvic, and stone cultures, making the decision for optimal antibiotic prophylaxis unclear. In particular, sepsis has been reported in 0.3% to 7.6% of PCNL cases and is the most common cause of perioperative mortality in patients undergoing PCNL.

Due to the increased risk for UTI, current American Urological Association (AUA) clinical practice statement recommends a perioperative dose of IV antibiotics within 60 minutes of the start of surgery; however, there is wide clinical variation in the use of pre-operative prophylactic antibiotics amongst urologists. Courses ranging from a single dose of perioperative IV antibiotics to extended courses of preoperative prophylactic oral antibiotics in the days to weeks leading up to surgery are being utilized. Prior studies have attempted to define the utility of prophylactic preoperative antibiotics in decreasing the incidence of post-operative infection; however, these have been limited by the exclusion of both the lowest and highest risk patients, or by a lack of randomization.

This study is a multi-institutional, randomized, controlled clinical trial of the use of a 7 day course of Nitrofurantoin monohydrate/macrocrystalline capsules (trade name Macrobid) 100 milligrams (mg) twice daily as a pre-operative prophylactic antibiotic and less than 24 hours perioperative IV antibiotics or less than 24 hours of perioperative IV antibiotics alone in patients who are undergoing PCNL and who are at low risk of infection. The rates of infectious complications following PCNL procedure are measured in both groups. Due to the nature of this study, we anticipate that the results from this study can provide evidence for the guidance of the use of preoperative antibiotic use prior to PCNL procedure in populations with low risk of infection and that the study will provide insight into the utility and safety of future studies in other populations.

3. Research Design and Methods:

3.1 Study Design

We performed a multi-institutional, prospective, randomized, controlled clinical trial investigating the use of preoperative prophylactic antibiotics in patients to receive PCNL surgery for the treatment of nephrolithiasis in decreasing risk of post-operative sepsis. The intervention arm was defined as patients receiving a 7 day course of Nitrofurantoin monohydrate/macrocrystalline capsules (trade name Macrobid) 100 milligrams (mg) twice daily pre-operative prophylactic antibiotic with final day of Macrobid course being 1 day prior to scheduled PCNL surgery and AUA recommended ≤24 hours perioperative intravenous (IV) ampicillin (2g) and IV gentamycin (5mg/kg) within 60 minutes prior to surgery start time. The control arm was defined as patients receiving AUA recommended ≤24 hours perioperative IV ampicillin (2g) and IV gentamicin (5mg/kg) within 60 minutes prior to PCNL surgery start time. In both the intervention arm (Macrobid + perioperative antibiotics) and the control arm (perioperative antibiotics only), patients

with a penicillin allergy received IV vancomycin (1g) instead of ampicillin and patients with aminoglycoside allergy received IV ceftriaxone (2g) instead of gentamycin.

A goal of 10 patients per participating academic medical institution (total n of 80 patients) were to be identified in each clinic by a urologist as patients who were already scheduled to have the PCNL procedure for the treatment of known nephrolithiasis. The participating institutions are academic medical centers in the United States and Canada that are part of the Endourologic Disease Group of Excellence (EDGE) research consortium, a research collaborative that has the goal of producing high quality, multi-institutional studies pertaining to the treatment of nephrolithiasis and include University of California San Diego (UCSD), Mayo Clinic Scottsdale, Mayo Clinic Rochester, Vanderbilt, Dartmouth University, Cleveland Clinic, Methodist Hospital Indiana University, and University of British Columbia. Each participating group obtained IRB approval from the IRB board at their respective institutions.

Patients were identified based on hospital admission or clinic visits at respective institutions and were counseled on standard treatment options for nephrolithiasis: extracorporeal shock wave lithotripsy (ESWL), percutaneous nephrolithotomy (PCNL), or ureteroscopy (URS), as well as expected routine post-surgical care. Medical records were not used as a method to identify potential candidates for study. Patients consenting for PCNL were considered for enrollment in the study if patients met inclusion criteria (for further detail of criteria, please refer to “Patient inclusion” section of this paper) and data was collected prospectively. Patients were consented prior to prescription of antibiotics and to PCNL procedure. After informed consent and prior to PCNL procedure, patients submitted urine analysis (UA), Complete Blood Count (CBC), metabolic chemistry panel (Chem7), urine culture (UCx), and abdominal pelvic computed tomography (CT) to determine pre-operative stone size, surgical planning, and for evaluation of renal and general physical health. If the patient did not consent to the study, he or she still underwent PCNL with preoperative antibiotics based on the routine clinical practice of the treating urologist at the participating institution.

Peri-operative and intra-operative data obtained and recorded are detailed under “Study assessments” section. Data collection and storage are further detailed under “Data Collection and Storage” section.

End points evaluated in this study include primary outcome of rate of postoperative sepsis in intervention arm and control arm. Sepsis is defined by the 2012 International Guidelines for the Management of Severe Sepsis and Septic Shock where 2 or more of the following variables are present and temporally associated:

- Temp >38.3C or <36C
- Heart Rate >90/min (at least 12 hours after surgery)
- Respiratory rate >20/min (at least 12 hours after surgery)
- Altered mental status: defined as lack of orientation to either name, place, or time/date
- Systolic Blood Pressure (SBP) <90mmHg, Mean Arterial Pressure <70mmHg, or SBP decrease >40mmHg in adults
- WBC >12000 or <4000

Secondary outcomes include the rate of nonseptic bacteriuria, stone-free rate, and length of hospital stay (LOS).

3.2 Patient inclusion

Inclusion criteria included men and women of all ethnicities, age ≥ 18 years, and PCNL being the agreed treatment for nephrolithiasis of the patient.

Exclusion criteria included eGFR <60mL/min/1.73 m^2, cirrhosis and/or hepatitis, pregnancy, positive preoperative urine culture within 2 weeks of initial evaluation for PCNL procedure, history of ≥ 38.3C fever associated with nephrolithiasis and/or sepsis thought to be due to urinary source within 12 months prior to current PCNL procedure, internalized ureteral stent, nephrostomy tube and/or nephroureteral stent prior to PCNL procedure, antibiotic use within 2 weeks

prior to randomization, and severe hydronephrosis (defined by ≥ 2 cm in the largest dimension) preoperatively as evaluated on CT scan, abdominal X-ray and/or renal ultrasonography. If patients met this any part of this exclusion criteria, the subject was considered to be of “high risk” for post-operative sepsis and was excluded from the study.

3.3 Study arm assignment

Patients were assigned treatment based on predetermined allocation sequence per computerized random number generator. Patients were stratified by institution in permuted blocks of varying size. Only UCSD study staff had access to the full allocation sequence during the duration of the study. No clinical staff involved in the recruiting and consenting of patients for the study at each participating institutions had knowledge of allocation sequence at their respective institutions.

3.4 Study assessments

Pre-operative CBC, Chem7, UA, UCx, and CT were obtained. PCNL was performed on all patients according to standard of care. Percutaneous access to the kidney was obtained either by Interventional Radiology or by the operating surgeon. Urine from the renal pelvis, urine from the bladder, and the stone itself were sent for culture and analysis at the time of surgery. Placement of renal drainage devices (ureteral stents, nephroureteral stents, nephrostomy tubes) were left up to the discretion of surgeon at each institution.

Post-operatively, the patients were admitted to the hospital or discharged home and post-operative CBC and Chem7 were obtained. Further laboratory tests were dictated by patients’ clinical status as per standard of care. For example, if patients exhibited signs of sepsis as defined by 2012 International Guidelines for Management of Severe Sepsis and Septic Shock (as described in section 3.1 “Study design”), further urine culture, blood culture and serum lactate will be obtained.

Patients were discharged from the hospital and underwent a follow-up non-contrast CT abdomen/pelvis, an abdominal plain radiograph and/or a renal ultrasound within 1-12 weeks after surgery and were seen in clinic for follow-up evaluation of stone burden and to review potential complications of their PCNL procedure.

3.5 Data collection and storage:

Data collection was obtained from Electronic Medical Records and/or Paper Medical Records at each participating institution upon enrollment of the patient. Demographic fields obtained preoperatively included age, race, gender, American Society of Anesthesiologists (ASA) score, body mass index (BMI), and history of prior stone disease. Disease fields included stone size (maximal axial and coronal dimensions), degree of hydronephrosis (mild/moderate/severe), and history of diabetes mellitus, cardiac disease, hypertension, prior urinary tract infection (UTI), bowel diversion or neurogenic bladder.

Perioperative fields included OR (surgical) time, type of anesthesia, number of access tracts, use of internalized ureteral stent, nephrostomy tube, or nephroureteral stent, estimated blood loss, and intraoperative complications.

Postoperative fields included postoperative maximum body temperature, heart rate, respiratory rate, respiratory rate, urine culture results, stone culture results, stone composition, white blood cell count, serum lactate, postoperative serum creatinine, need for admission to intensive care unit, hospital length of stay (LOS), and stone-free status at 1-12 week postoperative imaging. Patients were followed during routine clinical visits as part of their continuing care.

Data collected from each participating site was entered into a designated Research Electronic Data Capture (REDCap) Database, which is password protected with access rights restricted to lead investigator or their team (in our study, the lead investigating team was UCSD). This database is kept on a secure institutional server, allowing the study staff from participating sites to contribute. The research coordinator at each institution performed data entry. All patient specific information was de-identified and data collectors were blinded from treatment allocation.

4. Results:

All statistical analysis was conducted using STATA computer program with appropriate t-tests and chi-squared analysis conducted for continuous and categorical variables, respectively. Data was analyzed using 2-sided p values with statistical significance set at $p \leq 0.05$.

A total of 67 patients were enrolled for this study with 33 subjects randomized to intervention arm and 34 subjects randomized to control arm. In both arms, the patients were primarily white (intervention arm rate of 81.8% and control arm rate of 91.2%) and male (intervention arm rate of 57.6% and control arm rate of 64.7%). Mean BMI of patients in the intervention arm was 29.8 (Std. Dev = 6.99) and was 31.0 (Std. Dev = 9.49) in the control arm. The most frequently reported comorbidity in both groups was hypertension (frequency of 50.0%). Mean Charlson Comorbidity Index, a measurement used to predict the one-year mortality for a patient who may have comorbid conditions, was less than 1 in both groups. Summary statistics regarding demographics of the patients can be found in Table 1.

Mean axial and longitudinal stone diameters in the intervention arm were 18.9mm and 19.6mm, respectively. Mean axial and longitudinal stone diameters in the control arm were 19.6mm and 20.4mm, respectively. Patients who demonstrated complete or partial staghorn calculi, which refers to a branched kidney stone occupying much of the collecting system, was 34.3% and 36.4% in the intervention and control arms, respectively. Patients in both arms most frequently had one kidney stone on imaging (45.5% in the intervention arm and 38.2% in the control arm). 65.6% of patients in the intervention arm and 73.5% of patients in the control arm received perioperative IV ampicillin as one of their two antibiotics while 26 of 33 patients of the patients in the intervention arm and 30 of 34 patients in the control arm received IV gentamycin as one of their two perioperative antibiotics. Target stone characteristics, including mean dimensions of target stone and rate of partial or complete hydronephrosis, per study arm with associated summary statistics can be found in Table 2. Intraoperative data for each arm with associated p values and 95% CI can be found in Table 2.

Primary and secondary outcomes can be found in Table 3. The primary outcome of this study was the rate of postoperative sepsis (for information on criteria for definition of sepsis, refer to “3.1 Study Design”). The frequency of postoperative sepsis was 5 patients in the intervention arm and 6 patients in the control arm. A Chi-squared test was performed and showed no relationship between the intervention and control arms and the frequency of sepsis, X^2 (2, n=67) = 0.05, p value = 0.83. Secondary outcomes included the rate of nonseptic bacteriuria, stone-free rate upon follow-up, and LOS. Non-septic bacteriuria is defined as a positive post-operative urine culture without signs of sepsis in the subject. Stone-free rate is defined as imaging obtained from one to twelve weeks postoperatively that does show radiologic evidence of remaining nephrolithiasis. LOS refers to the number of days patient was admitted for observation and/or treatment during the post-operative period with day 1 referring to 24 hours after surgery. Of note, there was no significant relationship found between arm assignment and the frequency of nonseptic bacteriuria [X^2(2, n = 67) = 2.12, p = 0.145] and there was no statistically significant relationship between arm assignment and stonefree rate [X^2(2, n=67) = 0.29, p = 0.59].

The LOS mean in the intervention arm was 1.1 days and was 1.5 days in the control group. Patients in the intervention arm were more likely to have a 0.5 day shorter LOS compared to the control group, p=0.04 (95% CI: -0.92, -0.14). However, when controlling for patients meeting sepsis criteria (met sepsis criteria refers to the patient having at least two of the variables, as defined by 2012 International Guidelines for the Management of Severe Sepsis and Septic Shock, that are temporarily associated) using regression model, the difference of 0.5 days in LOS between the two arms is not statistically significant, p value = 0.050 (95% CI: -0.92, 0.00). Results from statistical analysis of data regarding the LOS prior to controlling for sepsis and after controlling for sepsis can be found in Table 3.

Table 1
Demographics and Baseline Characteristics (Total n = 67)

	Intervention Arm (n=33)	Control Arm (n=34)
Sex Frequency (percent) Male Female	 19 (57.6) 14 (42.4)	 22 (64.7) 12 (35.3)
Ethnicity Frequency (percent) Asian Hispanic or Latino White Other	 2 (6.1) 1 (3.0) 27 (81.8) 3 (9.1)	 2 (5.9) 1 (2.9) 31 (91.2) ---
BMI Mean (Std.Dev)	29.8 (6.99)	31.0 (9.49)
Comorbidities Frequency (percent) Diabetes Mellitus Hypertension Coronary Artery Disease Immunocompromised	 8 (24.2) 16 (50.0) 1 (3.0) 3 (9.4)	 7 (20.6) 16 (50.0) 3 (8.8) 2 (5.9)
Charlson Comorbidity Index Mean (Std. Dev) Min, Max Std. Error (95% CI)	 0.5 (0.79) 0, 3 0.14 (0.17, 0.74)	 0.6 (1.08) 0, 4 0.19 (0.25, 1.02)
History of Nephrolithiasis Frequency (Percent)	19 (57.6)	24 (70.6)

Table 2
Target Stone Characteristics and Intraoperative Data (n=67)

	Intervention Arm (n=33)	Control Arm (n=34)
Max axial stone diameter (mm) Mean (Std. Dev) Min, Max	 18.9 (11.66) 5.1, 65.4	 19.6 (12.02) 1.6, 55.7
Max longitudinal stone diameter (mm) Mean (Std. Dev) Min, Max	 19.6 (11.14) 3.5, 54.3	 20.4 (12.46) 1.6, 63.7
Complete or Partial Staghorn Calculi Frequency (percent)	11 (34.4)	12 (36.4)

Number of Stones Found on Pre-operative Imaging Frequency (Percent) 1 2 3 4 5 6 7 8 9 ≥10	 15 (45.5) 4 (12.1) 6 (18.2) 3 (9.1) 1 (3.0) 2 (6.1) ---- ---- 1 (3.0) 1 (3.0)	 13 (38.2) 9 (26.5) 8 (23.5) 1 (2.9) ---- ---- ---- 1 (2.9) ---- 2 (5.9)
Type of IV Perioperative Antibiotic 1 Frequency (Percent) Ampicillin Vancomycin Other	 21 (65.6) 7 (21.9) 4 (12.5)	 25 (73.5) 4 (11.8) 5 (14.7)
Type of IV Perioperative Antibiotic 2 if given Frequency (Percent) Gentamycin	 26 (100)	 30 (100)

Table 3
Primary and Secondary Outcome Data (n=67)

	Intervention Arm (n=33)	Control Arm (n=34)	p-value (95% CI)
Met Sepsis Criteria Frequency (%)	5 (15.6)	6 (17.7)	0.83
Non-septic Bacteruria Frequency (%)	2 (6.1)	0 (0)	0.15
Length of Stay (LOS) Frequency (%) 0 day (same day discharge) 1 day 2 days 3 days 4 days 5 days 6 days	 6 (18.2) 19 (57.6) 8 (24.2) ---- ---- ---- ---- 	 2 (5.9) 20 (58.8) 8 (23.5) 2 (5.9) 1 (2.9) ---- 1 (2.9)	0.04 (-0.92, -0.14)
LOS Mean (Std. Dev)	1.1 (0.66)	1.5 (0.19)	
LOS (days) controlling for met sepsis criteria	----		0.05 (-0.92, 0.00)
Stone Free Rate Frequency (%)	18 (60.0)	20(66.7)	0.59

5. Discussion and Conclusions:

Although the AUA guidelines for standard of care of PCNL includes one dose of perioperative IV antibiotics on day of surgery to decrease rate of postoperative sepsis in subjects, the role of a prolonged pre-operative prophylactic antibiotic course in decreasing risk of sepsis is still to be determined. The mortality rate of severe sepsis due to any cause is 20% to 42%, with 5-7% of cases having an identified urinary source. With the rate of urosepsis having previously been reported to occur in 0.9% to 4.7% of PCNL procedures, the need for data indicating the impact of preoperative prophylactic antibiotics on decreasing this risk in a low risk patient population can impact guidelines for standard of care.

Data from this multi-institutional, randomized, controlled trial indicates no difference between patients who received a 7 day course of Macrobid in addition to perioperative IV antibiotics and patients who received perioperative IV antibiotics alone in the rate of sepsis ($p = 0.83$). This suggests that prolonged pre-operative prophylactic antibiotics do not reduce the rate of post-operative sepsis following PCNL in low risk populations.

In addition, difference in stone-free rate one to twelve weeks post-operatively was not statistically significant in the intervention arm compared to the control arm ($p = 0.59$). There was also no statistically significant difference between the rate of non-septic bacteriuria between the intervention arm and control arm ($p = 0.145$).

Interestingly, LOS between the intervention and control arm was found to be statistically significant ($p = 0.04$, 95% CI: 0.92, -0.14) where patients in the intervention arm were hospitalized for 0.46 days less than patients in the control arm. It is important to note that this difference is no longer statistically significant when controlling for the met sepsis criteria variable ($p = 0.050$, 95% CI: -0.92, 0.00). The met sepsis criteria variable was defined as the patient having at least two of the variables defined by the 2012 International Guidelines for the Management of Severe Sepsis and Septic Shock at the same time point (for further information regarding these variables, refer to section 3.1 “Study Design”). Length of stay is dictated by the stability of the patient upon completion of surgery with patients being discharged if they are able to have stable vital signs at home, do not meet sepsis criteria, and do not have a post-operative complication that does not need medical intervention at a medical facility. Therefore, patients are hospitalized for a variety of reasons post-operatively, including if they were septic. It is important to note that 15.63% of patients in the intervention group and 17.65% of patients in the control group truly met sepsis criteria as defined by the 2012 International Guidelines for the Management of Severe Sepsis and Septic Shock. Therefore, individuals who were hospitalized longer than day 0 could have had other complications from surgery that impacted their overall length of stay.

Oral prophylactic antibiotic courses are not completely benign events. Side effects of antibiotics must be taken into effect and weighed against the potential benefit of preventing sepsis or infection postoperatively. Side effects of Macrobid range from diarrhea, nausea/vomiting, and headache to chest pain, anaphylaxis, hepatic injury, and Steven Johnson’s Syndrome. Case reports have also indicated chronic hepatitis resulting from long-term Macrobid use, although this complication appears to be incredibly rare. In addition, as rates of bacterial resistance to oral antibiotics increases, practitioners are more hesitant to prescribe antibiotics solely for the prevention of infection in low risk populations without a truly understood benefit. Therefore, prescribing a prophylactic pre-operative course of antibiotics that has no true impact on decreasing the risk of post-operative sepsis in low risk patients could cause harm.

Although sepsis has been defined by factors identified in the 2012 International Guidelines for the Management of Severe Sepsis and Septic Shock, there are other signs of sepsis that are not identified by these guidelines that could lead to diagnosis of sepsis. It is important to be able to recognize sepsis in aging patients as the mortality from sepsis has been reported as 2 times greater in older adults compared to the general population. A case report by Nag DS describes delirium in a patient as the main presenting symptom of post-operative sepsis after nephrolithotomy, as the patient did not otherwise meet the 2012 International Guidelines criteria for sepsis. Several patients in our study were found to have changed mentation post-operatively and were treated accordingly; however, they never met sepsis criteria, as defined by meeting at least 2 of the variables defined by the 2012 International Guidelines for the Management of Severe Sepsis and Septic Shock, throughout their hospital stay. These patients met one of the variables at any given time; however, they did not have at least 2 variables that were temporally associated in order to qualify as meeting sepsis criteria. Expanding upon the criteria for sepsis in populations with a higher mortality from sepsis could allow for increased rate of identification of true sepsis followed by earlier treatment.

With globally accepted sepsis mortality rates reported as high as 42% and the rate of post-operative sepsis following PCNL cases reported commonly as 1%, studies that indicate true impact of pre-operative antibiotics have been desired. Prior studies attempting to answer this question have been limited by methodological weakness that threaten the internal validity-- such as lack of heterogenous populations, absence of randomization, no evidence of allocation concealment, or unconventional sepsis definitions. Preliminary results from this multi-institutional, randomized, controlled clinical trial indicate that there could be no true benefit from prophylactic pre-operative antibiotics in decreasing the rate of post-operative sepsis following PCNL in patients with low risk of sepsis. Future expansion on this study to understand how prophylactic pre-operative antibiotics in patients at high risk of post-operative sepsis following PCNL could produce further understanding of the utility of these antibiotics in other populations.

This preliminary evaluation of the data obtained at this time from this clinical trial is primarily meant to fulfill the UCSD Independent Study Project (ISP) guidelines put forth by UCSD School of Medicine that need to be completed prior to a medical student’s graduation. The conclusions obtained from this data are preliminary and benefit from additional evaluation once this project is successfully completed. Therefore, further evaluation of the complete data set, once

available, will provide more insight to the impact of pre-operative antibiotics in the prophylaxis of sepsis prior to PCNL in a low risk population.

6. References:

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