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Modified Reporting of Positive Urine Cultures Collected from Long Term Care, a Randomized Controlled Trial Protocol

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Administrative Information

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Roles and responsibilities:

Protocol: Peter Daley, Associate Professor, Memorial University

Sponsor: Memorial University of Newfoundland, St. John's, NL, Canada

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Introduction

Background and rationale

Asymptomatic bacteriuria (ASB) is a condition in which bacteria from the bowel are detected in significant numbers by culture in a specimen of collected urine, but the patient does not have genitourinary symptoms or signs.(1) In contrast, urinary tract infection (UTI) is the presence of bacteria in urine specimens with defined symptoms or signs.(2, 3) Catheter-associated urinary tract infection (CA-UTI) is defined as presence of bacteria in urine specimens with defined symptoms or signs in the presence of an indwelling urinary catheter, and catheter-associated asymptomatic bacteriuria (CA-ASB) is defined as presence of bacteria in urine

specimens without defined symptoms or signs in the presence of an indwelling urinary catheter.(2)

The use of inappropriate antibiotic treatment for ASB is a systemic antibiotic stewardship problem, causing harm due to antibiotic adverse effects, selection of bacteria toward drug resistance, and wasted cost.(4)

UTI's are among the commonest indications for antimicrobial therapy. Prevalence of ASB varies from 1-5% among healthy premenopausal women, to 25-50% among women in long term care, to 100% among patients with chronic indwelling catheters.(5) Treatment of ASB with antimicrobial therapy does not reduce incidence of symptomatic UTI, complications or death, and is associated with adverse events.(6) Among women with ASB randomized to treatment, resistance to antibiotics among isolated bacteria increased.(7) Even among pregnant women, the treatment of ASB may not provide significant benefit.(8, 9) Various interventions have been proposed to reduce antibiotic treatment for ASB. Physicians have difficulty avoiding treatment of ASB when presented with positive culture results.

Recognizing the inappropriate treatment of ASB to be a problem in acute care, a novel intervention was defined, in which identification and susceptibility results for positive urine culture results were not made available to physicians, unless the physician called the microbiology laboratory.(10) This "modified reporting" was associated with a reduction in the rate of antibiotic treatment of AB from 48% to 12% (number needed to report for benefit = 3) among non-catheterized inpatients, using historical controls.

A randomized, unblinded controlled trial was performed in acute care in St. John's, among patients without indwelling catheters, using the same intervention.(11) Results of positive urine cultures from 110 consecutive inpatients at two urban hospitals were randomised to

standard report or modified report. Specimens randomized to the modified report were reported as follows: “This POSITIVE urine culture may represent asymptomatic bacteriuria or urinary tract infection. If urinary tract infection is suspected clinically, please call the microbiology laboratory for identification and susceptibility results.”

Exclusion criteria were age less than 18 years, pregnancy, presence of an indwelling urinary catheter, samples from patients already on antibiotics, neutropenia, or admission to an Intensive Care Unit. Patients were followed for seven days, and physician treatment decisions were observed. 76/110 (69%) of positive urine cultures represented ASB. The proportion of appropriate treatment (UTI treated plus ASB not treated) was higher in the modified arm than in the standard arm (44/55 (80.0%) vs 29/55 (52.7%), absolute difference=-27.3%, RR=0.42, p=0.002, Number needed to report for benefit=3.7).

There were two bacteremias in the modified report group, and one bacteremia in the standard report group, none of which were considered related to the intervention. There were two deaths in the modified report group, and one death in the standard report group, none of which were considered related to the intervention. Based on this trial, the intervention was considered safe over 7 days of followup, and effective to reduce inappropriate treatment, but further study would be required among populations excluded from the trial.

We propose to repeat the trial using an identical design and intervention, but including only urine collected from long term care facilities (LTCF). The control arm is standard of care. We hypothesize that the modified reporting intervention will also reduce treatment of ASB in the LTCF population, without causing harm.

Objectives

Research Question: Among patients with positive urine cultures collected from LTCF reported by Health Sciences microbiology laboratory, would restricted reporting, as compared to standard reporting, lead to a reduction in the rate of inappropriate antibiotic therapy without an increase in bacteremia or death over 30 days?

Trial design

Randomized controlled trial, 2 parallel groups with equal allocation, superiority analysis.

Methods: Participants, interventions, and outcomes

The proposed study is a randomized trial of two methods of laboratory reporting in which physicians are the main research participants. At the time of positive urine culture results, the specimen will be randomized in the laboratory using computer generated random numbers placed into serially numbered sealed, opaque envelopes, into two equal groups. One group will receive modified reporting, and the other group will receive standard reporting of bacterial identification and susceptibility. Physicians receiving modified reports will have the option to calling the laboratory to receive complete results, or not. Complete results will be released by laboratory information system to physicians who call to request them. Physicians will be informed about the study prior to initiation, and debriefed about the study after the results have been collected.

The primary efficacy outcome is proportion of appropriate antibiotic therapy prescribed by physicians, based on published diagnostic criteria for ASB and UTI among catheterized patients. Appropriate therapy is defined as any treatment for UTI, or no treatment for ASB. Inappropriate therapy is defined as no treatment for UTI, or treatment for ASB. The primary safety outcome is rate of bacteremia and death. The study investigators will determine the

diagnosis based on a chart assessment to determine if the patient has UTI, CA-UTI, ASB or CA-ASB.

The definition of UTI in LTCF will be based on 2017 Canadian LTCF surveillance guidelines.(12) For residents without an indwelling catheter, criteria 1 and 2 must be present with no other identified source of infection, OR criteria 2 and 3.

1. At least 1 of the following sign or symptom subcriteria:
    a. Acute pain, swelling, or tenderness of the testes, epididymis, or prostate in males
    b. Fever or leukocytosis and at least 1 of the following localizing urinary tract subcriteria:
        i. Acute dysuria
        ii. Acute costovertebral angle pain or tenderness
        iii. Suprapubic pain
        iv. Gross hematuria
        v. New or marked increase in incontinence
        vi. New or marked increase in urgency
        vii. New or marked increase in frequency
    c. In the absence of fever or leukocytosis, then 2 or more of the following localizing urinary tract subcriteria:
        i. Acute dysuria
        ii. Suprapubic pain
        iii. Gross hematuria
        iv. New or marked increase in incontinence
        v. New or marked increase in urgency
        vi. New or marked increase in frequency

2. $\geq 10^8$cfu/L of no more than 2 species of microorganisms from a midstream urine OR $\geq 10^5$ cfu/L of any number of organisms in a specimen collected by in-and-out catheter

3. A blood culture isolate is the same as the organism isolated from the urine and there is no alternate site of infection

For residents with an indwelling catheter (urine is collected from a single catheter urine specimen or a midstream voided urine specimen from a resident whose catheter has been removed within the previous 48 hours), criteria 1 and 2 must be present with no other identified source of infection, OR criteria 2 and 3.

1. At least 1 of the following sign or symptom subcriteria:

a. Fever, rigors, or new-onset hypotension, with no alternate site of infection

b. Either acute change in mental status or acute functional decline, with no alternate diagnosis and leukocytosis

c. New-onset suprapubic pain or costovertebral angle pain or tenderness

d. Purulent discharge from around the catheter

e. Acute pain, swelling, or tenderness of the testes, epididymis, or prostate in males

2. Urinary catheter specimen culture with $\geq 10^8$ cfu/L of any organism(s)

3. A blood culture isolate is the same species as the organism isolated from the urine, with the same resistance pattern, and there is no alternate site of infection

Study setting

Specimens will be collected from patients admitted to one (or more?) LTCF in St. John's, Newfoundland, Canada. The metropolitan area of St. John's has a population of 219,000 people (2017). Pleasantview Towers (430 beds) provides long term residential accommodation for frail

elderly with high care needs. One centralized microbiology laboratory performs all testing for the city.

Inclusion and exclusion criteria for participants

Consecutive positive urine cultures collected from patients admitted to LTCF will be included. All methods of urine collection will be included (midstream, in-and-out catheterization, indwelling catheter). Exclusion criteria will be urine cultures not collected from LTCF patients, pregnancy, antibiotic treatment at the time of collection, and patients known to have blood neutrophils <1.0 within 7 days.

Interventions

The modified report states "This POSITIVE urine culture may represent asymptomatic bacteriuria or urinary tract infection. If urinary tract infection is suspected clinically, please call the microbiology laboratory at 777-6936 between 0900 to 2300, or the microbiology technologist on-call at 570-9133 at night, for identification and susceptibility results." The standard report provides bacterial count, bacterial identification and bacterial susceptibility results.

The report is provided to the physician approximately 24 hours after receipt of the specimen, when cultures have been examined after overnight incubation. The intervention is a single report, so it is not possible to discontinue the intervention, or change allocation during the trial. There will no other influence on concomitant care or treatment.

Outcomes

Primary efficacy outcome:

Proportion of appropriate antibiotic therapy prescribed by physicians. Appropriateness is determined by investigators based on chart review, based on diagnosis of UTI or ASB. Appropriateness is determined within two days from positive urine culture.

Secondary efficacy outcomes:

Proportion of calls from physicians requesting complete report

Primary safety outcomes:

Mortality rate over thirty days from positive urine culture.

Bacteremia rate over thirty days from positive urine culture.

Adverse event rate over seven days from positive urine culture.

Participant timeline

	STUDY PERIOD				
	Enrolment	**Allocation**	**Post-allocation**		
TIMEPOINT	**Day -1**	**Day 0**	**Day 2**	**Day 7**	**Day 30**
ENROLMENT:	Urine specimen received at microbiology laboratory	Urine culture result reported to physician	Physician treatment decision made	Safety assessment	Safety assessment
Eligibility screen	X				
Allocation		X			
INTERVENTIONS:					
Reporting		X			
ASSESSMENTS:					
Appropriateness			X		
Adverse Events			X	X	X
Bacteremia			X	X	X
Mortality			X	X	X

Sample size

In the previous trial of the same intervention, modified reporting increased the appropriateness of treatment from 29/55 (52.7%) to 44/55 (80.0%) (p=0.002), for an absolute difference of +23%.(11) Accepting a risk of type 1 error of five percent, and a risk of type 2 error of twenty percent, the study will require 2N=90 patients. To account for missing data, recruitment will be increased to 100 patients.

The microbiology laboratory receives 130 urine specimens per day, with 30 percent reported as significant growth (40 specimens per day). Ten percent are submitted from LTCF (4 positive specimens per day). In the previous trial, approximately 40% of eligible specimens were excluded based on exclusion criteria. Recruitment of 100 specimens will require approximately 40-60 days.

The statistical test to be used is a comparison of proportions between two groups (T test, two-sided analysis). Because true diagnosis may be biased by lack of access to clinical information, an intention to treat analysis including all patients randomized will be performed.

Recruitment

Every urine specimen received for culture during the study period will be assessed for inclusion.

Allocation:

Sequence generation

Randomization sequence will be generated without blocking or stratification (Research Randomizer 4.0)(13).

Allocation concealment

Reporting assignments will be placed into serially numbered, sealed, opaque envelopes.

Implementation

Allocation sequence will be generated by investigators. Investigators will enroll specimens and assign specimens to reporting interventions.

Blinding

Trial participants (physicians) will not be blinded to the intervention because the laboratory report will reveal the intervention. Investigators will be blinded to assignment. Data analyst will not be blinded to assignment.

Data collection methods

After randomization and reporting, a physician investigator will assess inpatients for the true diagnosis of UTI or ASB at two days after reporting. Health records will be accessed including demographics, symptoms, treatment decisions and outcomes.

If patients are discharged from hospital before thirty days, primary care physicians will be contacted by phone for additional clinical information. If patients die before thirty days, available data will be analyzed.

Frequency of physician calls requesting complete reporting will be recorded.

Urine culture is reported according to laboratory protocol by licenced medical laboratory technologists, in categories of significant growth, non-significant growth, and no growth, based on quantity of growth and number of bacterial types detected. Antimicrobial susceptibility is reported according to laboratory protocol, including selected first and second-line antibiotics, as susceptible, intermediate or resistant. Drug cost and dosage suggestion are provided.

Data collection form attached.

Data management

Data collection will use a paper case report form, and entered into a trial database by a graduate student. Variables will be coded appropriately. The dataset will be protected using a

password and stored on a laptop computer during data entry. After data entry is completed, data integrity will be reviewed by a second investigator, and then the dataset will be locked for analysis.

Statistical methods

All specimens randomised and reported will be included in the Intention-to-treat (ITT) analysis. Specimens inappropriately included will be excluded from the Per-protocol (PP) analysis. The proportion of appropriate treatment will be compared using two-sided Pearson chi squared test (SPSS 23.0, IBM, USA). Adjusted analysis may be performed if appropriate. A subgroup defined as specimens in which physicians requested complete reporting will be analysed for appropriateness, compared to the standard reporting arm. Missing data will not be imputed.

Data monitoring

A data monitoring committee will not be used, as a single investigator will assume responsibility for data quality. A single interim analysis at approximately 50% recruitment will be performed, and the study stopped if the primary outcome achieves statistical significance.

Harms

Serious adverse events will be reported to the ethics committee within 24 hours. Adverse events will be collected by the investigators at day 2, day 7 and day 30. Patients with adverse events will be provided care in hospital.

Auditing

There will not be auditing of trial conduct during or after the trial.

Research ethics approval

The protocol will be submitted to the Provincial Health Research Ethics Board. Physician consent requirement will be requested to be waived because the intervention poses no more than minimal risk to participants. Patient consent requirement will be requested to be waived because physicians were the research subjects. A letter will be sent to all inpatient physicians informing them about the study prior to recruitment, and a debrief meeting, offering an opportunity to withdraw physician participation, will be provided.

The benefit of this study to patients includes a reduction in adverse events caused by inappropriate antibiotic treatment. The risk to patients includes possible untreated UTI. The benefit to physicians includes education toward appropriate treatment of ASB. The risk to physicians includes additional effort to access laboratory results for UTI.

Protocol amendments

Protocol amendments will be submitted to the ethics committee and trial registry and informed to investigators.

Consent or assent

Not applicable.

Confidentiality

Identification of patients will be required during data collection, but will be removed from trial dataset before analysis. No identifiers will be included in reporting of results.

Declaration of interests

The investigators and sponsor hold no financial interests in the trial.

Access to data

The trial dataset and protocol will be accessible to the investigators during the trial, and made publically available after the analysis is completed.

Ancillary and post-trial care

There will be no post-trial care provided.

Dissemination policy

Investigators will communicate trial results via unrestricted publication. All investigators are eligible for authorship, according to contribution.

Biological specimens

There will be no collection, testing or storage of biological specimens for genetic or molecular analysis.

Budget

The only expense of the project will be the graduate student to collect the data, perform the analysis and write the manuscript.

Implications

A reduction in inappropriate antibiotic treatment may reduce complications of treatment such as diarrhea due to *Clostridium difficile*, selection of bacteria towards drug resistance, and cost of treatment. If the intervention is determined to be safe, it may be considered for implementation in routine laboratory practice. The results will generalize to adult inpatients in Canada and around the world.

References

1. Lin K, Fajardo K, Force USPST. Screening for asymptomatic bacteriuria in adults: evidence for the U.S. Preventive Services Task Force reaffirmation recommendation statement. Ann Intern Med. 2008;149(1):W20-4. PubMed PMID: 18591632.
2. Hooton TM, Bradley SF, Cardenas DD, Colgan R, Geerlings SE, Rice JC, et al. Diagnosis, prevention, and treatment of catheter-associated urinary tract infection in adults: 2009 International Clinical Practice Guidelines from the Infectious Diseases Society of America. Clin Infect Dis. 2010;50(5):625-63. PubMed PMID: 20175247.
3. Nicolle LE, Bradley S, Colgan R, Rice JC, Schaeffer A, Hooton TM, et al. Infectious Diseases Society of America guidelines for the diagnosis and treatment of asymptomatic bacteriuria in adults. Clin Infect Dis. 2005;40(5):643-54. doi: 10.1086/427507. PubMed PMID: 15714408.
4. Gupta K, Hooton TM, Naber KG, Wullt B, Colgan R, Miller LG, et al. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: A 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. Clin Infect Dis. 2011;52(5):e103-20. doi: 10.1093/cid/ciq257. PubMed PMID: 21292654.
5. Colgan R, Nicolle LE, McGlone A, Hooton TM. Asymptomatic bacteriuria in adults. Am Fam Physician. 2006;74(6):985-90. PubMed PMID: 17002033.
6. Zalmanovici Trestioreanu A, Lador A, Sauerbrun-Cutler MT, Leibovici L. Antibiotics for asymptomatic bacteriuria. Cochrane Database Syst Rev. 2015;4:CD009534. doi: 10.1002/14651858.CD009534.pub2. PubMed PMID: 25851268.
7. Cai T, Nesi G, Mazzoli S, Meacci F, Lanzafame P, Caciagli P, et al. Asymptomatic Bacteriuria Treatment Is Associated With a Higher Prevalence of Antibiotic Resistant Strains in Women With Urinary Tract Infections. Clin Infect Dis. 2015. doi: 10.1093/cid/civ696. PubMed PMID: 26270684.
8. Smaill FM, Vazquez JC. Antibiotics for asymptomatic bacteriuria in pregnancy. Cochrane Database Syst Rev. 2015;8:CD000490. doi: 10.1002/14651858.CD000490.pub3. PubMed PMID: 26252501.
9. Kazemier BM, Koningstein FN, Schneeberger C, Ott A, Bossuyt PM, de Miranda E, et al. Maternal and neonatal consequences of treated and untreated asymptomatic bacteriuria in pregnancy: a prospective cohort study with an embedded randomised controlled trial. Lancet Infect Dis. 2015. doi: 10.1016/S1473-3099(15)00070-5. PubMed PMID: 26255208.
10. Leis JA, Rebick GW, Daneman N, Gold WL, Poutanen SM, Lo P, et al. Reducing antimicrobial therapy for asymptomatic bacteriuria among noncatheterized inpatients: a proof-of-concept study. Clin Infect Dis. 2014;58(7):980-3. doi: 10.1093/cid/ciu010. PubMed PMID: 24577290.
11. Daley P, Garcia DA, Inayatullah R, Penney C, Boyd S. Modified Reporting of Positive Urine Cultures to Reduce Inappropriate Treatment of Asymptomatic Bacteriuria Among Non-Pregnant Non-Catheterized Inpatients. A Randomised Controlled Trial. Infection Control and Hospital Epidemiology (accepted). 2018.
12. Happe J, Stoll F, Bilu L, Cargill K, Cuff A, Cerkowniak G, et al. Surveillance Definitions of Infections in Canadian Long Term Care Facilities. Can J Infect Control. 2017;Fall 2017 (Suppl):10-17.
13. Urbaniuk GC, Plous S. Research Randomizer (Version 4.0) [Computer software] 2015 [Retrieved on December 15, 2016]. Available from: http://www.randomizer.org/.