Reducing Urinary Tract Infection Rates using a Controlled Aseptic Protocol for Catheter Insertion
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I. Hypotheses and Specific Aims: Urinary Tract Infection (UTI) complications following catheter use in surgical patients remains high. Using an aseptic protocol has been shown to drastically reduce UTI incidence by 50%. [2] Reducing UTIs will prevent extended hospital stays, readmission, and antibiotic use associated with this complication and improve cost-effectiveness of care. We hypothesize that we can reduce the incidence of UTIs after catheter placement with the implementation of a QI protocol to prevent excess exposure to the environment exposure of the catheter before, during and after insertion.

II. Background and Significance:

Infections resulting from health-care complications are the greatest cause of morbidity and mortality in hospitalized patients in the US. [1] Urinary tract infection (UTI) is the most common health care complication following surgery. [2] Rates are high, causing longer hospital stays, readmissions, and antibiotic use. Rates at UCH are near 40%, high compared to the national standard. About 15% of post-op complications result in extended stays or readmissions and costly antibiotic treatments. These infections should be preventable with prophylaxis and pre-treatment protocols but there is no standard protocol at UCH for minimizing the risk of UTI infection. We propose a catheter management protocol in which the catheters are treated with betadine and then inserted while remaining protected within the plastic sleeve, reducing airborne/contact exposures to the catheter. Betadine is a topical antiseptic used in the prevention of infections. It is widely available and a cost-effective intervention. Similar aseptic protocols have been tested and implemented in other countries however we lag behind in having a systematic protocol for reducing the incidence of UTIs complications.[2-4] A study in rural-India found that antiseptic techniques were the best preventable measure for device-related infections.[5] Patients currently receive what will be considered standard of care intra-operative catheter placement which involves placement of catheter in a sterile field, drainage to a closed system and shortest possible duration of catheter placement. We hypothesize that the implementation of a controlled antiseptic protocol to inserting the urinary catheter will reduce UTI rates following surgery.

III. Preliminary Studies/Progress Report:

The Gynecologic Oncology service performs between 15-20 surgeries per week. There are 5 providers who would require training in the protocol. The providers all have similar practice patterns as they pertain to current standard of care catheter placement. Training would be relatively straight forward and protocol adherence is expected to be high. Adherence can be monitored on the service by the principle investigator. Faculty Mentors include Dr. Guntupalli who is an assistant professor in the department of Obstetrics and Gynecology at the UCH. He serves as the Principal Investigator for the Gynecologic Oncology Group, a national research consortium. His research has focused on all gynecologic cancer sites and surgical improvements.

IV. Project Design and Procedures.

a. **Performance Measurement.** The primary outcome is UTI within 14 +/- 2 days post-surgery. A UTI is defined as an infection in any part of your urinary system which may include the kidneys, ureters, bladder, and urethra. Most infections involve the lower urinary tract (bladder and urethra), and are treatable with antibiotics. If a UTI spreads to the kidney, it can become a more serious complication. Women are at a greater risk of developing a UTI than men are.
   Pre-operative antibiotics will be collected to determine if this directly affects the outcome of a UTI. Visits to the ED for urinary pain, incontinence, or fever will also be followed for determination of UTI. Participants will provide a urine sample 0-24 hours before surgery. The sample will be tested with a rapid urine analysis (UA) test. This measure was chosen so that study UAs results are not to be confused with standard UAs conducted with samples collected after catheter placement. Participants will be followed up by research staff ~24 hours post-surgery for a second UA test. A third UA will be conducted at the patients' post-op check. At follow-up visits, participants will also

be assessed for symptoms of UTI since surgery by assessment of: urethral discomfort, suprapubic tenderness or pelvic pain, sense of urinary urgency, frequency or dysuria, fever, antibiotic use, and clinical and laboratory data suggesting infection (UA with +leukocyte esterase +/- nitrates, urine culture with >10^5 bacterial colony forming units per mL (CFU)). Asymptomatic bacteriuria will be considered a UTI for this study (defined as >10^5 CFU/mL on urine culture). Patients who are treated with antibiotics for UTI without laboratory data suggesting infection will be included in UTI group. For participants reporting ED visits prior to 14 +/- 2 day visit, ED reports will be obtained and an assessment will be made regarding the symptomatic UTI diagnosis. Those meeting these criteria will be followed with symptom and laboratory analysis. All positive UA test will be confirmed by laboratory analysis for final diagnosis. Results of +leukocyte esterase +/- nitrites will be considered abnormal. If a diagnosis of UTI does not exist in the patient chart outside of study, the patient's clinical picture will be evaluated independently by 2 separate care providers to determine if meeting criteria for UTI (symptomatic bacteriuria as defined above). If there is discrepancy a third provider will be the determining opinion. Participants meeting the primary endpoint (UTI) will be discontinued from the study following.

Secondary outcomes include: hospital length of stay, readmissions, antibiotic use at the time of surgery and post-surgery. Measures of UTI, and secondary outcomes will be collected from observation during study visits and from the patient medical charts., If closed drainage system was disrupted during placement (to back fill bladder intra-operatively), and method of catheter discontinuation ("fill and pull" versus "pull and void" methods) will be collected for comparison between the groups for analysis as a possible confounding variables.

Additional secondary outcomes to be evaluated will include patient discomfort with catheter, tolerability of catheter, length of hospital stay, and number of post-operative evaluations required. A cost-analysis will be performed as a secondary endpoint based on this cost factors (length of hospital stay, readmission, additional clinic/ED visits, antibiotic costs). Costs of hospital days, clinic visits, other appointments, and antibiotics will be standardized for evaluation based on literature for cost analysis in gynecologic oncology literature.

b. Target population. Women undergoing extended surgery lasting >1 hour and requiring urinary catheter will be eligible for enrollment. All patients will have surgery performed by one of the trained Gynecologic Oncologists at the University of Colorado Hospital.
Inclusion criteria will include:

1) women 18-89 years of age
2) admitted for surgery lasting >1 hour and requiring urinary catheter,
3) have normal urine analysis within 24 hours pre-surgery, and
4) able to provide informed consent.

Women with dialysis, chronic urinary infection, and current infection will not be eligible to participate. Women who are pregnant or breast feeding will not be included in the study. Men will not be included because of their lower incidence of UTIs compared to our female population.

The null hypothesis is that there will be no difference in UTI rates between the standard of care catheter placement and the sterile protocol placement. If we use the current rates of UTI after catheter placement described above at 40%, we would need to enroll 100 patients per arm (total 200) to see a 50% reduction in UTI rates in the intervention group with an alpha of 0.05 and a power of 0.84. The Gynecologic Oncology services averages around 5 surgical patients who would be eligible for this study per week. We anticipate needing between 10-12 months to complete enrollment.

c. Study Design and Research Method. We will conduct a single-site Randomized Control Trial (RCT) in order to examine the use of an aseptic protocol for catheter insertion during gynecologic oncology surgeries for quality improvement. This study will take place at the UCH inpatient surgical unit of gynecologic oncology. The catheter protocol for QI will be conducted in the operating room prior to surgery and will not increase prep time or operating room time. Follow-up will be conducted during standard outpatient care visits and will also not increase clinic use time.

The intervention in this study is a controlled aseptic pre-treatment protocol for catheter use in the operating room involving dipping the tip of the catheter into betadine prior to insertion and maintaining catheter in the sterile plastic sleeve during preparation, insertion and post-operatively to avoid excess exposure to the environment. The Physician performing the operation will be responsible for inserting the catheter. Patients with normal UA pre-surgery will be randomized 1:1 to one of two arms prior to surgery:

1) Aseptic protocol for catheter insertion using betadine treated catheter and maintaining plastic sleeve on catheter *or*
2) SOC catheter insertion in which catheter is inserted right out of package/non-treated catheter.

Prior to study initiation, the PI will train providers on the proper use of the protocol. Catheter insertion procedures will be documented in the operation note following surgery. Compliance will be measured by adherence to both betadine use and maintenance of plastic sleeve. Standard of care practices for infection control are to be conducted by providers on all participants. This includes: hand hygiene, inserting catheters for appropriate indications, remove catheters when no longer needed, maintain a close system keeping bag and tubing below the bladder.

We will collect general patient demographics to assure similarities between the randomized groups. These will include age, race/ethnicity, BMI, insurance type, diagnosis (reason for surgery), history of diabetes, menopausal status, and smoking status. MRN data will be collected in order to pull data directly into the OnCore data management system.

d. Study Procedures

Participants will conduct the following study visits over 2 weeks. All costs associated with routine standard of care procedures for catheter insertions and diagnosing and treatment of a UTI will be the responsibility of the patient and/or their insurance provider. All costs associated with procedures conducted for research only will be paid for by the research study.

- **Visit 1 Screening and Enrollment:** Potential participants will be screened and consented for study up to 30 days prior to their surgical procedure. Inclusion/Exclusion criteria will be reviewed at the time of consent and baseline data including physical exam, health history, clinical diagnosis and concomitant medications will be collected following consent. A urine sample will be collected and analyzed 0-24 hours prior to procedure.
- **Visit 2 Randomization and Catheter Insertion:** Participants will be randomized to either the SOC catheter protocol or catheter insertion including Betadine on the day of procedure. Standard protocol will be followed for catheter preparation and insertion. Any adverse events following insertion will be recorded. Pre-operative antibiotics will also be recorded.
- **Visit 3, 24-hour post-op:** Patients will be assessed at 24 hours post-op in-patient. A urine sample will be collected and analyzed. Any positive urine analysis will be further analyzed and confirmed by the UCH laboratory per SOC procedures. Patients will be assessed for symptomatic signs of UTI and review of AEs following procedure.

- **Visit 4; 2-week post op:** Patients will be assessed 2-weeks post-op at their SOC post-op clinic visit. A urine sample will be collected and analyzed. Any positive urine analysis will be further analyzed and confirmed by the UCH laboratory per SOC procedures. A physical exam will also be collected. Patients will be assessed for symptomatic signs of UTI and review of AEs and ED visits since the last visit. Data including hospital stay, readmission, and antibiotic use will be collected. Patient satisfaction with catheter procedure will also be collected. Patient will be finished with study following visit 4.

e. Description, risks, and justification of procedures and data collection tools:

- Consent and randomization: Patients will be randomized to standard of care intraoperative catheter placement versus aseptic protocol for catheter insertion upon providing informed consent. Randomization will be performed using the REDCap randomization module and will be performed by the study coordinator or research manager.
- Urine analysis with urine dip: Patients will be asked to provide a clean catch urine sample in provided collection cup prior to surgery (done as standard of care), a catheter collected urine sample at 24hrs post-operatively (research procedure) and another clean catch specimen at their 2-week surgical follow-up (research procedure). This collection and analysis is low risk except for the possibility of unnecessary treatment if abnormal sample is obtained. Abnormal samples will be correlated with patient history/complaints and confirmed with formal urine analysis. Confirmation of UTI would also utilize urine culture. The urine analysis by dip gives a fast yet reliable indicator of urinary tract infections. Pre-operative/pre-randomization allows us to exclude patients who may have underlying UTI prior to initiation of the study.
- Catheter placement: The aseptic protocol involves dipping standard catheter in an aseptic betadine solution and leaving a pre-existing plastic cover in place over the catheter during insertion and while in place. We do not anticipate any added risk of the aseptic protocol to the patient although patients may experience some increased irritation due to the protective plastic cover.

Anticipated Risks

While the study anticipates minimal risks, the following outlines any potential minimum risk to subjects:

i. Breach of Confidentiality: Data obtained using information from medical records poses minimal risk. All procedures in which information is being obtained will be conducted per standard of care. There is a risk that a patient's privacy may not be protected. This risk is uncommon.

ii. Discomforts: Persons receiving catheter insertion can anticipate the following risks: primarily ascending infection of the urinary tract. This usually presents initially with symptoms such as pain with urination, urinary urgency, urinary frequency, abdominal pain, chills, and/or fever. As discussed above the number of patients with evidence of clinical (symptomatic) and subclinical (asymptomatic) UTI has been reported to be as high as 40%. Other risks of catheter placement include urinary leakage around the catheter and bladder spasm/irritation while the catheter is in place. These symptoms usually resolve when the catheter is removed. Uncommon risks include injury to the bladder or urethra, urethral narrowing or urinary stone formation. Patients in both arms will be monitored for these risks throughout the study period. The addition of Betadine on the catherter prior to insertion is not expected to pose an increase in the described risks or discomforts.

Participation in this study will not have any influence on the patient's current treatment. The study may include risks that are unknown at this time.

Event reporting
Adverse Events
An Adverse Event [AE] is defined as any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure, regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable or definite). An unanticipated event is defined as any adverse experience where the nature, severity or frequency is not identified in the investigational brochure described in the application form or detailed in the consent form. This can also include non-compliance issues such as over enrollment of subjects without prior COMIRB approval.

Investigators will report the following to COMIRB within 5 days:

- Adverse events which in the opinion of the principal investigator are both unexpected and probably or definitely related to the intervention/ drug or device.
- **Probably related**: In the opinion of the PI, it is more likely than not that the adverse event is related to the study intervention.
- **Definitely related**: In the opinion of the PI, it is very likely that the adverse event is related to the study intervention
- An unforeseen development that potentially increases the likelihood of harm to participants or others in the future.
- Information that indicates a change to the risks or potential benefits of the research

Adverse events that are deemed not related will be documented in the study AE log, subject study charts, and reported to COMIRB at the time of annual review, per their policy. The PI will review AEs on an ongoing basis.

Anticipated clinical adverse events associated with urine catheter is: urethral/bladder irritation requiring removal of catheter prematurely, bladder or urethral injuries related to catheter placement, folliculitis of the genital area, change in urine color and UTI infection. Symptoms of a UTI are anticipated and include: fever, chills, urethral discomfort, incontinence, dark urine, urinary pain, suprapubic tenderness or pelvic pain, urinary urgency, frequency or dysuria, antibiotic use, prolonged hospital stay or readmission following symptoms. Severe UTIs may result in spread to the kidneys and present with abnormal kidney function assessment.

Anticipated clinical adverse events associated with the use of Betadine are as follows:

- **Common:** skin irritation (burning, redness, or general irritation)
- **Rare but Severe:** severe allergic reaction including rash, gives, itching, difficult breathing, tightness of the chest, swelling of the face, lips or tongue.
- **Unlikely:** balance/hearing problems, hair bumps (folliculitis), change in the amount of urine

There are no known contraindicated medications associated with the use of Betadine.

Serious Adverse Event
A Serious Adverse Event (SAE) is any untoward medical occurrence at any dose that:

- Results in death
- Is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)

- Requires inpatient hospitalization or causes prolongation of existing hospitalization (see *NOTE**: below for exceptions)
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
  Is an important medical event, defined as a medical event that may not be immediately life-threatening or result in death or hospitalization but, based on appropriate medical and scientific judgment, may jeopardize the subject or may require intervention (e.g., medical, surgical) to prevent one of the other serious outcomes listed above.
  Suspected transmission of an infectious agent (e.g., pathogenic or non-pathogenic) via the study treatment is an SAE.

**NOTE: The following hospitalizations are not considered SAEs:*

- A visit to the emergency room or other hospital department lasting less than 24 hours that does not result in admission (unless considered an "important medical event" or a life-threatening event)
- Elective surgery planned before signing consent
- Admissions as per protocol for a planned medical/surgical procedure
- Routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy)
- Medical/surgical admission other than remedying ill health state that was planned before study entry. Appropriate documentation is required in these cases
- Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason)
- Admission for treatment of suspected/confirmed UTI as this is an anticipated risk and the primary outcome

Participants experiencing a SAE should be discontinued from the study and followed per clinical standard of care. SAEs should be documented on the AE CRF and reported to the IRB within 48 hours of notification of event.

There are no known reports of serious adverse events following standard practice of urine catheter insertion or associated with the use of Betadine.

Data Collection and Confidentiality

This study will obtain approval for conduct through the Colorado Multiple Institutional Review Board (COMIRB) for research involving human subjects. All patients within the Gynecologic Oncology clinic at the University of Colorado Cancer Center who meet the study criteria will be considered eligible for the study. We will not include any vulnerable populations as defined by ethical guidelines. Potential participants will be screened by the PI/Co-I and the research team and approached for consent. Consent will occur prior to the initiation of any study procedures at a scheduled clinic visit in the Gynecologic Oncology clinics of participating sites. Potential participants will be provided a private setting for in-person consent and will be adequately informed of the study intent, requirements, and potential risks and benefits. Patients will also be informed that any participation is voluntary and will not affect any clinical care they are to receive. Research

staff providing consent will be certified in Collaborative Institutional Training Initiative (CITI) and Human Insurance Portability and Accountability Act (HIPAA) trainings for ethics and human protection. Patients will have time to review the consent and ask any questions prior to signing consent.

Data Collection Tools

Data will be collected using clinical research forms (CRFs) followed by entry into the OnCore clinical trials management system. Research coordinators should verify all demographic and health history to the participant's medical records prior to entry into OnCore. OnCore is a secure, HIOAA compliant management system available to trained investigators on the UCD network server. OnCore provides: 1) secured interface for validated data entry, 2) audit trails for tracking data manipulations and data storage and export procedures, 3) automated export procedures for seamless data downloads to common statistical packages, and 4) a library of all approved regulatory documents including amendments and consents. The University of Colorado Denver Informational Technology (IT) department will provide the host services for OnCore. Data extracted from the database for analysis will de-identified and linked to the original source using only a coded study number. All analysis will be conducted using SPSS statistical software program.

Study documents include study consent, CRFs, and a study survey. A study file should be constructed for each participant for maintaining these documents. All paper records will be securely stored in the locked research offices with limited access. Study databases will be stored on secure computers of the research team and backed by the secured server of the University of Colorado Denver.

Data sources will not be shared with outside institutions. Data shared among the researchers will be sent in encrypted email messages. All data will be maintained until completion of study and properly stored per federal regulations after completion of study analysis. Any data remaining on research electronic devices (recording devices, computers hard drives) will be properly destroyed with the assistance of the University IT department.

V. Trial Oversight

The Principal Investigator will be responsible for the conduct of this study, overseeing participant safety, executing the data and safety monitoring (DSM) plan, and complying with all reporting requirements to local and federal authorities. This oversight will be accomplished through additional oversight from the Data and Safety Monitoring Committee (DSMC) at the University of Colorado Cancer Center (CU Cancer Center). The DSMC is responsible for ensuring data quality and study participant safety for all trials at the CU Cancer Center. A summary of the DSMC's activities is as follows:

- Conduct of internal audits
- Ongoing review of all serious adverse events (SAEs), unanticipated problems (UAPs) and reportable adverse events (AEs)
- Has the authority to close and/or suspend studies for safety or conduct issues
- May submit recommendations for corrective actions to the CU Cancer Center's Executive Committee

Per the CU Cancer Center Institutional DSM Plan, SAEs, UAPs and reportable AEs are reported to the DSMC, IRB and the sponsor (if applicable) per study protocol. All SAEs, UAPs and

reportable AEs are to be reported to the DSMC within 5 business days of the Principal Investigator receiving notification of the occurrence.

Study audits conducted by the DSMC will consist of a review of the regulatory documents, consent forms, and source data verification.

Documentation of the audit conducted by the DSMC will then need to be submitted to the IRB of record at the time of the IRB's continuing review of this trial.

Potential scientific problems:
This study proposes the use of a simplified peri-operative catheter insertion protocol aimed at reducing the rates of urinary tract infections after catheter placement. If effective this could be represent a low-cost, low-effort intervention however obtaining a clinically meaningful response may be the biggest limitation of this study. Although UTI rates are relatively high after post-surgical catheter placement and there have been several studies showing some reductions, there are numerous additional studies which have failed to show a difference. Our goal here is not to merely achieve a statistically significant but rather a clinically meaningful response. We therefore powered our study to look for at least a 50% reduction in the rate of UTI's.

Additionally, there is and will remain practice variations in catheter placement. While we hope to find a difference despite these differences, it is possible that the intervention may give a false impression of improvement simply by focusing attention on a protocol. While it is difficult to remove confounding from any study, randomization and analysis adjustments will be used to reduce as much as possible.

VI. Data Analysis Plan:
This study will assess a population of patients undergoing extended surgery requiring catheter placement to be performed by the Gynecologic Oncology service. De-identified patient data will be collected into OnCore and exported to SPSS for data analysis. Initial summary statistics will be performed to report the distribution of the data, including variable means, medians, proportions and missing data.

An intent-to-treat analysis will be conducted. All participants receiving treatment per protocol will be included in the final analysis. If there are any participants who are randomized but do not receive the intended treatment, we will document the reasons for their being withheld treatment.

For the primary outcome measure of UTI rate at each of the time points (24 hours and 14 +/- 2 days), we will perform a test of binomial proportions for testing the null hypothesis of no difference between the treatment arms. Because we are performing tests at two time points, we will adjust for the multiple comparisons using Bonferroni's method.

We will also explore the association between treatment arms and other covariates (symptomatic and demographics factors) using bivariate methods. The particular analysis method for testing the association between them will depend on the distribution of the covariates. For example, symptomatic presentation variables (fever, pelvic pain, sense of urgency or dysuria, and antibiotic use) are categorical, and their association with treatment arm will be evaluated with a chi-square statistic.

For demographic variables, Student's *t*-test (for continuous variables) and chi-square tests (for categorical variables) will be used to compare the two treatment arms. Variables found to be significant in these bivariate analyses will be included in multivariable analysis using logistic regression. Logistic regression models will be used to identify significant independent predictors associated with UTI

occurrence for each treatment arm. We will fit separate logistic regression models for UTI occurrence at the two time points. The logistic model will allow for control of study covariates simultaneously. A p-value of <0.005 will be used to demonstrate statistical significance. IBM SPSS version 23 will be used for all statistical analyses.

Secondary outcomes will include a cost-analysis of the two treatment protocols and a patient satisfaction query in regards to the catheter procedure.

- Cost-analysis: The cost-effectiveness of the interventions will be assessed using hospital stay, readmissions, clinic/ED visits, and antibiotic costs per patient during the study period. An estimate of patient care costs will be derived using standard cost data described in the literature. The two groups will be compared in terms of average cost of treatment with a 95% confidence interval using a Bayesian statistic.
- Satisfaction: Patient satisfaction with the catheter protocol will be measured using a Likert-like scale questionnaire. Responses between the two groups will be compared using a Mann-Whitney-Wilcoxon statistic.

VII. Summarized Knowledge to be gained:

This study aims to reduce the incidence of urinary tract infections in patients undergoing surgery on the Gynecologic Oncology service through an aseptic protocol for placement. Such quality improvement studies are needed to help reduce complication rates and health-care costs.

VIII. References:

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