

The Utility of Urinalysis Prior to In-office Procedures: A Randomized Clinical Trial

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Project Summary:

The current state of practice requires every patient to have a urinalysis (UA) and if positive then a urine culture (UC) prior to any in office urology procedure. This practice may cause diagnostic delays, unnecessary cancellation of procedures and the over use of antibiotics, promoting antibiotic resistance. We predict that there is no difference in the number of cases of urinary tract infections (UTI) in patients that undergo in office procedures with or without prior UA. While a few procedure specific studies have shown this trend, this will be the first time this hypothesis is tested on a broad spectrum of procedures in a randomized clinical trial setting. The trial will consist of two randomized groups of patients. The control arm will receive a standard of care urinalysis with a reflex culture if positive that their treating physician will be able to view before the procedure and may choose to delay/cancel the procedure if they deem necessary. The experimental arm will receive a urinalysis with a reflex culture if positive, but their treating physician will not view the urinalysis results before the subject's procedure. Both groups of patients will be followed-up via phone at one week and one month post-procedure to assess the intervention's impact on the number of post-procedure UTI cases. Any patients with positive urine cultures will be alerted and treated accordingly.

Background and Significance:

Currently all BCG patients undergo UA before their procedures, this practice is upheld at both the UW Urology Clinic and the VA. The reasoning behind the current practice is that any sign of a tentative infection could be aggravated by the treatment. Retrospective studies have suggested that there is no difference in the rates of UTI in people who were administered UA tests before BCG treatments versus people who were not administered UA tests before treatment.^[1] However, for patients that had a UA, BCG instillation was delayed for 2.5% of the cases.^[2] Additionally, a study aimed at understanding the role of preventative antibiotics prior to in office cystoscopy found that the risk of symptomatic UTI is only 4.5% of patients, therefore the vast majority of patients did not benefit from UA or preventative antibiotics.^[3] These studies suggest that a change in the standard protocol before in-office procedures is in order.

The current guidelines for urologic in-office procedures might be hindering patient care instead of improving it. A recent study by Zhao et al established that the cost of every UA is approximately \$4.24, which for the course of this proposed study alone (664 patients) could add up to \$1,300 approximately when accounting for the randomization of the study.^[1] The economic aspect shows a drain in resources that could be otherwise allocated to improve care. Furthermore, the results of these UA tests will occasionally lead to delays in procedures. If the UA was positive, then the procedure would be delayed at the physician's discretion. It is important to note that a previous study conducted at the Madison VA urology clinic has shown that >1% of urologic procedures have ever been cancelled due to a positive UA.^[4] Additionally, a study on the urine cultures of 150 men prior to prostate needle biopsy procedures found that fewer than 5% of men undergoing the procedure had a positive urine culture and none of the men with positive urine cultures showed evidence of developing an infection the morning following their procedures.^[5] Delays are cumbersome to the patients, but can also cause delays in more serious diagnosis, for potential cancer patients undergoing cystoscopy or prostate biopsies which could alter the care options available to the patient. **We hypothesize that eliminating UA before in-office procedures**

will not significantly affect the number of UTI cases reported post-procedure, but it will increase the efficiency of care provided.

An additional aspect of this study seeks to support antibiotic stewardship across patient care. Preventative antibiotics are potentially contributing to a worldwide rise in multidrug resistance.^[3] By eliminating UA prior to in-office procedures and thus the need to use antibiotics as a preventative measure, we will be making responsible use of antibiotics in the care provided. Antibiotic stewardship could be especially prudent in patients undergoing BCG treatments. One mechanism suggests that BCG treatments could be therapeutic by triggering cellular responses that lead to rapid epithelial cell shedding, reducing the case for infections.^[2] **We hypothesize that in the case of BCG treatment an immunomodulatory effect will reduce the bacterial load and potentially reduce the risk for UTI by comparing the outcomes between delayed and non-delayed procedures.**

Specific Aims/Study Objectives:

The aim of this study is to assess the usefulness of UA and urine cultures in patients prior to in-office urology procedures. Specifically, we want to challenge the current protocol of administering UA prior to in office cystoscopy, BCG treatments, and prostate biopsy procedures. A change in protocol could allow for improved clinical efficiency, antibiotic stewardship, and be economically advantageous.

Research Design and Methods:

1. Study design: Prospective cohort, 664 patients, randomized trial
2. Data Source: Urology Patients at the University of Wisconsin Hospital and the William S. Middleton Memorial Veterans Hospital
3. Study Population
 - a. Inclusion criteria:
 - i. Patients receiving an in-office cystoscopy, intravesical BCG treatment prior to first instillation, or prostate biopsy
 - b. Exclusion criteria:
 - i. Patients under 18
 - ii. Patients with symptomatic UTI infections at the time of recruitment
 - iii. Patients on antibiotics at the time of recruitment, not including prophylaxis
 - iv. Patients with a history of UTI within 1 year
 - v. Patients with indwelling catheters
 - vi. Patients with clean intermittent catheterization
 - vii. Patients undergoing stent removals or with ureteral stents
 - viii. Patients with history of asymptomatic bacteriuria
 - ix. Patients with high risk of infection
 - c. Subject Identification:
 - i. Subjects will be identified based on daily clinic schedules and screening will happen at the time of consent

- ii. Subjects will be given as much time as needed to decide if they would like to participate in the study or not
- iii. Patient medical history and current medication list will be confirmed at the time of consent
- iv. Patients will be randomized by sealed envelope using a random number generator populated with study identification numbers.
 - 1. Randomization specifications: Patients on this study receive a study identification number (Study ID), which corresponds to what number patient they are on the study. For example, Study ID 0049 is the 49th patient to sign a consent form. A random number generator was populated with the 664 study identification numbers used in this study. The generator divides the numbers into two equally sized groups, with one group being the “control arm” group and the other the “experimental arm” group. Sealed envelopes were created from that list with the study identification number on the front on the envelope and the group sealed inside. That way, when patients are consented into the study, their study identification number determines what study treatment they will receive, and the consenting/randomizing staff will have no way of guessing which arm the patient will get until they open the envelope.
- v. Patients will not know to which group they’re assigned
- d. Estimated number of patients to be included:
 - i. 664 patients recruited over approximately a year as estimated for an equivalence study
- e. Primary Cohorts:
 - i. Control: Patients who will receive UA prior to treatment and will be evaluated by the physician according to the test results as current standard of care dictates. A UC, which will be administered according to the results of the UA.
 - ii. Experimental: Patients will receive a UA prior to their procedure, but their physician will not evaluate the results of the UA and will instead proceed directly to conducting the procedure. The patient’s UA and reflex urine culture (if applicable) will be monitored by research staff and Dr. Richards will be alerted of any possible infections as soon as results are available. In this manner, we will know the necessary course of antibiotics for treatment ahead of time.
- f. Subset Cohort Analysis:
 - i. None
- g. Primary Outcome Measured: Number of UTI occurrences within study period. The definition of UTI for the study will be inclusive, consisting of a suspicious urinalysis with white blood cells, bacteria, or nitrites present and a positive culture >10,000 cfu/mL (excluding diptheroids) accompanied by symptoms.
- h. Secondary Outcome Measures:
 - i. Streamlining of patient care

1. Delayed procedures and reasoning behind delays will be recorded
 - ii. Improved usage of antibiotics
 1. Information on antibiotic use and type of antibiotics used will be recorded
4. Collaborating Sites
 - a. None
5. Information Collected from Patients:
 - a. Demographics
 - b. Prior history of UTIs
 - c. Prior history of urological procedures
 - d. Charlson Comorbidity Index
 - e. Lower Urinary Track Symptoms (LUTS) Questions: to be collected prior to procedure and at all follow ups.
 - i. Number of times voided the day before
 - ii. Number of times voided throughout the night before
 - iii. Current state of urine stream
 - iv. Perceived ability to completely empty the bladder
 - v. Number of times urgency for the bathroom occurred the day before
 - vi. Number of times urine leakage was experienced and was it related to urgency or routine (cough/strain/laughing)
 - vii. Dysuria, flank pain, or suprapubic pain
 - viii. Presence of hematuria
 - ix. Experiencing fever or chills
 - f. Procedure notes
 - g. If procedures are delayed, explanation of surgeons reasoning will also be recorded
 - h. UA results
 - i. Adverse events
6. Specimen/data collection/storage:
 - a. The data will be obtained from surveying urology patients at the VA and the UW urology clinics. Only the necessary data for the study will be obtained to answer the research question from patient charts. The data might include urologic history and general patient information including co-morbidities. Only the PI and authorized research assistants will have access to the data.
 - b. Study data will be kept in accordance with the Department of Veteran Affairs record control.

Risk-Benefit Analysis:

This trial poses minimal risk to the patient in the physical, psychological, social and legal aspects. While the physician will not have access to the experimental group's UA results at the time of the procedure, the results will be monitored so that patients can be alerted of any medical care needed in case of a UTI.

To reduce the risk further, every medication and medical history will be confirmed with the subject before consenting them into the study.

As previously stated, the definition of UTI for the study will be inclusive, consisting of a positive culture >10,000 cfu/mL, excluding diptheroids accompanied by symptoms. Any patients that develop symptomatic UTIs during the study will be treated with culture specific antibiotics per standard of care. If there is an infection detected for a patient in the experimental group Dr. Richards will notify the patients and arrange treatment 24 hours a day, 7 days a week. In the rare circumstance that Dr. Richards is not reachable, Dr. Sara Best will provide back up to ensure appropriate treatment and follow-up is in place. It is recommended that treatment for any infections that require urgent care after hours is administered at any ER if warranted at the convenience of the patient. The care provided from the point of admission will follow the standard of care protocol at the particular ER. Additionally, an example of standard practice for care of a UTI can be seen in the cited document from the UW Health ER SOP for sepsis treatment.^[6] For patients presenting to the emergency room or any other medical provider for the duration of the study, the study team wants to ensure effective communication in regards to any urine culture results or other important information related to participation in this study. Therefore, each participant will be provided an information sheet with basic details about the study, the contact information for the PI (and back-up), and a place to write down details about the findings when informed about the results by the PI. This would be provided to the patient when they enroll and could be provided to the physician in the ER.

Only the researchers approved by the IRB will have access to any information about the patients, protecting privacy. While any study poses a risk for breach of confidentiality, we plan on taking pre-emptive action to prevent this from happening and in the case of a breach; a report would be made to the IRB immediately and resolved with IRB guidance. Considering the benefits of the study, all assessed risks are minimal to the patient, and all possible preventative measures will be taken to avoid significant risks or harms. All study test results will be monitored as they become available by Dr. Richards' research assistant.

Data and Safety Monitoring Plan:

The PI and all study team members will be alerted to any unanticipated problems or complications that arise. They will be proactive, as described above, to avoid any unanticipated problems or complications. If an unanticipated problem or complication does arise, the IRB will be notified. Data analysis will also be performed every 100 patients and the experiment will be stopped if there is a statistically significant increase in the number of UTI incidences between the control and the variable groups. We will also plan to perform separate analysis for both safety and efficacy between the different treatment groups (i.e. BCG controls vs. BCG variable group; prostate biopsy controls vs. prostate biopsy variable group; cystoscopy controls vs. cystoscopy variable group).

Specific provisions are in place to address unanticipated problems or complications BEFORE THEY OCCUR, as described above and again herein: All risks of the study will be minimized by monitoring the patients test results prior to the study and taking immediate action, within 3 days of the urinalysis test, to prevent any UTI from affecting the patient. All standard privacy protective procedures will also be followed.

Specific provisions are in place to address unanticipated problems or complications AFTER THEY OCCUR. Namely, the PI and all study team members will document and report them to the IRB. Solutions to address any unanticipated problems or complications will be applied, based on advice from the IRB.

Statistical Considerations:

The study will enroll 664 patients as determined by the standards of an equivalence test with a proportion difference of 0.01 between the proportion of UTI for the group with urinalysis and reflexive culture visible to physicians (0.03) and the proportion of UTI for the urinalysis not ready for the physician to view prior to the in-office procedures. The null proportion difference is set at 0.05 and the alpha and power constants are set at 0.05 and 0.8 respectively as is common for studies of this type.

The results of the trial will be analyzed using a T-test for comparison of means, a Mann-Whitney U test for comparison of medians, Fisher's exact and chi-squared tests for comparison of categorical variables, and a logistic regression for predictors of UTI. All statistical tests will be two sided with p-values <0.05 considered significant.

Data and Record Keeping:

Measures that will be implemented by our research team to safeguard the identifiable subject information from unauthorized use or disclosure for both paper and electronic forms of information, including how and where data will be stored, include:

- 1.) Any data or information collected will only be available to IRB-approved study team members.
- 2.) Collection of sensitive information about subjects is limited to the amount necessary to achieve the aims of the research.
- 3.) All data or information collected will be stored only on VA servers or hard drive of VA-approved and serviced computers with appropriate security (i.e., firewall and password) protections.
- 4.) All paper files that store any data or information associated with this study will be housed inside locked offices in the security-protected VA office (B7112G).
- 5.) Any data or information stored in the excel database will be coded by using a unique study code to which only the PI and approved study team members have access.
- 6.) Study data and the corresponding master list of identifiers will be stored on a VA departmental server.
- 7.) VA research data and information will be retained in accordance with the applicable VA Records Control Schedule (NARA RCS 10-1).
- 8.) Per VA policy, a copy of all study data will reside within the VA protected environment (B7112G), including all codes used to re-identify subjects' PHI.

9.) VA sensitive data or information will only be transmitted using VA-approved solutions such as FIPS 140-2 validated encryption or PKI encryption for secure e-mail messages.

10.) Access to research study data will be removed for study personnel when they are no longer part of the research team.

11.) In accordance with VA policy, the ISO and PO and ACOS for Research will be notified within one hour of any actual or suspected data breach (i.e. unauthorized use, disclosure, transmission, removal, theft, loss, or destruction of VA research-related PHI, individually identifiable private information, or confidential information).

12.) VA information will be securely returned to the VA.

References:

1. Zhao LC, et al. Screening urine analysis before Bacille Calmette-Guerin instillation does not reduce the rate of infectious complications. *BJU International*. 2011. 109, 1819-1821
2. Herr, HW. Intravesical Bacille Calmette-Guerin Eradicates Bacteriuria in Antibiotic-naïve Bladder Cancer Patients. *European Association of Urology*. August 20, 2012
3. Herr, HW. Should Antibiotics be given prior to Outpatient Cystoscopy? A plea to Urologists to Practice Antibiotic Stewardship. *European Association of Urology*. August 30, 2013.
4. Richards KA, Cesario S, Lim, AH, et al. Utility of routine urinalysis and urine culture testing in an ambulatory urology clinic: a quality improvement initiative in a Veterans healthcare facility. *The Canadian Journal of Urology*. February 24, 2017. (1):8627-8633.
5. Qi DZ, et al. Pre-operative urine culture is unnecessary in asymptomatic men prior to prostate needle biopsy. *International Urology and Nephrology*. November 23, 2017.