A Randomized Controlled Trial of Modified Reporting of Urine Cultures to Reduce Inappropriate Treatment of Asymptomatic Bacteriuria

by

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ABSTRACT

45%-65% of patients with asymptomatic bacteriuria (ASB) are inappropriately treated with antimicrobials, leading to an increase in bacterial resistance, cost, and adverse health events. Positive urine culture seems to remarkably influence antimicrobial use in ASB. The purpose of this project is to answer the question of whether among inpatients with positive urine cultures, would modified reporting lead to a reduction in inappropriate therapy.

The study was a randomized, parallel group, superiority trial, comparing two different ways to report positive urine cultures.

In the intention-to-treat analysis, the proportion of appropriate treatment (UTI treated plus ASB not treated) in the modified arm was 44/55 (80.0%) vs. 29/55 (52.7%) in the standard arm, absolute difference= 27.3%, RR=0.42, p=0.002. Number needed to report for benefit=3.7. The overall difference in proportion of appropriate treatment was produced by a decrease in the number of ASB treated. Modified reporting did not increase the occurrence of adverse events.

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LIST OF ABBREVIATIONS AND SYMBOLS

IN ALPHABETICAL ORDER

ASB Asymptomatic Bacteriuria

CDC Centers for Disease Control and Prevention

CDI Clostridium Difficile 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

NNH Number Needed to Harm

PP Per-protocol

RR Relative Risk

SIRS Systemic Inflammatory Response Syndrome

UTI Urinary Tract Infection

Chapter 1 – INTRODUCTION

1.1 Preamble

The study published by Edward Kass in 1956: "Asymptomatic Infections of the Urinary Tract"[1] was the starting point for some fundamental concepts in this thesis. Kass was the first to establish the association between bacterial counts ≥100,000 colony-forming units (CFUs) per ml in urine cultures with patients presenting with symptoms of urinary tract infection (UTI). Since then, this number has remained the gold standard for the diagnosis of UTI. Additionally, Kass described a group of patients who, despite having urine cultures with bacterial counts ≥ 100,000CFU/ml, did not present symptoms of UTI; he coined the term “asymptomatic bacilluria” for these patients, later known as asymptomatic bacteriuria (ASB) or covert bacteriuria. Kass suggested that association between asymptomatic bacilluria and pyelonephritis (kidney infection) was not unlikely. From that point forward, the influence of ASB on health status and whether patients should be treated with antibiotics or not, were sources of controversy.

The cases described in Kass' study, currently known as ASB patients, constitute the population affected by the problem the intervention described in this thesis aims to improve. At present, they are patients whose urine samples are cultured for presenting any sign or symptom mistakenly attributed to a potential UTI, e.g., foul-smelling or cloudy urine; or for reasons not related to

clinical manifestations, such as routine admission or preoperative testing; and subsequently, in nearly half of the cases of these patients with positive urine cultures, they are treated with antimicrobials.[2]

ASB is a common clinical finding, particularly among inpatients, the elderly, and patients with indwelling urinary catheters.[3] In the 1980s, Dontas et al. stated that ASB was associated with a reduction of survival in the elderly.[4] Nonetheless, scientific evidence to date has shown that in general, ASB is not associated with adverse outcomes. In 2005, Clinical Practice Guidelines (CPGs) were published to assist practitioner decisions about appropriate management of ASB.[5] CPGs are systematically developed statements based on the best available scientific evidence. The aforesaid CPGs for the diagnosis and treatment of ASB in adults state that antimicrobial therapy has no role in most cases of ASB, and withholding treatment has no impact in mortality and morbidity. As discussed further on in this chapter, not only is ASB treatment not helpful, it may actually be harmful.

Certainly, patients with ASB are at an increased risk for symptomatic UTI;[5] however, the association of ASB with symptomatic UTI is likely caused by host factors that facilitate both entities, as opposed to symptomatic UTI being caused by ASB.[5]

It is not clear why physicians treat ASB with antimicrobials regardless of the presence of symptoms, but it may include the fear of consequences of ignoring a positive laboratory result.[6] In any case, it represents a lack of success in translating evidence into practice.

This Master's thesis describes a randomized controlled trial to evaluate the effect of an intervention conducted in a Microbiology Laboratory, which modifies the standard reporting of positive urine cultures, to improve ASB management.

1.2 UTI and ASB Definition, Pathophysiology and Epidemiology

UTI and ASB are two separate clinical syndromes, which have in common significant bacterial growth from a urine specimen. These syndromes are commonly confused, but have very different implications and treatment.

The Infectious Diseases Society of America (IDSA) defines ASB as the presence of bacteria in a non-contaminated urine sample collected from a patient without clinical manifestations of UTI.[5] In asymptomatic females, the determination of ASB requires the isolation of the same microorganism in 2 successive voided urine samples isolated in amounts ≥ 100,000 CFU/ml.[5] In asymptomatic men, one voided urine sample with 1 bacterial species isolated in amounts ≥100,000 CFUs/mL; or single catheterized sample with 1 bacterial

species isolated in quantitative counts ≥100 CFUs/mL in asymptomatic patients, regardless of sex, constitutes the diagnosis of ASB.[5, 7]

Conversely, acute cystitis (UTI affecting the bladder only) causes symptoms such as urinary frequency, urgency, dysuria (pain during urination), or suprapubic tenderness, with no anatomical anomalies in the genitourinary tract. Acute pyelonephritis (UTI affecting the kidney) causes symptoms such as fever, flank pain, nausea, vomiting, and rigours.[6] Complicated UTI occurs in patients whose genitourinary tract presents a functional or anatomical anomaly, e.g., vesicoureteral reflux (backward flow of urine from the bladder to the upper urinary tract), or urethral strictures.

The diagnosis of symptomatic UTI in some clinical conditions requires different considerations. Patients with indwelling urethral catheters have difficulty in localizing urinary symptoms.[8] therefore typical manifestations of UTI (pain, urgency, and dysuria) are uncommon. Clinical assessment of patients with limited communication such as advanced dementia or stroke can be challenging. In patient with spinal cord lesions, the sensitivity and specificity of symptoms and signs are poor.[9]

The microbiology of ASB/UTI mainly comprises gastrointestinal tract bacteria, since the mechanism of infection is ascending bacteria, from the bowel into the bladder. By far, the most frequently found bacterium is *Escherichia coli*

(75-95%); other causes include *Klebsiella spp, Proteus mirabilis, Enterococcus* and *Staphylococcus saprophyticus*.[10, 11]

It is considered that bacterial strains capable of triggering a remarkable inflammatory response of the urinary bladder epithelium and therefore the symptoms of UTI have different, or at least, a higher proportion of virulence factors in relation to the strains responsible for ASB.[11, 12] These factors include fimbriae, flagella, diverse adhesins, siderophores, toxins, polysaccharide coatings, among others, which help the microorganisms in overcoming host resistances.[10] Humans count on several urinary tract defenses against bacteria colonization such as mechanical flushing of urine flow, urine acidity and osmolality, various inhibitors of bacterial adherence, local secretion of cytokines and chemokines and bactericidal zinc in prostatic secretions.[13] Risk factors for urinary tract colonization are female sex, pregnancy, urological anomalies, frequent or recent sexual intercourse, indwelling catheter, spermicide use, diabetes, aging, genetic factors and some comorbidities.[10, 11, 14] The initial step in the genesis of ASB/UTI corresponds to bacterial colonization of the periurethral mucosa; followed by the bacterial ascent to the bladder. In cases of bacteria that possess the virulence factors to trigger tissue aggression, they cause inflammation of the urinary bladder epithelium (cystitis) and in some cases bacterial ascent to the kidney producing pyelonephritis.[11, 13] UTIs with involvement of kidneys or prostate are potential sources of bacteremia, and Systemic Inflammatory Response Syndrome (SIRS) and sepsis.[15] Bacteremia is

the presence of viable bacteria circulating in the blood, while SIRS is a widespread inflammatory process associated with infectious and noninfectious causes. When a SIRS is concomitant with a known or highly suspected infection, it defines a case of sepsis.[16]

UTIs are the most common bacterial infections in general; and the second most common in the non-institutionalized elderly. By the age of 24 years, almost one third of all women will experience 1 or more episodes of UTI requiring antimicrobials; and close to 50% will have one UTI within their lifetime.[17] Men are significantly less likely to experience UTI, accounting for approximately 20% of all UTIs.[18] According to The Centers for Disease Control and Prevention (CDC), UTIs represent over 12% of infections reported by acute care hospitals.[19]

Among healthy women, ASB prevalence varies from approximately 1% of preschool girls to almost 20% among women 80 years of age or older living in the community.[6] In a study including all preschool girls attending a medical office for “well child” checkup, none of whom presenting UTI symptoms, whose urine samples were cultured, ASB was found in 0,8% of cases.[20] In another study carried out in the geographical catchment area of a primary health care centre in a Swedish municipality, all residents aged ≥ 80 years old, not living in institutions, were invited to participate; they found ASB prevalence close to 20% among women.[21] ASB is infrequent in healthy young men; a Japanese study found no

cases of ASB among more than 1200 men younger than 50 years.[22] Obstructive uropathy (structural or functional hindrance of normal urine flow) increases the prevalence in older men.[23] Institutionalized patients regularly have significant numbers of bacteria in urine, with about 25–50% of females and 15–40% of males affected.[6] Urinary catheters enable microorganisms to accumulate, with a prevalence of bacteriuria of 9–23% in short-term and 100% in long-term catheterization.[6]

1.3 UTI Treatment

Antibiotic treatment is appropriate for UTIs, to prevent bacteria from ascending to the kidney or into the bloodstream.

In 2010, The IDSA and the European Society for Microbiology and Infectious Diseases updated the practice guidelines for treatment of UTI. They recommended a short-course of antibiotics to treat uncomplicated UTI in premenopausal, non-pregnant women. First line agents are: Nitrofurantoin x 5 days, Trimethoprim-sulfamethoxazole x 3 days (if local resistance rates of uropathogens do not exceed 20%) and Fosfomycin trometamol in a single dose. Despite the fact that fluoroquinolones are highly efficacious, these practice guidelines recommend considering them as alternative (second line) antimicrobials for acute cystitis to prevent the ecological adverse effects of selection of drug-resistant organisms and infection with multidrug-resistant

organisms.[24] According to the European Association of Urology, the prescription of short-course therapy (<7 days) is not generally accepted in postmenopausal women; and a minimum of 7 days should be prescribed in males.[25]

It is not necessary to request urine cultures in women with clinical presentation of uncomplicated UTI; empirical antibiotic treatment may be prescribed. The microbiology of these cases is predictable and by the time urine culture results are available, a short-course of antibiotic has usually been completed. Conversely, in males, pregnant females, and complicated UTIs, pretreatment urine culture is recommended, then treatment can be adjusted following the results of the culture. It is also appropriate to request urine cultures in suspected relapses (infection with the same organism following cure) or treatment failure, as well as cases of medication intolerance.[26]

1.4 ASB Treatment

Although the association between bacteriuria and symptomatic urinary infection has been reported, treatment of ASB does not diminish the number of symptomatic infection among patients with ASB, nor improve outcomes except for a temporary microbiological improvement. Hence, in general, screening for and treatment of ASB is not recommended in adult population.[5] Only pregnant women and patients undergoing traumatic urologic interventions can still be considered as candidates to be screened for ASB.[5]

There is a large body of evidence supporting the lack of benefit of ASB treatment. One study enrolled older female residents of continuing care retirement communities who submitted urine for culture. Participants were categorized as women with ASB who did not get antibiotic therapy and women with ASB who did get antibiotic therapy. Non-bacteriuric women served as control. The rate of development of UTI-symptoms for the treated group was higher than the rate for the group that was untreated during 6 months following treatment.[27]

In another study, 3,578 individuals (more than 90% were hospital visitors), aged 20-65, were screened for ASB and 107 cases were detected. Of the 107 bacteriuric subjects 49 (52%) were treated with nitrofurantoin during one week, and 45 (48%) with placebo. 10 (20%) of those treated with nitrofurantoin remained bacteriuric after 1 week of treatment, and received a second course of therapy with ampicillin. The rest of the subjects, the individuals who had responded to nitrofurantoin and the individuals who had been given placebo as first treatment, received altogether placebo as second treatment. During one year follow-up, 18 (37%) subjects from the treated group and 16 (36%) from the placebo group, developed symptomatic UTI. It was concluded that antibiotic therapy did not avert the development of symptomatic UTI.[28]

A randomized trial comparing antibiotic therapy with no antibiotic therapy in diabetic women with ASB who were followed for up to 36 months, found no

significant difference in rates of any symptomatic UTI, pyelonephritis, and hospitalization for UTI, as well as in time to a first symptomatic episode.[29]

A systematic review published in 2015 assessed the effectiveness of antibiotics for preventing development of symptomatic UTI, and UTI-related complications such as urosepsis and pyelonephritis, among adults with ASB. The authors did not find differences between antibiotics and no treatment of ASB for the development of symptomatic UTI or its complications. The results of the meta-analyses comparing antibiotics versus placebo or no treatment showed a relative risk (RR) = 1.1 (95% CI= 0.51 to 2.43) of developing symptomatic UTI and a RR= 0.80 (95% CI= 0.36 to 1.75) of developing UTI-related complications.[30]

Treatment of ASB is commonly associated with the overuse of antibiotics.[31] The use of antimicrobials inevitably causes the emergence of bacterial resistance, which has followed an uninterrupted steady increase historically. Since the advent of penicillin, the constant emergence of new antibiotics has lessened the impact of the continuous acquisition of bacterial resistance. However, the development of new antibiotics has decreased recently in comparison with previous decades;[32] thus decreasing the therapeutic alternatives against multidrug-resistant organisms, particularly Gram-negative bacteria. Bacterial resistance is a therapeutic challenge that can lead to treatment failures, adverse patient outcomes and an economic burden to society.

Steps therefore to diminish unnecessary use of antibiotics are required. Lee et al.[33] have advocated for several strategies to face the growing issue of bacterial resistance which may be summarized in three aspects: (I) creation and implementation of Antimicrobial Stewardship Programs; (II) education for patients, general public and relevant healthcare professionals; and (III) controlling antibiotic usage in veterinary medicine.

There is an association between treatment of ASB with antimicrobials and higher rates of bacterial resistance and reinfection, increased care cost, and significant collateral damage, including Clostridium difficile–associated diarrhea, bacterial vaginosis, and vaginal candidiasis.[7, 29] A systematic review published in 2014 concluded that among ASB trials that reported higher rates of treatment-related adverse effects, the number needed to harm (NNH) ranged from 2–10.[6] This systematic review included seventeen studies evaluating antimicrobial therapy for ASB. With the exception of one, the studies were all conducted before the publication of the CPGs for the diagnosis and treatment of ASB in 2005. The study conducted after 2005 also advocated against treatment for ASB.[34]

Clostridium Difficile is the most frequently reported nosocomial pathogen in the U.S. and its incidence has been increasing there,[35] as well as in Canada and Europe.[36] The U.S. Department of Health and Human Services estimated the incidence of Clostridium Difficile infections (CDI) for 2013 at 14.2 per 1000

hospital discharges.[37] Some authors have estimated the CDI mortality risk at close to 17%, with greater risk for the elderly.[38] In Canada, the increase in hospitalization cost of an initial episode of CDI is estimated at $11,930 and $15,330 for a recurrent episode.[39] Antibiotic use is the most important precursor of CDI. Although almost all antibiotics have been associated with CDI, the most frequent are ampicillin, amoxicillin, cephalosporins, clindamycin, and fluoroquinolones.[35] A prospective study conducted in 2009 exploring the appropriateness of fluoroquinolones use among hospitalized patients found that 51% of all fluoroquinolone regimens classified as unnecessary were prescribed to treat ASB.[40]

It has been observed that repeated antimicrobial courses are associated with the fact that bacterial strains isolated from older subjects have an increased frequency of resistance relative to younger populations.[8] Treatment for ASB is not only ineffective, but an increased risk for resistant infections may prompt poorer outcomes in people who contract symptomatic UTI.[6] A study published in 1998, when uncertainty about how to manage ASB existed, assessed two modalities of ofloxacin treatment for ASB. The results of this study are striking, not because of the intervention's ability to eliminate ASB (which we currently know is not beneficial), but because of the unfortunate adverse effect of promoting bacterial resistance. A group of bacteriuric and asymptomatic participants were randomized to receive three possible interventions for three months: continuous ofloxacin therapy, pulse ofloxacin therapy, or no treatment.

At the end of the study the microbiology of urine cultures classified as persistence, relapse or reinfection was assessed (although this was not the purpose of the study). They found 55.2% vs. 4.5% of resistance to ofloxacin among bacterial isolates from patients treated vs. not treated.[41]

A randomized trial of treatment of ASB among women with recurrent urinary tract infections revealed that treatment of ASB is associated with a higher rate of symptomatic UTI over one year. Oral antibiotics for treatment of UTI can negatively influence the ordinary intestinal microflora, boosting the development of antimicrobial-resistant strains, such as resistant potential pathogens that may spread within the body and cause severe diseases.[34]

Based on the concept of bacterial interference, ASB may play a beneficial role.[6] Bacterial interference makes reference to the antagonism between bacterial species during the surface colonization and acquisition of nutrients.[42] Zdziarski et al. have proposed that genetic changes such as point mutations, DNA rearrangements, and deletions, may prompt some Escherichia coli strains to experience a decrease in virulence factors and evolve toward a state of adaptation to prolonged in vivo growth in human hosts,[43] which may be defensive against superinfection and symptomatic UTI.

The 2005-CPGs specify that pregnant women with ASB are at increased risk for unfavourable outcomes such as pyelonephritis and preterm labour, and

antibiotic therapy can prevent this situation; thus, screening for ASB is needed during pregnancy.[5] However, some controversy has arisen in relation to screening and treatment of ASB during pregnancy. Based on the fact that the evidence in favour of screening pregnant women is derived from studies performed more than 30 years ago, a multicenter, prospective cohort study published in 2015, evaluated 16-22 week pregnant women in 13 health facilities in the Netherlands. 40 pregnant women with ASB were randomized to receive nitrofurantoin, and 45 were randomized to placebo, two times daily for five days. 163 pregnant women with ASB from the same cohort who decided not to participate in the study were followed and served as a control group. It was observed that the proportion of preterm labour was not significantly different among women with ASB treated, those receiving placebo, and the control group. Likewise, there was no significant variation in the incidence of preterm labour compared to pregnant women without ASB within the same cohort. ASB did show a significant association with pyelonephritis among women with ASB treated with placebo or untreated, although with low absolute risk. The author concluded that due to the low level of evidence supporting the benefits of ASB treatment, coupled with the possibility of side effects caused by antibiotic treatment, doubts were raised about the routine screening and treatment of ASB among pregnant women.[44]

ASB should be treated preceding traumatic urologic interventions with mucosal bleeding, since it increases the risk of bacteremia and sepsis in patients undergoing such interventions.[5]

Regardless of consistent lack of demonstrable benefit in the majority of cases, doctors still treat ASB regularly, with several studies reporting that 45%–65% of patients get unnecessary antibiotic treatment.[2] A way to positively impact public health and patient safety is to promote measures aimed at preventing antimicrobial use for the treatment of ASB in patients for which no advantage has been shown.[6]

1.5 Interpretation of Positive Urine Culture to Prevent Inappropriate Treatment of ASB

Positive urine culture seems to remarkably influence antimicrobial use in ASB treatment. Symptomatic patients are usually treated from the moment they seek medical attention, without waiting for the results of the urine culture, while asymptomatic patients are usually treated in response to a positive culture.[45] In general, urine cultures should only be requested in patients with presence or suspicion of UTI related symptoms. Nevertheless, urine cultures are often requested because of other reasons not recommended by CPGs including foul-smelling or cloudy urine, routine admission and follow-up screening, or non-

specific symptoms of clinical decline such as malaise, behavioural changes, lethargy, generalized weakness, falls, or poor appetite.[6]

Although some authors have supported the idea of requesting urine cultures routinely prior to non-urologic procedures, such as cardiothoracic, orthopedic, and vascular procedures, several recent studies have shown that there is no benefit in treating ASB prior to such procedures.[6, 46-48]

Physicians appear to have difficulty avoiding treatment when presented with patients' positive culture results. Various interventions have been proposed to reduce inappropriate antibiotic treatment for ASB. A cluster randomized trial of an algorithm for diagnosis and treatment of UTI failed to reduce urine culture collection rate.[49] 169 residents and staff physicians demonstrated poor knowledge of published ASB treatment guidelines, suggesting education may be of benefit.[50] Prospective audit and feedback to physicians reduced treatment duration, but not treatment initiation decisions, in one study;[51] and reduced culture orders and treatment during and after an intervention period in another study.[52] An educational intervention reduced inappropriate treatment during the intervention period.[53] Audit and educational interventions require considerable effort and may not lead to sustainable change.

The update of the IDSA and the Society for Healthcare Epidemiology of America guidelines published in 2016[54] suggests a more active role by microbiology laboratories in antimicrobial stewardship programs. They recommend, with low-to-moderate levels of evidence, the use of selective or cascade reporting to promote the wise use of antimicrobials. Cascades are algorithm-driven reports that contain only a reduced number of tested antimicrobial susceptibilities based on availability, local susceptibilities, and costs. They further recommend reporting of susceptibility to broader-spectrum drugs only when isolates are resistant to drugs in the first "cascade."[55] This type of intervention, based on a controlled release of information, aims to influence the prescription of antibiotics towards those considered more appropriate according to the case.

In a pilot study conducted by Leis and colleagues, non-catheterized inpatients with positive urine cultures were reported by the microbiology laboratory with a general statement suggesting the physician call the lab if there was really clinical suspicion of urinary infection.[45] This provided a barrier to access to positive culture results. In the intervention group modified reporting reduced inappropriate therapy from 48% to 12%, with no incidence of UTI or sepsis among untreated patients. Among 37 positive cultures reported in the modified way, only 5 calls were received to the laboratory requesting complete culture report. The authors described the design as a controlled before–after study. Because the study was not randomized, the ability of this design to control

the confounding effect may be compromised. An ideal design would include randomization of positive cultures between modified and standard reporting.

1.5 Purpose and Rationale

The purpose of this randomized controlled trial is to address the question of whether modified reporting, as compared to standard reporting, of positive urine cultures by the Health Sciences microbiology laboratory, would lead to a reduction in the rate of inappropriate antibiotic therapy without an increase in adverse events.

The Health Sciences microbiology laboratory is part of Eastern Health, and in charge of performing all inpatient and outpatient bacteriology testing for St. John's, Newfoundland. Eastern Health is the largest Regional Health Authority (RHA) of four RHAs in the province of Newfoundland and Labrador, serving St. John's and the Eastern region. The city of St. John's has three large tertiary care centers; the Health Sciences Centre, St. Clare's Mercy Hospital and the Janeway Children's Health and Rehabilitation Centre.

In Eastern Health microbiology laboratories, urine represents half of all specimens received, with 30 percent of specimens requiring bacterial identification and antibiotic susceptibility testing. In view of the resemblance to a study conducted in Ontario,[56] it can be also expected that many of these

specimens belong to asymptomatic patients. Preventing ordering of urine cultures without clinical indication is an ideal condition, but that is a complicated undertaking, requiring changes in long-standing practices and convictions among health care providers.[45] Modifying the way urine cultures are reported may be a cheaper and easier intervention. Given that positive results from urine cultures for ASB are likely to trigger inappropriate prescribing behaviour, modified reporting may lead to a reduction in inappropriate antibiotic treatment and its complications such as diarrhea due to *Clostridium difficile*, selection of drug resistance bacteria, and cost of treatment. In addition, a demonstration that untreated UTI or pyelonephritis are improbable consequences of changing the reporting of positive culture results may reassure physicians and nurses regarding a more selective procedure in urine collection. This could reduce workload and cost in the microbiology laboratory. The role of David Garcia in this project was participating in team meetings discussing the protocol and ethics application, coordinating and participating in recruitment and randomization, participating in data collection, designing the dataset and entering the data, running statistical analyses, and writing the thesis.

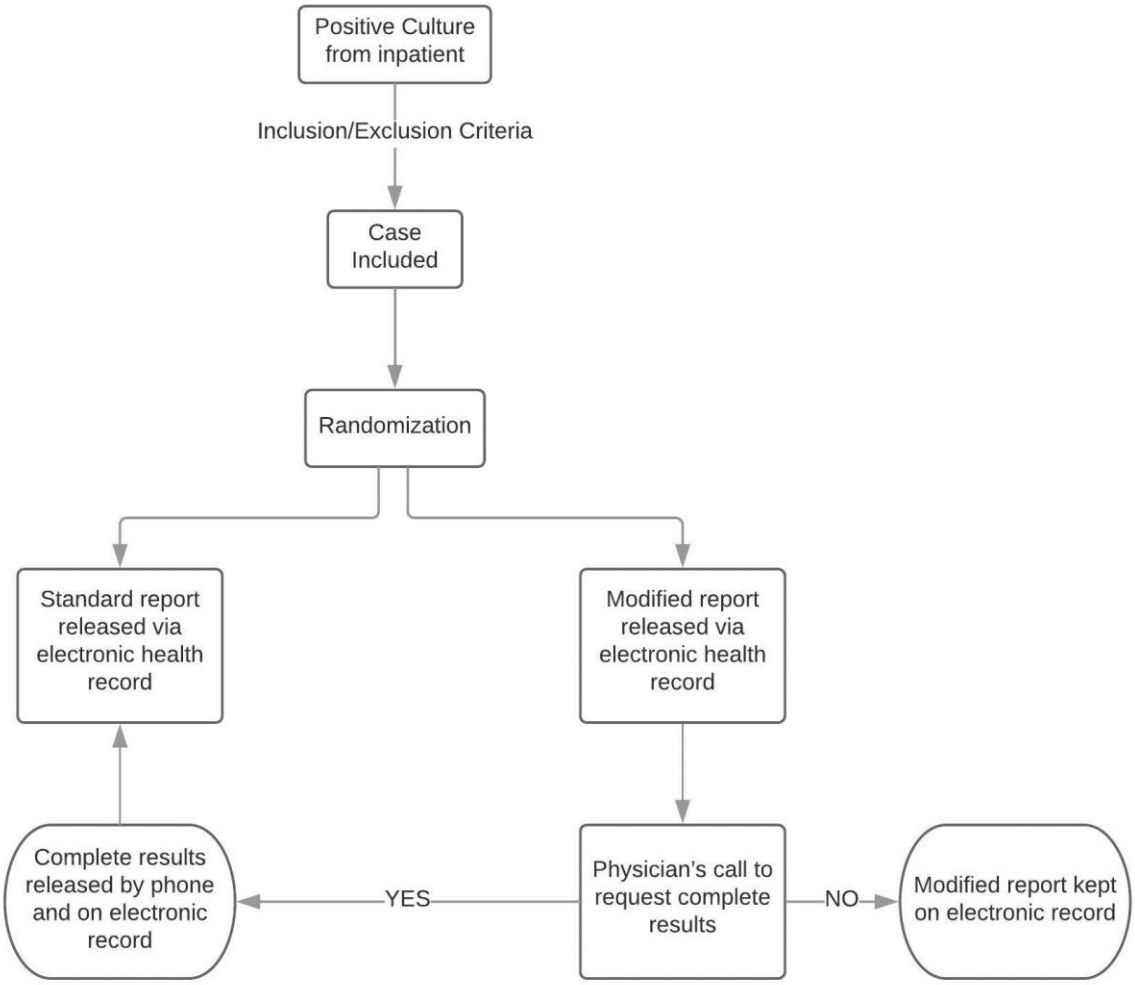
Chapter 2 – METHOD

2.1 Design

The study was a randomized, parallel group, superiority trial, which compared two different methods of reporting positive urine cultures, with an allocation ratio of 1:1 for two groups of patients.

Urine specimens received for urine culture were inoculated onto blood and MacConkey agars, incubated overnight and interpreted quantitatively by the regular staff of the Health Sciences microbiology laboratory according to their protocol. Eligible positive urine cultures were randomized by three trained members of the research team (D. Garcia, S. Boyd, or C. Penney) into standard reporting or modified reporting, prior to entry into the laboratory information system. Complete results from patients with modified reporting were available to clinicians 24 hours a day by telephone, and this was clearly communicated in lieu of the standard report. Laboratory staff released complete results by telephone and on the electronic chart to physicians who called to request them (Figure 1. Intervention Flow).

Figure 1. Intervention Flow



2.2 Participants:

Between January 3, 2017, and March 27th, 2017, all consecutive positive urine cultures processed by the microbiology laboratory were assessed. Urine cultures were considered positive if a bacterium was isolated in amounts greater than or equal to 100,000 CFUs/ml. Specimens included were collected only from

inpatients admitted to one of the two tertiary adult care academic teaching hospitals in St John's: Health Sciences Centre and St. Clare's Mercy Hospital. Eligibility was assessed by review of medical records by study personnel (D. Garcia, S. Boyd, or C. Penney). In cases whose medical records were not explicit enough to ensure eligibility of the participant, e.g. no clear method of sample collection, the nurse in charge of the patient was called from the laboratory to complete the information (without discussing the research project).

Inclusion criteria were:

- Inpatients admitted to one of the two included acute care facilities.

Exclusion criteria were:

- Pregnancy
- Receiving antibiotics at the time of collection
- Absolute neutrophil count < $1x10^9$/liter
- Admitted to the Intensive Care Unit
- Indwelling catheter
- Age less than 18 years

Pregnant women were excluded because ASB treatment is appropriate for them. Patients receiving antibiotics at time of collection were excluded to simplify the assessment of physician's prescribing behaviour after the report of urine cultures. Neutropenic patients were excluded because there is still no clear

consensus on whether or not they must be treated.[5, 57] ICU patients were excluded because they are critically ill patients who habitually have indwelling catheters, and a large portion of them have endotracheal tubes or alterations in level of consciousness, which makes it difficult to assess UTI manifestations. The definition of UTI in patients with indwelling catheters includes criteria different than those used in this project, therefore they also were excluded.[58]

2.3 **Intervention**

Included patients were randomized equally into standard or modified report arms. The standard report (control arm) included bacterial count, bacterial identification and susceptibility information including drug dosage and cost, in the regular format, while the modified report (intervention arm) withheld the standard report information, and expressed verbatim: *"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 to2300, or the microbiology technologist on-call at xxx-xxxx at night, for identification and susceptibility results."*

2.4 Outcomes

The primary outcome was the proportion of inappropriate antibiotic treatment. Inappropriate treatment was defined as treated ASB or untreated UTI, and appropriate treatment was defined as untreated ASB or treated UTI.

After randomization, medical records of included cases were assessed by a study physician (P. Daley or R. Inayatullah) for a clinical diagnosis of UTI or ASB, using criteria from the CDC for non-catheterized urine specimens.[19] These criteria state that diagnosis of UTI requires the presence of at least one of the following signs or symptoms: fever >38°C, suprapubic tenderness, costovertebral angle pain or tenderness, urinary frequency, urinary urgency, or dysuria. Conversely, ASB was defined as the absence of any of these signs or symptoms. Reassessments of each case were scheduled at 72 hours and at seven days after randomization to collect data on treatment decisions (time of prescription, drug given, and indication), and adverse events for safety assessment. ASB was considered treated when an antimicrobial was prescribed in patients who did not present any other condition that required the usage of the antibiotic. Presence of any of the CDC UTI criteria in a patient with no antimicrobial treatment was considered as UTI untreated.

As measures of secondary efficacy outcomes, the study team recorded the number of calls from physicians requesting access to complete reports, and calculated the cost saving from reduction in antimicrobial treatment.

As safety outcomes, we determined bacteremia rate, number of deaths and adverse events at 72 hours and at 7 days. As adverse events at 72 hours, we searched for evidence of SIRS, such as changes in vital signs (body temperature >38.3^{o}C or <36^{o}C, pulse > 90/min, and respirations > 20/min) and mental status, abnormal white blood cells count (>12,000 or < 4,000 per microliter of blood), positive fluid balance (fluid intake higher than output), and hyperglycemia (fasting plasma glucose ≥7.0 mmol/L). At seven days, any other new symptoms were recorded.

Investigators did not speak with attending physicians. If patients were discharged during the follow-up period, health records were reviewed, and primary care doctors were telephoned by P. Daley to collect information about adverse events.

In cases when doctors asked for standard reporting after receiving a modified report, the patient was analyzed as randomized and kept in follow-up.

2.5 Sample Size

In agreement with the report of Leis et al,[45] the expected rate of inappropriate treatment was 45% in the standard reporting arm and 15% in the modified reporting arm. Power analysis for chi-squared test of proportions, with a two-sided 5% significance level and type 2 error of 20%, suggested a total sample size of approximately 90 patients. Allowing for attrition/losses to follow-up, 110 eligible consecutive in-patient samples were included in the study. This calculation was based on the number of urine samples, disregarding the number of health personnel involved in the care of these patients; therefore it is possible that a single individual requested more than one of the included samples, and some physicians could have been exposed to the intervention more than once.

2.6 Interim Analysis and Stopping Rules

There was no predefined stopping rule. The study was stopped once the planned sample size was achieved.

2.7 Randomization

A non-member of the research team used randomization software (Research Randomizer 4.0) to randomize the sequence numbers from 1 to 110. The even numbers were used to generate cards assigning participants to the

standard arm and the odd numbers to the modified arm. Cards containing the participant allocation were placed in serially numbered, sealed, opaque envelopes. After a specimen was determined as eligible by an investigator, it was included in the study and the corresponding envelope was opened. The envelopes were opened strictly as numbered.

2.8 Blinding

To comply with ethics requirements, a general notice was sent to all inpatient physicians informing them about the study prior to recruitment. Since investigators in charge of outcome assessment had access to urine culture reports, they were not blinded to randomization arm. Patients were not aware of the study.

2.9 Statistical Analysis

The proportion of appropriate treatment in each arm was compared using two-sided Pearson chi squared test (SPSS 23.0, IBM, USA) in an Intention-to-treat (ITT) analysis; thus, all 110 randomized cases were included and analyzed as originally allocated. A Per-protocol (PP) analysis was also conducted, in which only cases that fulfilled the protocol in terms of eligibility were analyzed, and inappropriately included samples were excluded. Additionally, a subgroup analysis by diagnosis (UTI/ASB) was conducted to determine the impact of each

subgroup on outcomes. In order to estimate the difference in antibiotic cost between arms, the total cost of antibiotics to treat UTI was calculated in each included case, all randomized patients were included, untreated UTI and untreated ASB were considered as cost = 0. We determined median cost and mean cost per episode in each arm. Since the variable “cost” was not normally distributed, a Mann Whitney U test was used to compare the medians between groups.

2.10 Ethics

The protocol was approved by the Provincial Health Research Ethics Board on June 30, 2016 (reference #2016.157). Physician consent requirement was waived because the intervention incurred no more than minimal risk to participants, it was unlikely that it affected participants’ well-being, and pursuing doctors’ consent would have likely influenced their behavior, however, a letter was sent to all inpatients’ physicians advising them about the study prior to recruitment, and a debrief meeting offering a chance to withdraw participation was provided. Patient consent requirement was waived because physicians were the research subjects. Debrief letters were sent to patients, and they were also offered the opportunity to be removed from the study.

Chapter 3 – RESULTS

3.1 Participant Flow

Between January 3rd, 2017, and March 27th, 2017, 286 sequential positive urine cultures were surveyed. After determining they did not meet the inclusion criteria, 176 specimens were excluded (see Figure 2. Participant Flow). The total sample size comprised 110 urine cultures that were randomized and included in the ITT analysis; 55 were randomized to standard reporting and 55 were randomized to modified reporting. Four cases randomized to standard reporting (one collected from indwelling catheter, one duplicate, one on antibiotics, one culture negative) and two cases randomized to modified reporting (two duplicate) did not follow protocol and were excluded from the PP analysis. The last patient follow-up period ended on April 3rd, 2017.

3.2 Baseline Demographics

The two groups were comparable in demographics (see Table 1), with similar mean age and percentage females. However, as a result of randomization a slightly higher percentage of UTIs were obtained in the modified reporting arm: 20/55 (36.3%) vs. 14/55 (25.4%) in the standard reporting arm. Of all positive urine cultures, 69.1% (76/110) were defined as ASB, not UTI.

Figure 2. Participant Flow

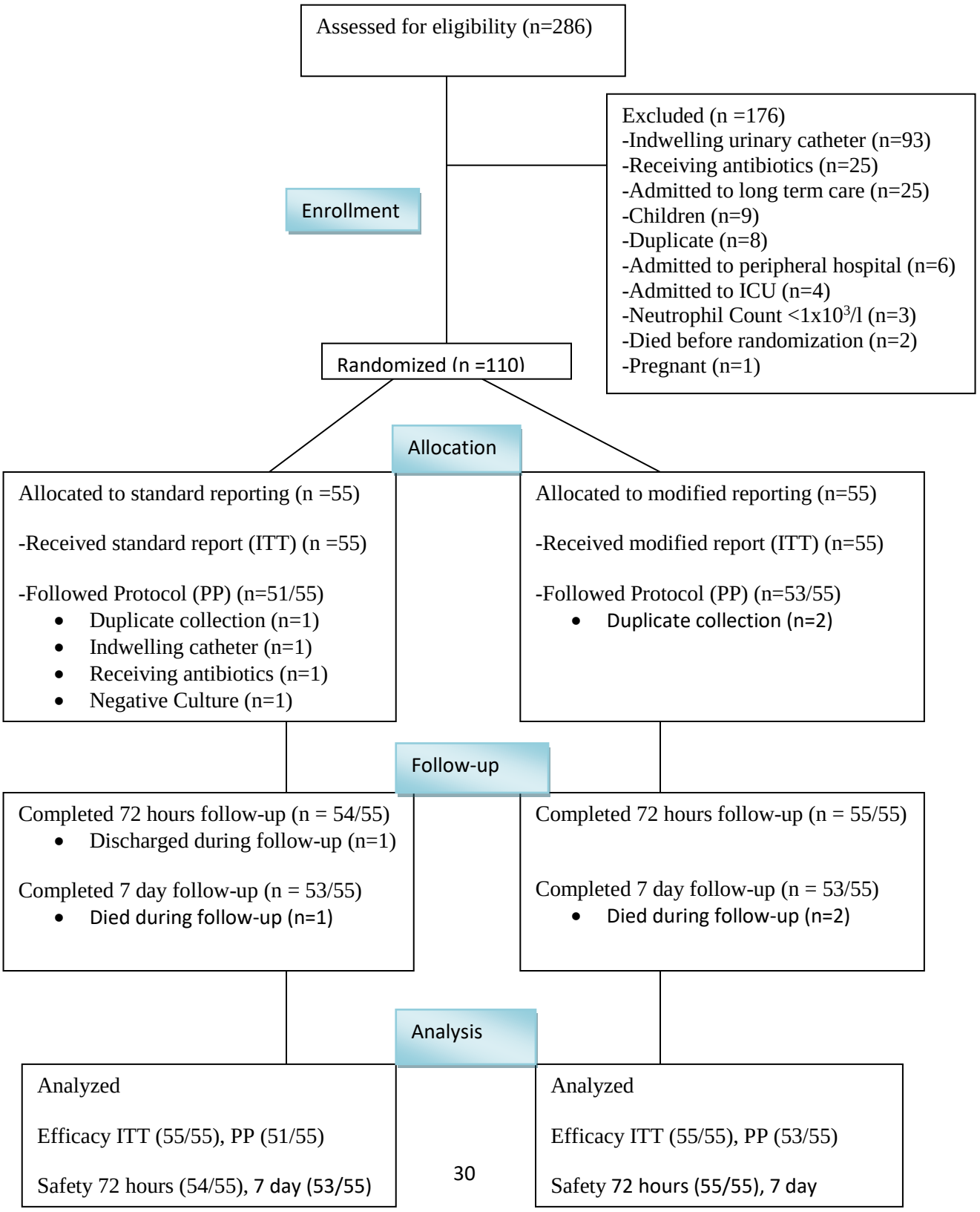


Table 1. Patient Demographics

	Standard Reporting (n=55)	Modified Reporting (n=55)
Age (mean +/- SD)	68.6 +/- 16.0 years	67.7 +/- 16.3 years
Females	36/55 (64.5%)	35/55 (63.6%)
Urinary tract infection (UTI)	14/55 (25.5%)	20/55 (36.4%)
Asymptomatic bacteriuria (ASB)	41/55 (74.5%)	35/55 (63.6%)

3.3 Efficacy

The primary outcome of appropriate treatment (UTI treated plus ASB not treated) was very similar in both the ITT and PP analysis; namely, it was significantly higher in the modified arm than in the standard arm (Table 2. Proportion of patients receiving appropriate treatment). In the ITT analysis, the proportion of appropriate treatment in the modified arm was 44/55 (80.0%) vs. 29/55 (52.7%) in the standard arm, absolute difference= 27.3%, RR=0.42 (95% CI= 0.23 to 0.77), p=0.002, Number needed to report for benefit=3.7. Likewise, The PP analysis showed appropriate treatment in 42/53 (79.2%) cases vs. 26/51

(51.0%), absolute difference= 28.2%, RR=0.42 (95% CI= 0.23 to 0.77), p=0.002, Number needed to report for benefit=3.5.

Table 2.Proportion of patients receiving appropriate treatment

	Report		Absolute Risk Reduction	Relative Risk (95% CI)
	Standard	Modified		
ITT population	29/55 (52.7%)	44/55 (80%)	27.3%	0.42 (0.23, 0.77)
PP population	26/51 (51%)	42/53 (79.2%)	28.2%	0.42 (0.23, 0.77)

In the subgroup analysis, it was observed that the overall difference in proportion of appropriate treatment was mainly caused by a change in the proportion of treatment of ASB, not in the proportion of treatment of UTI (see Table 3). In the ITT analysis, there was a significant increase of ASB not treated among patients randomized to the modified reporting arm in comparison to patients with standard report, 26/35 (74,3%) vs. 17/41 (41.5%) respectively; absolute difference= 32.8%, RR=0.44 (p=0.004). It is worth noting that the number of UTI untreated was the same in both arms (2 cases in each arm). In the PP analysis the rate of ASB not treated increased from 15/38 (39.5%) in the

standard arm to 25/34 (73.5%) in the modified arm; absolute difference= 34%, RR=0.44 (p=0.004).

Table3. Subgroup analysis according to diagnosis.
Proportion of patients receiving appropriate treatment

	Report		Absolute Risk Reduction	Relative Risk (95% CI)
	Standard	Modified		
ITT population				
ITU (n=34)	12/14 (85.7%)	18/20 (90%)	4.3%	0.7 (0.11,4.4)
ASB (n=76)	17/41 (41.5%)	26/35 (74.3%)	32.8%	0.44 (0.24,0.82)
PP population				
ITU (n=32)	11/13 (84.6%)	17/19 (89.5%)	4.9%	0.68 (0.11,4.3)
ASB (n=72)	15/38 (39.5%)	25/34 (73.5%)	34%	0.44 (0.24,0.81)

Among 53 specimens in the PP analysis randomized to modified reporting, in fourteen cases (26.4%), the attending physician called the laboratory to request the complete report.

3.4 Safety

There were three bacteremias observed during the study, two in the standard reporting arm (both treated UTI) and one in the modified reporting arm (treated UTI). All bacteremias occurred on blood cultures collected at the time of admission to hospital; i.e. before inclusion of cases in the study. Therefore, none were considered related to the study intervention. The bacteremic patient randomized to modified reporting presented neither features of SIRS nor any other new symptom during the follow-up. See Table 4. Bacteremias. There were three deaths observed, one in the standard reporting arm (untreated ASB) and two in the modified reporting arm (one untreated ASB and one treated UTI). None were considered related to the study intervention. See Table 5. Deaths. The bacterium isolated from urine culture of the patient who died with UTI and modified report (study number 81) was *Escherichia coli*. The patient was treated with ceftriaxone, which had adequate action against this bacterium according to susceptibility information.

There were complete data available for 72-hour safety assessment on 109/110 patients (one discharged during follow-up). There were complete data available for seven-day safety assessment on 107/110 patients (three deaths during follow-up). See Figure 2. Participant Flow. There was not any noticeable trend in occurrence of adverse events during the follow-up period comparing standard and modified reporting. At 72 hours, features of SIRS were uncommon in both arms. See Table 6. Adverse Events at 72 Hours. At seven days, new symptoms were observed in both arms; most of them were unrelated to UTI;

although dysuria, chills, delirium and nausea were seldom observed. See Table 7. Adverse Events at Seven Days.

3.5 Cost

The mean cost of antibiotic treatment given per episode of UTI/ASB was $35.78 +/- $109.77 (Median= $3.64) in the standard reporting arm, compared to $19.84+/- 64.88 (Median= $1.1) in the modified reporting arm (mean cost savings = $14.94/episode), p=0.231.

Table 4. Bacteremias

Study Number	40	44	56
Study arm	Modified	Standard	Standard
Age	79	81	61
Gender	Male	Female	Female
Reason for Admission	Urinary Tract Infection	Urinary Tract Infection	Diverticulitis
Comorbidities	Bladder carcinoma	Psoriatic arthritis, Spinal stenosis, Pulmonary embolus	Alcoholism
Reason for Urine Culture Collection	Fever	Fever	Fever
Urine Culture Date and Result	February 1: *E.coli*	February 3: *E.coli*	February 14: *E.coli*
Reason for Blood Culture Collection	Fever	Fever	Fever
Blood Culture Date and Result	February 1: *E.coli*	February 3: *E.coli*	February 14: *E.coli*
Study Diagnosis	UTI treated	UTI treated	UTI treated
Antimicrobial Therapy	Ceftriaxone IV, Ciprofloxacin IV, Vancomycin IV	Piperacillin/Tazobactam IV	Piperacillin/Tazobactam IV
Presumed Cause of Bacteremia	UTI	UTI	Diverticulitis
Bacteremia Related to Intervention	No	No	No

Table 5. Deaths

Study Number	37	67	81
Study arm	Standard	Modified	Modified
Age	70	67	86
Gender	Male	Male	Male
Reason for Admission	Hip Fracture, Rhabdomyolysis	Bowel Obstruction	Urinary Tract Infection
Comorbidities	Cirrhosis	Metastatic Bowel Sarcoma, Atrial Fibrillation	Aortic Stenosis, Congestive Heart Failure
Reason for Urine Culture Collection	Unknown	Incontinence	Septic Shock
Urine Culture Date and Result	January 29:*E.faecalis*	February 23: *E. faecalis*	March 4:*E. coli*
Blood Culture Date and Result	None	None	March 4: Negative
Study Diagnosis	ASB untreated	ASB untreated	UTI treated
Study Day of Death	3	6	2
Antimicrobial Therapy	Metronidazole IV	None	Ceftriaxone IV
Presumed Cause of Death	Renal failure	Sarcoma	UTI
Bacteremia Related to Intervention	No	No	No

Table 6. Adverse Events at 72 Hours

	Modified Reporting	Standard Reporting
Tachycardia	4	5
Abnormal Temperature	0	0
Hyperglycemia	0	0
Edema	1	1
Elevated White Blood Cell Count	0	3
Altered Mental Status	2	5
Tachypnea	0	3

Table 7. Adverse Events at Seven Days

	Modified Reporting	Standard Reporting
Surgical Site Infection	**1**	**0**
Delirium	**0**	**1**
Diarrhea	**0**	**1**
Chills	**0**	**1**
Increased Wound Drainage	**1**	**0**
Diaphoresis	**1**	**0**
Sputum	**1**	**0**
Trigeminal Neuralgia	**1**	**0**
Headache and Abdominal Pain	**0**	**1**
Dysuria	**1**	**0**
Nausea	**0**	**1**

Chapter 4 – DISCUSSION

The modification in the report of positive urine cultures applied in this study is based on the proof of concept study conducted by Leis. In order to diminish potential source of bias to the maximum, we conducted a randomized trial design and proved the efficacy of this laboratory intervention to improve antibiotic stewardship regarding UTI / ASB.

The significant reduction in treatment inappropriateness of patients with positive urine cultures who received modified reporting is produced by a decrease in the number of ASB treated. Treated and untreated UTI numbers remained technically the same between the study groups. The subgroup analysis showed the intervention did not affect UTI cases management, it presented a relative risk of inappropriate treatment of UTI within a wide 95% confidence interval (0.11-4.4); thus modified reporting did not cause significant difference in the risk of inappropriate treatment of UTIs.

Regarding safety, the intervention was not associated with harm to patients whose samples were included. The occurrence of adverse events was the same in both arms. None of the outcomes related to safety (bacteremia,

death, features of SIRS, and new symptoms at 7 days) presented a difference in occurrence greater than one between the groups.

The intervention did not result in cases with untreated UTI. This statement is based on the fact that the number of UTIs untreated was the same in both arms. We observed four cases of symptomatic patients who did not receive antibiotic therapy throughout the study, two of them received modified reporting and two received standard reporting.

Modified reporting might represent a potential risk of favouring empirical treatment, which in turn could favour the use of inappropriate antibiotics in terms of microbial susceptibility. We did not record if the antibiotics prescribed to patients with UTI-treated in the modified reporting arm showed adequate action according to the susceptibility report; however, the fact that the progress of patients in terms of occurrence of adverse events was very similar between the two study arms, makes it very unlikely that the intervention resulted in the prescription of antibiotics without activity against any of the bacteria within patients with UTI. It is, however, possible that this intervention, in areas or countries with higher rates of bacterial resistance, would lead to a higher risk of adverse events.

Several reasons have been reported as rationale to collect inappropriate urines samples. Daley et al. in a study conducted on residents of long-term care facilities located in Newfoundland and Labrador, Canada, found that nurses requested urine cultures due to changes in patient behaviour, change in mental status, change in colour or character of urine, previous UTI, or patient request, among others[59]. Leis et al. studying inpatients in two teaching hospitals in Ontario, Canada, mentioned as reasons to inappropriately order urine cultures: confusion, unexplained leukocytosis, previous history of UTI, abnormal smell or colour of urine, recent catheterization, urinary retention, weakness or dizziness, and dysglycemia.[56] These reasons lead physicians to face positive culture results coming from patients with no clinical indication to be either tested or treated, and possibly not requested by them but by nursing staff. The intervention described in this study demonstrated ability to reduce these events and therefore the reflexive prescription of antibiotics. The modified report advises the doctor that the culture is positive and recommends contact with the laboratory in case of clinical suspicion of UTI to access identification and bacterial susceptibility. It is possible that this kind of report may increase mindfulness regarding the appropriateness of antimicrobial therapy. The doctor can choose to reassess patient history, contact the laboratory for additional results, or treat empirically.

The majority (69%) of cultures in our study were regarded as ASB. This indicates the potential extent of the problem.

The reduction of unnecessary antibiotic usage, in addition to obvious savings in pharmacy expenses, leads to other potential outcomes as important or

even more important, such as avoiding bacterial resistance, Clostridium Difficile-associated diarrhea, bacterial vaginosis and vulvovaginal candidiasis.

We relied on data collected directly from medical records and data provided by nursing staff to make clinical diagnoses of ASB vs. UTI among patients whose samples were included. In cases where medical records may not have been thoroughly prepared or in cases of patients who may have had some difficulty in communicating the presence of urinary symptoms, our diagnosis could have been biased towards ASB. Moreover, it is possible that nurses may have misinterpreted some symptoms and reported such patients as having UTI symptoms. However, given that we used randomization, this source of bias should be balanced between both groups.

Although ethics required circulating an email to inform physicians about the study existence before starting the recruitment, making treating-doctors' blinding impossible, the impact that such email might have had on our results does not seem to change the applicability of this intervention in a "real world" situation. In fact, in a hypothetical scenario of a larger scale application of this intervention, it may be expected that the addition of some educational intervention to make physicians aware about correct indications of urine cultures and management of patients with ASB might produce even more favorable results.[60]

The application of this modified reporting in a "real world" situation would suppose an increase on microbiology staff workload. For doctors, it would

represent some loss in their autonomy, and time consumption when contacting the laboratory is needed.

Another lab step that could also be suitable to be intervened is the acceptance of urine specimens to be cultured; by establishing as a requirement the confirmation that the specimen really comes from a patient with indication to be tested. In order to achieve this, an effective communication between the laboratory and the collection site would have to be set up. This would be an intuitive approach, since inappropriate test requesting is a common issue.[56] Rejecting non-indicated urine cultures would result in a considerable decrease of workload. Modifying request forms have been proposed to improve the appropriateness of test submissions.[61, 62] The use of requests forms asking providers to indicate the reason for urine culture, coupled with the availability to telephone call from the microbiology laboratory in cases when the information on the form is not sufficient, might be an approach to be considered. However, this intervention would require extra effort to contact the test requestor, who might indeed be unavailable, and therefore it could require third parties' involvement to obtain the clinical information. Additionally, this intervention, unlike modifying reporting, might result in the rejection of samples with legitimate reasons to be tested. On the other hand, using the Health Sciences Microbiology Laboratory as an example, the fact that out of the approximately 130 daily urine cultures, 70% are negative, and over-half of positive cultures may represent ASB, in addition to

a cost of about $15 per urine culture,[63] makes a strong case that any effort to identify and reject unnecessary samples may be financially beneficial.

Several limitations of this study must be mentioned. We did not measure the variable “time to symptoms resolution”; therefore we are not able to ensure that the intervention did not delay the relief of urinary symptoms among patients with UTI. The expected frequency of ASB cases is much higher than the expected frequency of urosepsis in the study population; hence, our sample size is underpowered to rule out a clinically significant difference (if any) in the occurrence of SIRS symptoms between a group with standard reporting and one with modified reporting. Follow up in larger populations would be required to state unequivocally that this difference does not exist. Lastly, blinding of outcome assessment could not be ensured, so determination of outcomes may have been biased towards a beneficial effect of the intervention.

There is no reason to think that our results could not be generalized to some populations that were not included in our recruitment, such as: children older than two years old, residents of long-term care facilities, carriers of indwelling catheters, and outpatients. Thus, future research could expand the application of this intervention to include those populations. Demonstration of safety and efficacy of modified reporting in those populations is an important step forward in its implementation by increasing its scope of application and facilitating the screening of samples.

There are some changes and additions that can be considered in future research to improve this study design: (i) blinding of outcome assessment, (ii) prolongation of follow-up period, (iii) measurement of some other outcomes such as time to symptoms resolution, and the emergence of resistant strains after antimicrobial treatment, (iv) inclusion of a qualitative component to capture the experiences and perspectives of physicians.

In conclusion, this study has demonstrated through a randomized controlled design that modified urine culture reporting is associated with a significant reduction in inappropriate treatment, without an increase in adverse events. Our results support the idea that the microbiology laboratory can have a more active role in improving adequacy of treatment given to patients with ASB / ITU by applying a simple and sustainable intervention such as modified reporting.

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