A Randomized Controlled Trial of Modified Reporting of Positive Urine Cultures to Reduce Inappropriate Treatment of Asymptomatic Bacteriuria in Long Term Care Facilities

by

© Zahra Rehan, BSc.

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Abstract

There is a high rate of inappropriate antibiotic treatment in long-term care facilities, prescribed for asymptomatic bacteriuria (ASB). We conducted a prospective, randomized and unblinded superiority trial to test whether modified reporting of positive urine cultures reduced inappropriate antibiotic treatment without increasing adverse events or mortality. Consecutive positive urine cultures collected from non-catheterized patients from 8 long-term care facilities in St. John's, NL were randomized in the laboratory between a standard (identification and susceptibility) or modified (without identification and susceptibility) report, between November 2018 and June 2019. The patients were followed for thirty days after the report. The diagnosis of a urinary tract infection (UTI) and ASB were made following standard criteria using prospective chart review. 100 positive urine cultures were included in intention-to-treat analysis and 96 were included in per-protocol analysis. 62/100 (62%) patients were diagnosed with ASB and 38/100 (38%) with UTI. 41/62 (66%) patients with ASB were treated and 35/38 (92%) of patients with UTI were treated. In the modified reporting arm, the lab was called to report the identification and susceptibility in 30/51 (59%) reports. The rate of appropriate treatment (untreated ASB + treated UTI) was higher in the modified report arm compared to the standard report arm: 30/48 (63%) vs. 24/48 (50%), (+13%, RR=1.25, 95% CI (0.88, 1.79). There were 2/51 (3.9%) deaths in the modified arm and 0/49 (0%) deaths in the standard arm. Modified reporting reduced treatment of ASB, but without statistical significance. Modified reporting is a safe method to reduce inappropriate antibiotic treatment in long-term care facilities.

General Summary

There is a high rate of unnecessary antibiotic treatment in healthcare, especially in long-term care facilities (LTCF). To reduce inappropriate antibiotic treatment, this study introduced a modified report for urine cultures which were ordered for suspicion of urinary tract infection (UTI) in the elderly. Urine cultures collected from patients in LTCFs in St. John's, NL were sent to a microbiology laboratory for reading and reporting of results. The laboratory provided either a standard (information identifying bacteria and drug that would target this micro-organism) or a modified (withholding the aforementioned information) report. 100 urine cultures were included in the study, 38 patients were diagnosed with UTI and 62 patients were diagnosed with a bacterial infection, but no clinical symptoms. We found that appropriate treatment was higher in the modified report (treated UTI, untreated bacterial infection with no symptoms) compared to the standard report. We concluded that modified reports reduce inappropriate treatment, but not with statistical significance; however, modified reporting is a safe method to reduce inappropriate antibiotic use in LTCFs.

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I would like to identify that there is a manuscript undergoing revisions which reports the same research findings as outlined in this thesis project.

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List of Abbreviations and Symbols

ASB Asymptomatic Bacteriuria

AR Antibiotic resistance

AMS Antimicrobial stewardship

ARTI Acute Respiratory Tract Infection

CFUs Colony-forming Units

CI Confidence Interval

CPGs Clinical Practice Guidelines

ICU Intensive Care Unit

IDSA Infectious Diseases Society of America

ITT Intention-to-treat

PP Per-protocol

RR Relative Risk

SIRS Systemic Inflammatory Response Syndrome

UTI Urinary Tract Infection

Chapter 1: Introduction

1.1 Urinary Tract Infection (UTI): Pathophysiology and Epidemiology

The pathophysiology of UTI is periurethral contamination by a bacterial pathogen residing in the gut, that accesses and ascends the urethra, and migrates to the bladder[1]. If the pathogen continues to multiply and evades the host immune response, it will ascend to the kidneys, and may cross the tubular epithelial barrier to gain access to the blood stream causing bacteremia[2]. The most common urinary pathogen is the Gram-negative bacillus *Escherichia Coli* (*E. coli*), which is primarily responsible for community-acquired infections and is the most common cause of UTI in all settings[3]. Other common pathogens include *Staphylococcus*, *Klebsiella*, *Enterobacter, Proteus* and *Enterococcus*; these organisms are primarily catheter-associated and responsible for hospital and community acquired infections[3].

Host defense mechanisms in the urinary tract eliminate bacteria and prevent bacterial adherence. In females, estrogen stimulates vaginal mucosa to proliferate; this allows for the removal of bacteria through a sloughing mechanism[4]. In males, the most effective local defenses are urethral length and the mechanical action of urine flow[5]. There are non-pathogenic microorganisms that create a local environment which is hostile for pathogenic bacteria, such as an acidic pH that inhibits Gram-negative bacterial proliferation[5]. Furthermore, urine is inhibitory to bacterial growth because of high osmolality. Urea is another substance in urine that is highly inhibitory to microorganisms[5]. The ureter itself serves as a mechanical barrier to bacterial attachment as a result of its peristaltic activity. Another host defense is the immune

system; the local immune response is mediated by polymorphonuclear leukocytes which remove bacteria through phagocytosis, and the humoral response that produces antibodies against antigens[2].

Cystitis is an infection of the bladder only, and presents with urinary frequency, urgency, incontinence, dysuria and suprapubic tenderness. Pyelonephritis is an infection of one or both kidneys that presents with fever, flank, pain, nausea, vomiting and rigors[4]. An uncomplicated UTI affects individuals who are healthy, with no structural or obstructive abnormalities of the urinary tract; a complicated UTI is an infection in the presence of a structural or functional abnormality including neurological disease, stones or tumours, immunosuppression, pregnancy or the presence of foreign bodies such as indwelling catheters[1].

UTIs are the most common bacterial infections of humans, affecting 150 million people worldwide every year[2]. In Canada, UTI remains in the top ten causes for inpatient hospitalizations and outpatient care in the elderly (65+) and the number one reason for emergency department visits[6]. The prevalence of UTI is higher among women and increases with age[7]. Females have a shorter urethral length and a vaginal environment that is conducive to microbial colonization[1]. The frequency of UTI among females increases during the years of maximal sexual activity. In postmenopausal women, other risk factors for UTI contribute, including bladder catheterization, history of antibiotic use and current health status[8]. At extremes of age and with co-morbidities, males have a higher incidence of UTI and greater UTI-related mortality than females do[9].

UTIs are the leading cause of bacteremia in the elderly; the likelihood of bacteremia steeply increases with the presence of an indwelling catheter[10]. A study from the USA reported estimated cost associated with UTI of $2 billion annually[7]. In acute care settings, the cost of care varies from $600 for UTI to over $50,000 for bacteremia[11]. In long-term care facilities (LTCF), UTIs are a common indication for resident hospitalization and antibiotic use[12].

The risk factors for UTI can be classified into factors that expose a host to pathogens and factors that enhance colonization by pathogens. Most pathogens have virulence factors that allow them to survive in the urinary tract, including biofilm formation, adhesins, toxins and urothelial cell invasion[9]. Factors that enhance colonization include host immunocompromise, such as an indwelling catheter which bypasses host defence mechanisms. Subpopulations at increased risk of UTI include infants, pregnant women, the elderly, patients with spinal cord injuries, diabetes, obesity, multiple sclerosis, compromised immune system, patients with underlying structural abnormalities of the urinary tract and patients with history of prior infections[7].

Antibiotics are used to treat UTIs. The Infectious Diseases Society of America (IDSA) has published clinical guidelines for the management of acute uncomplicated cystitis and pyelonephritis in women[13]. The recommended treatment for acute uncomplicated cystitis is nitrofurantoin, trimethoprim/ sulfamethoxazole or fosfomycin[14]. The second-line antibiotics used for treatment failure or intolerance are fluoroquinolones, and third-line antibiotics include beta-lactams, amoxicillin/clavulanate, cefdinir and cefaclor[14]. Selection of antibiotic treatment is based on antibiotic resistance (AR) in the organism and risk of adverse effects in the host[15]. Other factors to consider

when prescribing include cost, availability, allergies and patient compliance[16]. Antibiotics negatively influence the ordinary intestinal microflora, creating selection of AR strains[17].

1.2 Urinary Tract Infections in LTCF

Residents of LTCF are frail and prone to developing infections. In fact, antibiotics are amongst the most commonly prescribed medications in nursing homes and infections are a major source of resident morbidity and mortality[18]. Elderly people are at increased risk of acquiring AR bacteria which lead to poorer health outcomes. These health outcomes can include increased length of hospital stay, functional decline, increased healthcare expenditure and all-cause mortality[19]. In USA, hospital admissions increased by 48.8% from 1997 to 2006 for elderly people with resistant infections[20]. The older population are more susceptible to AR due to physiological changes and comorbidities. Further, LTCFs may contribute to AR as they are reservoirs of resistant bacteria and have high rates of antibiotic prescriptions[21]. There is an increased risk of spreading these organisms to other residents due to crowding, and to patients in other health care settings during care transitions[18]. Establishing improvements in antibiotic prescribing practices in LTCF may address these risks.

1.3 Asymptomatic Bacteriuria: Definitions and Management

UTI is diagnosed using bacterial culture of urine. Where pathogenic bacteria are detected in significant numbers and the patient presents with signs or symptoms of

genitourinary infection, UTI is diagnosed. Asymptomatic bacteriuria (ASB) is defined as significant numbers of bacteria in a urine culture, in the absence of clinical manifestations of UTI[22]. In patients without indwelling catheters, ASB is defined as the isolation of 10^5 colony-forming units of bacteria (CFU)/mL in a voided urine specimen[22]. In non-catheterized females, two consecutive positive urine cultures constitute a diagnosis of ASB, but in non-catheterized males, a single specimen is sufficient for diagnosis[22].

The prevalence of ASB is influenced by factors such as age, sex, genitourinary abnormalities and comorbidities[23]. ASB is more common among women, diabetics, patients with chronic indwelling catheters and the elderly. The prevalence of ASB in healthy, young, nonpregnant women is 1-5%, whereas in elderly women, ASB prevalence is 32-50%[3]. In healthy young men, ASB is infrequent but the prevalence increases in older men[23]. ASB frequency increases in institutionalized patients with greater functional impairment, affecting 25-50% of females and 15-35% of males in institutionalized facilities[3].

A urinary catheter facilitates colonization by microbes and is associated with a prevalence of ASB of 9-23% in short-term catheter use, and 100% in long-term catheter use[23].

Testing and treatment of ASB is only appropriate if adverse outcomes from bacteriuria can be prevented by antibiotics[24]. The treatment of ASB has not been shown to prevent occurence of symptomatic UTI, complications or death[25]. In fact, antibiotic therapy for ASB increases adverse drug effects and AR[24]. In premenopausal, nonpregnant and diabetic women, screening for and treatment of ASB is not indicated.

For older people residing in the community or LTCF, routine screening and treatment of ASB is not recommended. For patients with spinal cord injuries or urethral indwelling catheters, screening for and treatment of ASB is not recommended[24].

There are limited populations in which screening and treatment of ASB is recommended. Among pregnant women, who are at an increased risk for adverse outcomes of UTI including pyelonephritis and premature labor, clinical trials demonstrate antibiotic therapy for ASB to be effective in preventing these outcomes[15]. Among patients undergoing traumatic urologic interventions with a high probability of mucosal bleeding, ASB increases the risk of bacteremia, therefore, the recommendation is to treat ASB[24].

1.4 Asymptomatic Bacteriuria: Antibiotic Usage and Antimicrobial Stewardship

There is an ongoing global crisis of AR infections[19]. A few decades ago, this problem was not a widespread concern because pharmaceutical companies were continuously investing in the research and development of new antibiotics. With a limited profit timeframe, discovery and development of new antibiotics is no longer a lucrative investment for pharmaceutical companies[26]. The future effectiveness of antibiotics is threatened by resistant microbes, because new antibiotic research and development has slowed. Infections caused by multidrug-resistant bacteria increase morbidity, mortality and cost of care; these organisms are considered to be a substantial threat to human health[27]. Many factors contribute to AR including selection pressure from antibiotic use, gene transfer between organisms, societal pressures, inadequate

diagnostics, insufficient surveillance, prevention and control, and ineffective regulation of antibiotic use in agriculture[27].

Misuse of antibiotics in human medicine is common. Inappropriate patterns of prescribing include prescribing antibiotics for viral infections, overprescribing for mild bacterial infections, and overshooting treatment durations[28]. It is estimated that a half of prescriptions are inappropriate and given for conditions for which antibiotics provide no benefit, such as acute respiratory tract infections (ARTI)[29]. Further, unnecessary use of antibiotics exposes the patient to adverse drug and health outcomes. Because of a fast-approaching threat of losing antibiotics as treatment for bacterial infections, there are antibiotic stewardship interventions being put into place to protect patients and the public from antibiotic resistance and adverse outcomes[30]. The inappropriate use of antibiotics for treating ASB is an antibiotic stewardship problem.

Antimicrobial stewardship (AMS) is the process of prescribing the correct antibiotic, at an optimal dose and duration, to the appropriate patient while minimizing risks and adverse events associated with unnecessary antibiotic use[18]. The methods of AMS include measuring antibiotic use and appropriateness, designing interventions to improve antibiotic use, and measuring the effectiveness for these interventions. AMS programs aim to improve prescribing patterns, reduce antimicrobial resistance, drug costs, and hospital acquired infections[31]. An area of medicine that may benefit from AMS is the appropriate avoidance of treatment of ASB in LTCF. A variety of AMS interventions have been proposed to reduce antibiotic treatment for ASB including microbiology laboratory-based solutions, educating physicians and drawing peer comparisons[32].

Some strategies for AMS are antibiotic “timeouts”, prior authorization, and prospective audit and feedback[31]. An antibiotic “timeout” is designed to prompt a reassessment of the need and choice of antibiotics after diagnostic and clinical information is available. With prior authorization, the use of certain antibiotics can be restricted based on the spectrum of activity, cost or associated toxicity profile, to ensure appropriate use before initiating therapy by consulting with an expert. A prospective audit and feedback strategy is where audits are conducted by external experts or staff who do not play a role in treatment delivery. Other AMS interventions include education, providing local treatment guidelines, automatic changes from intravenous to oral antibiotics, dose adjustments, dose optimization, automatic alerts in situations where therapy may be duplicative, time-sensitive automatic stop orders and detection or prevention of antibiotic-related drug-drug interactions[31]. AMS interventions for ASB include avoiding unnecessary urine culture collection and ASB treatment[31].

Laboratory-based AMS interventions may be effective. In a case-control study by Leis et al., the microbiology laboratory reported positive urine cultures with a general statement requesting the treating physician to call the laboratory for further information, if there was a clinical suspicion of UTI[35]. This modified reporting significantly reduced inappropriate therapy from 48% to 12% ($p=0.002$), with no adverse outcomes among untreated patients. This demonstrated that modified reporting can reduce antimicrobial therapy for ASB.

We performed a randomized trial of modified reporting in non-catheterized acute care inpatients[36]. The modified arm resulted in a higher proportion of appropriate

treatment compared to the standard arm (80.0% vs 52.7%, p=0.002) without an increase in mortality and/or adverse events (10.0% vs 14.3%, p=0.37).

1.5 Urine Culture Implications

A positive urine culture plays an important role in promoting antimicrobial use in ASB. Symptomatic patients are more likely to receive therapy at the time of presentation, compared to asymptomatic patients who are treated in response to positive culture (Leis et al., 2014). According to clinical practice guidelines (CPGs), urine cultures should only be collected in the presence of UTI symptoms[37]. However, urine cultures are often collected in the absence of urinary symptoms and for inappropriate reasons including foul-smelling or cloudy urine, routine admission and follow-up screening or nonspecific symptoms of clinical decline such as malaise, behavioral changes, lethargy, weakness, falls or poor appetite[23].

In LTCF, a positive urine culture is often interpreted as the cause for a change in a patient's clinical status. In a prospective cohort study involving nursing home residents and cases of clinically suspected UTI episodes, there was a poor correlation between the presenting symptoms, urine culture results and decision to initiate antibiotics. The study demonstrated a weak association between dysuria, change in character of urine and change in mental status with bacteria and pyuria[12]. In this setting, another factor that influences the pattern of ordering urine cultures is a greater prevalence of cognitive impairment in residents' which can impede their ability to articulate symptoms[37]. Cultures are ordered for changes in cognitive status, not true urinary symptoms. There

is no consensus on which signs are reliable markers of UTIs[23]. Further research on symptom characterization will be necessary to reliably diagnose UTI and reduce the treatment of ASB in the elderly population. Physicians have difficulty avoiding treatment of ASB when presented with a positive urine culture report[38].

Other interventions to reduce treatment of ASB included an algorithm, which failed to reduce urine culture collection rate[33] and prospective audit and feedback, which had no effect on the decision to initiate treatment[35].

In Eastern Health microbiology laboratories, urine samples represent half of all specimens received, and the majority are reported as significant growth above a pre-determined threshold without providing an accurate range to quantify the microbes. The literature has established that most of these samples represent ASB. This study will focus on a laboratory-based intervention that influences decision-making through the strategic reporting of microbiology results while preserving physician autonomy.

The research question is: For adult non-catheterized patients with positive urine cultures, does the introduction of laboratory-based intervention of modified reporting reduce inappropriate antibiotic therapy compared to standard reporting in LTCF?

Chapter 2 – METHODS

2.1 Design

The study was a prospective, randomized, parallel, unblinded superiority trial comparing two different methods of reporting for positive urine cultures.

All consecutive urine specimens received for urine culture were inoculated onto blood and MacConkey agar plates, incubated overnight and interpreted according to the standard laboratory procedures. Consecutive eligible positive urine cultures were randomized to standard reporting or modified reporting, prior to result entry into the electronic health record system. For patients allocated to modified reporting, complete results were available to physicians by telephone at all hours of the day. Upon request by physicians, complete results were released over telephone and documented in the electronic medical chart. Eligible patients enrolled in the study were followed for thirty days after reporting, using electronic medical records. If information was missing from electronic records, paper charts were reviewed by an investigator from study personnel.

After randomization, the clinical diagnosis of UTI or ASB was determined at 72 hours, based on 2017 Canadian LTCF surveillance guidelines[39]. The criteria is outlined in Table 1.

Table 1: Clinical Diagnosis Criteria

Criteria
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 increased 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

ASB was defined as the absence of any of these signs or symptoms. Each patient was reassessed at 72 hours to collect data on treatment decisions (time of prescription, drug given, dosage and indication). Each patient was reassessed at seven days and thirty

days to collect data on adverse events (bacteremia, mortality and adverse effects). ASB was considered to be treated if an antibiotic was prescribed for patients who did not present with another indication that required the use of an antibiotic. Conversely, UTI was considered to be untreated if patients presented with the signs or symptoms above but were not prescribed antimicrobial treatment.

Appropriate therapy was defined as any treatment for UTI, or no treatment for ASB. Inappropriate therapy was defined as no treatment for UTI, or treatment for ASB. The duration of therapy or type of antibiotic chosen given susceptibility patterns was not considered in this classification.

2.2 Participants:

Between November 5, 2018, and June 29, 2019, consecutive positive urine cultures were processed and assessed by the Public Health Microbiology Laboratory (PHML). All urine specimens submitted for culture were from 8 LTCF facilities situated in St. John's, Newfoundland, Canada. The PHML is responsible for performing all microbiology testing for St. John's; approximately 10% of urine culture submissions are from LTCFs.

The eligibility of specimens was assessed prospectively using electronic medical records. In cases where medical records were not explicit enough to determine eligibility of the patient, the ward was called by a study investigator to complete the missing information. The inclusion criteria were positive urine cultures collected midstream or from in-and-out catheterization from patients admitted to LTCF facilities. The exclusion criteria

were urine cultures collected from an indwelling catheter, urine cultures collected from patients not residing in LTCF facilities, pregnancy, age ≤18 years, admission to acute care hospitals, antibiotic treatment at the time of collection, neutropenia and admission to ICU or urology service.

2.3 **Intervention**

The eligible patients were randomized into two arms: standard report (SR) or modified report (MR). The standard report included bacterial count, bacterial identification and bacterial susceptibility information. The MR stated: “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 xxx-xxxx between 0900 to 2300, or the microbiology technologist on-call at xxx-xxxx at night, for identification and susceptibility results”. If a physician requested for the full report, the full report was received immediately by telephone and documented in the electronic health record.

2.4 Outcome

The primary efficacy outcome was the proportion of appropriate antibiotic treatment prescribed. The secondary efficacy outcome was the proportion of requests for complete reports in the MR arm.

The following safety outcomes were recorded: bacteremia rate over thirty days, mortality rate over thirty days, and adverse event rate over 72 hours and over thirty days. We searched for adverse events using the Systemic Inflammatory Response Syndrome

(SIRS) criteria, such as changes in vital signs and mental status, hyperglycemia, abnormal rate of respirations and white blood cell count, and significant edema. Additionally, any other adverse effects that did not fall under the SIRS criteria were also recorded up to thirty days after the positive urine culture.

There were no interactions between study investigators and attending physicians. If patients were discharged during the thirty-day follow-up period, health records were reviewed, and the primary care physician was contacted to gather adverse events.

2.5 Sample Size

In the absence of other literature testing the same intervention, the sample size was calculated based on the effect size observed in our previous study[36]. The previous trial reported an increase in appropriateness of treatment from 29/55 (52.7%) in the standard arm to 44/55 (80.0%) in the modified arm for an absolute difference of +27%. For a comparison of two proportions, accepting a significance level (α) of 5% and a risk of type 2 error (β) of 20%, a sample size of 2N=90 specimens was determined. To account for missing data or loss to follow-up, 100 eligible specimens were recruited.

2.6 Stopping Rules

There was no predefined stopping rule; the study was stopped once the planned sample size was achieved. No interim analyses were planned or completed.

2.7 Randomization

A list of random numbers was used to generate a randomization sequence without blocking or stratification, using Microsoft Excel, Version 1903. The allocation concealment was executed by placing the reporting assignments into serially numbered, sealed and opaque envelopes. The allocation sequence was revealed by study investigators as they enrolled eligible specimens and assigned specimens to reporting interventions. The envelopes were opened strictly as numbered.

2.8 Blinding

Trial participants (physicians) were not blinded to the intervention because the laboratory report revealed the intervention arm. The patients were not aware of the study. Assessors of diagnosis were not blinded to assignment, as the report was available in the medical record. The data analysts were not blinded to assignment.

Prior to study recruitment, a general notice was sent to all physicians working in LTCFs informing them about the study. After trial completion, a debrief meeting was scheduled which offered physicians the opportunity to withdraw participation.

2.9 Statistical Analysis

All specimens randomized and reported were analyzed using intention-to-treat (ITT) analysis. Inappropriately included specimens were excluded from a per-protocol

(PP) analysis. The proportion of appropriate treatment in each arm was compared by running a two-sided Pearson Chi-squared test using the SPSS Statistics software. Similarly, subgroup analysis was conducted using the secondary efficacy outcome (proportion of requests for complete reports) to assess the efficacy of the intervention and analyse for appropriateness within the MR arm.

2.10 Ethics

The protocol was approved by the Provincial Health Research Ethics Board on July 16, 2018 (file 2018.121). The requirement for patient consent was waived because physicians were the research subjects. The requirement for physician consent was waived because the intervention posed minimal risk to participants, and awareness of the study may have influenced therapy decisions.

All serious adverse events were reported to the ethics committee within 24 hours, including mortality. Adverse events were collected by study investigators at Day 3 and up to Day 30.

Chapter 3 – RESULTS

3.1 Participant Flow

170 consecutive positive urine cultures were assessed between November 5th, 2018 and June 29th, 2019. 70 specimens were excluded because they did not meet the inclusion criteria (Figure 1). 100 samples were randomized and included in the ITT analysis: 49 were randomized to SR arm and 51 were randomized to MR arm. Four samples were excluded from the study; one was randomized to standard reporting (admitted to acute care hospital) and three were randomized to modified reporting (samples collected from indwelling catheters). These samples did not follow the protocol; therefore, they were included in ITT analysis but excluded in PP analysis. The last patient follow-up period ended on July 29th, 2019. All participants were analyzed in originally assigned groups.

Figure 1. Participant Flow

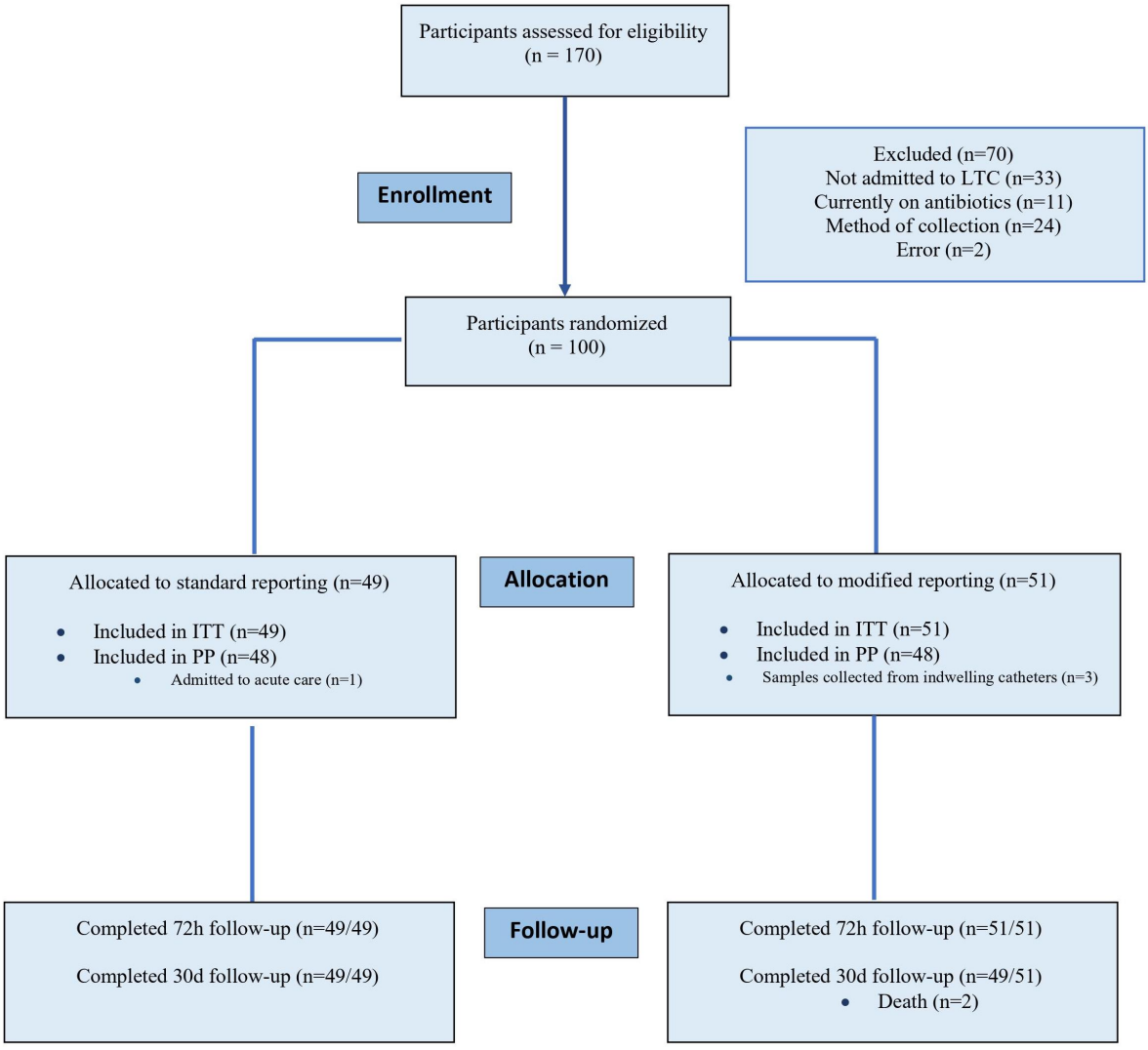

Figure 1 Selection process for participant inclusion.

3.2 Baseline Demographics

The two groups were comparable in demographics (Table 2), with similar mean age ± SD (SR 74.0 ± 17.7 years, MR 76.1 ± 12.5 years) and proportion of females (SR 71.4%, MR 66.7%). 38% (38/100) of all positive urine cultures were defined as UTI and 62% (62/100) of all positive urine cultures were defined as ASB. In terms of the true diagnosis, the proportion of UTI (SR 38.8%, MR 37.3%) and ASB (SR 61.2%, MR 62.7%) were comparable in both reporting arms. 76% (76/100) were treated with antibiotics: 41/62 (66.1%) were treated for ASB and 35/38 (92.1%) were treated for UTI.

Table 2. Patient Demographics

	Standard Reporting (n=49)	Modified Reporting (n=51)
Age (mean +/- SD)	74.0 +/- 17.7 years	76.1 +/- 12.5 years
Females	35/49 (71.4%)	34/51 (66.7%)
Urinary Tract Infection (UTI)	19/49 (38.8%)	19/51 (37.3%)
Asymptomatic Bacteriuria (ASB)	30/49 (61.2%)	32/51 (62.7%)

3.3 Efficacy Outcomes

The primary efficacy outcome of appropriate treatment was slightly higher in the modified arm than in the standard arm (Table 3). For the ITT analysis, the proportion of appropriate treatment in the modified arm was 31/51 (60.8%) vs. 25/49 (51.0%) in the standard arm, absolute difference= +9.8%, RR=1.19, 95% CI (0.84, 1.69). In the PP analysis, the proportion of appropriate treatment in the modified arm was 30/48 (62.5%) vs. 24/48 (50.0%) in the standard arm, absolute difference= +12.5%, RR=1.25, 95% CI (0.87, 1.79).

Table 3. Appropriate Treatment: Standard Arm vs. Modified Arm

	Report		Absolute Risk Reduction	Relative Risk (95% CI)
	Standard	Modified		
ITT population	25/49 (51.0%)	31/51 (60.8%)	+9.8%	1.19 (0.84, 1.69)
PP population	24/48 (50.0%)	30/48 (62.5%)	+12.5%	1.25 (0.87, 1.79)

The secondary efficacy outcome of appropriate treatment was slightly higher in the modified arm where there were no callbacks for complete reports (Table 4). For the ITT analysis, the proportion of appropriate treatment in the callback modified arm was 16/29 (55.2%) vs. 15/22 (68.2%) in the no callback modified arm, absolute difference= -13.0%, RR=0.81, 95% CI (0.52, 1.25). In the PP analysis, the proportion of appropriate treatment

in the callback modified arm was 15/28 (53.6%) vs. 15/20 (75.0%) in the no callback modified arm, absolute difference= -21.4%, RR=0.71, 95% CI (0.47, 1.10).

Table 4. Appropriate Treatment: Requests For Complete Reports in Modified Arm

	Modified Report		Absolute Risk Reduction	Relative Risk (95% CI)
	Callback	No Callback		
ITT population	16/29 (55.2%)	15/22 (68.2%)	-13.0%	0.81 (0.52, 1.25)
PP population	15/28 (53.6%)	15/20 (75.0%)	-21.4%	0.71 (0.47, 1.10)

Breaking down the analysis to subgroups, it was observed that the overall difference in proportion of appropriate treatment was caused by a change in the proportion of treatment of ASB and a slight change in the proportion of treatment of UTI (Table 5). For the ITT analysis, there was a greater proportion of untreated ASB in the modified arm in comparison to the standard arm, 13/32 (40.6%) vs. 8/30 (26.7%) respectively; absolute difference = +13.9%, RR=1.57 (p=0.25). Similarly, in PP analysis, the rate of untreated ASB was greater in the modified arm in comparison to the standard arm, 12/29 (41.4%) vs. 7/29 (24.1%) respectively; absolute difference = 17.3%, RR=1.71 (p=0.16). With both ITT analysis and PP analysis, there were a greater proportion of untreated UTI in the standard arm (2 cases) compared to the modified arm (1 case).

Table 5. Subgroup Analysis According to Diagnosis.
Proportion of Appropriate Treatment

	Report		Absolute Risk Reduction	Relative Risk (95% CI)
	Standard	Modified		
ITT population				
UTI (n=38)	17/19 (89.5%)	18/19 (94.7%)	+5.2%	1.06 (0.87,1.28)
ASB (n=62)	8/30 (26.7%)	13/32 (40.6%)	+13.9%	1.57 (0.76,3.26)
PP population				
UTI (n=38)	17/19 (89.5%)	18/19 (94.7%)	+5.2%	1.06 (0.87,1.28)
ASB (n=62)	7/29 (24.1%)	12/29 (41.4%)	+17.3%	1.71 (0.79,3.73)

3.4 Safety Outcomes

There was no bacteremia in the modified reporting arm and one bacteremia observed in the standard reporting arm (Table 6). The positive blood culture was collected on Day 22 of the study follow-up period. Because the patient was randomized to the standard arm and received treatment for ASB, the bacteremia was not considered related to the study intervention. There were two deaths observed, both in the modified reporting arm (one untreated ASB and one treated ASB). Both deaths were not considered related

to the study intervention (Table 7). For the untreated ASB patient, the death was reported as a result of congestive heart failure. For the treated ASB patient, the death was reported as a clinical decline. There was no death observed in the standard reporting arm. Each case of death and bacteremia was investigated by an infectious diseases specialist; none were found to be related to the MR.

There was complete data available for a 72-hour safety assessment on all 100 patients. There were complete data available for thirty-day safety assessments on 98 patients (two deaths during follow-up). At 72 hours, features of SIRS were common in both arms, SR 6/14 (42.8%), MR 8/14 (57.1%), p=0.45 (Table 8). At thirty days, features of SIRS were also common in both arms (SR 27/61 (44.2%), MR 34/61 (55.7%) p=0.20); majority of these symptoms included tachycardia, high temperature and altered mental status (Table 9). Adverse events at thirty days were more frequent in the MR arm compared to the SR arm (MR 55.7%, SR 44.2%, p=0.20). There was no significant trend in occurrence of adverse events between the two arms during the follow-up period.

3.5 Ancillary Analysis

In the PP analysis, there were 48 specimens randomized to the modified reporting arm. For 29 specimens (60.4%), the microbiology laboratory was called to disclose the complete report.

Table 6. Bacteremia

Study Number	62
Study Arm	Standard
Age	82
Gender	Male
Reason for Admission	CVA
Reason for Urine Culture Collection	Incontinence
Urine Culture Date and Result*	March 21, 2019: *E.faecalis*
Reason for Blood Culture Collection	Fever
Blood Culture Date and Result	April 13: *E.faecalis*
Study Diagnosis	ASB treated
Antimicrobial Therapy	Amoxicillin PO; Vancomycin IV
Bacteremia Related to Intervention	No

Table 7. Deaths.

Study Number	48	49
Study Arm	Modified	Modified
Age	82	85
Gender	Female	Male
Reason for Admission	Clinical Decline	COPD Exacerbation, Pneumonia, Decreased LOC
Reason for Urine Culture Collection	Unknown	Unknown
Urine Culture Date	February 11, 2019	February 12, 2019
Blood Culture Date and Result	None	None
Study Diagnosis	ASB treated	ASB untreated
Study Day of Death	4	26
Antimicrobial Therapy	Septra DS	None
Presumed Cause of Death	Decline	CHF
Bacteremia Related to Intervention	No	No

Table 8. Adverse Events Over 72 Hours

	Modified Reporting	Standard Reporting
Tachycardia	**5**	**1**
Abnormal Temperature	**2**	**1**
Hyperglycemia	**0**	**0**
Edema	**0**	**0**
Elevated White Blood Cell Count	**1**	**1**
Altered Mental Status	**0**	**3**
Tachypnea	**0**	**0**

Table 9. Adverse Events Over Thirty Days

	Modified Reporting	Standard Reporting
Tachycardia	**14**	**8**
Abnormal Temperature	**8**	**5**
Hyperglycemia	**0**	**1**
Edema	**1**	**0**
Elevated White Blood Cell Count	**3**	**4**
Altered Mental Status	**5**	**4**
Tachypnea	**3**	**5**

Chapter 4 – DISCUSSION

We conducted a randomized trial and tested the efficacy of MR to improve appropriateness of treatment. There was a non-significant increase in appropriateness of treatment due to MR. The proportion of inappropriate treatment in the modified arm was slightly lower: 20 of 51 (39%) in the modified reporting arm, and 24 of 49 (49%) in the standard reporting arm. The intention of MR was to influence the interpretation of the positive urine culture away from a decision to treat. Although the reduction of inappropriate treatment was statistically non-significant in the MR arm, these findings confirm that physicians continue to make treatment decisions based on positive urine cultures as opposed to following the diagnostic guidelines; this practice contributes to overprescribing antibiotics. Further, MR did provide a clinically significant difference; there was a small reduction of inappropriate treatment observed in the intervention arm.

In previous literature, MR intervention proved to be effective in reducing inappropriate therapy. In a case-control study, the microbiology laboratory reported positive urine cultures with a general statement, recommending physicians call the laboratory for further information, if there was a high suspicion for UTI[35]. In this study, the intervention significantly reduced inappropriate therapy from 48% to 12% (p=0.002). From 37 modified reports, the laboratory only received 5 calls requesting a complete culture report. In another randomized controlled trial, modified reporting intervention was tested in non-catheterized acute care inpatients[36]. The modified arm demonstrated a higher proportion of appropriate treatment compared to the standard arm (80.0% vs 52.7%, p=0.002). These studies indicated that modified reporting may reduce antimicrobial therapy for ASB.

With our study, the benefit was not as large as the previous study in acute care[36]; there are a few plausible explanations. Older people usually have multiple comorbidities and new onset of infections can have severe consequences for patient morbidity and mortality[37]. Younger patients usually have stronger immune systems and are less likely to be immunocompromised; this could certainly impact a physician's decision to treat ASB. Further, older populations are often unable to voice or describe their symptoms. Because UTI is a diagnosis based on a symptomatic presentation, physicians are more inclined to treat older patients in fear of missing a true diagnosis.

Of the 100 urines collected, a majority (62/100, 62%) of urine cultures in our study represented ASB. This indicates that urine cultures continue to be ordered without indication in a long-term care setting. The inappropriate collection of urine cultures promotes treatment of ASB and disregard for physical symptoms and exam findings; further intervention may reduce this behavior significantly.

Between the two study arms, there were no significant differences in safety and adverse events. In the modified reporting arm, there were three cases of untreated UTI, these did not result in increased morbidity or mortality. Because of our small sample size and cases of untreated UTI, we cannot make a general claim that modified reporting is completely safe in long-term care populations. Further, there were a great number of patients meeting SIRS criteria in the modified reporting arm; however, SIRS criteria are not solely indicative of UTI and may be positive for other medical processes, especially with an older patient population in long-term care facilities. The SIRS criteria are sensitive but nonspecific, caused by and not limited to influenza, ischemia, inflammation, trauma, or a combination of insults.

MR may not be suitable for LTCF implementation because nurses and physicians called the lab to request the identification and susceptibility information in 60.4% (29/48) of reports, causing unblinding of the MR arm. Despite a substantial effect size observed with an increase in appropriate treatment of ASB in the modified reporting arm, the lack of significance of this result speaks to low power. Low power suggests that assumptions may not have been met by using effect size observed from a previous clinical trial to calculate the estimated sample size for this study[36]. Perhaps, an effect size observed in the previous trial did not provide an accurate estimated sample size in a different population. Both findings indicate that the MR may not be effective for treatment decisions in this setting. This research is still important because it provides an objective assessment of the modified report as a generalizable intervention across LTCFs.

In LTCFs, interventions such as education and algorithms have not proven to be effective in improving urine culture order patterns or increasing appropriate antimicrobial use[35]. In a cluster-randomized trial including 12 LTCF, Loeb et al. evaluated the impact of implementing guidelines with diagnostic and therapeutic algorithms for UTI treatment[33]. The interventions included nursing education, written material and videos, outreach visits, audits and one-on-one physician teaching. The study found a significant decrease in the rate of antimicrobial use for suspected UTIs in the intervention arm compared to the usual care arm (1.17 courses of antimicrobials/ 1000 patient days vs. 1.59, 95% CI [-0.06, -0,93]); however, the difference was reduced over time. Zabarsky et al., provided education to healthcare workers about appropriate urine specimen collection and treatment of ASB[34]. Six months following the educational intervention, there were significant decreases in the proportion of inappropriate urine specimen

collection (3.7 to 1.5/ 1000 patient days, 95% CI [0.27, 0.64]); these reductions were sustained more than two years later. Educational interventions require considerable resources, and policy interventions may be more efficient and sustainable.

It is worthwhile to conduct further research on other interventions which may be more suitable in LTCFs. Perhaps, restriction and monitoring may be more suitable in LTCFs[40]. With this intervention, restriction could happen at a physician level where the approval of an infectious disease staff would be necessary to order a urine culture or on ordering repeat cultures. Before implementing such a strategy, it may be useful to audit culture order forms and determine whether orders are being placed appropriately. Another strategy could include working with allied healthcare workers such as pharmacists to ensure appropriate treatment of UTIs and discontinuation of ASB therapy in LTCFs. Furthermore, it may be helpful to explore physician attitudes towards prescribing antibiotics, stewardship, and factors which encourage participation in clinical trials; these are all important for designing future antimicrobial stewardship initiatives.

Limitations

We relied on data collected from medical records and data provided by nursing staff to make the clinical diagnosis of ASB or UTI. In some cases, medical records may not have been thoroughly completed or patients may have had difficulty in communicating the presence of urinary symptoms, our diagnosis could have been biased towards ASB. Given the samples were randomized, this source of bias would have a balanced impact in both groups. Further, there could be inconsistencies in charting which may have created a bias towards ASB if symptoms were not documented in progress notes.

Similarly, documentation of adverse events also relied on data collected from medical records and data provided by nursing staff. If there was a failure to record adverse events or the data was incomplete, our estimate of adverse events could be lower than the true value, which would negatively affect safety outcomes.

It was not possible to blind the investigators because they had to access urine culture reports to make the outcome assessment. The lack of blinding of these investigators did not influence treatment because investigators were not involved in the treatment decisions. The outcome assessment was determined using a standardized case report form, which limited possible bias caused by not blinding the investigators. Although assessment of outcome and treatment were based on objective criteria, lack of blinding could potentially bias our conclusions.

A weakness of the study design would be the failure to apply the criteria guidelines that specify two consecutive positive urine cultures constituting a diagnosis of ASB in non-catheterized females. In our study, only one positive urine culture was collected to constitute a diagnosis of ASB in non-catheterized males and females. As such, it is possible that UTI could have been under-diagnosed in females.

Another factor that could have limited our ability to identify UTI is incomplete collection of essential criteria. Although medical records and paper charts were prospectively examined, some criteria were not collected for every patient with a positive urine culture, such as temperature or complete blood count; this could have led to under-diagnosis of UTI in our patient population. The under-diagnosis of true UTI could have negatively affected safety outcomes, if left untreated.

This study excluded patients under the care of the urology department by their request, this may have biased our patient selection towards a healthier population. Due to the narrow eligibility criteria, these findings may not be generalizable across LTCFs or across all non-catheterized residents.

Conclusion

In our study, we tested the efficacy of MR to reduce inappropriate treatment of ASB. There was a statistically non-significant and clinically significant increase in appropriateness of treatment due to MR. In the two study arms, there were no significant differences in safety and adverse events. A few limitations of our study included an inadequate sample size, incomplete criteria collection, and reliance on data from external sources. It may be worthwhile to repeat our study in a long-term care setting with an adequate sample size and accurate determination of symptoms and signs of UTI.

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Appendices

A. Ethics Approval

HREB

Ethics Office
Suite 200, Eastern Trust Building
95 Bonaventure Avenue
St. John's, NL
A1B 2X5

July 16, 2018

ADDRESS: Room 1J421 Health Sciences Centre
300 Prince Phillip Dr.
St. John's, NL A1B 3V6
Canada

Dear Dr. Daley:

Researcher Portal File # 20190395
Reference # 2018.121

RE: "Modified Reporting for Positive Urine Cultures Collected from Long Term Care, a Randomized Controlled Trial"

This will acknowledge receipt of your correspondence dated July 4, 2018.

Your application was reviewed by the Health Research Ethics Board (HREB) at the meeting held on June 28, 2018. Your revised application has been reviewed by the Co-Chair under the direction of the HREB.

Ethics approval of this research study is granted for one year effective July 16, 2018. This ethics approval will be reported to the board at the next scheduled HREB meeting.

This is your ethics approval only. Organizational approval may also be required. It is your responsibility to seek the necessary organizational approval from the Regional Health Authority (RHA) or other organization as appropriate. You can refer to the HREA website for further guidance on organizational approvals.

This is to confirm that the HREB reviewed and approved or acknowledged the following documents (as indicated):

Doc / Agreement	Version Date	Status	Description
Information	2018/07/01	Approved	Debriefing email to