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Modified Reporting of Positive Urine Cultures Collected from Indwelling Catheters Among Inpatients, 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 of 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 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 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 acute care 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 indwelling catheters. The control arm is standard of care. We hypothesize that the modified reporting intervention will also demonstrate effectiveness at reducing treatment of ASB in this population, without causing harm.

Objectives

Research Question: Among inpatients with positive urine cultures collected from indwelling catheters 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?

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 by computer generated random number 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 identification and susceptibility. Physicians will then have the option of calling the laboratory to receive the results or not. Complete results will be released by telephone and 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 definition of CA-UTI will be based on the Infectious Diseases Society of America guidelines,(2) not the Centers for Disease Control National Health Safety Network surveillance definition, which is not designed for clinical care.(12) The definitions to be used in patients with indwelling urethral, indwelling suprapubic, or intermittent catheterization are as follows:

CA-UTI

1. presence of symptoms or signs compatible with UTI with no other identified source of infection AND
2. $\geqslant 10^3$ colony-forming units (cfu)/mL of $\geqslant 1$ bacterial species in a single catheter urine specimen or in a midstream voided urine specimen from a patient whose

urethral, suprapubic, or condom catheter has been removed within the previous 48 h

CA-ASB

1. presence of ⩾105 cfu/mL of ⩾1 bacterial species in a single catheter urine specimen in a patient without symptoms compatible with UTI.

Signs and symptoms compatible with CA-UTI include new onset or worsening of fever, rigors, altered mental status, malaise, or lethargy with no other identified cause; flank pain; costovertebral angle tenderness; acute hematuria; pelvic discomfort; and in those whose catheters have been removed, dysuria, urgent or frequent urination, or suprapubic pain or tenderness. In patients with spinal cord injury, increased spasticity, autonomic dysreflexia, or sense of unease are also compatible with CA-UTI.

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. The primary safety outcome is rate of bacteremia and death.

Study setting

Specimens will be collected from inpatients admitted to one of the two tertiary care academic hospitals in St. John's, Newfoundland, Canada. Health Sciences Center (346 acute care beds) provides medicine, pediatric and surgery inpatient services, critical care, cardiac surgery, neurosurgery, plastic surgery, burn unit, obstetrics/gynecology and acute psychiatry. St. Clare's Mercy Hospital (205 acute care beds) provides medicine and surgical inpatient services, critical care, general surgery, vascular surgery, thoracic surgery, otolaryngology, orthopedics,

and ambulatory services. The metropolitan area of St. John's has a population of 219,000 people (2017). One centralized microbiology laboratory performs all testing for the city.

Inclusion and exclusion criteria for participants

Consecutive positive urine cultures collected from indwelling catheters from patients greater than or equal to 18 years of age, admitted to acute care will be included. Inpatients must be admitted to Health Sciences Center or St. Clare's Mercy hospitals only, to facilitate access to inpatient records. Exclusion criteria will include urine cultures not collected from indwelling catheters, pregnancy, antibiotic treatment at the time of collection, patients in the Intensive Care Unit and patients with blood neutrophils <1.0 within 7 days, which will help protect immunocompromised individuals, and admission to a urologist.

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 CA-UTI or CA-ASB. Appropriateness is determined within seven days from positive urine culture.

Secondary efficacy outcomes:

Proportion of calls from physicians requesting complete report

Primary safety outcomes:

Mortality rate over seven days from positive urine culture.

Bacteremia rate over seven 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**
ENROLMENT:	Urine specimen received at microbiology laboratory	Urine culture result reported to physician	Physician treatment decision made	Safety assessment
Eligibility screen	X			
Allocation		X		
INTERVENTIONS:				
Reporting		X		
ASSESSMENTS:				
Appropriateness			X	
Adverse Events			X	X
Bacteremia			X	X
Mortality			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). Twenty-five percent are submitted from inpatients (10 specimens per day). Approximately 33% of inpatient urines are collected from catheters, however collection method is not always provided to the laboratory. This leaves approximately three urine specimens per day which may be eligible for inclusion. In the previous trial, approximately 40% of eligible specimens were excluded based on exclusion criteria. Recruitment of 100 specimens will require approximately 60-90 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. One investigator will serve as outcome assessor, and will be blinded to assignment. Data analyst will not be blinded to assignment.

Data collection methods

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

If patients are discharged from hospital before seven days, primary care physicians will be contacted by phone for additional clinical information. If patients die before seven 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 will be entered into the trial dataset by a single investigator. Data collection will use a paper case report form, and entered into a trial database by a single investigator. 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 will not be performed. 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 significan

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 and day 7. 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 CA-UTI. The benefit to physicians includes education toward appropriate treatment of CA-ASB. The risk to physicians includes additional effort to access laboratory results for CA-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.

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