

**A Randomized Trial of Betadine Bladder Irrigations vs. Standard of Care
Prior to Indwelling Catheter Removal to Reduce Bacteriuria and Catheter-
Associated Urinary Tract Infections**

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I. BACKGROUND AND RATIONALE

Indwelling urinary catheters are routinely used in the care of hospitalized patients for a variety of reasons, including monitoring of urine output in critically ill patients, relief of urinary obstruction, and prevention of contamination of decubitus ulcers. Bacteriuria increases by 3-10% each day a catheter is left in place^{1, 2} meaning that by 30 days, generally 100% of patients with indwelling catheters will have bacteria in their urine. The majority of these people do not have urinary tract infections (UTIs), they are merely colonized and do not require treatment.

Over the last decade, there has been great emphasis on reducing the incidence of hospital-acquired infections, including catheter-associated UTI (CAUTI). Hospitals have had relatively good results, though there is certainly still room for improvement. To define a standard (and ultimately to compare hospitals against each other), a surveillance definition for CAUTI³ has been developed by the National Healthcare Safety Network (NHSN). While useful for surveillance, the definition does not correlate with clinical UTIs, leading to over diagnosis and over-reporting of UTIs (in other words, those with merely bladder colonization being diagnosed as having a UTI). Despite continuing progress in standard methods of reducing infection rates (including decreasing the number of catheters inserted, ensuring proper catheter maintenance, and removing catheters when no longer necessary) we continue to have unacceptably high rates of CAUTIs. As hospital-acquired infection rates are increasingly tied to reimbursement from governmental agencies, there is a great need to reduce infection, either by meeting surveillance criteria or through novel clinical approaches.

Studies from the 1980s and 1990s investigated a variety of compounds for local instillations into the bladder in attempts to decrease bacteriuria and prevent infections. One of the more promising solutions instilled was povidone-iodine. A single preoperative instillation of 1% povidone-iodine prior to prostatectomy in patients with indwelling catheters reduced the rate of post-operative bacteriuria from 100% to 22.5%⁴. Similarly, bladder irrigation with 2% povidone-iodine prior to prostatectomy in patients with indwelling catheters was well tolerated and achieved urine sterilization in 75% of patients in another study⁵. While neither of these studies looked at reducing rates of CAUTI, we hypothesize that they could provide a benefit, given their effectiveness at decreasing bacteriuria in patients with indwelling catheters. Both studies

reported that a low concentration of 1 or 2% was well tolerated by patients. A study from the Netherlands evaluated use of pre-removal povidone-iodine bladder irrigation⁶. No reduction in bacteriuria was found in cultures at days 4 to 14 after removal, though there was a trend towards less bacteriuria in the first 3 days after removal. Additionally, more than half of the patients had only had catheters in place for 3 days or less prior to removal, and only 13.6% of patients had positive urine cultures prior to removal, which may have minimized the potential differences.

A single dose of povidone-iodine prior to catheter removal seems a novel and promising practice for several reasons. First, we suspect it will be helpful in reducing rates of NHSN defined CAUTI, as these are still diagnosed for 2 days after the catheter is removed. Results of a recent review revealed that 15-20% of diagnosed CAUTIs at Beaumont occurred during this window. Second, using multiple doses of povidone-iodine would be inadvisable, since we suspect bacteria over time would become resistant even to this antiseptic. Third, we suspect use of an antiseptic is preferable to an antibacterial for preventing further antimicrobial resistance development. Finally, use of this method, as opposed to the suggested use of systemic antibiotics at time of removal⁷, is potentially preferable from the downstream standpoint of less antimicrobial resistance and reduced risk of *Clostridium difficile* infection.

II. OBJECTIVE AND ENDPOINT

Objective:

To evaluate the effectiveness of Betadine irrigation solution (2% povidone-iodine) instilled into the bladder immediately prior to indwelling catheter removal to decrease the risk of subsequent bacteriuria, leading to decreased rates of NHSN defined CAUTI.

Endpoint:

Presence or absence of NHSN defined CAUTI at 48-72 hours after indwelling urinary catheter removal, as assessed by urinalysis (UA), urine culture (UC), and UTI Symptom Assessment questionnaire (UTISA)⁸.

III. METHODOLOGY

A total of 110 men will be enrolled in this randomized trial, which will be conducted at Beaumont Hospital, Royal Oak. Eligible patients will be consented and randomized into 1 of 2

groups. Ideally, fifty-five men will be in each group. 120 men may need to be enrolled to achieve the desired number of patients completing the 48-72-hour post-catheter removal visit, which is the study endpoint.

Despite optimal “clean catch” collection techniques, it is often difficult to obtain a non-contaminated urine sample from females without performing sterile catheterization due to the chronically colonized vaginal flora. In order to minimize patient risks and difficulty with recruitment associated with additional catheterization, we have chosen to exclude females from this initial study. The male anatomy allows for adequate sample collection via “clean-catch” alone. By enrolling only males we hope to reduce the possibility of contamination in the clean-catch specimens collected at the 48-72 hour follow up visit⁹. Future studies would include females as well.

Study staff will review patient charts from all Beaumont Hospital, Royal Oak units (including rehabilitation units) in order to identify patients who may be eligible to participate. Appropriate patients will be approached, the study will be described to them in detail, and informed consent will be obtained. Eligibility criteria will be reviewed, including current antibiotic use, which is exclusionary. If the patient meets all of the inclusion criteria and none of the exclusion criteria, a urine sample will be obtained for UA and UC. All urine test results will be for research purposes only and not part of the patient’s clinical chart/electronic medical record. All UA and UC results, collected for research, will be reviewed by one of the study investigators. If a patient develops symptoms at any point in the study, a UA and UC could be obtained at the care provider’s discretion.

Patients will be randomized 1:1 to receive either standard of care (catheter removal with no bladder irrigation) or bladder irrigation with 2% povidone-iodine solution immediately prior to catheter removal. Randomization envelopes will be provided by the biostatistician and stored in a secure location in Urology Research. At the time research staff contact the pharmacist with the Betadine request, group assignment will be verified.

The first group will receive standard of care (SOC) only (indwelling catheter removal without any other interventions). If the patient is randomized to the SOC arm, the research nurse will simply remove the indwelling catheter. The second group will receive a single dose of approximately 60 cc of 2% povidone-iodine (Betadine) placed into the bladder. When the patient is randomized to the Betadine rinse arm, the research pharmacist will be contacted. The pharmacist will prepare and deliver the Betadine filled syringe to the research staff for instillation. The Betadine solution will be instilled through the catheter and left to dwell for 10 minutes, drained, and then the catheter will be removed. Research staff will be trained by a physician to remove the catheter using aseptic technique and prevent introduction of bacteria. To ensure patients are able to adequately void after catheter removal, designated study personnel (Urologists), will manage the study patient's voiding trial.

48-72 hours after catheter removal a urine sample will be obtained to repeat UA and UC. If enrolled patients are still inpatient at this time point, study staff will see the patient in the hospital and conduct the Visit 2 activities. If the patient has been discharged from the hospital, this visit will occur in the Urology Research office. While not ideal or preferred, if the patient is not available for an in-person visit, the questionnaire may be completed over the phone, or sent to the patient and returned by mail (returned by USPS, email, or fax). In addition to the UA and UC, the UTISA questionnaire will also be completed. The UTISA questionnaire is a validated tool which will be utilized to assess the "severity" and "bothersomeness" of the most frequently reported signs and symptoms of uncomplicated UTI⁸. The Beaumont laboratory will evaluate all collected specimens. If a patient develops symptoms suggestive of a UTI, then further testing may be performed at the discretion of their managing physician or one of the study investigators. Research staff will also contact patients by phone at 7 and 28 days after catheter removal. At that time the UTISA will be administered to assess urinary symptoms, including diagnosed UTIs since the time of catheter removal. The UTISA may be completed verbally over the phone or by mail (returned by USPS, mail, or fax). If the patient's responses indicate a possible UTI, the patient will be referred to their primary care provider and/or other health care provider for evaluation.

Patients requiring reinsertion of an indwelling catheter prior to study completion will be withdrawn from the study. Patients that do not comply with the study protocol may also be withdrawn from the study by the Principal Investigator (PI).

SCHEDULE OF ACTIVITIES

	Screening & Treatment Visit <i>Inpatient Visit</i>	Visit 2 <i>48-72 Hours Clinic or Inpatient Visit</i>	Visit 3 <i>7 ± 3 days Phone Call</i>	Visit 4 <i>28 ± 3 days Phone Call</i>
Informed Consent	X			
Review Inclusion and Exclusion Criteria	X			
Review of Current Antibiotic Medication Use	X	X	X	X
Urine collection: UA & UC	X	X		
UTISA Questionnaire		X ^a	X ^b	X ^b
Indwelling Catheter Removal	X			
Betadine Bladder Irrigation	X ^c			
Assess for Adverse Events	X	X	X	X

^aAt Visit 2 the UTISA may be completed in person, over the phone, or by mail (returned via USPS, email, or fax).

^bAt visits 3 and 4 the UTISA may be completed over the phone or by mail (returned via USPS, email, or fax).

^cBetadine Bladder Irrigation will only be completed with those patients who are randomized to the treatment group.

IV. RISKS AND BENEFITS

Potential Benefits: This intervention may be beneficial for both patients and the hospital. The rate of hospital acquired CAUTIs may be reduced without increasing the risk of antimicrobial resistance.

Potential Risks:

Risks of Urinary Catheterization:

Less Frequent (occurring from 1% to 10% of the time):

- Temporary inability to urinate
- Bleeding
- Mild cramping
- Urinary tract infection

Risks of Betadine:**Less Frequent (occurring from 1% to 10% of the time):**

- Local irritation of the bladder

Rare (occurring less than 1% of the time):

- Allergic reaction

Unknown Risk:

- Brown discoloration of urine

Risks of Bladder Irrigation:**Less Frequent (occurring from 1% to 10% of the time):**

- Discomfort while the indwelling urinary catheter is clamped

All patients will be closely monitored by the research staff during the instillation, if applicable, and during catheter removal. All unanticipated problems will be reported to Beaumont's Investigational Review Board (IRB) per policy.

V. COMPENSATION

Patients will be reimbursed for time and travel during the course of the study, as outlined in the table below. Stipend checks will be sent, via US mail, in the amount listed below after each completed visit which is eligible to receive a stipend. If patients are unable to complete all study visits, they will be paid only for the visits they were able to complete.

Visit	Stipend Per Visit
Screening and Treatment Visit	\$25.00
Study Visit 2	\$25.00
Study Visit 3	\$0.00
Study Visit 4	\$0.00
Maximum Total (if all visits are included)	\$50.00

VI. ELIGIBILITY CRITERIA

Inclusion:

- 1) Provide written informed consent and the willingness and ability to comply with all aspects of study requirements
- 2) Male
- 3) Inpatients ≥ 18 years of age with an indwelling catheter in place for at least 5 days with a plan for removal

Exclusion:

- 1) Patients planned for discharge with an indwelling catheter in place
- 2) Patients unable to report urinary symptoms accurately
- 3) Patients with hyper-sensitivity or allergic reaction to Betadine, iodine, shellfish or other related compounds
- 4) Clinical signs or symptoms of urinary tract infection at the time of consent
- 5) Patients currently being treated for UTI
- 6) Patients currently taking any antibiotic medication, other than those listed in **Appendix B**
- 7) Patients already taking medications known to potentially irritate the bladder, such as, but not limited to, cyclophosphamide, ifosfamide, and other chemotherapeutic agents
- 8) Patients with history of bladder cancer, pelvic radiation or interstitial cystitis
- 9) Patients unable to comply with study requirements
- 10) Any other condition which, per investigators' judgment, may increase patient risk and/or impede the reliability of study data

VII. DATA ANALYSIS

An infection rate of 25% is anticipated at day 2 post catheter removal for the SOC group. A difference has been shown of a 75% drop in infection rate using povidone-iodine bladder irrigation⁵. A power analysis using these estimates yields 55 patients needed in each arm to have 80% power at a 0.05 significance level to detect a difference of 25% versus 6.25%. We estimate at most a 10% dropout rate and plan to enroll 60 patients per arm to account for this.

Descriptive statistics will be provided for all data collected. Categorical variables will be reported as counts and percent frequencies. All continuous variables will be reported as means

+/- the standard deviation followed by the median, minimum to maximum or the median (25th, 75th percentiles) then minimum to maximum dependent on the normality of the data.

The endpoint of presence or absence of bacteriuria at 48-72 hours post catheter removal will be examined with a Fisher's exact tests, odds ratio and 95% confidence intervals. If any differences are found in what appear to be confounders for UA, a multivariate logistic regression analysis may be completed adjusting for these differences.

The categorical variables will be examined using Pearson's Chi-square tests where appropriate (expected frequency >5), otherwise Fisher's exact tests will be used. Continuous variables will be examined for normality. Normally distributed variables will be analyzed using t-tests. Non-normally distributed variables will be examined using non-parametric Kruskal-Wallis tests.

REDCap (Research Electronic Data Capture) is the web-based software program that will be utilized for data collection and management. Urology Research will be responsible for all data management responsibilities including, but not limited to, database creation, data entry and query resolution. Data analyses will be performed by a Beaumont Biostatistician utilizing statistical software.

VIII. DATA SAFETY MONITORING PLAN

Ongoing safety monitoring will be performed by the study staff, including the PI and co-investigators. The PI will have ultimate responsibility of assuring patient safety. A Medical Safety Monitor (MSM) will be assigned by the PI. The MSM will be a physician who is not involved in the study and who has no conflict of interest. The MSM will review Serious Adverse Events (SAEs) and will determine expectedness and causality of the event. The MSM may suggest protocol modifications to prevent the occurrence of adverse events (e.g., modifying the protocol to require frequent measurement of laboratory values predictive of the event or to improve expeditious identification of SAEs). If the MSM is unavailable for an extended period (i.e. extended vacation, illness, etc.) a back-up MSM will be nominated by the study PI. Safety issues will also be addressed in the annual reports to Beaumont's IRB.

Additional data safety monitoring procedures include:

- Research Administration's Clinical Research Quality and Process Improvement Program (CRQIP) will perform in-house monitoring of the first patient enrolled after the completion of visit 1
- Safety data review at study team meetings

IX. REFERENCES

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Appendix A: Urinary Tract Infection Symptom Assessment (UTISA)

About Your Symptoms and Their Impact on Your Life								
Please indicate whether you have had the following symptoms/problems in the past 24 hours and how severe they were: (Please circle one number for each symptom)				SYMPTOMS	If you have experienced these symptoms/problems in the past 24 hours, please indicate how bothersome they were? (Please circle one number for each symptom)			
Did not have	Mild	Moderate	Severe		Not at all	A little	Moderately	A lot
0	1	2	3	Frequency of urination (going to the toilet very often)	0	1	2	3
0	1	2	3	Urgency of urination (a strong and uncontrollable urge to pass urine)	0	1	2	3
0	1	2	3	Pain or burning when passing urine	0	1	2	3
0	1	2	3	Not being able to empty your bladder completely/passing only small amounts of urine	0	1	2	3
0	1	2	3	Pain or uncomfortable pressure in the lower abdomen/pelvic area caused by your urinary tract infection	0	1	2	3
0	1	2	3	Lower back pain caused by your urinary tract infection	0	1	2	3
0	1	2	3	Blood in your urine	0	1	2	3

8. Please give an overall rating of the severity of your urinary tract infection symptoms as they are at this moment *(Please circle the number of your answer)*

0 No symptoms 1 Mild 2 Moderate 3 Severe

Additional questions at Visits 3 and 4:

9. Since you last completed this questionnaire, have there been any changes in your urinary tract infection symptoms? *(Please circle the number of your answer)*

- 0 about the same
- 1 better (if patient responded 1=better, go to question 10)
- 2 worse

10. Please indicate how much better *(Please circle the number of your answer)*

- 6 a very great deal better
- 5 a great deal better
- 4 a good deal better
- 3 moderately better
- 2 somewhat better
- 1 a little better

Appendix B: Antibiotic Medications which are NOT Exclusionary

- Vancomycin (Vancocin)
- Linezolid (Zyvox)
- Daptomycin (Cubicin)
- Clindamycin (Cleocin, Evoclin)
- Metronidazole (Flagyl)