A Randomized Trial of Preoperative Prophylactic Antibiotics Prior to Kidney Stone Surgery (Percutaneous Nephrolithotomy [PCNL])

NCT #02384200

Document Date - July 3, 2016

This study will be a multi-institutional randomized, controlled clinical trial of a course of a 1 week course of preoperative nitrofurantoin monohydrate/macrocrystalline capsules (trade name Macrobid) 100 milligrams twice daily leading up to PCNL. The control group will be no preoperative oral antibiotics. The participating institutions are academic medical centers in the United States and Canada that are part of the EDGE (Endourologic Disease Group of Excellence) research consortium, a research collaborative that has the goal of producing high quality, multi-institutional studies of nephrolithiasis. Separate IRB approvals will be obtained at each institution. UCSD will be the coordinating institution. Member institutions of EDGE maintain frequent email contact with one another and hold a monthly teleconference to discuss safety updates, interim results, issues with accrual, and modifications to research protocols and consents (if necessary).

Treatment Assignment:
Patients will be assigned to control or intervention arm based on a predetermined allocation sequence that will be generated by a computerized random number generator. Patients will be stratified by institution in permuted blocks of varying size. Only study staff at the coordinating institution (UCSD) will have access to the full allocation sequence. i.e. no clinical staff involved in recruiting and consenting patients for the study at UCSD or other participating institutions will have knowledge of the allocation sequence at their institution prior to enrollment of each patient. To further aid allocation concealment, the block size will be varied.

Standard of care procedures:
Patients will be identified based on clinic visits or hospital admission. All patients will be counseled on standard treatment options— extracorporeal shock wave lithotripsy (ESWL), percutaneous nephrolithotomy (PCNL) and ureteroscopy (URS). The discussion regarding treatment options and subsequent care will not deviate from routine care. Patients consenting for PCNL will be considered for enrollment into the study and will be enrolled to have data collected prospectively. Patients will be consented prior to prescription of antibiotics and to the surgery for collection of demographics, disease, perioperative, and postoperative data. Abdominal pelvic computed tomography (CT), if not already obtained, will be used to delineate pre-operative stone size and for preoperative planning. If the patient does not consent to the study the use of antibiotics will be based on the routine clinical practice of the treating urologist. Both prophylaxis with preoperative antibiotics and no prophylaxis (i.e. periprocedural only) are considered standard of care and this study will examine the difference between these two common practices.

Investigational portion of treatment:
Patients randomized to the intervention arm will be prescribed nitrofurantoin monohydrate/macrocrystalline 100 mg twice daily for 7 days prior to PCNL with the final day of prophylactic course being 1 day prior to surgery. Nitrofurantoin monohydrate/macrocrystalline is currently indicated for the treatment of acute uncomplicated urinary tract infections. Antibiotics the day of surgery will be a dose of ampicillin IV (2 g) and gentamicin IV (5 mg/kg) within 120 minutes of surgery start time. Patients with penicillin allergy will receive vancomycin IV (1 g) instead of ampicillin and patients with gentamicin/aminoglycoside allergy will receive ceftriaxone IV (2 g) instead of gentamicin. Postoperative antibiotics in the absence of infection will be <24 hours of IV antibiotics. Control patients will receive perioperative ampicillin IV (2 g) and gentamicin IV (5 mg/kg) (or vancomycin(1 g) /ceftriaxone (2 g), if indicated) as in the intervention arm, but control patients will not be prescribed a course of preoperative oral antibiotics. Central randomization will take place with UCSD as the lead site. Randomization will occur in block randomization in block sizes of 4.

Standard of care procedures
Patients will have PCNL performed in standard fashion, without deviation from standard of care. Per the usual practice of the treating surgeon, percutaneous access into the kidney will be obtained either by

Interventional Radiology or by the operating surgeon. At time of surgery, urine from the renal pelvis, urine from the bladder, and the stone itself will be sent for culture. Placement of renal drainage devices (ureteral stents, nephrostomy tubes, nephroureteral stents) will be left up to the discretion of the surgeon. Post-operatively, the patients will be admitted to the hospital and monitored per usual clinical procedure. Pre-operative CBC, basic metabolic panel (chem 7) as well as Postoperative day 1, a CBC, basic metabolic panel (chem 7). further laboratory tests will be dictated by the patients' clinical status as per the standard of care—i.e. for patients that exhibit signs of sepsis such as tachycardia (>90/min), low systolic blood pressure (<90 mmHg), fever >38.3C, hypothermia <36C, altered mental status, respiratory rate>20 min or leukocytosis >12000 or leukopenia (<4000), further urine culture, blood culture and serum lactate will be obtained (as per standard of care).

The patient will be discharged from the hospital per the usual clinical protocols. Post-discharge the patient will be seen in clinic 1-12 weeks after surgery. Patients will undergo a non-contrast CT abdomen/pelvis, an abdominal plain radiograph, and/or a renal ultrasound during this postoperative period.

Demographic fields that will be obtained preoperatively include age, race, gender, ASA (American Society of Anesthesiologists) score (for comorbidity assessment), body mass index (BMI), and prior stone disease. Disease fields that will be obtained include stone size (maximal axial and coronal dimensions), degree of hydronephrosis (mild/moderate/severe), and history of diabetes mellitus, history of cardiac disease, hypertension, prior urinary tract infection, history of bowel diversion, or neurogenic bladder.

Perioperative fields will include 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 will include postoperative maximum body temperature, heart 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 weeks postoperative imaging. Patients will be followed during routine clinical visits as part of their continuing care.

b. Data Collection

Data will be collected by each participating site and entered into a designated and shared REDCap (Research Electronic Data Capture) database. All patient specific information will be de-identified and the database will be password protected with access rights restricted to the lead investigator or their team at each site. Data collectors will be blinded from treatment allocation.

c. Data Handling

The electronic data will be stored in the external REDCap database. This database will be saved at a separate server that allows the study staff from non-UCSD sites to contribute their database. Study staff will create the database and is responsible for analyzing the study data. The coordinator at each site will perform data entry.

d. Data Analysis

The summary statistics will be used to describe the data. Mean/95% confidence intervals will be reported for continuous variables, and frequency/percentage will be reported for nominal variables. The primary outcome, rate of postoperative sepsis, and the corresponding 95% confidence interval (CI) will be reported, and compared between the intervention and control groups at the for the postoperative period using a Chi-squared test. Secondary outcomes will include rate of nonseptic bacteruria, stone-free rate, and LOS and will be compared with using Chi-squared tests or t-test as indicated. The patient characteristics and outcomes between those who have one-year follow up records and those who do not will also be investigated. Using 2-sided P values, statistical significance will be set at $p \leq 0.05$.

Sepsis will be defined by the 2012 International Guidelines for Management of Severe Sepsis and Septic Shock where 2 or more of the following variables are present and temporally associated

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

e. Feasibility and Time Frame

This study enrollment period will be 2 years, with presumed enrollment expected to be completed prior to that date. Each site is a high-volume stone center that performs more than 30 PCNLs per year.

f. Strengths

This study is unique in that it randomizes patients at low to moderate risk of postoperative infection and it uses the most updated definition of sepsis as the primary outcome. The limitations of previous studies have been a lack of randomization, exclusion of patients at moderate-high risk of infection, and less contemporary definitions of sepsis. It aims to answer very important and relevant questions as it pertains both to the surgical management of kidney stone disease and to the prophylactic use of preoperative antibiotics in patients with an increased risk of infection. It will also represent a broad geographic distribution of patients from the US and Canada due to the location of the participating sites.

g. Limitations

The inclusion of a placebo pill would strengthen the study but was not able to be included due to logistical difficulties with obtaining a placebo of identical appearance that would have been adequate for blinding. Furthermore, there is little benefit of a “placebo effect” for the objective outcomes that we seek to study which are signs and symptoms of sepsis and septic shock.