Modified Reporting of Positive Urine Cultures to Reduce Treatment of Catheter-Associated Asymptomatic Bacteriuria (CA-ASB) Among Inpatients: A Randomized Controlled Trial

By

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Abstract

We conducted a randomized, unblinded superiority trial to determine if modified laboratory reporting of positive urine cultures (UC) increased the appropriateness of antibiotic treatment among catheterized inpatients. Efficacy outcome was treatment appropriateness. Safety outcomes included adverse events, bacteremia, and death. Between November 2018 and June 2019, 100 consecutive positive UCs were randomized to the standard report (SR) (bacterial count, identification and susceptibility) or modified report (MR) (standardized comment). Exclusion criteria were pregnancy, current antibiotic treatment, intensive care unit (ICU) or urology admission, or neutropenia. Current antibiotic treatment was excluded because their use may affect culture interpretation. True diagnosis of catheter-associated urinary tract infection (CA-UTI) or catheter-associated asymptomatic bacteriuria (CA-ASB) was based on published criteria and prospective chart review. Patients were followed for 7 days after reporting. Of 543 positive UC considered, 443 were excluded. The intention-to-treat (ITT) analysis included 100 UCs, while per protocol (PP) included 90. CA-ASB was diagnosed in 75% of all urines and 60% of these cases were treated with antibiotics. All CA-UTI cases were treated. There was a trend towards increased appropriate treatment (untreated CA-ASB + treated CA-UTI) in the MR than the SR: 31/54 (57.4%) vs 23/46 (50.0%), (+7.4%, p=0.45, RR=1.15) by ITT analysis. PP analysis gave similar results. There were 4/54 (7.4%) deaths and 16/54 (29.6%) adverse events in the MR, and 3/46 (6.5%) deaths and 19/46 (41.3%) adverse events in the SR (-11.7% adverse events, p=0.216). We conclude that MR trends towards treatment appropriateness and may be safe. Larger studies are required.

General Summary

We asked if modified reporting of positive urine cultures (UC) was effective in reducing inappropriate antibiotic treatment of catheterized hospital patients without causing harm. A MR indicated a positive UC, while a SR describes the identified bacteria, count, and potential medication(s) to treat the bacteria. Our conclusion depended on the proportion of appropriate antibiotic treatment based on diagnosis (e.g. treated catheter-associated urinary tract infection (CA-UTI) or untreated catheter-associated asymptomatic bacteriuria (CA-ASB)). Of 543 UCs considered, 443 were excluded based on our defined exclusion criteria (admitted to the intensive care unit or urology wards, pregnancy, using antibiotics at the time of urine collection, and low white blood cell (WBC) count). Of 100 UCs, 75% had CA-ASB, and 60% of these patients were inappropriately treated with antibiotics. The MR saw more appropriate treatment than the SR: 31/54 (57.4%) vs 23/46 (50.0%), suggesting a trend towards improved antibiotic treatment following a MR. The safety outcomes for both groups were comparable, and differences between them were not statistically significant (MR deaths and adverse events: 7.4% and 29.6%, respectively; SR deaths and adverse events: 6.5% and 41.3%, respectively). The MR trended towards more appropriate antibiotic treatment in comparison to the SR and may be safe. However, larger studies are needed to make a better assessment.

Acknowledgements and Co-Authorship Statement

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Co-Authorship Statement

Dr. Peter Daley, an infectious disease and medical microbiology specialist, was the principal investigator of this project and collected data on treatment regimen, determined true diagnosis, and assessed treatment appropriateness and adverse events over 7 days, as well as revised many copies of this thesis. Dr. Lydia Xing, an internal medicine resident, also collected data on treatment regimens, determined true diagnosis, and assessed treatment appropriateness and adverse events over 7 days. Zahra Rehan, a master's candidate in clinical epidemiology, was involved in patient recruitment and data collection. Laura Gilbert, a public health informatician in the microbiology lab, performed the randomization and recruitment preparation. Brenda Fillier, a microbiology laboratory technician, coordinated this clinical trial at the Public Health Microbiology Lab (PHML), and the staff at the urine bench processed all cultures and reported recruited cultures according to randomization. My contribution to this project included patient recruitment, data collection and analysis, as well as the writing and editing of all chapters of this thesis, following revisions by Dr. Peter Daley.

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List of Abbreviations

AAA – Abdominal Aortic Aneurysm

AKI – Acute Kidney Infection

AMS – Antimicrobial Stewardship

ASB – Asymptomatic Bacteriuria

CA-ASB – Catheter-Associated Asymptomatic Bacteriuria

CA-UTI – Catheter-Associated Urinary Tract Infection

CFU/ml – Colony Forming Units Per Milliliter

CHF – Congestive Heart Failure

CIC – Chronic Indwelling Catheter

COPD – Chronic Obstructive Pulmonary Disease

DM2 – Diabetes Mellitus Type 2

GERD - Gastroesophageal Reflux Disease

HTN - Hypertension

ITT – Intention To Treat

IV - Intravenous

LUT – Lower Urinary Tract

MRSA – Methicillin Resistant *Staphylococcus Aureus*

N/A – Not Available

PHML – Public Health Microbiology Laboratory

PO – Oral

PP – Per Protocol

TAT – Turnaround Time

UC – Urine Culture

UT – Urinary Tract

UTI – Urinary Tract Infection

UUT – Upper Urinary Tract

WBC – White Blood Cells

Chapter 1: General Introduction

1.1 Thesis Structure and Style

This thesis will proceed following the manuscript style of presentation. Figure 1: Pathogenesis of Urinary Tract Infection has been used in this body of work with permission from Springer Nature.

1.2 Study Objective

The purpose of this study is to determine if modified reporting of positive urine cultures collected from indwelling catheters improves the appropriateness of treatment for suspected CA-UTI and CA-ASB, without causing harm to patients.

1.3 Chapter Summary

The present chapter briefly outlines the style, structure, and flow of this thesis by outlining the main objective of each chapter. Chapter 2 intends to provide background information that will further the reader's understanding of this study's objectives (Section 1.2). The background information includes: the anatomical structure and function of the genitourinary system, the pathophysiology of urinary tract infection (UTI) and asymptomatic bacteriuria (ASB), as well as the indications and functions of indwelling catheterization. It also describes antimicrobial resistance (AMR) and the process of antimicrobial stewardship (AMS). Chapter 3 is a literature review describing previous antibiotic stewardship interventions involving the microbiology laboratory and/or changes to the ordering and reporting of urine cultures. Chapter 4 outlines the methodology of the study and includes: study design, study setting, urine culture assessment,

patient recruitment, population and inclusion criteria, the intervention and control groups, outcomes, and statistical analyses. It also discusses the randomization process, blinding, sample size, debriefing plan, and ethics approval information. Chapter 5 reports the study results including: participant flow, patient demographics, efficacy and safety outcomes. Chapter 6 is the discussion which provides an interpretation of the results, strengths and weaknesses of the study design, areas of improvement and future research goals. Chapter 7 concludes the study by summarizing the previously outlined objectives, outcome results, and their value to clinical practice and current antibiotic stewardship research. Chapter 8 and following appendices include references for all cited works, and additional information (i.e., study tools, approval forms, and permission forms) for reader reference, respectively.

Chapter 2: Background Information and Study Rationale

2.1 The Genitourinary System

The genitourinary system is responsible for regulating body fluid balance and excretion of metabolic products through the kidney, ureter, urinary bladder, and urethra (Patton & Thibodeau, 2016). The upper urinary tract (UUT) consists of the kidneys and ureters, while the lower urinary tract (LUT) consists of the urethra and urinary bladder. During bladder catheterization, a urethral catheter is inserted transurethrally into the bladder (Schaeffer, 2019). Bladder catheterization is indicated for adults with urinary retention with or without bladder obstruction, when monitoring urine output, and during pharmacological therapy of the bladder (Schaeffer, 2019). In addition, bladder catheterization is used to manage hematuria associated with blood clots, immobilized patients, and open wounds in the perianal or sacral regions of incontinent patients (Schaeffer, 2019).

2.2 Urinary Tract Infection (UTI)

Urinary tract infections occur when bacteria from the colon ascend the urethra and colonize the bladder (Mclellan, Hunstad, & Sciences, 2017). The bacteria (or uropathogens) adhere to the outermost epithelial layer of cells, eventually forming biofilm-like masses (Mclellan et al., 2017). These changes in the cellular environment trigger defense mechanisms in the urinary tract cells: inflammation, leukocytosis, the expulsion of uropathogen-containing lysosomes, and the exfoliation of infected epithelial cells into the urine (Mclellan et al., 2017) (Figure 1). Such defense mechanisms are initiated once the uropathogens have passed the urinary system's front-line defenses including mucous production, urination, and the urinary microbiome (Spencer, Schwaderer, Becknell, Watson, & Hains, 2014). The most common uropathogen is *Escherichia coli* (*E. coli*), which accounts for 75-95% of uncomplicated UTIs, although *Staphylococcus, Klebsiella, Enterobacter, Proteus,* and *Enterococcus* genera are also common (Colgan et al., 2018; Mclellan et al., 2017). These pathogens colonize the bladder by adhering to the periurethral area and ascending to the urethra and bladder through pili, flagella, and recognition of adhesin proteins on bladder epithelium (Flores-Mireles, Walker, Caparon, & Hultgren, 2000). Along with other proteins and carbohydrates, pili and flagella are also involved in the production of a biofilm which protects the bacteria from antibiotic entry (Flores-Mireles et al., 2000). The process of catheterization induces an inflammatory response in the bladder that damages the mucosa, further providing the uropathogens with surfaces to which they can easily adhere (Lo, Nicolle, Classen, & Arias, 2008; Mclellan et al., 2017). This immune response causes an accumulation of fibrinogen on the catheter, which facilitates colonization and biofilm formation as many bacteria

express fibrinogen-binding proteins (Flores-Mireles et al., 2000)**.** Considering this facilitated route, it is no surprise that over 75% of hospital-acquired UTIs occur in patients with a chronic indwelling catheter (CIC) (Centers for Disease Control and Prevention, 2015; Lo et al., 2008; Mclellan et al., 2017; Tambyah & Maki, 2000). Risk factors for an UTI include female sex, history of UTIs, sexual activity, vaginal infection, diabetes, and genetic susceptibility (Flores-Mireles et al., 2000). However, risk factors for CA-UTI include failure to maintain a closed drainage system, female sex, older age, and duration of catheter use (Lo et al., 2008).

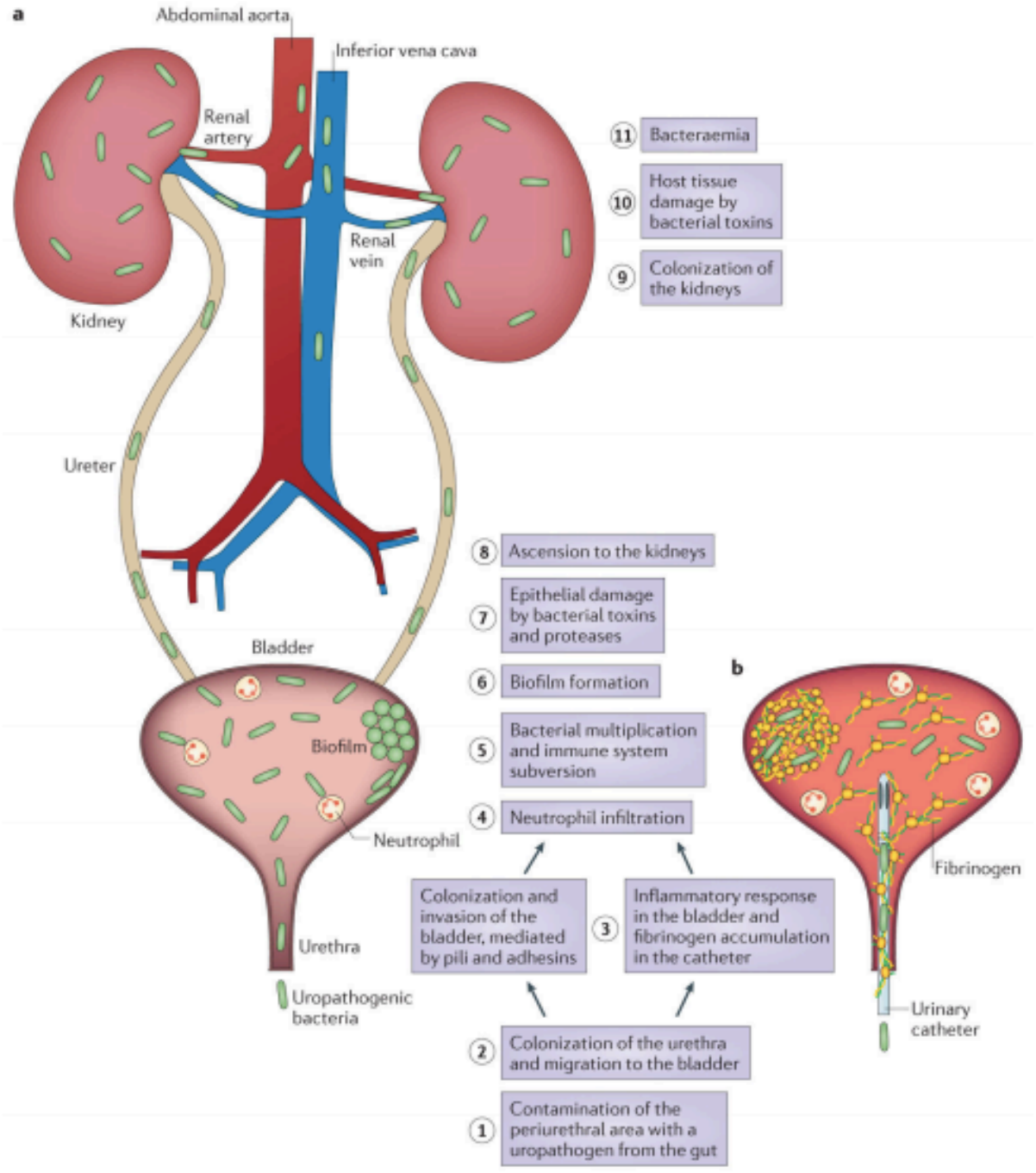

Figure 1: Pathogenesis of Urinary Tract Infection (Flores-Mireles et al., 2000). Used with permission.

Urinary tract infections can be classified based on location: cystitis occurs in the LUT, pyelonephritis occurs in the UUT (Colgan et al., 2018; Mazzulli, 2012; Mclellan et al., 2017). Bacterial infections can be classified as either ASB, uncomplicated UTI, or complicated UTI, though they may be difficult to distinguish. Asymptomatic bacteriuria occurs when there is a significant amount of bacteria present in the urinary tract as determined by laboratory results, but the patient does not experience any symptoms (Section 1.3) (Mazzulli, 2012). Uncomplicated UTIs occur in functioning urinary tracts, while complicated UTIs are defined as UTIs associated with functionally or structurally abnormal urinary tracts, in the presence of a CIC, during transplantation of urinary structure(s), male sex, elderly age, infection by an antimicrobial resistant organisms, or pregnancy (Mazzulli, 2012)**.** Finally, if a UTI is diagnosed in the presence of a urinary catheter, it is referred to as a CA-UTI (Tambyah & Maki, 2000). Given the variety of UTI definitions, correct diagnosis is critical as its indication guides the appropriate treatment.

While CA-UTI patients can experience fever, pain, dysuria, frequent urination, and a change in urgency, these symptoms are non-specific and should not be the sole basis of diagnosis (Hooton et al., 2010). The presence of new costovertebral tenderness, rigors, or a new onset of delirium should also be considered when ordering an UC and subsequent treatment decisions (Hooton et al., 2010; Jaeger et al., 2019). Urinalysis via dipstick testing can be used to assess whether a UC is needed based on urine nitrites, white blood cells, and leukocyte esterase results (Centers for Disease Control and Prevention, 2015; Jaeger et al., 2019). There are three different ways in which a urine sample can be collected: midstream or clean catch, in/out catheterization, or indwelling catheterization (though not generally recommended). While the former two

methods are most common, 12% to 16% of acute care inpatients will have a catheter inserted during admission to hospital (Lo et al., 2008). The diagnostic criteria for CA-UTI defined by the Infection Diseases Society of America (IDSA) are as follows:

1. Has an indwelling urethral, suprapubic, or intermittent catheter,
2. Is positive for signs and symptoms compatible with UTI diagnosis and no other known source of infection (fever ≥ 38°C, suprapubic tenderness, costovertebral angle (CVA) pain or tenderness, urinary urgency, urinary frequency, or dysuria)
3. Positive UC defined by growth of a minimum of 10^3 colony-forming units per milliliter (CFU/mL) of at least one organism in a single catheter urine specimen, or in a midstream urine specimen taken from a patient with a catheter removed within the last 48 hours (Hooton et al., 2010).

It is common to begin antibiotic treatment at the same time that a urine is sent for culture and antimicrobial susceptibility results ("empiric" treatment). Treatment should be adjusted after UC results that identify significant growth of a uropathogen and associated susceptibility testing results are received ("targeted" treatment) (Mazzulli, 2012). Empiric treatment may be informed by the local antibiogram; In Newfoundland and Labrador, appropriate empiric treatment in females with an uncomplicated UTI could include nitrofurantoin PO, cephalexin PO, TMP/SMX PO, or ciprofloxacin PO for 3-5 days without the need for UC testing (Daley, 2018). Treatment guidelines for CA-UTI are poorly defined, as the catheterized population is heterogenous and ranges from healthy surgery patients to severely ill patients with many complications (Hooton et al., 2010). While both empiric and targeted treatment may be

appropriate, targeted treatment is preferred because it limits unnecessary antibiotic use that could lead to antibiotic-resistant bacteria in the patient, as well as reduces unnecessary cost (Mazzulli, 2012).

2.3 Asymptomatic Bacteriuria (ASB)

Asymptomatic Bacteriuria is the presence of bacteria in the urinary tract in the absence of genitourinary signs or symptoms (Daley, 2018; Givler & Givler, 2019; Nicolle et al., 2005). It occurs more often in females than males and is typically caused by uropathogenic *E. coli* (Givler & Givler, 2019; Nicolle et al., 2005). Increased age, diabetes, the presence of genitourinary abnormalities, and the presence of an indwelling catheter are additional risk factors (Claeys, Blanco, Morgan, Leekha, & Sullivan, 2019; Givler & Givler, 2019). In the absence of symptoms, the diagnosis of ASB requires two consecutive positive UCs for women or one positive UC for men (Claeys et al., 2019). For inpatients with an indwelling urinary catheter, catheter-associated ASB (CA-ASB) can be diagnosed in asymptomatic catheterized patients based on a single positive UC, regardless of sex (Claeys et al., 2019).

ASB is often inappropriately tested and treated with antibiotics; evidence has shown that treatment of ASB does not lead to reduction in mortality or pyelonephritis in most patients, with the exception of patients undergoing urological procedures expected to cause mucosal bleeding and perhaps pregnant women (Claeys et al., 2019; Givler & Givler, 2019; Nicolle et al., 2005; F. Smaill & Vasquez, 2019). The use of antibiotic treatment for ASB during pregnancy to reduce pyelonephritis, low birthweight, and preterm birth, is based on low-quality evidence and it's

indication varies across management recommendations (Nicolle et al., 2019; F. M. Smaill & Vazquez, 2015; F. Smaill & Vasquez, 2019). Treatment of ASB may cause harm, including adverse drug reactions, *Clostridiodes difficile* diarrhea, and an increased incidence of infections caused by antibiotic resistant uropathogens (Daley, Garcia, Inayatullah, Penney, & Boyd, 2018; Givler & Givler, 2019; Leis et al., 2014; Nicolle et al., 2005).

2.4 Bladder Catheterization

Urinary catheters are inserted in the urethra to access the urinary bladder, allowing urine to pass from the bladder to an external collection bag (Newman, 2002). Collection bags are fitted with an emptying spout for drainage; drainage is important in reducing the risk of antimicrobial infection for CIC patients (Lo et al., 2008). The increased risk of infection resulting from catheterization is due to the passage that the catheter provides for uropathogens, which is free of first- and second-line defenses of the urinary tract (Mclellan et al., 2017).

2.5 Diagnosis of CA-UTI and CA-ASB

Catheter-associated urinary tract infection and CA-ASB may be difficult to distinguish clinically because indwelling catheters themselves can cause urinary symptoms (e.g. urgency, frequency, and dysuria) and because the characteristics symptoms of a UTI are non-specific (Claeys et al., 2019; Lo et al., 2008). In addition, catheterized inpatients often have comorbidities that complicate diagnosis, and CA-ASB rate increases by 3-10% each day following catheterization, eventually affecting 100% of patients (Claeys et al., 2019). Urine culture alone cannot distinguish CA-ASB from CA-UTI as both conditions show significant growth, meaning the

diagnosis must be made clinically. Risk factors for the treatment of ASB have been defined. (Daley et al., 2018).

2.6 Antimicrobial Resistance (AMR)

Antimicrobial resistance has long been identified as a significant threat to global health, stability, and national security (Bourdellon, Thilly, Fougnot, & Pulcini, 2017; World Health Organization, 2001). By definition, "antimicrobial resistance" encompasses the resistance of different microorganisms, including bacteria, viruses, fungi, and parasites, to the medications used to treat infections they cause (World Health Organization, 2001). The prevalence of drug-resistant bacteria has been increasing globally over years in both inpatient and outpatient settings (Bourdellon et al., 2017; Tsuboi et al., 2017). This is a product of different factors but is largely due to misuse (encompassing both unnecessary and inappropriate usage) of antibiotics given for UTI and upper respiratory tract infections (Bourdellon et al., 2017; Macvane, Hurst, & Steed, 2016). Extended-spectrum beta lactamase (ESBL) producing *Enterobacteriaceae* are one example of a very common cause of antibiotic-resistant UTIs, which must be treated with broad-spectrum antibiotics (Choi & Yoo, 2019).

In order to combat the immediate threat of AMR, antimicrobial stewardship (AMS) attempts to modify current practices in order to reduce the unnecessary use of antimicrobials and their resultant selective pressure favoring bacterial species.

2.7 Antimicrobial Stewardship (AMS)

Antimicrobial stewardship is now considered an urgent need in infectious disease management (Tsuboi et al., 2017). Antimicrobial stewardship is formally defined as antibiotic treatment that results in the best clinical outcome, as well as a system-wide approach to promoting and monitoring proper antimicrobial usage to preserve the future effectiveness of antimicrobials (Nathwani et al., 2018). These stewardship initiatives are versatile in their applications and are implemented in different areas of the health care system. Initially starting with pharmacy and infectious disease clinicians, these they have expanded into the daily routine of public policy makers, nurses, physicians, and microbiologists (Bourdellon et al., 2017; Macvane et al., 2016). Inclusion of the microbiology lab has gained attention as it has the ability to influence treatment decisions before treatment is prescribed (Langford et al., 2019). Consultation with infectious disease physicians, educational interventions, guideline review, and restricted reporting are just some of the ways in which AMS can positively influence better patient outcomes by improving the appropriateness of antimicrobial therapy (Daley et al., 2018; Maclaggan et al., 2018; Macvane et al., 2016). With attention on UTIs, some AMS initiatives have focused on reducing the number of orders for UCs, improving the rate of appropriate treatment for asymptomatic patients, and optimizing antibiotic therapy (Gonzalez & Razzano, 2017).

Chapter 3: Literature Review

The Effectiveness of Antibiotic Stewardship Initiatives Implemented During the Ordering and Processing of UCs

3.1 Introduction

The process of performing an UC begins with urine collection by midstream, clean catch, an in/out catheter, or an indwelling catheter into a sterile container (Daley, 2018; Miller, 1985). Urine is transferred to culture media within 2 hours of collection at room temperature, or within 24 hours if preserved (Daley, 2018; Miller, 1985). Bacterial growth is quantified in the microbiology lab using a fixed volume of urine and counting of bacterial colonies (colony forming units, CFU) (Daley, 2018; Miller, 1985). Bacterial identification and susceptibility results are reported if one or two types of bacteria are detected at greater than 10×10^3 CFU/mL, or if two or more types are detected with greater than 100×10^3 CFU/mL (Daley, 2018). Other patterns of growth are reported as mixed growth from specimen contamination, and identification and susceptibility testing results are not reported (Daley, 2018).

The overuse of antibiotics is a major global health concern that is in part the result of inappropriate treatment decisions, such as in response to a positive UC alone or inappropriate decisions to collect urine (Daley et al., 2018; Leis et al., 2014; Macvane et al., 2016; Nicolle et al., 2005; Pharm et al., 2019; Stagg et al., 2018; World Health Organization, 2001). For example, ASB is frequently screened and treated unnecessarily; one of the most common explanations for treatment of ASB is reflexive treatment of the positive laboratory result rather than the treatment of presenting clinical features(Maclaggan et al., 2018)(Maclaggan et al., 2018) (Leis et

al., 2014; Maclaggan et al., 2018; Nicolle et al., 2005, 2019). The unnecessary but frequent collection and ordering of UCs leads to the over-detection of ASB (Jaeger et al., 2019). Urine cultures should be reserved for patients with urinary symptoms, however some settings order routine pre-operative UC or add reflex UCs based on a positive urinalysis (Jaeger et al., 2019). Antimicrobial stewardship initiatives may target treatment of ASB or the ordering behaviour of UCs, and may come in many forms including audit-and-feedback, algorithms, and educational interventions (Daley et al., 2018; Leis et al., 2014). The microbiology laboratory report is rarely considered an AMS strategy, although "nudging" strategies within laboratory reports are gaining more traction (Daley et al., 2018; Langford et al., 2019; Pharm et al., 2019; Stagg et al., 2018). Nudging strategies are those that use strategic placement of "choice architecture" in reporting to influence prescriber behaviour and treatment decision without compromising their autonomy (Langford et al., 2019). Nudging highlights the role of the microbiology laboratory report in AMS. (Langford et al., 2019; Maclaggan et al., 2018; Macvane et al., 2016).

This literature review aims to summarize previous AMS initiatives in the microbiology laboratory, and asks the following question: In what ways has the microbiology laboratory been integrated in AMS interventions that are aimed at reducing antibiotic usage through the ordering and processing and reporting of UCs? Furthermore, have these interventions been effective and is their implementation realistic in everyday practice? The purpose of this literature review is to determine whether AMS initiatives in the microbiology laboratory are worth pursuing based on previous findings, or if future efforts are better spent in a different setting. This question warrants

exploring because of the increasing risk posed by AMR, which will need to be managed by a set of diverse approaches to cover such a broad problem.

3.2 Methods

The following string was searched in PubMed and Embase to yield 1 result: ’urinary tract infection' AND 'asymptomatic bacteriuria' AND 'indwelling catheter' AND 'antibiotic treatment' AND 'acute care inpatients'. Due to the low yield of this search, the MeSH string was expanded to the following and searched in Embase and PubMed: “laboratory AND intervention AND 'antimicrobial stewardship' AND 'urinary tract infection'”. Papers were excluded if their intervention was inappropriate (unrelated to UC ordering, processing, or reporting) (n=10) or if they were review papers rather than papers describing experiments (n=2). The expanded search yielded 14 results, of which 12 were excluded (Figure 2). The PubMed search was done with the following filters to search results: clinical trial, full text, published in the last 10 years, and studies in humans. This yielded 2 results, one of which was included from the Embase search, and the other was excluded as an inappropriate intervention. Other articles were identified by searching the reference section of Daley et al. (2018) (Figure 2). From this resource, 2 additional publications were identified using the same inclusion and exclusion criteria as the database results (unrelated intervention n=2, review paper n=5). A final paper was obtained through recommendation by the principal investigator, resulting in a total of 6 papers included (Figure 2).

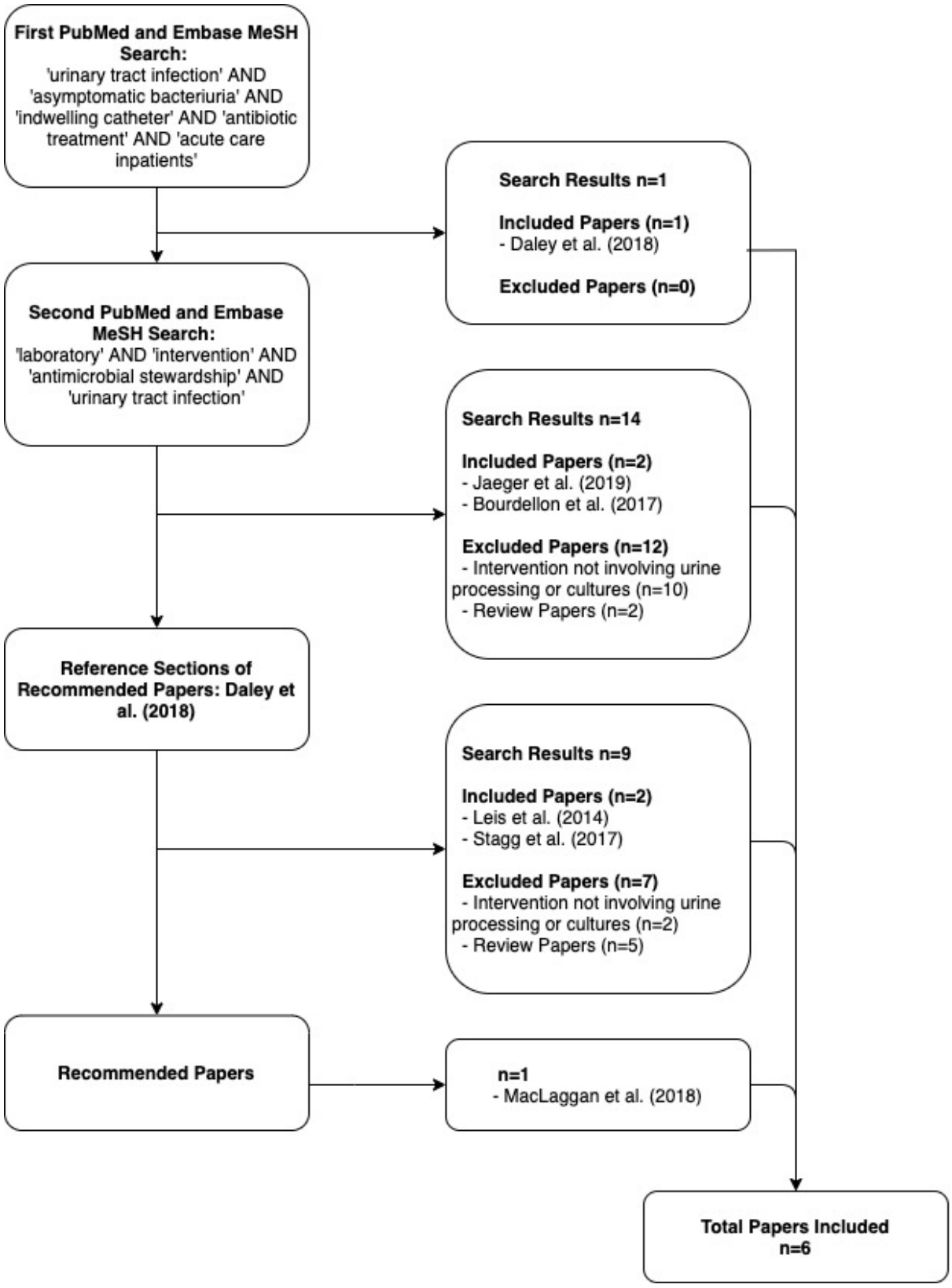

Figure 2: Flowchart of Literature Selection

3.3 Results/Discussion

3.3.1 *Application of Interventions*

Six different stewardship interventions were used during the process of UC ordering, processing, and reporting. These interventions can be broadly categorized as (i) changes to the UC ordering process (2 papers) and (ii) reporting strategies (4 papers).

(i) Changes to the UC Ordering Process

The first study described was a before and after comparison of two-step ordering in an acute care urban hospital (Stagg et al., 2018). The control was the standard process, which involved urine collection and culture ordering in a single step by a nurse or physician (Stagg et al., 2018). The two steps of the intervention included “Step 1”: the ordering of a UC by a triage nurse, and “Step 2”: the submission of the specimen to the laboratory after assessment by a physician within 48 hours (Stagg et al., 2018). Between Steps 1 and 2, the urine was held at the lab until the physician ordered Step 2, and in the meantime urinalysis was preformed (Stagg et al., 2018). The hypothesis was that two-step ordering would help reduce the over-ordering of UCs and treatment of ASB in relation to the numbers of UCs processed in the emergency department (ED) (Stagg et al., 2018). The second study was set in a tertiary care hospital emergency department that used reflex UC testing (Jaeger et al., 2019). The study design was not disclosed and there were insufficient details to infer. The order sheets for certain indications had UC pre-selected, regardless of the reflex to culture threshold based on screening results with urinalysis (Jaeger et al., 2019). For this intervention, the researchers modified the threshold from >3 WBC to >4 WBC

and un-selected the pre-selected UC order sets for indications that had the highest rate of negative culture (Jaeger et al., 2019).

(ii) Reporting Strategies

Two papers used a modified reporting style (MR) for positive UCs. The MRs disclosed that the culture detected significant growth but withheld bacterial identification, bacterial counts, and susceptibility results (Daley et al., 2018; Leis et al., 2014). Leis et al. hypothesized that the pretest probability of UTIs would be low and this reporting style would show that physicians treat a positive UC rather than clinical status (Leis et al., 2014). Daley et al. hypothesized that the modified reporting among acute care inpatients would reduce inappropriate treatment of ASB without an increase in adverse events (Daley et al., 2018). Both of these interventions were tested in non-catheterized inpatients in acute care teaching hospitals, however Leis et al. used a proof-of-concept before/after study design, while Daley et al. used a unblinded parallel randomized control trial study design (Daley et al., 2018; Leis et al., 2014).

A third study included this same reporting style in their overall intervention, which was a UTI management bundle also including education for nurses and prescribers and pharmacy prospective audit-and-feedback (Maclaggan et al., 2018). The authors hypothesized that this reporting style would decrease inappropriate treatment of ASB and the unintended consequences of unnecessary antimicrobial therapy, as well as improve appropriate collection of UCs and the selection and duration of antimicrobial therapy for UTI (Maclaggan et al., 2018). This was tested using a retrospective before and after study in a tertiary care hospital (Maclaggan et al., 2018). Lastly, the fourth publication altered UC results by selectively limiting the amount of

susceptibility results listed, to determine if this improved the appropriateness of antibiotic therapy selected, using a randomized control trial of case-vignettes (Bourdellon et al., 2017). As selective reporting is commonly used in practice today, this study is included to assess the quality of evidence supporting this reporting style. The case-vignettes disclosed identification and quantitative results unlike the previous interventions discussed.

3.3.2 *Major Findings of Stewardship Interventions*

(i) Changes to UC ordering processes

Stagg et al. reported that only 19.1% of all urines ordered in Step 1 had the second step ordered by physicians, the amount of ED visits requiring callback significantly decreased, and the turnaround time (TAT) for urinalysis significantly decreased by 21.01 minutes (Stagg et al., 2018). Furthermore, overall antimicrobial therapy and antibiotics prescribed for urinary indication significantly decreased for admitted ED patients (Stagg et al., 2018). In terms of urinalysis reflex to culture, Jaeger et al. also had favorable results, although the quality of this study was questionable. They reported a significant decrease of urinalysis reflex to UCs from a mean of 92 to 49 per day, while the number of urinalysis without reflex to culture significantly increased from 3 to 41 per day (Jaeger et al., 2019). The number of negative UCs per day significantly decreased by 54% (Jaeger et al., 2019). From the report, there was insufficient information to assess methods and the criteria used to update order sets and thresholds (Jaeger et al., 2019).

(ii) Reporting Strategies

The findings of Leis et al. and Daley et al. were in agreement as both found that the MR had a higher proportion of appropriate treatment compared to standard reports for non-

catheterized inpatients (Daley et al., 2018; Leis et al., 2014). Leis et al. reported a significant absolute risk reduction (ARR) of inappropriate treatment of 36% with no cases of untreated UTI, while Daley et al. reported ARR=27.3% with a higher proportion of untreated UTI in the standard arm compared to the modified arm (Daley et al., 2018; Leis et al., 2014). Similarly, MacLaggan et al. found that the MR included in the UTI management bundle lead to a significant decrease in inappropriate treatment of ASB (ARR=50.8%) (Maclaggan et al., 2018). They also found decreases in the average days of antimicrobial therapy (4.73 days to 1.05 days), the number of cultures collected without a doctor's orders (-28.8%), and fluoroquinolone use (31.1% to 12.2% of empiric treatment, 30.5% to 18% of directed treatment), while ceftriaxone use in empiric treatment increased (9.5% to 36.6%) (Maclaggan et al., 2018).

The findings of Bourdellon et al. also support the implementation of modifications to the standard UC report; results showed that limited susceptibility reports lead to higher rates of appropriate antibiotic selection in three out of four case-vignettes, while in the remaining case there was no difference between full and restricted results (Bourdellon et al., 2017). Of the case-vignettes with higher appropriate antibiotic selection following the restricted reports, the percentage of appropriate antibiotic selection increased by 22.4% (Case 1), 67.5% (Case 3), and 36.3% (Case 4)(Bourdellon et al., 2017).

3.4 Practicality

These types of interventions are only as effective as the study results if they are implemented in the same manner and setting. In order for the interventions to be applied in every-day practice, they should not drastically change the workflow of those involved in UC

ordering and processing, and ideally, they should be well-received by microbiologists and physicians alike. It appears that the interventions were designed with this in mind, as the modified reporting of positive UCs required a simple change to the script that was sent to the electronic medical record. If this reporting style is used going forward, the lab would have to pay more attention to the ward from which the inpatient who submitted the sample was residing, as the ICU and obstetrics were not included in these trials (Daley et al., 2018; Leis et al., 2014; Maclaggan et al., 2018). This could likely be a simple fix, such as adding a reminder prompt in the laboratory information system for microbiology staff, but would still require a change in workflow. The limited reporting of susceptibility results has similar implications but would not cause a change in workflow for those involved. Furthermore, limited susceptibility had a favourable response from participating physicians, as over half of the participants considered limited reporting as an improvement to the quality of the antibiotic therapy they prescribed, and 80.9% favoured its used in every day practice (Bourdellon et al., 2017). Out of all the interventions examined, it seems as though the urinalysis reflex to culture would require the least amount of change in workflow and employee demand, as it would be a matter of changing setting thresholds in an already automated process (Jaeger et al., 2019). The changes that would be required in order to implement each of the interventions described seems minimal and reasonable.

It is notable that these interventions have all been tested recently with the earliest paper being published in 2014 (Leis et al., 2014). This suggests a growing focus on laboratory-based interventions which will influence and potentially improve their practicality, as they will be

developed with new resources and consideration of previous experience. At this point the quality of the data produced is variable as it encompasses a combination of randomized control trials (RCTs) and before/after comparisons. Randomized control trials produce high quality evidence, but before/after comparisons create bias due to unmeasured system changes between the before and after periods. (Murad, Noor, Alsawas, & Alahab, 2016; Thiese, 2014).

3.5 Limitations and Safety

None of the studies described were implemented in a hospital-wide setting (Bourdellon et al., 2017; Daley et al., 2018; Jaeger et al., 2019; Leis et al., 2014; Maclaggan et al., 2018; Stagg et al., 2018). Similarly, no studies included catheterized patients which makes the findings ungeneralizable to this study's population. Some of these interventions were limited to adults (age ≥ 18), meaning that it cannot be assumed that they would work in pediatric or youth populations (Daley et al., 2018; Leis et al., 2014). Therefore, further investigation of AMS initiatives involving the microbiology lab and catheterized patients is warranted. Studies with interventions that required physicians to call for full reports had a low call-back rate, indicating that there was a risk of failure to treat UTIs (Daley et al., 2018; Leis et al., 2014; Maclaggan et al., 2018). In one paper, there were two cases of untreated UTI, one of which progressed to bacteremia at 72 hours, however this was treated without any significant clinical sequalae (Maclaggan et al., 2018). Any adverse events in the Daley et al. and Leis et al. papers were individually investigated in their respective studies and deemed to be unrelated to the MR, indicating that the MR did not cause any harm to patients. (Daley et al., 2018; Leis et al., 2014). Strategies that delay transportation of urine between the clinic and the laboratory beyond 2 hours will be associated with changes in the UC results, causing a potential safety concern if urine

preservation is not used (Rabinovitch, Arzoumanian, Curcio, Dougherty, & Halim, 2009). Published CLSI criteria limit the time between collection and culture to 2 hours, due to false positivity of UC because of overgrowth during transportation (Bartlett, 2004).

The publication describing urinalysis with reflex to culture was very limited in its details: patient demographics, data collection method, and study design were not adequately described, so the strength and generalizability of their evidence could not be assessed (Jaeger et al., 2019). Regarding Bourdellon et al., the primary outcome was based on a general practitioner's response to a hypothetical scenario, rather than real life. Theoretical case vignettes may produce a biased assessment of true behaviour in patient care; while these cases were based on realistic scenarios, the results could not be directly applied to physician response in a real scenario. Furthermore, Bourdellon et al. described a randomized control trial case-vignette study, which includes two different study designs. Because of this, the results should have been reported separately: once in corresponding to the RCT, and again in correspondence to case-vignette results.

3.6 Conclusion

Laboratory AMS interventions in ordering and reporting of UCs have shown benefit without harm (Bourdellon et al., 2017; Daley et al., 2018; Jaeger et al., 2019; Leis et al., 2014; Maclaggan et al., 2018; Stagg et al., 2018). All of the included studies reported reductions in inappropriate treatment or ordering of UCs in limited populations, however these strategies have not yet been widely implemented. Reported benefits imply that research involving AMS interventions in the microbiology lab and UC ordering should continue to be pursued. Further

studies should focus on the populations missing from the current data, such as catheterized patients, critically ill, pregnant and pediatric populations, or include entire inpatient populations.

CHAPTER 4: METHODS

4.1 Study Design

This study was a prospective, superiority, parallel, unblinded randomized control trial comparing two different reporting styles for positive UCs using appropriate treatment following the report as the outcome. Urine cultures were obtained from inpatients at acute care hospitals in St. John's, NL. Consecutive positive UCs were assessed for eligibility and those that met inclusion criteria were randomized into one of two arms, MR or SR, before culture results were released on the electronic health system (Meditech). Once randomized, results were released in Meditech following the format for the group they had been assigned to. Patients that provided the positive UCs were followed for 7 days to assess appropriateness of antimicrobial therapy and safety outcomes. For urines randomized to the MR group, physicians were able to obtain complete results via telephone 24 hours a day, 7 days a week.

4.2 Study Setting

This study took place in St. John's, Newfoundland and Labrador. Recruitment and data collection were performed at the Public Health Microbiology Laboratory (PHML), while patient assessment was completed at either the Health Sciences Center (HSC) or Saint Clare's Mercy Hospitals (SCMH).

4.3 UC Assessment

Urines were cultured using only MacConkey Agars, a selective and differential medium that supports growth of Gram-negative bacilli while inhibiting most Gram-positive bacteria

(Miller, 1985). Cultures were incubated for 24 hours at 35°C under ambient air, and interpreted according to laboratory policy (Miller, 1985).

4.4 Recruitment

Following UC assessment, the microbiology technologist provided a tracking form (Appendix A) to the graduate students with the Accession Number (AN, a number that could refer back to the exact plate being assessed), and the Medical Care Plan number (MCP, a unique number that identifies patients and their history) for each positive UC to be assessed for eligibility. The graduate students assessed eligibility by searching the patient history of the inpatient associated with each sample using Meditech and inclusion/exclusion criteria (Section 4.5). The appropriate ward was called before inclusion to confirm method of collection for the urine sample. Once confirmed, students randomized the sample to either the SR or MR according to the method described in Section 4.9. Students provided reporting assignment to the microbiologist by email using a secure server.

4.5 Population and Inclusion Criteria

Urines included in this study were collected from patients who met the following inclusion criteria:

i. Is at least 18 years of age
ii. Is admitted to either HSC or SCMH
iii. Is not pregnant (tested negative or not reproductive age)
iv. Has a neutrophil count greater than 1.0 within 7 days of collection
v. Is not taking antibiotics at the time of collection

vi. Provides a urine collected from an indwelling catheter present in the bladder for a minimum of 48 hours

vii. Provides a urine that was **not** ordered by a urologist

viii. Is not admitted to an intensive care unit (ICU)

Patients taking antibiotics at the time of urine collection were excluded because current antibiotic usage may interfere with culture growth and interpretation (Wilson, Badarudeen, & Godwin, 2011).

4.6 Intervention and Control Groups

The intervention in this study was a modified positive UC report that attempted to influence ordering behaviour and reduce inappropriate antibiotic treatment. The SR for a positive UC identifies the bacteria isolated, the quantity in CFU, and antibiotic susceptibility. The MR informs the ordering physician or nurse that the culture is positive while withholding all other identifying, quantifying, and susceptibility information. It reads 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 at ###-### for identification and susceptibility results".

4.7 Outcomes

Outcome results were determined by licensed physicians using prospective chart review. The primary efficacy outcome was the proportion of appropriate antibiotic treatment prescribed, based on published treatment guidelines. Cather-associated asymptomatic bacteriuria was distinguished from CA-UTI by the absence of documented symptoms. Inappropriate treatment

was any treatment for CA-ASB or no treatment for CA-UTI. The secondary efficacy outcome was the rate of physician calls to the lab requesting complete results (this outcome is limited to the MR arm). A licensed physician member of the research team determined and collected data for the safety outcomes: rate of bacteremia, number of deaths, adverse events at 72 hours, and patients meeting the Systemic Inflammatory Response Syndrome (SIRS) criteria. Adverse events were defined as meeting 2 or more of the criteria diagnostic of systemic inflammatory response syndrome (SIRS): body temperature > 38.3°C or < 36°C, heart rate > 90bpm, respiratory rate >20/min, leukocyte count > 12,000 or < 4,000, altered mental status, significant edema or positive fluid balance, and hyperglycemia in the absence of diabetes (Boka, 2018). Adverse events at 7 days were defined as the onset of any new signs or symptoms during the 7-day follow-up.

4.8 Determination of Outcomes

Two physicians (a physician specializing in infectious diseases and medical microbiology, and an internal medicine resident), assessed the efficacy and safety outcomes using prospective chart review. The patient care records written by the attending nurses and physicians were accessed using the local electronic medical records and paper charts. These records included patient care notes, laboratory work, medications, vital signs, etc. If there was dispute between physicians regarding the outcomes, the case was further investigated until a conclusion was made. Physicians were not blinded to each other's outcome conclusions. The adverse events at 7 days and bacteremia rates were assessed by both physicians. All deaths were investigated by the infectious disease and medical microbiology specialist and reported to ethics appropriately.

4.9 Interim Analysis

Interim analysis was performed when we recruited 50% of our sample size (N=50) to assess safety outcomes. There were no predefined stopping rules.

4.10 Randomization

A statistician at PHML randomized group assignment for recruited cultures using Excel for Office 365 (Version 1903). A list of numbers 1-100 (inclusive) were randomly assigned to "Normal Report" or "Modified Report" using this software, and the result for each number was printed and stuffed into individual and serially labelled envelopes with chronological study numbers. Graduate students responsible for recruitment were not involved in randomization and so were blinded to the assigned study arm until the culture was recruited and the according envelope was opened. Once a urine sample was recruited into the study, the according envelope was opened, and the sample was randomized based on the directions in the envelope.

4.11 Blinding

Blinding was difficult to enforce because investigators saw the report during the patient follow up. For this reason, investigators were not blinded to allocation.

4.12 Sample Size

Sample size was calculated based on a previously observed absolute difference of +23% appropriateness in the modified arm compared to the standard arm and an expected rate of inappropriate treatment of 45% and 15% in the standard and modified reporting arms, respectively (Daley et al., 2018). Using α=0.05 and β=0.20, the required sample size for this study

was calculated to be N=90 per arm. An additional 10 samples were added to account for missing data/loss to follow-up, for a total sample size of N=100 per arm.

4.12 Statistical Methods

Intention-to-treat (ITT) analysis was used to analyze all specimens randomized into the study. In addition, per-protocol (PP) analysis was used to analyze the specimens that followed protocol. Interim analysis was performed when 50% of our sample size was recruited, to assess safety outcomes only. There were no preliminary stopping rules. Outcomes were analyzed using a 2-sided Pearson Chi-squared test using SPSS version 26.0 software (IBM, Markham, ON). Fisher's Exact Test was used to assess the significance of differences in proportions between groups. Confidence intervals for bacteremia rate in the standard arm was assess with a one-sided 97.5 confidence interval based on the results from a confidence interval for a proportion calculator (Kohn & Senyak, 2020). Two-sided 95% confidence intervals were used to assess the significance of differences in means between groups. An adjusted analysis was not performed.

4.14 Ethics

The study was approved by the Health Research Ethics Board for Clinical Trials on July 16, 2018 (file 2018.098). The requirement for patient and physician consent was waived, because awareness of the study may have influenced treatment decisions.

4.15 Debriefing Plan for Physicians and Patients

Physicians were informed of the study prior to initiation and debriefed about the study following completion. Physicians and residents of inpatients at HSC and SCMH received an email inviting them to a debrief session with the principal investigator. Physicians and residents were provided with study results and given the option to withdraw their patient data if desired. Patients who submitted an UC that was included in the study were sent a letter that explained the study, waived consent as per ethics, and the option to withdraw their data after the data was collected.

CHAPTER 5: RESULTS

5.1 Participant Flow

Recruitment began on November 6th, 2018 and was completed on June 5th, 2019. During these 9 months, 543 samples were assessed for eligibility and 443 (81.6%) were excluded because they did not meet inclusion criteria. Intention to treat analysis included 100 samples; 46 samples were randomized to the SR, and 54 samples were randomized to MR. Of these 100, 10 samples were excluded post-randomization leaving 90 samples to be included in the per protocol (PP) analysis (SR N=43, MR N=47) (Figure 3). In the SR, the losses to follow-up were due to death before 72 hours (n=3), discharge before 72 hours (n=6), and lab error (n=2). In the MR, the losses to follow-up were due to death before 72 hours (n=3), discharge before 72 hours (n=6), recruitment errors (n=2), and lab errors (n=5). Lab error occurred when the UC result was changed by the lab after the culture had already been randomized or when the report released did not follow randomization. Recruitment error occurred when the sample was recruited into the study but violated inclusion criteria (Figure 3).

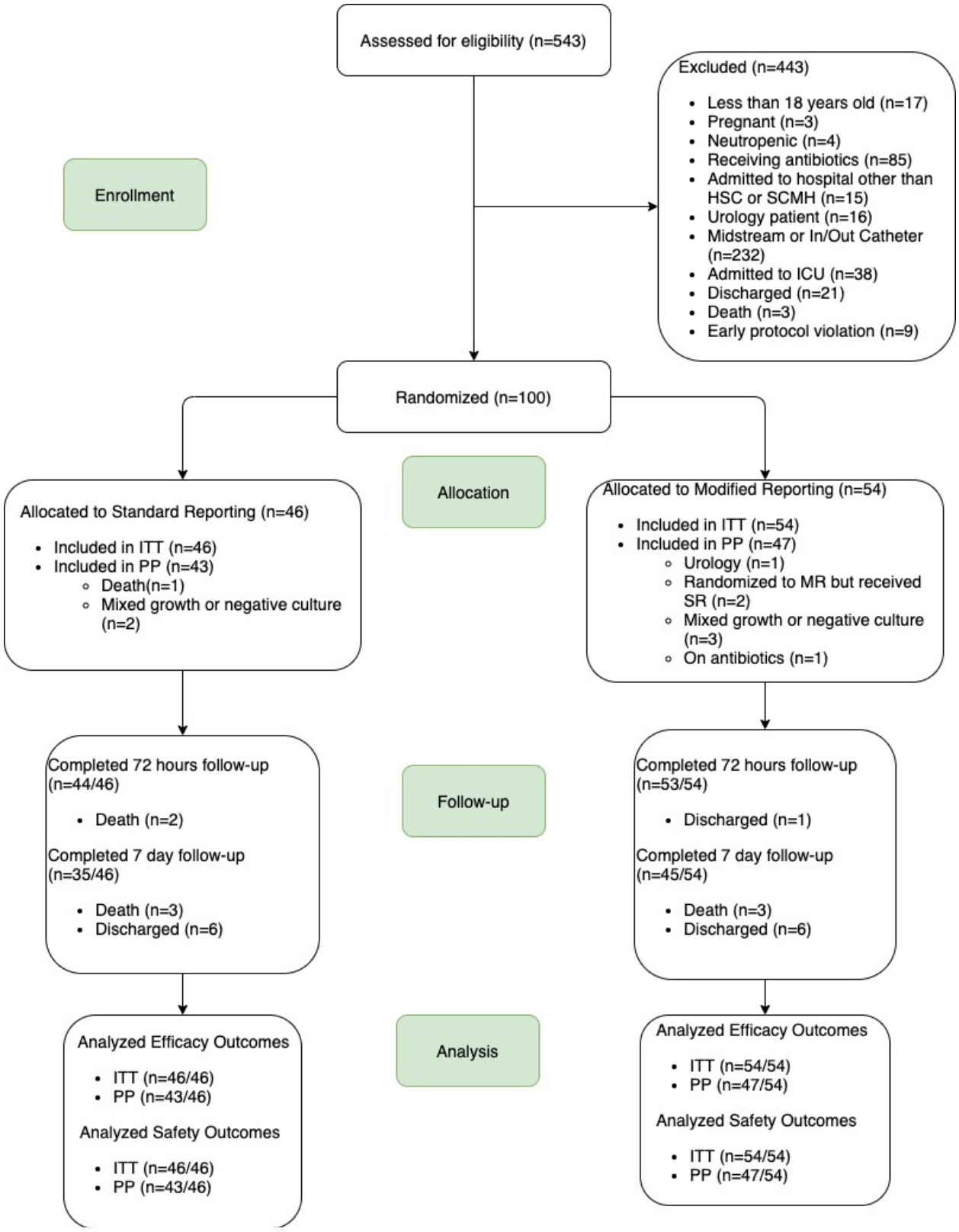

Figure 3: Participant Flow

5.2 Patient Demographics

Demographics were comparable between SR and MR groups. The groups were comparable in mean age ± SD (ITT-SR 73.6 ± 13.9 years, ITT-MR 71.4 ± 13.1 years), proportion of CA-UTI (ITT-SR 26.1%, ITT-MR 22.2%), and proportion of CA-ASB (ITT-SR 71.4%, ITT-MR 77.8%). There was a lower proportion of females in the SR than the MR (ITT-SR 39.1%, ITT-MR 51.9%). The proportion of CA-UTI was higher in the SR (ITT-SR 26.1%, ITT-MR 22.2%) while the proportion of CA-ASB was lower in the SR (ITT-SR 71.7%, ITT-MR 77.8%) (Table 1).

Table 1: Patient Demographics

	Intention-to-Treat			Per-Protocol		
	Standard (n=46)	Modified (n=54)	P value *	Standard (n=43)	Modified (n=47)	P value*
Age (mean ± SD)	73.3 ± 13.7	70.8 ± 12.6	0.330**	73.3 ± 14.0	72.0 ± 12.7	0.617**
Females	18/46 (39.1%)	28/54 (51.9%)	0.231	17/43 (39.5%)	24/47 (50.1%)	0.297
CA-UTI	12/46 (26.1%)	12/54 (22.2%)	0.065	12/43 (27.9%)	12/47 (25.0%)	0.093
CA-ASB	33/46 (71.7%)	42/54 (77.8%)	0.065	31/43 (72.1%)	35/47 (74.5%)	0.093

* P value (Fisher's Exact Test)
** P value (two-sided 95% confidence interval)

5.3 Efficacy Outcomes

Treatment appropriateness was calculated based on the sum of the proportion of patients with treated UTI and untreated ASB. For both ITT and PP analysis, appropriate treatment occurred more often with the MR than in the SR. Using ITT analysis, the proportion of appropriate treatment in the modified arm was 57.4%, while appropriateness in the standard arm was lower at 50.0% (Table 2). This produced an absolute increase of 7.4% and relative risk RR=1.15 (0.746,1.765) (Table 2). Using PP analysis, the proportion of appropriate treatment in the

modified arm was 61.4%, while appropriateness in the standard arm was lower at 53.5% (Table 2). This produced an absolute increase of 8.2% and relative risk RR=0.867 (0.606,1.240) (Table 2).

Table 2: Proportion of Appropriate Treatment

				Absolute Risk Reduction	Relative Risk (95% CI)
	SR	MR	P value*		
ITT	23/46 (50.0%)	31/54 (57.4%)	0.547	7.4%	1.15 (0.746, 1.765)
PP	23/43 (53.5%)	29/47 (61.7%)	0.523	8.2%	0.867 (0.606, 1.240)

*P value for Fisher's Exact Test

The secondary efficacy outcome was the proportion of physicians that called for the complete report after receiving the MR. Using ITT analysis, a full report was requested in 33.3% cases, and in 36.1% of cases in PP analysis. The majority of the calls were made by physicians or residents, followed by nurses and pharmacists (Table 5).

Treatment timing trended towards less treatment at the time of urine collection, (32/70, 45.7%) and towards more treatment after receiving the UC report (38/70, 54.3%) (Table 3). Of all antibiotics given, ciprofloxacin (MR-14.8%, SR-26.1%) nitrofurantoin (MR-13.0%, SR-15.2%), and ceftriaxone (MR-9.3%, SR-9.3%) were most common in both arms. All antibiotic treatments used can be found in Appendix B (Table 10). Treatment duration was variable but shorter in the MR (ITT-MR 3.6 ± 3.6 days, ITT-SR 4.2 ± 4.4 days) (Table 4).

Table 3: Antibiotic Treatment Timing

Intention To Treat, p=0.080					
	No Treatment	At Urine Collection	After ID Reported	After Susceptibility Reported	Total
SR	12 (26.1%)	15 (32.6%)	9 (19.6%)	10 (21.7%)	46 (100%)
MR	18 (33.3%)	17 (31.5%)	15 (27.8%)	4 (7.4%)	54 (100%)
Total	30	32	24	14	100
Per Protocol, p=0.115					
	No Treatment	At Urine Collection	After ID Reported	After Susceptibility Reported	Total
SR	12 (27.9%)	13 (30.2%)	9 (20.9%)	9 (20.9%)	43 (100%)
MR	16 (34.0%)	15 (31.9%)	13 (27.7%)	3 (6.4%)	47 (100%)
Total	28	28	22	12	90

Table 4: Common Antibiotic Treatment Regimen

Antibiotics Used			
	Ciprofloxacin	Nitrofurantoin	Ceftriaxone
SR	12/46 (26.1%)	17/46 (15.2%)	6/46 (13.0%)
MR	8/54 (14.8%)	7/54 (13.0%)	5/54 (9.3%)
Average Treatment Duration			
	SR (mean ± SD), (range)	MR (mean ± SD)	P-value*
ITT	4.2 ± 4.4 days, (1, 21)	3.6 ± 3.6 days, (1, 13)	0.455
PP	4.3 ± 4.5 days, (1, 21)	3.5 ± 3.5 days, (1, 12)	0.347

*P value (two-sided 95% confidence interval)

Table 5: Calls Received Requesting Standard Report

	Healthcare Worker			Total
	Physician/Resident	Nurse	Pharmacist	
ITT	10	7	1	18/54 (33.3%)
PP	9	7	1	17/47 (36.1%)

5.4 Safety

There were 3 deaths in the SR arm and 4 deaths in the MR arm (Table 7). Each death was investigated independently by a physician and none were found to be related to the MR (Table 7). There were no bacteremias in the SR arm and 3 bacteremias in the MR arm. Each bacteremia was investigated independently by a physician and none were found to be related to the MR. All positive blood cultures were collected at the time of UC collection, meaning that no new bacteremias occurred during patient follow-up (Table 8). The occurrence of 2 or more SIRS criteria at 72 hours follow-up was more frequent in the MR compared to the SR (ITT-MR 24.1%, ITT-SR 17.4%, p=0.414). This was consistent in the PP analysis, PP-MR 22.9% and PP-SR 18.6%, p=0.577 (Table 6). Adverse events at 7 days were more common in the SR (19/46, 95% CI (0.270,0.568) versus 16/54, 95% CI (0.180,0.436) in the MR). There was no significant difference in adverse events at 7 days between groups (Table 6). Specific adverse events are listed in Table 9.

Table 6: Safety

Deaths			
	Standard (95% CI)	Modified (95% CI)	P value*
ITT	3/46 (6.5%)	4/54 (7.4%)	0.863
PP	2/43 (4.7%)	3/47 (6.4%)	0.720
Bacteremias			
	Standard	Modified	
ITT	0/46 (0.000,0.077)**	3/54 (0.012,0.154)	0.247
PP	0/43 (0.000,0.082)**	3/47 (0.013,0.175)	0.243
SIRS at 72 Hours***			
	Standard	Modified	
ITT	8/46 (0.078,0.314)	13/54 (0.135,0.376)	0.414
PP	8/43 (0.084,0.334)	11/47 (0.123,0.380)	0.577
Adverse Events at 7 days			
ITT	19/46 (0.270,0.568)	16/54 (0.180,0.436)	0.216
PP	19/43 (0.291,0.601)	13/47 (0.156,0.426)	0.159

*P value (Fisher's Exact Test)
** Indicates one-sided 97.5% confidence interval.
***SIRS criteria met if patient exhibited 2 or more of body temperature > 38.3°C or < 36°C, pulse >90/min, respirations >20/min, WBC count >12,000 or <4,000, altered mental status, significant edema or positive fluid, or hyperglycemia without diabetes.

Table 7: Deaths

Study Number	2	12	17	40*	76	80	81
Study Arm	SR	MR	MR	MR	SR	MR	SR
Age	83	85	73	77	83	74	83
Sex	F	F	F	M	M	M	F
Reason for Admission	Myocardial infarction	Congestive heart failure (CHF)	Small bowel obstruction	UTI	Acute kidney injury (AKI) with delirium	Vertigo	Atrial fibrillation
Comorbidities	Hypertension (HTN), diabetes mellitus 2 (DM2), diverticulosis, gastroesophageal reflux disease (GERD), depression, anxiety, coronary artery disease (CAD)	Non-ST elevated myocardial infarction, DM2, chronic diarrhea, iron deficiency anemia, lichen planus, chronic scarring from tuberculosis	Rheumatoid arthritis, witamin B12 deficiency, osteoporosis, rheumatoid lung, bronchiectasis, hyperthyroidism	Abdominal aortic aneurism (AAA), bladder cancer, recurrent UTI, depression	COPD, interstitial lung disease, renal failure, dementia, ST-elevated myocardial infarction, upper gastrointestinal bleeding	Benign paroxysmal positional vertigo, atrial fibrillation, CHF, HTN, GERD	Progressive multiple sclerosis, CHF, Hypothyroidism
Reason for Collecting UC	Delirium	UTI	Cloudy urine	N/A	Suspected infection	Unknown infection	Unknown infection
Date for Complete UC Result: Bacterial ID	Nov 06, 2018	Nov 18, 2018	Nov 23, 2018	Dec 14, 2018	Mar 01, 2019	Mar 18, 2018	Mar 20, 2018
	E. faecalis	Restricted report	*K. pneumoniae*	Gram negative bacteria	*P. mirabilis*	Repeat culture, restricted report	*K. oxytoca*
Reason for Collecting Blood Culture	N/A	Sepsis	Pneumonia	N/A	N/A	N/A	N/A
Diagnosis at 72 hours	N/A	UTI	ASB	ASB	ASB	ASB	ASB
Antimicrobial Therapy	Pip/Tazo, intravenous (IV)	Ceftriaxone IV, Azithromycin, oral (PO)	Cipro PO, Pip/Tazo IV, Vancomycin IV	Pip/Tazo IV	None	None	Nitrofurantoin PO
Presumed Cause of Death	Bradycardia, Cardiogenic Shock	CHF, general decline	Pneumonia, general decline	Ischemic bowel, AAA, General decline	AKI, palliative care	Renal failure	CHF
Was death related to the intervention?	No	No	No	No	No	No	No

* Excluded from PP analysis.

Table 8: Bacteremias

Study Number	10	23	88
Study Arm	MR	MR	MR
Age	80	70	85
Sex	M	M	M
Reason for Admission	Urosepsis	UTI cap	Urosepsis
Comorbidities	Urethral stricture, recurrent UTI, COPD, HTN, bladder stones, dementia	COPD, constipation, heartburn, neurogenic atonic bladder, depression	COPD, palliative kidney cancer, CHF, pacemaker, fasciculations, urinary retention/clotting
Reason for Collecting UC	Fever	Weakness/unwell	Urosepsis
Date for Complete UC Result: Bacterial ID	Nov. 16, 2018 P. aeruginosa	Nov 26, 2018, Restricted report	Apr. 15, 2018 E. faecalis, P. aeruginosa
Reason for Collecting Blood Culture	Fever	Weakness/unwell	Shortness of breath
Date for Complete Blood Culture Result: Bacterial ID	Nov. 20, 2018 *P. aeruginosa*	Nov. 27, 2018 MRSA	Apr. 15, 2018 *E. faecalis*
Diagnosis at 72 hours	UTI	ASB	UTI
Antimicrobial Therapy	Pip/tazo IV	Azithromycin PO, Ceftriaxone IV, Vancomycin IV	Pip/tazo IV, Ampicillin IV, Cefuroxime PO
Presumed Cause of Bacteremia	Urosepsis	Urosepsis	Urosepsis
Was bacteremia related to the intervention?	No	No	No

Table 9: Adverse Events at 7 Days

Adverse Event	MR	SR
Acute Kidney Injury	1	0
Anxiety	0	1
Aspiration Pneumonia	0	1
Auditory Hallucinations	0	1
Candidemia	0	1
Chest Pain	1	0
Confusion	0	1
Constipation	0	1
Decreased level of consciousness	0	1
Decreased white blood cell	0	1
Delirium	1	1
Diarrhea	1	0
Dizziness	0	1
Edema	0	1
Fall	0	1
Fever	1	0
Fluid Overload	0	1
Gross Hematuria	0	1
Hypokalemia	1	1
Increased liver enzymes	0	1
Increased penile discharge	0	1
Respiratory Secretions	1	0
Sacral tear	1	0
Shortness of Breath	1	1
Stool Impaction	0	1
Suicidality	1	0
Suprapubic Tenderness	1	0
Tachycardia	1	0
Wound Infection	1	0

CHAPTER 6: DISCUSSION

6.1 Patient Flow and Randomization

Because the study only included catheterized patients, many urine specimens were excluded. Non-catheterized urine specimens were analyzed in a previous study (Daley et al., 2018). Demographics were evenly distributed between groups with the exception of female sex. Female sex is a risk factor for UTI and ASB, but this would not bias our analysis because all patients were catheterized, and catheterization bypasses the female genital anatomy which predisposes to bacterial penetration of the bladder (Hooton et al., 2010; Letica-Kriegel et al., 2019).

Any losses to follow-up were a result of discharge or death within 7 days. However, the retention for assessing overall safety outcomes was high as most patients remained in the study for at least 72 hours, or were included in the death analysis (Figure 4). The MR observed two incidences of recruitment error that violated inclusion criteria. One of these urines were ordered by a urologist, however that was not known at the time of inclusion because this physician was not included on the list of urologists provided to the graduate students for recruitment. Following this, the list was revised to ensure that all urologists were listed. The second recruitment error was due to a patient being on antibiotics at the time of collection. This error occurred because the antibiotic treatment was not appropriately documented in the online medical record used to assess medication status and was found elsewhere after randomization. Based on the ITT and PP analyses, the losses to follow-up did not significantly impact our results.

6.2 Efficacy outcomes

The MR appears to have a positive trend towards more appropriate treatment as indicated by the higher proportion of appropriate treatment compared to the standard arm. However, the proportion of inappropriate treatment in both arms was high (22/46 47.8% SR, 23/54 42.6% MR). This confirms that physicians continue to treat positive UCs without considering the patient's symptom history, as seen in a previous study (Daley et al., 2018). In both arms, the proportion of CA-ASB was higher than CA-UTI, indicating that the majority of included UCs should not have been ordered. The rate of CA-ASB observed (75.0%) is higher than in the previous study done in non-catheterized inpatients (69.1%), confirming that the over-ordering of UCs is a significant issue in acute care and a desirable target for future stewardship initiatives (Daley et al., 2018; Jaeger et al., 2019; Redwood et al., 2018). ASB treatment rate was similar in the catheterized and non-catheterized population, however the proportion of inappropriate treatment in the MR was much higher in the catheterized population (51.1% compared to 25.7% in non-catheterized) (Daley et al., 2018). This is likely due to the increased risk of CA-UTI posed by catheterization and the difficulty in differentiating CA-ASB from CA-UTI in these patients, compared to non-catheterized patients (Lo et al., 2014).

Twenty-eight treatments out of ninety (31.1%) were given at the time of urine collection in both arms, suggesting that a MR intervention occurs too late to influence these treatment decisions. However, the MR is a suitable intervention when treatment is given after identification and susceptibility reporting, which cumulatively accounted for the majority of treatment decisions in both arms (ITT-MR: 19/54 (35.2%), ITT-SR: 19/46 (41.3%)). Treatment duration was

extremely variable in both groups and averaged 3.6 days in the MR and 4.2 days in the SR (range=(1,13) days in MR, range=(1,21) days in SR). Comparison of treatment duration was done to observe if physicians seemed to reassess antimicrobial treatment when given the MR as opposed to the SR. While the average treatment duration observed may seem short compared to the suggested 7-14 days stated in guidelines, this may be appropriate as physicians should reassess the antimicrobial treatment given at 3 days with the opportunity to change or terminate therapy (Spectrum Mobile Health Inc., 2018). As it was not determined during our investigations, future studies should examine the ordering physician's rationale for their treatment decisions. This would provide valuable information that can expand our knowledge of the interaction between the use of evidence-based guidelines and the surrounding medical culture, and the resultant effect on treatment decisions.

The existing medical culture in acute care settings facilitates the inappropriate treatment of CA-ASB seen in our study. The over-ordering and treatment of results rather than symptoms, as well as the increased risk of developing CA-UTI in catheterized patients may have influenced a clinical bias towards treatment. This appears to be supported by our findings that only 37% of MRs called the laboratory for complete results and that the proportion of inappropriate treatment remained high in the MR arm.

6.3 Safety outcomes

Our results support previous findings that MR is a safe intervention in acute care settings, however because our data did not result in significant findings, we cannot confidently say that the MR is fully safe in the catheterized population. There were no cases of untreated UTI,

meaning that no cases were allowed to progress to pyelonephritis due to the MR. The MR was also safer than the standard report based on the lower proportion of cumulative adverse events, and safe in that no cases of death or bacteremia were associated with the MR. However, the proportion of patients that met SIRS criteria was higher in the MR arm. SIRS criteria are non-specific and may be caused by underlying illness, not only CA-UTI (Boka, 2018). The implication of other sources of SIRS is possible as the majority of patients submitting positive UCs were seniors and on other medications at the time of admission (Boka, 2018). Regardless, a higher rate of SIRS in the MR is concerning, and if the modified report is to be used in clinical practice, patients should continue to be monitored for SIRS criteria and investigated appropriately.

6.4 Strengths and Limitations

MR is a useful and effective AMS intervention because it has the ability to prevent inappropriate treatment and is extremely practical (Daley et al., 2018; Leis et al., 2014). Based on current findings, the realistic implementation of a MR would require institution-specific guidelines as to which patients and wards would be eligible. The actual change and implementation of MR would not require excessive additional work for hospital and microbiology staff, as a simple change in report script would be the main requirement. Our study design was a randomized controlled trial which reduced the risk of confounders presented by other ongoing AMS initiatives (Langford et al., 2019).

The main limitation in this study was the extensive inclusion/exclusion criteria which diminished the generalizability of our findings. These criteria also limit the practicality of the

intervention, as it would be very difficult for the microbiology laboratory to assess eligibility with the current urine culture collection, processing, and reporting protocol. Furthermore, the diagnosis of CA-UTI and CA-ASB in our study are based on chart review; inconsistencies in charting may have led to missing information, possibly creating a bias towards the diagnosis of CA-ASB. Incomplete records also caused difficulty in confirming the method of collection of each urine, despite calling the ward to discuss with nursing. As this study repeated an intervention from a previous study showing very significant benefit, the calculated sample size used was done using an expected amount of appropriate treatment from the previous study (Daley et al., 2018). This unfortunately led to an underpowered study due to a smaller observed effect size compared to the previous study, and indicates that this study may not have been sufficiently powered to best analyze adverse events. Participation from the urology department would have been beneficial as this department treats many CA-UTIs and has many patients with a CIC.

With these limitations in mind and the lack of evidence in laboratory AMS interventions, future studies should be more inclusive where possible and have a larger sample size. Future research should focus on interventions at a different point in the process of inpatient UTI care, such as before ordering a urine culture or before giving treatment, as well as consider the bias towards overtreatment observed in acute care.

CHAPTER 7.0: Conclusion

We measured the impact of MR on treatment appropriateness for CA-UTI and CA-ASB. We found that CA-ASB was common and often inappropriately treated. Our findings were clinically significant as they demonstrated the MR to have a higher proportion of appropriate treatment compared to the SR, with similar rates of adverse events and no association with bacteremia or death. It is noteworthy however that the MR did have a higher proportion of patients meeting SIRS criteria compared to the standard report, which is concerning and should be taken into consideration for future testing or implementation of a MR. These findings agree with previous research (Daley et al., 2018; Leis et al., 2014). We have learned that a MR is not as effective in a catheterized population compared to a non-catheterized population. The catheterized population receives treatment much more frequently, likely due to their unique risk factors for bacterial infection that are absent in non-catheterized patients.

Antimicrobial resistance is in part a societal issue for which the behaviour around antibiotic treatment needs to change. Future research can support these goals by testing interventions that occur at different points in patient care and are practical. Furthermore, interventions should be as generalizable to a hospital-wide setting where possible. The MR should continue to be investigated, as it is known to influence treatment, is practical, and requires more data on its safety in the catheterized population. A better knowledge of the MR's safety outcomes can inform the implementation of its use in everyday practice. The MR can also be included as a part of a combined intervention to help reduce unnecessary use of antibiotics.

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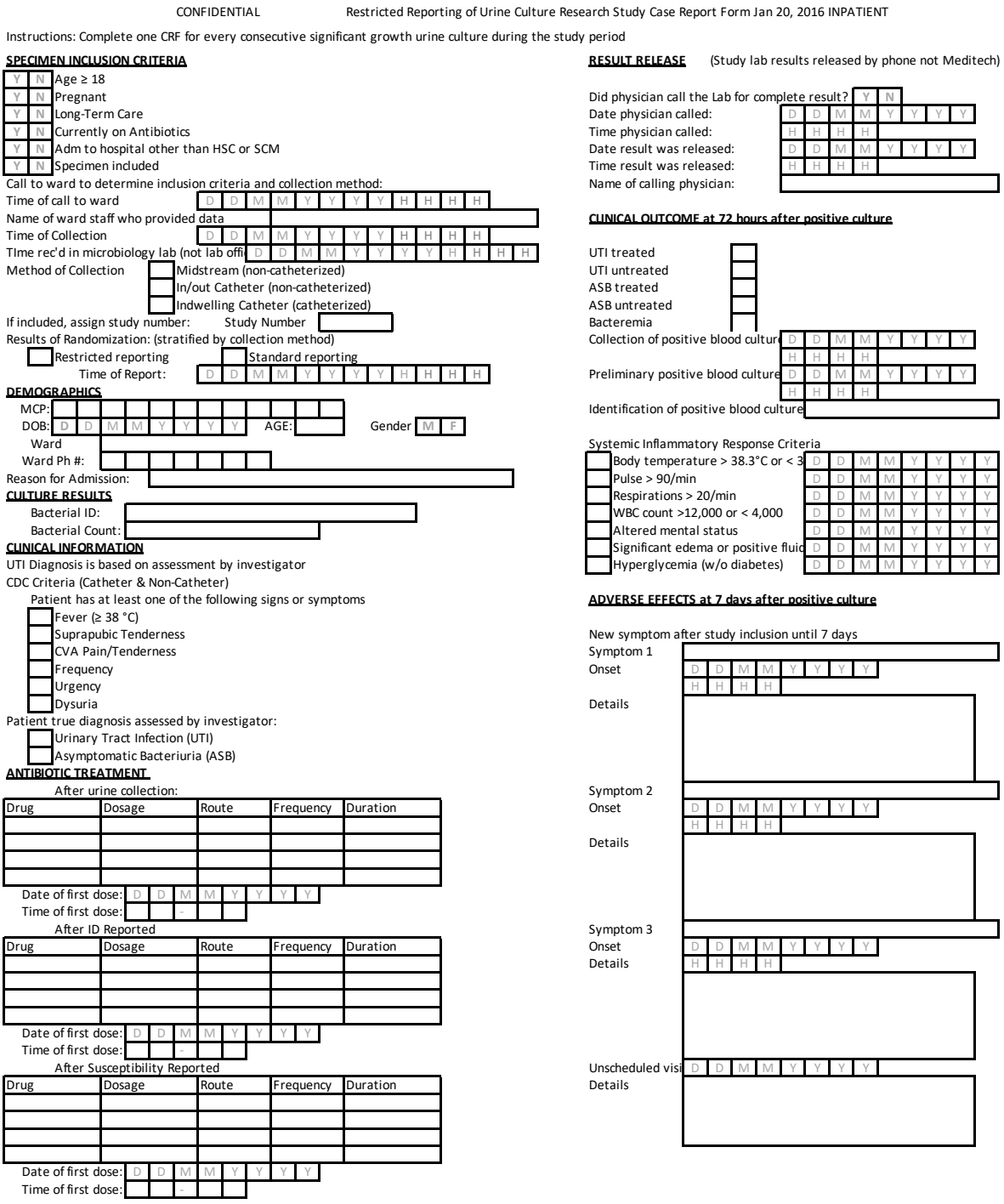
Appendix A: Study Forms



CONFIDENTIAL Restricted Reporting of Urine Culture Research Study Case Report Form Jan 20, 2016 INPATIENT

Instructions: Complete one CRF for every consecutive significant growth urine culture during the study period

SPECIMEN INCLUSION CRITERIA

Y N Age ≥ 18
Y N Pregnant
Y N Long-Term Care
Y N Currently on Antibiotics
Y N Adm to hospital other than HSC or SCM
Y N Specimen included

Call to ward to determine inclusion criteria and collection method:
Time of call to ward D D M M Y Y Y Y H H H H
Name of ward staff who provided data
Time of Collection D D M M Y Y Y Y H H H H
TIme rec'd in microbiology lab (not lab offi D D M M Y Y Y Y H H H H
Method of Collection ☐ Midstream (non-catheterized)
☐ In/out Catheter (non-catheterized)
☐ Indwelling Catheter (catheterized)
If included, assign study number: Study Number
Results of Randomization: (stratified by collection method)
☐ Restricted reporting ☐ Standard reporting
Time of Report: D D M M Y Y Y Y H H H H

DEMOGRAPHICS

MCP:
DOB: D D M M Y Y Y Y AGE: Gender M F
Ward
Ward Ph #:
Reason for Admission:

CULTURE RESULTS

Bacterial ID:
Bacterial Count:

CLINICAL INFORMATION

UTI Diagnosis is based on assessment by investigator
CDC Criteria (Catheter & Non-Catheter)
Patient has at least one of the following signs or symptoms
☐ Fever (≥ 38 °C)
☐ Suprapubic Tenderness
☐ CVA Pain/Tenderness
☐ Frequency
☐ Urgency
☐ Dysuria
Patient true diagnosis assessed by investigator:
☐ Urinary Tract Infection (UTI)
☐ Asymptomatic Bacteriuria (ASB)

ANTIBIOTIC TREATMENT

After urine collection:

Drug	Dosage	Route	Frequency	Duration

Date of first dose: D D M M Y Y Y Y
Time of first dose: : (24 hr)

After ID Reported

Drug	Dosage	Route	Frequency	Duration

Date of first dose: D D M M Y Y Y Y
Time of first dose: : (24 hr)

After Susceptibility Reported

Drug	Dosage	Route	Frequency	Duration

Date of first dose: D D M M Y Y Y Y
Time of first dose: : (24 hr)

RESULT RELEASE (Study lab results released by phone not Meditech)

Did physician call the Lab for complete result? Y N
Date physician called: D D M M Y Y Y Y
Time physician called: H H H H
Date result was released: D D M M Y Y Y Y
Time result was released: H H H H
Name of calling physician:

CLINICAL OUTCOME at 72 hours after positive culture

UTI treated
UTI untreated
ASB treated
ASB untreated
Bacteremia
Collection of positive blood cultur D D M M Y Y Y Y
H H H H
Preliminary positive blood culture D D M M Y Y Y Y
H H H H
Identification of positive blood culture

Systemic Inflammatory Response Criteria
☐ Body temperature > 38.3°C or < 3 D D M M Y Y Y Y
☐ Pulse > 90/min D D M M Y Y Y Y
☐ Respirations > 20/min D D M M Y Y Y Y
☐ WBC count >12,000 or < 4,000 D D M M Y Y Y Y
☐ Altered mental status D D M M Y Y Y Y
☐ Significant edema or positive fluic D D M M Y Y Y Y
☐ Hyperglycemia (w/o diabetes) D D M M Y Y Y Y

ADVERSE EFFECTS at 7 days after positive culture

New symptom after study inclusion until 7 days
Symptom 1
Onset D D M M Y Y Y Y
H H H H
Details

Symptom 2
Onset D D M M Y Y Y Y
H H H H
Details

Symptom 3
Onset D D M M Y Y Y Y
Details H H H H

Unscheduled visi D D M M Y Y Y Y
Details

Figure 4: Case Report Form Used During Recruitment and Follow-Up

Date	Time	Date Standard Report was Released	Time Standard Report was Released	Name of Physician
DD/MM/YYYY	HH:MM	DD/MM/YYYY	HH:MM	
DD/MM/YYYY	HH:MM	DD/MM/YYYY	HH:MM	
DD/MM/YYYY	HH:MM	DD/MM/YYYY	HH:MM	
DD/MM/YYYY	HH:MM	DD/MM/YYYY	HH:MM	
DD/MM/YYYY	HH:MM	DD/MM/YYYY	HH:MM	
DD/MM/YYYY	HH:MM	DD/MM/YYYY	HH:MM	
DD/MM/YYYY	HH:MM	DD/MM/YYYY	HH:MM	
DD/MM/YYYY	HH:MM	DD/MM/YYYY	HH:MM	
DD/MM/YYYY	HH:MM	DD/MM/YYYY	HH:MM	
DD/MM/YYYY	HH:MM	DD/MM/YYYY	HH:MM	
DD/MM/YYYY	HH:MM	DD/MM/YYYY	HH:MM	
DD/MM/YYYY	HH:MM	DD/MM/YYYY	HH:MM	
DD/MM/YYYY	HH:MM	DD/MM/YYYY	HH:MM	
DD/MM/YYYY	HH:MM	DD/MM/YYYY	HH:MM	
DD/MM/YYYY	HH:MM	DD/MM/YYYY	HH:MM	
DD/MM/YYYY	HH:MM	DD/MM/YYYY	HH:MM	
DD/MM/YYYY	HH:MM	DD/MM/YYYY	HH:MM	
DD/MM/YYYY	HH:MM	DD/MM/YYYY	HH:MM	
DD/MM/YYYY	HH:MM	DD/MM/YYYY	HH:MM	
DD/MM/YYYY	HH:MM	DD/MM/YYYY	HH:MM	
DD/MM/YYYY	HH:MM	DD/MM/YYYY	HH:MM	
DD/MM/YYYY	HH:MM	DD/MM/YYYY	HH:MM	
DD/MM/YYYY	HH:MM	DD/MM/YYYY	HH:MM	
DD/MM/YYYY	HH:MM	DD/MM/YYYY	HH:MM	
DD/MM/YYYY	HH:MM	DD/MM/YYYY	HH:MM	
DD/MM/YYYY	HH:MM	DD/MM/YYYY	HH:MM	
DD/MM/YYYY	HH:MM	DD/MM/YYYY	HH:MM	
DD/MM/YYYY	HH:MM	DD/MM/YYYY	HH:MM	
DD/MM/YYYY	HH:MM	DD/MM/YYYY	HH:MM	
DD/MM/YYYY	HH:MM	DD/MM/YYYY	HH:MM	

Figure 5: Physician Call Back Log Sheet

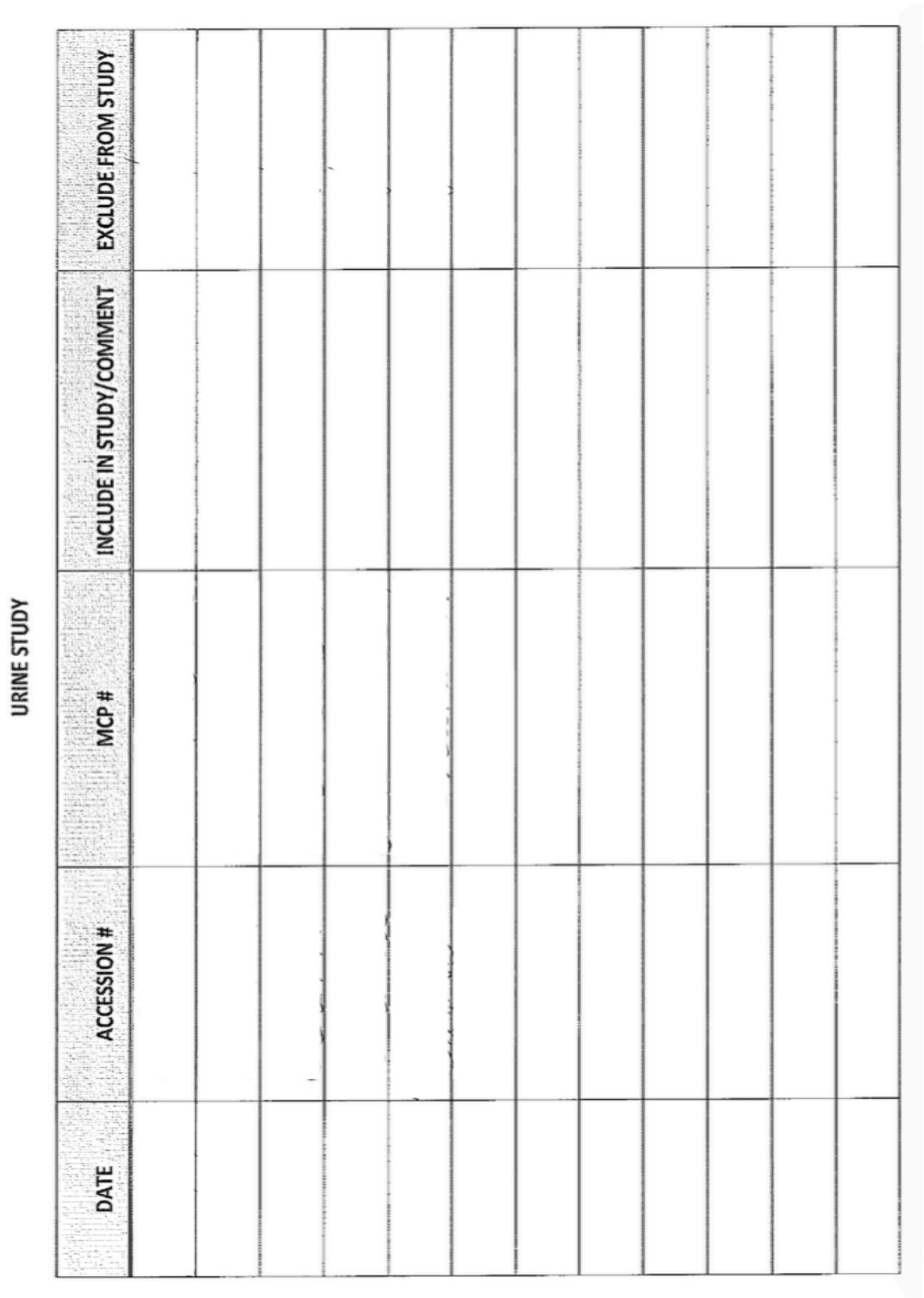


Figure 6: Accession Number Sheet Used to Communicate Included and Excluded Cultures

Appendix B: Antibiotics Used

Table 10: All Antibiotics Used for Treatment

Standard Report			
Drug	Frequency	Percent	Cumulative Percent
Amoxicillin/Clavulanate	1	2.2	2.2
Ampicillin	1	2.2	4.4
Ceftriaxone	6	13.0	17.4
Ciprofloxacin	12	26.1	43.5
Nitrofurantoin	7	15.2	58.7
None + N/A	12	26.0	84.7
Pip/Tazo	3	6.5	91.4
Septra DS	4	8.8	100.0
Total	46	100	100.0
Modified Report			
Drug	Frequency	Percent	Cumulative Percent
Amoxicillin	2	3.7	3.7
Amoxicillin/Clavanulate	1	1.9	5.6
Azithromycin	1	1.9	7.5
Caspofungin	1	1.9	9.4
Ceftriaxone	5	9.3	18.7
Ciprofloxacin	8	14.8	33.5
Clindamycin	1	1.9	35.4
Ertapenem	1	1.9	37.3
Gentamicin	1	1.9	39.2
Nitrofurantoin	7	13.0	52.2
None + N/A	17	31.1	83.3
Piperacillin/Tazobactam	3	5.6	88.9
Septra	2	3.7	92.6
Septra DS	4	7.4	100.0
Total	54	100.0	100.0

Appendix C: Ethics Approval

HREB

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

July 16, 2018

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

Dear Dr. Daley:

Researcher Portal File # 20190283
Reference # 2018.098

RE: "Modified Reporting for Positive Urine Cultures Collected from Indwelling Catheters, a Randomized Controlled Trial"

This will acknowledge receipt of your correspondence dated July 5m 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 [*insert the date of this letter (i.e. the date that this letter was signed)*]. 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	File Name	Description

Figure 7: Proof of Ethics Approval

	Date		
Debriefing Script/Sheet	2018/05/11	Approved	Invitation to debrief
Debriefing Script/Sheet	2018/05/11	Approved	Patient Debrief Letter
Debriefing Script/Sheet	2018/07/05	Approved	Corrected Debrief Email
Information Sheet/Letter	2018/05/11	Approved	Briefing email to be sent to physicians and residents
Letter of Acknowledgement from Data Custodian	2018/05/11	Acknowledged	Request to Data Custodian
Other	2018/05/11	Acknowledged	Lab SOP
Research Instrument	2018/05/11	Acknowledged	Case Report Form
Research Proposal/Protocol	2018/04/12	Acknowledged	Protocol
Response Summary	2018/07/05	Approved	Response to ethics committee received July 4

MARK THE DATE

This ethics approval will lapse on July 16, 2019. It is your responsibility to ensure that the Ethics Renewal form is submitted prior to the renewal date; you may not receive a reminder. The Ethics Renewal form can be found on the Researcher Portal as an Event Form.

If you do not submit the completed Ethics Renewal form prior to date of renewal:

- **You will no longer have ethics approval**
- You will be required to stop research activity immediately
- You may not be permitted to restart the study until you reapply for and receive approval to undertake the study again
- Lapse in ethics approval ***may result in interruption or termination of funding***.

You are solely responsible for providing a copy of this letter, along with your approved HREB application form; to **Research Grant and Contract Services** should your research depend on funding

Figure 7: Proof of Ethics Approval (continued)

administered through that office.

Modifications of the protocol/consent are not permitted without prior approval from the HREB. **Implementing changes in the protocol/consent without HREB approval may result in your ethics approval being revoked, meaning your research must stop.** Request for modification to the protocol/consent must be outlined on an amendment form available on the Researcher Portal website as an Event Form and submitted to the HREB for review. Please refer to the attached guidance document regarding on-going reporting requirements to the HREB.

The HREB operates according to the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS2), ICH Guidance E6: Good Clinical Practice Guidelines (GCP), the Health Research Ethics Authority Act (HREA Act) and applicable laws and regulations.

You are responsible for the ethical conduct of this research, notwithstanding the approval of the HREB.

We wish you every success with your study.

Sincerely,

Dr. Joh Fardy (Acting Co-Chair, Clinical Trials)
Health Research Ethics Board

You Have Received Ethics Approval, Now What?: HREB Reporting Requirements

Once a study has received ethics approval from the Health Research Ethics Board (HREB), there are still associated reporting requirements. In the conduct of approved research researchers are required to report to the HREB, in a timely manner, proposed changes from approved research that affect participants at any stage of the process. This includes, but is not limited to, changes to the consent form, changes to the tasks or interventions involved in the research, or changes to measures to protect privacy and confidentiality.

Any substantive change to the research should not be implemented prior to documented approval by the HREB, except when necessary to eliminate an immediate risk(s) to the participants. Below are examples of post approval documentation that must be submitted to the HREB:

Amendments

Figure 7: Proof of Ethics Approval (continued)

Any proposed change in the conduct of a study must be submitted to the HREB, and approved, before the change may be implemented. Such changes might include modification of recruitment procedures, inclusion or exclusion criteria, revised sample size, addition or deletion of study sites, changes to an intervention, consent forms, questionnaires or scripts, etc. If there are changes in project team members or changes to funding source(s)/sponsor(s), there are specific forms to complete to report this to the HREB.

Adverse Events

Serious and unanticipated adverse events that occur within Newfoundland and Labrador are required to be reported to the HREB. Such events may occur in both clinical trials and in other types of research, e.g. collapse during a rehabilitation program, emotional breakdown requiring follow up care during an interview, or breach of privacy during correspondence. Serious adverse events that are fatal or life-threatening are required to be reported to the HREB as soon as the research team is aware of the event.

Protocol Deviations

Deviations from an approved study protocol must be reported to the HREB. Changes that eliminate immediate hazards to participants do not require prior approval, but must be reported soon as reasonably possible.

Safety Reports

Safety reports providing information on all serious adverse events (SAEs) occurring in a clinical trial must be provided by the sponsor to the HREB, normally on a three or six monthly basis (i.e. in accordance with the specified reporting timelines that were outlined in the approved ethics application).

Investigator Brochure (IB) and Product Monograph (PM)

Throughout the course of a clinical trial, changes may be implemented to study documents. All revisions to approved study documents must be submitted to the HREB to ensure the record is up to date. If the revisions include new risk or safety information there may be a requirement to notify research participants.

Ethics Renewal/Study Closure

Ethics approval lasts for one year. Ethics renewal is required annually, on the anniversary of the date of the HREB notification of approval. Once data collection is no longer ongoing, a study closure form is required to be submitted to the HREB for the study to remain active or to be closed in good standing.

Figure 7: Proof of Ethics Approval (continued)

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