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STRIVING FOR APPROPRIATE ANTIBIOTIC USE: A BIOMARKER INITIATIVE, AND OUTCOMES ASSOCIATED WITH AZITHROMYCIN EXPOSURE

DISSERTATION

A dissertation submitted in partial fulfillment of the
requirements for the degree of Doctor of Philosophy in the
College of Pharmacy
at the University of Kentucky

By

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Lexington, Kentucky

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2023

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ABSTRACT OF DISSERTATION

STRIVING FOR APPROPRIATE ANTIBIOTIC USE: A BIOMARKER INITIATIVE, AND OUTCOMES ASSOCIATED WITH AZITHROMYCIN EXPOSURE

The introduction of antibiotics into clinical practice is considered the greatest medical breakthrough of the 20th century[1]. However, the use of antibiotics can contribute to the development of resistance[2]. In the United States (U.S.), approximately 2.8 million people are infected with antibiotic-resistant bacteria each year, and more than 35,000 people die as a result[3]. Moreover, some antibiotics are known to cause cardiac side effects including QT prolongation, hypotension, and ventricular arrythmias[4]. The U.S. Centers for Disease Control and Prevention (CDC) defines appropriate antibiotic use as the effort to use "the right antibiotic, at the right dose, for the right duration, at the right time, and reduce unnecessary antibiotic use"[5]. The aspects of CDC's appropriate antibiotic use definition covered in this dissertation are antibiotic duration and reducing unnecessary antibiotic use in Chapter 2, and the right antibiotic at the right time in Chapters 3 and 4.

Chapter 2 and Chapter 3 contain summaries of literature regarding relevant scientific background, clinical background, historical context, and gaps in the literature. Chapter 2 additionally covers the biomarker intervention studied at UKHC, a pre-intervention cohort study, and a pre-post cohort study. Chapter 3 additionally includes a cohort study examining AZM exposure around a myocardial infarction and long-term cardiac outcomes. Chapter 4 includes a cohort study examining AZM exposure around a myocardial infarction and short-term cardiac outcomes. Finally, Chapter 5 discusses implications, future directions, and recommendations from the findings provided in this work.

KEYWORDS: OUTCOMES, ANTIBIOTICS, PROCALCITONIN, AZITHROMYCIN, REAL-WORLD EVIDENCE

Amanda Vida Gusovsky
(Name of Student)

03/28/2023

STRIVING FOR APPROPRIATE ANTIBIOTIC USE: A BIOMARKER INITIATIVE,

AND OUTCOMES ASSOCIATED WITH AZITHROMYCIN EXPOSURE

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03/28/2023

DEDICATION

I dedicate this dissertation to four people who have inspired my education.

Firstly, to my mom and dad, to whom my success is greatly attributable thanks to their support, guidance, and love.

To my grandmother Virginia who was the valedictorian of her high school class, and believed education is the key to the world.

And lastly, to my grandfather Samuel who I never had the chance to meet, but seem to have so much in common with. A piece of him was with me while writing this dissertation.

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Lastly, I must express my gratitude to the University of Kentucky College of Pharmacy and all its staff. I can still clearly remember the day I received my letter of acceptance, and I can now say with certainty that attending this institution has been one of the best decisions of my life.

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CHAPTER 1. INTRODUCTION

1.1 Introduction to Appropriate Antibiotic Use

The introduction of antibiotics into clinical practice is considered the greatest medical breakthrough of the 20th century[1]. Antibiotics have enabled the treatment of infectious diseases and performing of medical procedures, both of which have greatly advanced modern medicine[1]. However, the use of antibiotics can contribute to the development of resistance[2]. When a patient is treated with antibiotics, the antibiotic-resistant germs with resistance traits in their deoxyribonucleic acid (DNA) survive and multiply[2]. As a consequence, germs develop the ability to defeat antibiotics, creating resistant infections which are difficult, and sometimes impossible, to treat[6]. As new antibiotics have been approved and released, germs have been developing resistance to them rapidly[7]. In the United States (U.S.), approximately 2.8 million people are infected with antibiotic-resistant bacteria each year, and more than 35,000 people die as a result[3]. Furthermore, as with any pharmaceutical therapy, there are certain risks to the patient associated with antibiotics[8]. Antibiotic use is associated with a number of adverse drug events which are estimated to cause more than 140,000 emergency department visits per year in the U.S[8]. Moreover, some antibiotics are known to cause cardiac side effects including QT prolongation, hypotension, and ventricular arrythmias[4].

The U.S. Centers for Disease Control and Prevention (CDC) defines appropriate antibiotic use as the effort to use "the right antibiotic, at the right dose, for the right duration, at the right time, and reduce unnecessary antibiotic use"[5]. Total inappropriate antibiotic use, inclusive of unnecessary use, inappropriate selection, dosing, and duration

is estimated at 50% of all outpatient antibiotic prescriptions[9,10]. There is a need to examine and scrutinize current antibiotic use to slow the spread of antibiotic resistance and protect patient safety. The aspects of CDC's appropriate antibiotic use definition covered in this dissertation are antibiotic duration and reducing unnecessary antibiotic use in Chapter 2, and the right antibiotic at the right time in Chapters 3 and 4.

1.2 Improving Antibiotic Duration and Unnecessary Use

The CDC definition of appropriate antibiotic use mentions duration and unnecessary use, upon which may be improved in practice by the use of biomarker testing to guide antibiotic decision-making[11]. Specifically, procalcitonin (PCT) has been shown to decrease antibiotic duration; thereby reducing unnecessary use and, in some cases, reducing duration[11]. This was implemented at University of Kentucky HealthCare (UKHC) by examining the association of antibiotic duration with PCT before and after the implementation of a hospital protocol (PCT-guided antibiotic prescribing (PRO-GAP)) recommending the use of PCT for antibiotic decision-making in LRTI patients. A summary of relevant PCT and LRTI literature, the PRO-GAP intervention at UKHC, and the analyses using UKHC electronic health records are described in Chapter 2 of this dissertation.

1.3 Examining outcomes associated with exposure to an antibiotic (azithromycin)

Azithromycin (AZM) is an antibiotic used for the treatment of respiratory infections, cancers, auto-immune diseases, and inflammatory diseases[12–14]; and is prescribed to more than 30 million patients annually in the U.S[15]. In 2012, the U.S. Food and Drug Administration (FDA) released a warning that AZM may cause potentially fatal heart rhythm, particularly in patients with known cardiac risk factors[16]. Irrespective of this FDA

warning, AZM remains so commonly prescribed (both appropriately and inappropriately) that some patients in the real world are likely to be on a course of AZM close to the time of an MI. Using a large claims data source coupled with epidemiological methods enabled investigation of the exposure of AZM in a 10-day window of an MI and its association with both long- and short-term cardiac and hospital utilization outcomes. A summary of relevant AZM and MI literature and the analyses to examine long-term outcomes are described in chapter 3; and the analyses to describe short-term outcomes are described in chapter 4. This work contributes to understanding whether AZM is the "right antibiotic" for some patients, and whether prescribing it around the time of an MI is the "right time," as mentioned in the CDC definition of appropriate antibiotic use.

1.4 Conclusion

Appropriate antibiotic use is a complicated and subjective topic in healthcare[17]. This dissertation addresses questions regarding appropriate antibiotic use and exposures in patients with LRTI and MI, two different yet highly prevalent disease states; and contributes to knowledge of appropriate antibiotic use in regard to reducing unnecessary antibiotic use, the right duration, the right antibiotic, and at the right time.

CHAPTER 2. PROCALCITONIN

2.1 Introduction and Literature Summary

2.1.1 Scientific Background

In 1975 a group of researchers studied chicken cells *in vitro* and suggested the existence of a precursor to calcitonin, and they named this precursor procalcitonin (PCT)[18]. In 1981, researchers demonstrated that human calcitonin is synthesized as a precursor polyprotein[19]. PCT is a protein consisting of 116 amino acids[20]. In healthy individuals, PCT is produced in thyroid C cells from a CALC-1 gene located on chromosome 11[21]. The production of PCT during inflammation is linked to the bacterial endotoxin and to inflammatory cytokines[20]. As a result, PCT is released into the blood stream and serum levels of PCT are elevated due to a bacterial infection[22(p6)].

2.1.2 Laboratory Test

PCT can be measured using a quantitative homogenous assay, BRAHMS (Hennigsdorf, Germany), based on Time Resolved Amplified Cryptate Emission (TRACE) technology[23]. Samples suitable for the assay can be serum or plasma[23]. A nitrogen laser is directed at a sample containing PCT, and "donor" and "acceptor" molecules are brought in close proximity by binding to PCT[23]. The result is a prolonged signal that can be measured[23].

2.1.3 History of Clinical Use

Clinical use of procalcitonin was scarce until the early 1990s when research was conducted to determine its utility[24]. A few months before the Gulf War began, a group of French army physicians were interested in markers of severe lung injury brought about by the inhalation

of toxic gasses[24]. These French military researchers studied burn patients with and without inhalational trauma, and found that some had high levels of PCT[24]. It was later realized that the patients with high levels of PCT suffered from severe sepsis and septic shock[24]. It was that study from 1991 that revealed the first inkling of a relationship between heightened PCT and sepsis[24]. In another early study published in 1993, pediatric patients with bacterial infections, and not viral infections, were found to have a marked increase of PCT. This study concluded that PCT serum concentrations appeared to be correlated with the severity of microbial invasion[25]. After the 1993 study was published, several subsequent scientific studies confirmed the findings[24]. A study by Muller et. al. explored the use of PCT to guide the diagnosis of community-acquired pneumonia (CAP) and found that PCT could improve the accuracy of CAP diagnosis and is useful in the severity assessment of CAP[26]. Another study by Young et. al. found that initial elevated PCT levels are an early predictor of septic shock in patients with acute pyelonephritis secondary to ureteral caculi[27]. These early studies were foundational for PCT use in clinical practice.

2.1.4 Procalcitonin and Antibiotic Best Practices

Antimicrobial (or antibiotic) resistance occurs when bacteria or fungi develop the ability to defeat the drugs designed to kill them[3]. Infections caused by antibiotic-resistant bacteria are difficult, and at times impossible to treat[3]. In short, if antibiotics lose their effectiveness, we lose the ability to treat infections[3]. Each year in the U.S., at least 2.8 million people are infected with antibiotic-resistant bacteria, and more than 35,000 people die as a result[3]. Antibiotic resistance has the potential to affect anyone at any stage of life[3], and poses a threat to life expectancy and the progress that has been made in health care[7]. In addition to

human healthcare, antibiotic resistance is a threat to veterinary and agricultural industries, as they also rely on antibiotic use in practice[7].

The most important preventable risk factor for antibiotic resistance is inappropriate prescribing of antibiotics[28]. Antibiotic stewardship is the effort to measure and improve how antibiotics are prescribed and taken[28]. The goal of stewardship is to maximize the benefit of antibiotic treatment while minimizing harm both to individuals and communities at large[28].

One piece of antibiotic stewardship is diagnostic stewardship, defined as the appropriate use of laboratory testing to guide patient management[29]. Rapid real-time laboratory tests enable modifications in decision-making, which may result in improved antibiotic use[29]. Rapid and precise diagnostic tests have the potential to curb the antibiotic resistance crisis by improving antibiotic decision-making, leading to more judicious use of antibiotics[29]. Such laboratory testing provides important information promptly that may aid prescribers when faced with uncertainty in prescribing decisions[22(p6)].

For some infections, the causative agent cannot be anticipated based on a patient's clinical presentation[22(p6)]. Biomarkers are surrogates of infection that may be utilized to assist clinicians in prescribing decisions in a context of clinical uncertainty[22(p6)]. The decision to initiate empirical antimicrobial therapy or safely stop antimicrobial therapy may be guided by the use of biomarkers[22(p6)]. Because PCT becomes elevated in response to bacterial infection, but not viral infection, it can be utilized as a biomarker to guide antibiotic decision making[22(p6)]. High levels of PCT suggest a bacterial infection, while low levels suggest a viral infection or non-infectious causes[30]. PCT has levels below the limit of detection in healthy individuals, and becomes markedly and persistently elevated in

response to bacterial infection very quickly (within 2 to 4 hours) until recovery[31,32]. Because of PCT's relatively swift elevation and/or decline, taking more than one PCT value for a patient during their hospital stay enables detection of a change point in PCT value and can inform early discontinuation of antibiotics[31].

More than 12 randomized controlled trials were conducted to evaluate PCT as an aid to guide antibiotic therapy, and found that utilizing PCT can safely reduce antibiotic use[33]. For example, Christ-Crain et. al. randomized patients with suspected lower respiratory tract infections to receive standard care or PCT-guided treatment, and found that antibiotic use was significantly reduced in the PCT group[34]. Briel et. al. studied patients with acute respiratory tract infections who, in the opinion of a physician, were in need of antibiotics; and randomized patients to receive a PCT-guided approach or a standardized approach. They found that PCT-guided therapy markedly reduced antibiotic use without compromising patient outcomes[35]. Stolz et. al. studied chronic obstructive pulmonary disease (COPD) exacerbation patients by randomizing them to receive either PCT-guided or standard antibiotic therapy; and found that PCT guidance reduced antibiotic prescriptions at the index exacerbation compared to standard therapy and allowed a sustained reduction in total antibiotic exposure for up to 6 months[36]. In 2017 the U.S. Food and Drug Administration approved the expanded use of the BRAHMS laboratory assay to guide health care providers in determining antibiotic initiation and cessation in lower respiratory tract patients[30].

2.1.5 Procalcitonin use in Lower Respiratory Tract Infections

Lower respiratory tract infections (LRTIs) are the leading cause of death among infectious diseases worldwide, the fifth overall cause of death, and the second overall cause of

disability-adjusted life years[37]. One study found that LRTIs account for the largest proportion (34.4%) of all infectious disease hospitalizations[38]. LRTIs affect the airways below the level of the larynx; involving the trachea, bronchi, and lung parenchyma[39,37]. "LRTI" tends to have varying definitions, however the most common definitions are a broad list of disease states including: pneumonia, acute exacerbations of chronic obstructive pulmonary disease (COPD), influenza, bronchitis, and bronchiolitis[37].

Antibiotic overuse is common in LRTIs because it is difficult to distinguish bacterial from viral cause of infection[40]. Patients admitted to the hospital with a LRTI often have an unclear clinical prognosis upon admission but are prescribed antibiotics by default, although a large portion of these patients may have a non-bacterial cause of symptoms that is not appropriate for antibiotic use[41]. One study found 74% of LRTI cases were positive for a virus[42]. Additionally, fixed antibiotic regimens may result in unnecessarily long treatment durations, although an appropriate treatment length can vary patient to patient[41]. It is estimated that more than two-thirds of LRTI patients in the U.S. and Europe are prescribed antibiotics[43]. Improving antibiotic use in LRTIs is important due to the broad impact of LRTIs worldwide, and the high volume of unnecessary antibiotics associated with them. One way to improve antibiotic decision-making in LRTIs is via diagnostic stewardship, or the appropriate use of laboratory testing to guide patient management[29].

One diagnostic stewardship approach to improve antibiotic use in LRTI is measuring PCT levels in order to estimate the probability that an infection has bacterial origin[44]. Several clinical trials have been run to test the impact of PCT antibiotic prescribing guidelines on antibiotic use in LRTI patients. The first large multicenter trial to examine whether a PCT algorithm could reduce antibiotic exposure in LRTI patients

was the 2009 ProHOSP Randomized Controlled Trial[44]. This trial took place in academic and nonacademic hospitals in Switzerland[44]. LRTI patients in the emergency departments between 2006 and 2008 were enrolled and randomized to receive antibiotics based on a PCT algorithm or according to guidelines (control group)[44]. The PCT algorithm used dictates that initiation or continuation of antibiotics is strongly discouraged if levels are 0.25 ug/L or lower[44]. Initiation or continuation of antibiotics is strongly encouraged if PCT is higher than 0.5 μg/L and encouraged if PCT levels in the blood are higher than 0.25 μg/L[44]. Hospitalized patients are clinically re- evaluated and PCT measurement was repeated after 6 to 24 hours[44]. Ultimately, the authors conclude that a strategy of PCT guidance compared with standard guidelines result in lower rates of antibiotic exposure and lower rates of antibiotic-associated adverse events[44].

There are few observational studies studying PCT use and antibiotic prescribing for LRTI patients using real world data. One example is a study that observed at hospitals from a large U.S. hospital system and categorized them into "treatment" and "control" hospitals based on their PCT testing capacity[45]. LRTI patients from treatment hospitals were matched 1:1 to patients from control hospitals[45]. The authors concluded that PCT along with treatment recommendations may lead to shortened hospital stays with no adverse outcomes[45].

2.1.6 Differing Schools of Thought

Although several clinical trials have demonstrated the use of PCT with improved antibiotic use, the use of PCT in practice remains controversial among the clinical community for a number of reasons. Firstly, there are some cases where PCT becomes elevated due to a non-bacterial cause, including major stressors that cause systemic inflammation (e.g.

severe trauma, cardiac arrest or circulatory shock, surgery, burns, pancreatitis, and intracranial hemorrhage); certain autoimmune diseases (e.g. Kawasaki disease); and some other infectious nonbacterial etiologies (e.g. malaria and invasive *Candida* infections)[33,46]. Additionally, concerns exist in regards to the utility of PCT in patients with cellular injury and bacterial inflammation[47,48]. Highly elevated bilirubin and triglycerides also interfere with PCT level measurement[48]. There is conflicting evidence on the use of PCT in patients with renal failure[48]. Due to the high incidence of renal failure in patients admitted to critical care units, some argue the utility of PCT is limited in such a setting[48]. Further, localized infections such as cellulitis, appendicitis, abscess, and empyema may show falsely low PCT values[48].

In addition to testing errors, there is one example of conflicting evidence from a clinical trial. The PCT Antibiotic Consensus Trial (ProACT) was the first trial conducted in the U.S. to assess whether a PCT antibiotic prescribing guideline for the treatment of LRTI would result in less exposure to antibiotics than usual care, and found that it did not result in less exposure to antibiotics than did usual care[40]. This trial was conducted in 14 hospitals with high adherence to quality measures for the treatment of pneumonia[40]. One explanation for this finding is that the PCT-based prescribing guideline provided fewer opportunities to change antibiotic decisions than in earlier trials because antibiotics are being used judiciously even in the usual care group[40].

The results from the ProACT trial may not, however, be generalizable to all healthcare settings. Firstly, the trial was run in 14 hospitals with already high adherence to quality measures for the treatment of pneumonia, meaning there was not much room for improvement in appropriate antibiotic prescribing in patients with pneumonia. If the trial

were run in hospitals with a larger need for improvement of appropriate antibiotic use, there may have been a greater chance for PCT to move the needle on antibiotic use. Additionally, because this was a randomized trial, the results may not be generalizable to the real world. There is a need to confirm the results of this trial using a source of real world data to elucidate the true impact of PCT guidance on antibiotic prescribing.

2.1.7 Filling Gaps in the Literature

The literature summarized presently demonstrates that, under the correct circumstances, PCT may be used to guide antibiotic-decision making for LRTI patients; which may result in improved antibiotic use. PCT is a datapoint that appears to be quite useful for clinicians as they make real-time antibiotic prescribing decisions, and should be taken into account alongside clinicians' best judgment.

Although clinical trials have shown the utility of PCT-guided antibiotic use in LRTI patients, there are few observational studies using real-world data to observe this association. Results from said clinical trials may not be broadly generalizable due to their strict exclusion criteria and/or differing conditions in daily practice. What is scarce in the literature is the observation of PCT and antibiotic use among LRTI patients under ordinary conditions in hospitals where PCT testing is available in-house. The work described is a novel case study observing PCT and antibiotic use at one institution before and after a hospital protocol (PRO-GAP) was adopted; with the aim of observing differences that may be attributable to the intervention. The work described in this chapter examines PCT and antibiotic use at UKHC using electronic health records data. Chapter 2.2 is an analysis of before PRO-GAP, and Chapter 2.3 is an analysis comparing before and after PRO-GAP.

2.2 Procalcitonin-Guided Antibiotic Prescribing (PRO-GAP) Intervention at University of Kentucky HealthCare

2.2.1 Protocol Development and Implementation

In recent years, there has been great interest in biomarkers that are able to indicate the risk for bacterial infection in a short time after admission and thus, can help to reduce antibiotic overuse and potentially diminish antibiotic associated side effects, mortality and treatment failure. The use of PCT for this purpose was approved by the US Food and Drug Administration (FDA)[30]. Several academic hospitals across the U.S. have adopted protocols for procalcitonin-guided antibiotic prescribing including (but not limited to): University of Nebraska, University of Michigan, University of California- LA, University of California-SF, and University of Wisconsin.

University of Kentucky HealthCare (UKHC) is a system of all University of Kentucky hospitals and clinics comprising of a flagship facility with 945 beds, and four other facilities with 400 or fewer beds. UKHC has an Antimicrobial Stewardship program, which is a multidisciplinary team of providers with the aim of optimizing the use of antimicrobials to improve clinical outcomes and decrease the spread of antimicrobial resistance through collaboration, education, research, and innovation. According to internal data, at UKHC more than 430 tests for PCT were ordered per month on average in 2019. However, it is unclear if these tests were being interpreted and utilized for antibiotic decision-making by providers because there was no PCT guideline in place advising so.

In order to optimize PCT use, a multidisciplinary team within the UKHC network worked to develop a new institutional protocol recommending the use of PCT as a guide for antibiotic prescribing in lower respiratory tract infection (LRTI) patients, which was

implemented in December 2020. The protocol is titled PCT-guided antibiotic prescribing (PRO-GAP).

The algorithms for the PRO-GAP protocol at UKHC were developed based on evidence from the literature regarding PCT cutoff thresholds and were tailored to the needs of UKHC. The following aspects of the protocol stemmed from recommendations from in-network UKHC pharmacists, physicians, and clinical chemists. The algorithms are categorized by patient risk level: low and moderate acuity vs. high acuity (Appendix 2.3). Simplicity was emphasized when developing the algorithms, with the intention to provide an uncomplicated and easy-to-use guideline for clinicians. The protocol includes a caution for potential non-bacterial causes of PCT elevation (massive stress, malaria, systemic vasculitis, agents that stimulate cytokines, end-stage renal disease, immunocompromise) for clinicians to keep in mind while interpreting the PCT value, and a warning that patients with chronic infections including (but not limited to) osteomyelitis, abscess, and subacute endocarditis may not have a reliable PCT value and therefore it should not be used for antibiotic decision-making. (Appendix 2.3).

The algorithms provide ranges of PCT levels and their associated antibiotic recommendation (from low to high PCT value: strongly discouraged, discouraged, encouraged, strongly encouraged)(Appendix 2.3). In the high acuity algorithm these ranges of values are more conservative, as these patients should be handled cautiously(Appendix 2.3). See the full PRO-GAP protocol in Appendix 2.3.

2.2.2 Provider Education Efforts

The PRO-GAP protocol was passed by the antimicrobial stewardship, lab formulary, intensive care unit (ICU), and pharmacy and therapeutics (P&T) committees at UKHC in December 2020, and the educational rollout occurred in January and February 2021.

One study demonstrated improvement of antibiotic use with the implementation of a PCT guideline by sending blast emails and presenting educational lectures to hospital departments[49]. We utilized these strategies by presenting at hospital departmental meetings (emergency department, infectious disease, internal medicine/hospitalist, ICU, and trauma) and sending email blasts with the protocol information. In total, five education sessions were held with an estimated reach of ~130 participants, and five corresponding email blasts containing the algorithms (Figure 2.4.1) were sent out to ensure providers had the information and to reach anyone unable to attend the session. Additionally, an online decision tool was developed for PCT-guided antibiotic prescribing. The online decision tool contains multiple-choice questions regarding basic patient information and PCT laboratory value, and then provides an antibiotic recommendation for the clinician (Figure 2.4.1). The online decision tool is accessible by mobile and desktop, and can be accessed at this link: https://pharmacy.uky.edu/office-research-operations/cornerstones/research-centers/ipop/data-visualizations/pct-page.

2.2.3 Introduction to Protocol Evaluation

The overarching goal of the PRO-GAP protocol adoption was to improve the meaningful interpretation of PCT for antibiotic decision-making at our institution. In order to examine whether the PRO-GAP protocol was successful in achieving this goal, we designed a study

examining LRTI patients at UKHC, patients that would be impacted by the PRO-GAP protocol, during 2019 and 2020 (prior to PRO-GAP) and 2021 (after PRO-GAP).

Chapters 2.3 and 2.4 describe how we leveraged electronic health records data and methods of outcomes research to examine whether there was a difference in antibiotic duration at our institution before and after PRO-GAP.

2.3 Procalcitonin and Antibiotic Use in Lower Respiratory Tract Infections: Analysis of Electronic Health Records, 2019-2020

2.3.1 Abstract

Background: Procalcitonin (PCT) may be used to guide antibiotic decision-making in lower respiratory tract infection (LRTI) patients because it becomes elevated in response to bacterial infection and persists until recovery.

Objective: The present study aims to measure PCT ordering and antibiotic duration at one academic health center while considering the COVID-19 pandemic.

Methods: This retrospective cohort analysis includes adult LRTI inpatients. Baseline characteristics were examined overall and stratified by: (1) PCT order volume and (2) year. The association of the number of PCT orders with antibiotic duration was modeled using negative binomial regression. Differences between the cohorts (March-September 2019 vs. March-September 2020) were examined in baseline characteristics and for three different outcomes: (1) antibiotic duration, (2) receipt of a discharge antibiotic prescription, and (3) PCT orders.

Results: Overall, 70.6% of patients had 0 PCT orders (N=303), 24.7% had 1 (N=106), and 4.7% had >1 (N=20). There was no significant difference in antibiotic duration between

patients who received 0 vs. 1 PCT order (RR=1.02 [95% CI: 0.91, 1.15], p=0.70) or between those who received 0 vs. >1 PCT order (RR=0.90 [95% CI: 0.73, 1.12], p=0.36). There were no statistically significant differences in antibiotic duration, receipt of a discharge antibiotic prescription, or PCT ordering across the 2019 and 2020 cohorts.

Conclusion: The lack of a significant association of PCT ordering and antibiotic duration alongside the evidence of infrequent PCT ordering indicates an opportunity to improve meaningful use of PCT at our institution as a means of antibiotic stewardship.

2.3.2 Background

In the United States (U.S.), approximately 2.8 million people are infected with antibiotic-resistant bacteria each year, and more than 35,000 people die as a result.[3] The most important preventable risk factors for antibiotic resistance are inappropriate and unnecessary antibiotic use. Data from the U.S. Centers for Disease Prevention and Control (CDC) has shown that Kentucky's rate of outpatient antibiotic prescriptions is above the national average and is among the highest in the country[50,51,52,53]. In 2021 CDC reported Kentucky's rate of outpatient prescribing at 938 dispensed per 1,000 compared to the national average of 636 dispensed per 1,000[53]. For that reason, there is a need for sustained antibiotic stewardship efforts in Kentucky[52]. Furthermore, the early months of the coronavirus disease 2019 (COVID-19) pandemic posed potential threats to antimicrobial resistance by taking emergent priority over antibiotic stewardship activities[54]. Early in the pandemic there were high rates of antibiotic utilization in COVID-19 patients despite their lack of effectiveness.[55] Certain pandemic-related factors including increased hand hygiene, decreased travel, and decreased elective procedures may have reduced the spread of antimicrobial resistance in the short term; however more wide use of antibiotics would

have resulted in the opposite effect.[54] As of now the true impact of the COVID-19 pandemic on antimicrobial resistance remains to be seen.[56,54]

Lower respiratory tract infection (LRTI) is defined as an acute illness presenting with no more than 3 weeks duration with usually cough as the main symptom along with at least one other symptom of the lower respiratory tract (i.e., sputum formation, breathlessness, wheezing, or chest pain).[57] Pneumonia and COPD with acute exacerbation/bronchitis (i.e., complication) are LRTIs that present with similar symptoms including shortness of breath and tightening of the chest.[58] Symptoms that are more distinctly characteristic of pneumonia are chills, high fever, and head and body aches.[58] Patients admitted to the hospital with pneumonia or COPD with complication often have an unclear clinical prognosis upon admission, but are prescribed a fixed antibiotic course by default because clinical assessment cannot always decipher between bacterial and viral infections.[59] LRTIs are exceedingly common and cause considerable morbidity and mortality worldwide.[37] One study found that LRTIs account for the largest proportion (34.4%) of all infectious disease-related hospitalizations.[38] Appropriate antibiotic treatment length can vary by patient and severity of disease.[41]

A biomarker that is generally sensitive and specific for bacterial infection may be used to guide antibiotic decision-making.[31] Procalcitonin (PCT) is a peptide that has levels below the limit of detection in healthy individuals, but becomes markedly elevated in response to bacterial infection very quickly (within 2 to 4 hours) until recovery.[31,32] Measuring more than one PCT value for a patient during their hospital stay enables detection of a change point in PCT value and can inform early discontinuation of

antibiotics. Studies have found that utilizing PCT values as a guide for antibiotic prescribing decreased rates of antibiotic initiation and duration.[60,61,62]

The present study includes LRTI patients from one academic health center in Kentucky and aims to examine the association of antibiotic duration with PCT order volume among LRTI patients in the absence of an institutional PCT-guided prescribing protocol, while also taking into account potentially indirect consequences of the early stages of the COVID-19 pandemic. This overarching aim was executed by 1) describing characteristics of patients who received differing volumes of PCT orders during their hospital stay; 2) observing if there was an association between PCT ordering and shortened antibiotic duration; and lastly 3) evaluating differences in PCT ordering and antibiotic prescribing before versus during the early stages of the COVID-19 pandemic. Findings will inform opportunities for improved antibiotic stewardship using PCT.

2.3.3 Methods

This was a retrospective cohort analysis using electronic health records from University of Kentucky HealthCare (UKHC), which comes from an Enterprise Data Warehouse containing clinical data from the local inpatient population. UKHC includes all University of Kentucky hospitals and clinics comprising of a flagship facility with 945 beds, and four other facilities with 400 or fewer beds. UKHC has an Antimicrobial Stewardship program, which is a multidisciplinary team of providers with the aim of optimizing the use of antimicrobials to improve clinical outcomes and decrease the spread of antimicrobial resistance through collaboration, education, research, and innovation.

This analysis consists of adult inpatients with a primary diagnosis LRTI (defined as ICD-10 code for pneumonia or COPD with complication (Appendix 2.1) on the first position on the record) that received at least one antibiotic prescription (prescriptions were reviewed by pharmacists to ensure they were meant to treat LRTI). Data were obtained from the University of Kentucky Center for Clinical and Translational Science, and the study was approved as IRB-exempt (IRB #62976) by the University of Kentucky Office of Research Integrity. Two cohorts of patients were defined by admission and discharge dates between March 1-September 30, 2019 or March 1-September 30, 2020.

Patients were included if they: 1) were 18 years of age or older at admission, 2) had a primary diagnosis of pneumonia or COPD with complication (Appendix 2.1), 3) were administered at least one antibiotic, and 4) were admitted and discharged during their respective cohort. Patients were excluded if they had the following comorbidities: asthma, emphysema, secondary bacterial infection (tuberculosis, pulmonary mycobacterial infection, unspecified infection, streptococcus, staphylococcus, enterococcus, bacterial vaginosis), neutropenia, or active immunosuppression (Appendix 2.1); as these patients were deemed more likely to have a complicated hospital course with antibiotic prescriptions unrelated to LRTI. Unique patients' first encounter in each cohort was evaluated, and subsequent encounters were excluded.

The number of PCT orders for each patient was divided into three categories: 0 PCT, 1 PCT, or >1 PCT. The purpose of grouping patients with >1 PCT orders together is to identify association of having multiple PCT measurements for the same patient on antibiotic duration compared to having a single measurement. To examine baseline characteristics across the three PCT categories, chi-squared tests were used for categorical

variables, and ANOVA tests were used for all continuous variables except length of stay and antibiotic duration where Kruskal-Wallis tests were used due to abnormal distributions[63]. The threshold for statistical significance was 0.05. The association between the number of PCT orders and antibiotic duration was modeled using negative binomial regression. Antibiotic duration was defined as the total number of days a patient received any antibiotics, irrespective of the number or frequency of prescriptions or dose. There was no adjustment for other drugs or duration of the drug elimination period because the total days of antibiotic therapy aims to capture the days for which a patient was administered an antibiotic. To account for length of stay in the association between the number of PCT orders and antibiotic duration, the log of length of stay was included as an offset in the model[64].

Differences between the cohorts before COVID-19 and during COVID-19 (March-September 2019 vs. March-September 2020) were examined in baseline characteristics characteristics (age, sex, race (White vs. non-White), qualifying diagnosis) using chi-squared and t-tests for categorical and continuous variables, respectively. Additionally, differences between the two cohorts were examined for three different outcomes: (1) antibiotic duration during hospital stay, (2) receipt of a discharge antibiotic prescription, and (3) receipt of a PCT order(s) during hospital stay. These outcomes were modeled using negative binomial regression with an offset for log of length of stay for the first outcome, and logistic regression for the latter outcomes resulting in reported rate ratios (RRs) and odds ratios (ORs), respectively, with 95% confidence intervals.

Baseline characteristics (age, sex, race (White vs. non-White), qualifying diagnosis) were included as covariates in regression models if they were deemed to be

potential confounders of the primary exposure-outcome relationship. A variable was considered to be a potential confounder if the following criteria were satisfied: (1) the variable is not a downstream effect of the primary exposure or outcome, and (2) the variable exhibits at least moderate association with both the exposure and the outcome, defined as $p<0.2$ in bivariate analyses.[65] The threshold for statistical significance for in each model was 0.05. Analyses were performed using SAS v. 9.4.

2.3.4 Results

A total of 429 patients were included with 70.6% of the patients having 0 PCT orders (N=303), 24.7% having 1 order (N=106), and 4.7% having >1 order (N=20) (Table 2.1). Overall, 64.1% of the patients were in the 2019 cohort year, 47.8% were female, and 86.0% were White. The mean age overall was 61.3 years old (SD=13.6). The median days of antibiotic therapy was 4.0 days (Q1=3.0, Q3=6.0) overall. Stratified by PCT order volume, median days of antibiotic therapy was 4.0, 5.0, and 5.0 days in patients with 0, 1, or >1 PCT order, respectively. This association was statistically significant (p=0.01), however it is not adjusted for length of stay. No other baseline demographic or clinical characteristics were significantly different between PCT order volume groups.

In examining the association between PCT ordering and antibiotic duration, race and qualifying diagnosis were identified as potential confounders and included as covariates in the model in addition to an offset for the log of length of stay (Table 2.2). There was no significant difference in antibiotic duration between patients who received 0 vs. 1 PCT order or >1 vs. 0 PCT orders, after controlling for race, qualifying diagnosis, and length of stay (RR=1.02 [95% CI: 0.91, 1.15], p=0.70) (Table 2.3).

In those who received >1 PCT order, the duration of antibiotic therapy was 10% lower (RR=0.90 [95% CI: 0.73, 1.12]) than in those who received 0 PCT orders after controlling for race, qualifying diagnosis, and length of stay; though this association was not statistically significant (p=0.35) (Table 2.2).

In examining differences across the 2019 and 2020 cohorts, the mean age was significantly lower in the 2020 cohort (62.4 y.o. vs. 59.5 y.o., p=0.03), but otherwise there were no statistically significant differences in the demographic characteristics examined (Appendix 2.2). The median total days of antibiotic therapy was 4.0 (Q1=3.0, Q3=6.0) in both 2019 and 2020. In the 2019 cohort, 71 patients (25.8%) received a discharge antibiotic prescription, and in the 2020 cohort, 51 people (33.1%) received a discharge antibiotic prescription (p= 0.08). Moreover, 75 (27.3%) patients in the 2019 cohort and 51 (33.1%) patients in the 2020 cohort received at least one PCT order (p=0.20).

2.3.5 Discussion

Approximately 30% of the LRTI patients had any PCT testing, with less than 5% receiving multiple PCT orders. The findings of our study are inconclusive on the association of multiple PCT orders with shorter antibiotic durations. Overall, PCT ordering occurs at the observed hospital infrequently, and multiple PCT orders per patient are scarce. One retrospective cohort study using a large U.S. hospital-based electronic database found that 5% of sepsis patients had any PCT levels measured, and among those only 1 in 3 on average received more than one PCT order.[66] Additionally, they found that PCT use was not associated with reduced antibiotic use. The authors concluded that programs to improve PCT implementation are warranted. Although this study looked at sepsis patients instead of LRTI patients, the conclusions drawn are ultimately the same: there is an opportunity to

expand and leverage the use of PCT to guide antibiotic decision-making. The lack of a significant association of PCT ordering and antibiotic duration alongside the evidence of infrequent PCT ordering indicates an opportunity to improve meaningful use of PCT at our institution as a means of antibiotic stewardship.

PCT ordering and antibiotic duration appeared to be similar regardless of the COVID-19 pandemic just having begun. Next steps include utilizing these findings as a baseline for analyses on the following year (2021) after which the institution adopted a protocol for PCT-guided antibiotic prescribing.

There are some limitations in this study. Firstly, the months observed in both cohorts omit the Winter months, which is the high-volume season for LRTIs. This cohort was selected to observe status quo of PCT ordering and antibiotic prescribing practices in a lower volume time period, and to capture the earliest months of the COVID-19 pandemic. Secondly, we are uncertain if PCT lab values were intentionally used for antibiotic decision-making because there was no formally adopted protocol for PCT-guided antibiotic prescribing at the time.

The findings of this paper shed light on an opportunity to improve meaningful use of PCT for antibiotic stewardship. At our institution, we have taken action by formally adopting a protocol and educating providers on meaningful interpretation of PCT values. This protocol is not meant to simply increase the volume of PCT orders or promote unnecessary serial PCT ordering; but rather to expand awareness of PCT-guided decision-making and improve the meaningful interpretation of PCT values. The target population of this study, however, is cases where antibiotic course has been initiated, and PCT may be useful in early discontinuation.

The protocol for PCT-guided antibiotic prescribing was officially adopted in December 2020 and education sessions were held through February 2021. The new protocol applies to adult LRTI inpatients and contains guidance on PCT value cutoffs for antibiotic initiation and discontinuation. The present study provides a foundational analysis in the absence of a PCT-guided prescribing protocol, as well as baseline and clinical characteristics of the two years leading up to the adoption of the protocol. Looking ahead, we plan to analyze 2021 data from our institution on a similar patient population in order to detect differences in PCT ordering practices that may be attributable to the implementation of the protocol. The overarching goal of this protocol is to leverage PCT ordering to improve antibiotic use at our institution in Kentucky. The findings of this study demonstrate an opportunity to expand meaningful PCT utilization to guide antibiotic prescribing.

2.3.6 Tables and Figures

Table 2.3.1 Baseline characteristics of lower respiratory tract infection (LRTI) patients overall and stratified by number of procalcitonin (PCT) orders.

	Overall (N=429)	0 PCT Orders (N=303)	1 PCT Order (N=106)	>1 PCT Order (N=20)	Unadjusted p-value¶
Cohort year					
2019	275 (64.1)	200 (66.0)	67 (63.2)	8 (40.0)	0.06
2020	154 (35.9)	103 (34.0)	39 (36.8)	12 (60.0)	
Age	61.3 (13.6)	61.6 (13.6)	60.5 (13.4)	62.0 (15.9)	0.74
Sex					
Female	205 (47.8)	149 (49.2)	48 (45.3)	8 (40.0)	0.61
Male	224 (52.2)	154 (50.8)	58 (54.7)	12 (60.0)	
Race					
Asian	2 (0.5)	2 (0.7)	0 (0.0)	0 (0.0)	0.10
Black/African American	58 (13.5)	35 (11.6)	22 (20.8)	1 (5.0)	
White	369 (86.0)	266 (87.8)	84 (79.3)	19 (95.0)	
Qualifying Dx					

COPD w/ complication	175 (40.8)	133 (43.9)	37 (34.9)	5 (25.0)	0.09
Pneumonia	254 (59.2)	170 (56.1)	69 (65.1)	15 (75.0)	
Length of stay*	4.0 [2.0, 6.0]	4.0 [2.0, 6.0]	5.0 [2.0, 7.0]	6.0 [4.0, 12.5]	0.01
Discharge antibiotic Rx	122 (28.4)	94 (31.0)	26 (24.5)	2 (10.0)	0.08
Total days of antibiotic therapy*	4.0 [3.0, 6.0]	4.0 [3.0, 6.0]	5.0 [3.0, 6.0]	5.0 [4.0, 8.0]	0.01

Characteristics are summarized as mean (SD) for continuous variables and n (%) for categorical variables unless otherwise noted.

¶*P-values represent ANOVAs for continuous variables and chi-squared tests for categorical variables unless otherwise noted.*

**Summarized as median [Q1, Q3]; differences analyzed using a Kruskal-Wallis test.*

Table 2.3.2 Negative binomial model results for antibiotic duration

	Adjusted Rate Ratio (95% CI)	Adjusted P-value
1 PCT order vs. 0 PCT orders*	1.02 (0.91, 1.15)	0.70
>1 PCT orders vs. 0 PCT orders*	0.90 (0.73, 1.12)	0.35
Non-White vs. White	1.01 (0.86, 1.19)	0.89
COPD with complication vs. pneumonia	0.87 (0.78, 0.97)	0.01

**Rate ratios for PCT order volume are interpreted as the expected multiplicative change in total days of antibiotic therapy as the number of PCT orders increases from 0 to 1 or from 0 to >1, holding other covariates constant (race and qualifying diagnosis). Model includes an offset for length of stay.*

Table 2.3.3. Cohort associations for antibiotic and PCT outcomes.

	Outcome	2019 cohort	2020 cohort	P-value
Model 1	Total days of antibiotic therapy (continuous)*	4.79 [3.00, 6.00]	5.18 [3.00, 6.00]	0.78
Model 2	Receipt of discharge antibiotic prescription (binary)[†]	71 (25.82)	51 (33.12)	0.08
Model 3	Receipt of any PCT orders (binary)[§]	75 (27.27)	51 (33.12)	0.20

**Negative binomial regression model. Mean [Q1, Q3] reported. P-value is for cohort variable; receipt of PCT order included for adjustment. Model includes an offset for length of stay.*

[†] *Logistic regression model. N (%) reported. P-value is for cohort variable; receipt of PCT order and age included for adjustment.*

[§]*Logistic regression model. N (%) reported. P-value is for cohort variable; no variables included for adjustment.*

2.4 Procalcitonin-Guided Antibiotic Prescribing (PRO-GAP): Examining a biomarker's association with antibiotic therapy before and after hospital protocol implementation.

2.4.1 Abstract

Background: Procalcitonin (PCT) may help guide antibiotic decision-making in patients with lower respiratory tract infection (LRTI) because it becomes elevated in response to bacterial infection and persists until recovery. A new institutional protocol for PCT-guided antibiotic prescribing (PRO-GAP) was adopted at an academic medical center in December 2020.

Objective: The present study aims to examine the association of PCT ordering with antibiotic duration and whether that association changed after the implementation of the PRO-GAP protocol.

Methods: This retrospective cohort analysis includes adult LRTI inpatients. Cohorts were defined by admission before (March-September 2019 and 2020) and after (March-September 2021) the PRO-GAP protocol. Negative binomial regression was used to examine the association of PRO-GAP implementation with days of antibiotic therapy, adjusting for patient characteristics.

Results: In total, 429 patients were in the pre-protocol cohort and 322 in the post-protocol cohort. Average age was 61.3 (SD=13.6) pre-protocol and 59.4 (SD=15.1) post-protocol; and both cohorts were ≥47.8% female, ≥79.8% White, and had a median length of stay of 5.0 days. 29.4% and 32.9% of patients had ≥1 PCT order pre- and post-protocol, respectively. Average days of antibiotic therapy was 4.2 days (SD=4.6) pre-protocol and 3.9 days (SD=4.8) post-protocol. In the pre-protocol cohort, antibiotic duration was not

significantly different between those with 1 PCT (RR [95%CI]=1.07 [0.93, 1.22), P=0.354) or >1 PCT(RR [95%CI]=1.00 [0.78, 1.28], P=0.988) compared to 0 PCT. Among those with 0 PCT, antibiotic duration was significantly reduced after protocol implementation (RR [95%CI]=0.70 [0.62, 0.79], P<0.001), and the expected decrease in duration of antibiotic therapy after protocol implementation was equally reduced in those with 1 PCT (RR [95%CI]=0.88 [0.71, 1.10], P=0.273) and significantly further reduced in those with >1 PCT (RR [95%CI]=0.68 [0.49, 0.95], P=0.025) order compared to those with 0 PCT orders

Conclusion: The findings of this study indicate that antibiotic duration was reduced overall after implementing PRO-GAP, with evidence of additional reduction in patients with >1 PCT order compared to none. Other hospital systems that have existing PCT testing available without a protocol in place may consider developing and implementing a hospital protocol for PCT-guided antibiotic prescribing.

2.4.2 Background

In the United States (U.S.), approximately 2.8 million people are infected with antibiotic-resistant bacteria each year, and more than 35,000 people die as a result.[3] The most important preventable risk factors for antibiotic resistance are inappropriate and unnecessary antibiotic use. Data from the U.S. Centers for Disease Prevention and Control (CDC) (2019) has shown that Kentucky's rate of antibiotic prescriptions is well above the national average and is among the highest in the country.[50,51,52] For that reason, there is a need for sustained antibiotic stewardship efforts at healthcare facilities in Kentucky.[52]

Lower respiratory tract infection (LRTI) is defined as an acute illness presenting with no more than 3 weeks duration with usually cough as the main symptom along with at least one other symptom of the lower respiratory tract (i.e., sputum formation, breathlessness, wheezing, or chest pain).[57] Pneumonia and COPD with acute exacerbation/bronchitis (i.e., complication) are LRTIs that present with some similar symptoms including shortness of breath and tightening of the chest.[58] Patients admitted to the hospital with pneumonia or COPD with complication often have an unclear clinical prognosis upon admission, but are prescribed a fixed antibiotic course by default because clinical assessment cannot always decipher between bacterial and viral infections.[59] LRTIs are exceedingly common and cause considerable morbidity and mortality worldwide.[37] One study found that LRTIs account for the largest proportion (34.4%) of all infectious disease-related hospitalizations.[38] Appropriate antibiotic treatment length can vary by patient and severity of disease.[41]

Procalcitonin (PCT) is a peptide that has levels below the limit of detection in healthy individuals, but becomes markedly elevated in response to bacterial infection very

quickly (within 2 to 4 hours) until recovery.[31,32] Measuring more than one PCT value for a patient during their hospital stay enables detection of a change point in PCT value and can inform early discontinuation of antibiotics. Studies have found that utilizing PCT values as a guide for antibiotic prescribing decreased rates of antibiotic initiation and duration.[60,61,62] The use of PCT for this purpose was approved by the US Food and Drug Administration (FDA).[30] Several academic hospitals across the U.S. have adopted protocols for procalcitonin-guided antibiotic prescribing, containing recommendations for both initiation and early discontinuation of antibiotics.

University of Kentucky HealthCare (UKHC) is a system of all University of Kentucky hospitals and clinics comprising of a flagship facility with 945 beds, and four other facilities with 400 or fewer beds. According to internal data, in 2019 and the first half of 2020 more than 420 tests for PCT were ordered per month on average at UKHC. However, it is unclear if these tests were being interpreted and utilized for antibiotic decision-making by providers because there was no PCT guideline in place advising so.

In order to improve meaningful PCT use, a multidisciplinary team within the UKHC network developed a new institutional protocol, PCT-guided antibiotic prescribing (PRO-GAP), that recommends, alongside clinical judgement, the use of PCT as a guide for antibiotic prescribing in lower respiratory tract infection (LRTI) and sepsis patients, which was adopted at the institution in December 2020 (Figure 2.4.1). The algorithms for the protocol at UKHC were developed based on evidence from the literature regarding PCT cutoff thresholds and were tailored to the needs of UKHC by recommendations from in-network pharmacists, physicians, and clinical chemists. The algorithms are categorized by patient risk level: low and moderate acuity vs. high acuity. Simplicity was emphasized

when developing the algorithms, with the intention to provide an uncomplicated and easy-to-use guideline for clinicians. The protocol includes a caution for potential non-bacterial causes of PCT elevation (massive stress, malaria, systemic vasculitis, agents that stimulate cytokines, end-stage renal disease, immunocompromise) for clinicians to keep in mind while interpreting the PCT value, and a warning that patients with chronic infections including (but not limited to) osteomyelitis, abscess, and subacute endocarditis may not have a reliable PCT value and therefore it should not be used for antibiotic decision-making. (Figure 2.4.1). The algorithms provide ranges of PCT levels and their associated antibiotic recommendation (from low to high PCT value: strongly discouraged, discouraged, encouraged, strongly encouraged). In the high acuity algorithm these ranges of PCT values are more conservative, as these patients are more severe and should be handled cautiously. The protocol was passed by all necessary committees at UKHC in December 2020, and the educational provider rollout occurred in January and February 2021. The overarching goal of the PRO-GAP protocol adoption was to improve the meaningful interpretation of PCT for antibiotic decision-making at our institution. The present study aims to examine the association of PCT ordering with days of antibiotic therapy and whether that association changed after the implementation of the PRO-GAP protocol.

2.4.3 Methods

This was a retrospective cohort analysis using UKHC electronic health records, which come from an Enterprise Data Warehouse containing clinical data from the local inpatient population. Data were obtained from the University of Kentucky Center for Clinical and Translational Science, and the study was approved as IRB-exempt (IRB #62976) by the

University of Kentucky Office of Research Integrity. Adult (≥ 18 years old) inpatients admitted and discharged in the months of March through September in 2019, 2020, or 2021 with a primary diagnosis of pneumonia or COPD with complication (Appendix 2.1), with evidence of ≥1 antibiotic prescription to treat LRTI were included in the analysis. Patients were excluded if they had any of the following comorbidities: asthma, emphysema, secondary bacterial infection (tuberculosis, pulmonary mycobacterial infection, unspecified infection, streptococcus, staphylococcus, enterococcus, bacterial vaginosis), neutropenia, or active immunosuppression (Appendix 2.1); as these patients were deemed more likely to have a complicated hospital course with antibiotic prescriptions unrelated to LRTI. Only the patient's first encounter was included.

Study cohorts were defined by admission in March-September of 2019 and 2020 (pre-protocol) and March-September 2021 (post-protocol). The months March-September were selected because PRO-GAP provider education occurred in January and February 2021, and therefore those months were omitted from all three years; and to observe the status quo of PCT ordering and antibiotic prescribing practices in a lower volume time period by omitting Winter months. Age, sex, race, qualifying diagnosis, length of stay, and number of PCT orders (0, 1, or >1) during hospital stay were summarized by cohort and differences were examined using Kruskal-Wallis and chi-square tests for continuous and categorical variables, respectively.

The primary outcome of interest was total days of antibiotic therapy, defined as the total number of days a patient received any antibiotics in hospital, irrespective of the number or frequency of prescriptions or dose (there was no adjustment for other drugs or duration of the drug elimination period because the total days of antibiotic therapy aimed

to capture the days for which a patient was administered an antibiotic). Negative binomial regression was used to examine differences in duration of antibiotic therapy pre- and post-protocol implementation and by the number of PCT orders. Because of the hypothesized difference in the association between PCT ordering and days of antibiotic therapy due to the protocol; an interaction term between PCT orders and cohort (pre- vs. post-protocol) was included. To account for differences in length of stay, the log of length of stay was included as an offset in the model. Variables examined as potential confounders were: age, sex, race, qualifying diagnosis, and length of stay. Variables were selected as covariates if they were deemed to be potential confounders of the primary exposure-outcome relationship. A variable was considered to be a potential confounder if the following criteria were satisfied: (1) the variable is not a downstream effect of the primary exposure or outcome, and (2) the variable exhibits at least moderate association with both the exposure and the outcome, defined as $p<0.2$ in bivariate analyses.[65] The threshold for statistical significance for in each model was 0.05. Analyses were performed using SAS v. 9.4.

2.4.4 Results

A total of 751 patients met study criteria, with 429 in the pre-protocol cohort and 322 in the post-protocol cohort. The median age was 63.0 (IQR=[54.0, 71.0]) in the pre-protocol cohort and 61.0 (IQR=[50.0, 69.0]) in the post-protocol cohort, and this difference was not significant (P=0.084). Both cohorts were ≥47.8% female (P=0.921). Both cohorts had a median length of stay 5.0 days, but it was significantly longer in the post-protocol cohort (P=0.008). The pre-protocol cohort was 86.0% White, and the post-protocol cohort

was 79.8% White (P=0.004). In the pre-protocol cohort, 40.8% had a qualifying diagnosis of COPD with complication versus 30.7% in the post-protocol cohort (P=0.005).

Pre-protocol, 29.4% of patients had ≥1 PCT compared to 32.9% post-protocol. The pre- and post-protocol cohorts had 24.7% and 24.8% with 1 PCT order, and 4.7% and 8.1% had >1 PCT order in the pre- and post-protocol cohorts, respectively (P=0.147) (Table 2.4.1). Median days of antibiotic therapy was 3.0 days (IQR=[2.0, 5.0]) pre-protocol and 2.0 days (IQR=[1.0, 5.0]) post-protocol (Table 2.4.1). In the pre-protocol cohort, duration of antibiotic therapy was not significantly different between those with 1 PCT (RR [95%CI]=1.07 [0.93, 1.22), P=0.354) or >1 PCT(RR [95%CI]=1.00 [0.78, 1.28], P=0.988) compared to 0 PCT (Table 2.4.2). Among those with 0 PCT, duration of antibiotic therapy was significantly reduced after protocol implementation (RR [95%CI]=0.70 [0.62, 0.79], P<0.001), and the expected decrease in duration of antibiotic therapy after protocol implementation was equally reduced in those with 1 PCT (RR [95%CI]=0.88 [0.71, 1.10], P=0.273) and significantly further reduced in those with >1 PCT (RR [95%CI]=0.68 [0.49, 0.95], P=0.025) order compared to those with 0 PCT orders (Table 2.4.2).

2.4.5 Discussion

The findings of this study indicate that duration of antibiotic therapy was reduced after implementation of the PRO-GAP protocol, and this reduction in duration of antibiotic therapy was even further reduced in those with >1 PCT order compared to those with 0 PCT orders.

PCT testing was available at UKHC before PRO-GAP, but it is unknown if PCT orders were used for meaningful interpretation for antibiotic decision-making. For

example, in some parts of the hospital PCT was automatically ordered for upon admission (although undistinguishable in the data from other PCT orders). This could be one contributing factor to the finding that before PRO-GAP, those with 1 PCT and >1 PCT order had no significant association with antibiotic duration. Default automatic ordering has been shown to result in redundant testing, and excessive laboratory testing can result in both harm to the patient and unnecessary costs to the medical system[67]. Furthermore, with the availability of PCT testing but no protocol, there was a missed opportunity to leverage this biomarker for antibiotic best practices. The original goal of PRO-GAP was not necessarily to increase the sheer number of PCT values taken at the institution, but rather to promote meaningful PCT interpretation for antibiotic decision-making and ultimately make improvements to antibiotic use. The findings of the present study show that after the PRO-GAP protocol was implemented and provider education was complete, >1 PCT order had an improved association with antibiotic duration.

There have been clinical trials run to examine PCT guidance and antibiotic use. The first large multicenter trial to examine whether a PCT algorithm could reduce antibiotic exposure in LRTI patients was the 2009 ProHOSP Randomized Controlled Trial examining patients with LRTI in the emergency department in Switzerland[44]. The findings showed PCT guidance resulted in lower rates of antibiotic exposure compared with standard guidelines [44]. Conversely, the 2017 PCT Antibiotic Consensus Trial (ProACT) observed a PCT antibiotic prescribing guideline for the treatment of LRTI, and found that it did not result in less exposure to antibiotics than did usual care[40]. This trial was conducted in 14 hospitals with high adherence to quality measures for the treatment of pneumonia[40]. One explanation for this finding is that the PCT-based prescribing guideline

provided fewer opportunities to change antibiotic decisions than in earlier trials because antibiotics are being used judiciously even in the usual care group[40]. The results from the ProACT trial may not, however, be generalizable to all healthcare settings. Firstly, the trial was run in 14 hospitals with already high adherence to quality measures for the treatment of pneumonia, meaning there was not much room for improvement in appropriate antibiotic prescribing in patients with pneumonia. If the trial were run in hospitals with a larger need for improvement of appropriate antibiotic use, such as a hospital located in a state with known heightened antibiotic use, there may have been a greater chance for PCT to move the needle on antibiotic use. Additionally, applicable to both the ProACT and ProHOSP trials, because they were randomized trials, the findings may not be necessarily generalizable to how providers behave in the real world while not under observation for antibiotic decision-making. Because the ProACT and ProHOSP trials have opposing findings, examining PCT and antibiotic use in a similar patient population (LRTI) using real world data from one hospital would help elucidate the true utility of PCT as a guidance for antibiotic decision-making under normal conditions.

The present study used real world data to test whether a PCT hospital protocol moved the needle on antibiotic use in LRTI patients in one hospital in Kentucky. The findings were that >1 PCT order was associated with decreased antibiotic duration after the PRO-GAP protocol, consistent with the findings of the ProHOSP trial and contradictory to the findings of the ProACT trial. One of the hypothesized reasons for this is because UKHC is located in Kentucky, which is known to be above the national average antibiotic use[53], compared to the 14 hospitals with already high adherence to quality measures for pneumonia that were examined in the ProACT trial. Because this study examines one

hospital in Kentucky (UKHC) before and after the adoption of a protocol, there may have been more room for improvement in antibiotic use than in the hospitals included in the ProACT trial. These findings may suggest that PCT is a particularly useful tool in settings with a great need for antibiotic improvement. More research is warranted using multi-institutional real-world data in order to examine the differential impact that PCT guidance makes on antibiotic use based on the baseline state of antibiotic prescribing.

There are some limitations in this study. Firstly, this is a pre-post cohort study design, making it difficult to discern whether observed effects were attributable to the intervention of interest.[68] Further, the PRO-GAP training was not monitored in a way that enabled tracking of which providers did and did not receive training and their respective prescribing behavior. One way we aimed to account for this limitation was by including two years of data leading up to the implementation of PRO-GAP instead of just one year. Even so, with the limitations of pre-post study design, it is not possible to ascribe the observed effects with certainty as a direct result of the PRO-GAP protocol. Secondly, the COVID-19 pandemic hit the United States during the study period. There were many differences in hospital care attributable to this unprecedented global crisis, particularly in the first several months of the pandemic. We aimed to account for this issue by including 2019 in addition to 2020; and when comparing the two pre-protocol years, no differences were observed in patient characteristics, PCT ordering, and antibiotic duration across 2019 and 2020 (Appendix 2.2)[69]. Thirdly, the months observed in both cohorts are March through September, which are not the high-volume season for LRTIs. This cohort was selected to observe the impact of PRO-GAP as soon as the educational intervention was complete, and to observe the status quo of PCT ordering and antibiotic prescribing

practices in a lower volume time period, and the findings of this study should be interpreted with that context in mind. Assessment of the omitted months is a future direction of this work. Lastly, due to the nature of electronic health records data we cannot be certain if all PCT lab values were intentionally used for antibiotic decision-making even after implementation of PRO-GAP in 2021.

There are other methods that would enable comparison before and after an event takes place. For example, segmented regression is a method that statistically models interrupted time series data. Two of the assumptions of segmented regression are that the trend over time is linear, and that the cohort's characteristics remain unchanged through the study period. Neither of these assumptions are met in this study. Firstly, we cannot assume that the days of antibiotic therapy is a linear decreasing trend over the 3 years in the study period. Secondly, the cohort's characteristics did not remain unchanged, with race and qualifying diagnosis being significantly different pre- and post-protocol (Table 2.4.1). For these reasons, segmented regression, although a technique with merit, would not be appropriate for this analysis.

There is a need for additional research beyond the scope of this study. Firstly, as mentioned, there is a need to examine PCT and antibiotic use in hospitals with differing levels of antibiotic best practices at baseline, in order to better inform hospitals that would be good candidates for PCT guidance. To explore provider decision-making behavior in regard to PCT and antibiotic duration, the association of the PCT lab value and its corresponding antibiotic prescription must be examined, which is a study that could be done using the same data source as the present study (UKHC electronic health records).

Additionally, provider attitudes towards PCT for antibiotic decision-making are very important to consider, which could be quantified and examined via institutional surveys.

Developing and implementing the PRO-GAP protocol was designed to increase awareness to providers about optimizing the existing PCT laboratory test for this purpose, with the aim of consequentially improving antibiotic use. Other hospital systems that have existing PCT testing available without a protocol in place should consider implementing PRO-GAP, or a similar hospital protocol. A full version of the PRO-GAP protocol is in Appendix 2.3. The findings of this study indicate that antibiotic duration was reduced overall after implementing PRO-GAP, with evidence of additional reduction in patients with >1 PCT order compared to none. Other hospital systems that have existing PCT testing available without a protocol in place may consider developing and implementing a hospital protocol for PCT-guided antibiotic prescribing.

2.4.6 Tables and Figures

Figure 2.4.1 Procalcitonin-Guided Antibiotic Prescribing (PRO-GAP) Algorithms

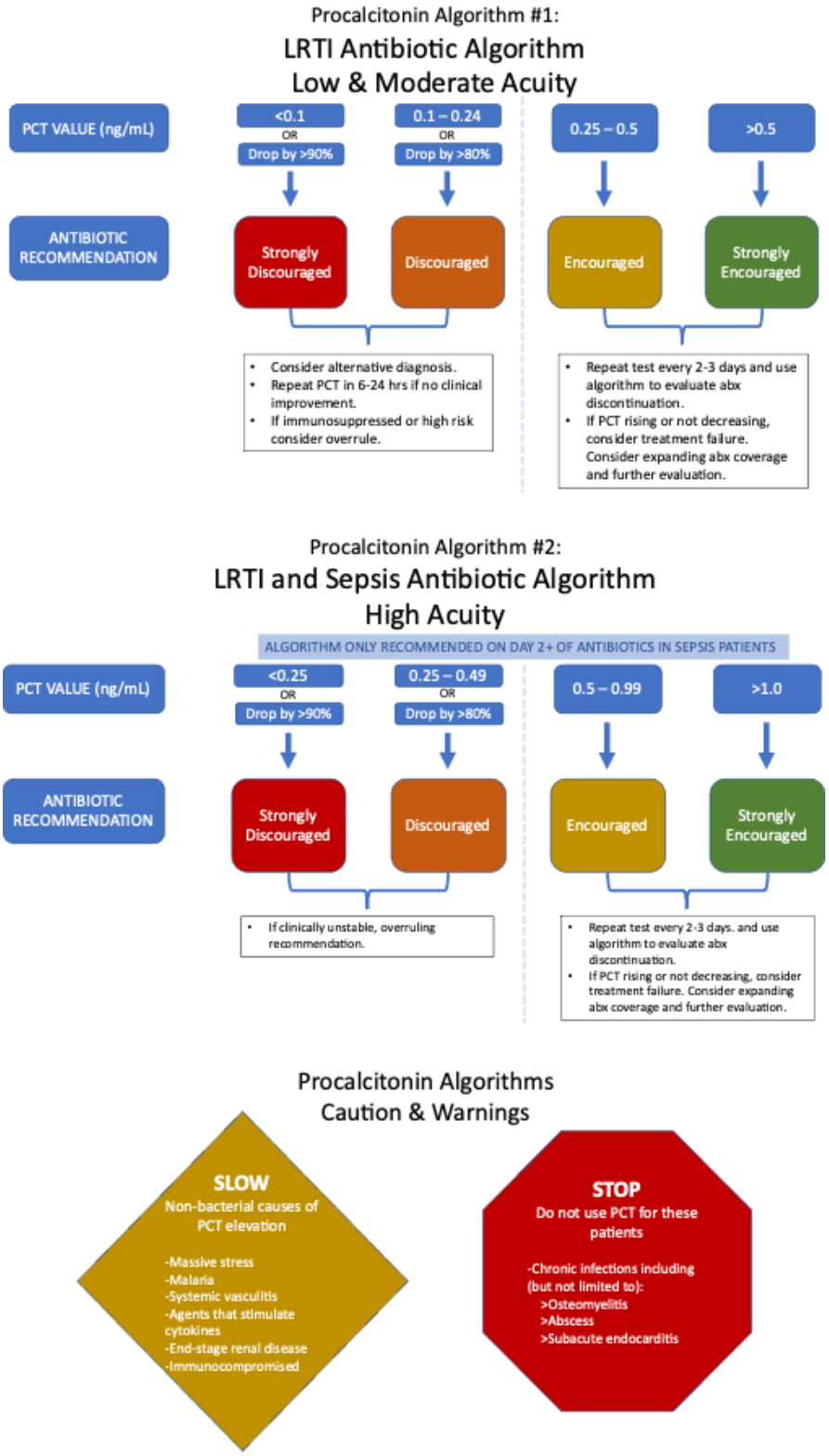


Table 2.4.1 Patient characteristics by cohort

Characteristic	**Pre-protocol cohort*** **(N=429)**	**Post-protocol cohort¶** **(N=322)**	**P-value†**
Age, median [Q1, Q3]	63.0 [54.0, 71.0]	61.0 [50.0, 69.0]	0.084
Sex, N (%)			
Female	205 (47.8)	155 (48.1)	0.921
Male	224 (52.2)	167 (51.9)	
Race, N (%)			
Asian	2 (0.5)	1 (0.3)	0.004
Black	58 (13.5)	56 (17.4)	
White	369 (86.0)	257 (79.8)	
Unreported/Other	0 (0.0)	8 (2.5)	
Qualifying diagnosis, N (%)			0.005
COPD with complication	175 (40.8)	99 (30.7)	
Pneumonia	254 (59.2)	223 (69.3)	
Length of stay, median [Q1, Q3]	5.0 [3.0, 7.0]	5.0 [3.0, 11.0]	0.008
Number of PCT Orders, N (%)			
0	303 (70.6)	216 (67.1)	0.147

1	106 (24.7)	80 (24.8)	
>1	20 (4.7)	26 (8.1)	
Total days of antibiotic therapy, median [Q1, Q3]	3.0 [2.0, 5.0]	2.0 [1.0, 5.0]	<0.001

**Pre-protocol cohort contains patients admitted in March-September 2019 & 2020*

¶*Post-protocol cohort contains patients admitted in March-September 2021*

†*P-values were obtained from Kruskal-Wallis tests for continuous variables and chi-squared tests for categorical variables.*

Table 2.4.2 Negative binomial regression results for days of antibiotic therapy

	N=740 **RR (95% CI)***	**P-value**
Post-protocol (reference = pre-protocol)	0.70 (0.62, 0.79)	<0.001
1 PCT (reference = 0 PCT)	1.07 (0.93, 1.22)	0.354
>1 PCT (reference = 0 PCT)	1.00 (0.78, 1.28)	0.988
Post-protocol * 1 PCT	0.88 (0.71, 1.10)	0.273
Post-protocol * >1 PCT	0.68 (0.49, 0.95)	0.025
COPD with complication (reference= pneumonia)	0.85 (0.77, 0.94)	0.001
Non-White (reference= White)	0.93 (0.81, 1.06)	0.258

**Offset for log of length of stay included.*

CHAPTER 3. AZITHROMYCIN EXPOSURE AND LONG-TERM OUTCOMES

3.1 Introduction and Literature Summary

3.1.1 Scientific Background- Azithromycin

Azithromycin (AZM) is an azalide, a subclass of macrolide antibiotics[12]. In the 1970s macrolides were established as an immunomodulatory therapy for respiratory infections, and have become the best-known of the macrocyclic structures[12]. Beyond the treatment of infectious respiratory infections, macrolides are used in treatment of cancer, auto-immune, and inflammatory diseases due to their significant anti-inflammatory, immunomodulatory, and a number of other properties[13,14]. Macrolides are a class of natural compounds produced by *Streptomyces* species, and are the most commonly used class of antibiotics[14]. Macrolides consist of a 14-, 15-, or 16-membered macrocyclic lactone ring to which one or more deoxy sugars may be attached[12].

Erythromycin is the first-discovered 14-membered macrolide, and has been in use in human medicine since 1952[14]. Its antimicrobial spectrum is similar to penicillin, and was widely used in patients with a penicillin allergy[14]. AZM was derived from erythromycin, and is the first-discovered 15-membered macrolide characterized by a basic nitrogen atom inserted into the macrocyclic ring[14]. AZM was first synthesized in 1980 by a team of Croatian pharmacists at PLIVA Laboratories, and was patented shortly thereafter.[14,12] It was discovered that AZM exhibited excellent tissue distribution and extended half-life compared to other macrolides, and that its localization to phagocytes aids killing of *S. aureus*, *L. pneumophilia*, and *H. influenzae* in vitro[12]. AZM prevents

bacteria from growing by interfering with protein synthesis[13]. In vivo tests showed AZM is less than half as toxic as erythromycin, and has significant superiority against systemic infections in mice in both subcutaneous and oral administration routes[14]. Pharmacokinetic studies in several animal species (mice, rats, rabbits, and dogs) showed AZM retention time was significantly longer than erythromycin[14]. The following clinical data exhibited that AZM was very well tolerated, and a single daily dose of AZM could be effective in the treatment of systemic infections[14].

In 1988 AZM was introduced to market by a joint collaborative agreement between PLIVA and Pfizer under branded names Sumamed® and Zithromax®[70]. Clinical AZM use expanded in the 1990s, when it was used as a treatment for chlamydia, trachoma, and prophylactic use against malaria; and expanded even more broadly to treat respiratory tract, genitourinary, and enteric infections in the 2000s.[12] In the year 2000, AZM became the market leader of antibiotics for respiratory tract infections[14]. Zithromax® was one of the best-selling branded antibiotics worldwide, but its sales began to decline due to loss of patent protection in 2006[14]. Today, AZM is prescribed to more than 40 million patients annually[70].

AZM is particularly potent against *Chlamydia trachomatis*, the bacteria that causes trachoma[71]. The global burden of trachoma is majorly in Africa, concentrated in 14 countries[71]. Pfizer has partnered with international organizations to provide Zithromax® free of charge to the trachoma endemic countries in need. To date, more than 500 million AZM doses have been donated[71]. Since this effort began, a study has shown that mass

distribution of AZM is associated with reduced childhood mortality in Sub-Saharan Africa[72].

Like other antibiotics, misuse of AZM is an important cause of the development of resistant bacteria[70]. The administration of improper dose or duration of AZM contributes to the spread of resistant bacteria[70]. One U.S. study found AZM to be the most commonly prescribed antibiotic in the outpatient setting by a primary care provider, and 78.4% of those AZM prescriptions were found to be inappropriate[73]. AZM has been used for mass drug administration in Africa, causing concern for the development of resistance.[74] A cluster-randomized trial examined proportions of macrolide-resistant pneumococcus in children in Niger who received AZM versus placebo twice per year for two years, and found increased resistance to macrolides in the AZM group.[74] However, there was no evidence of increased resistance to other classes of antibiotics.[74] In September 2020, the World Health Organization (WHO) issued new guidelines recommending that mass administration of AZM be considered for children <1 year old in some high-risk Sub-Saharan African countries, but recommended against universally implementing mass AZM administration for children in low-and middle-income countries.[75] WHO is utilizing a targeted approach aiming to utilize AZM to its full potential to save lives while protecting its use for the future.

Despite the lack of strong evidence, it was hypothesized that AZM may be adopted as a repurposed drug for the treatment of COVID-19.[76] This led to early adoption of AZM in routine COVID-19 care in some facilities in 2020, although the empirical practice of AZM treatment for COVID-19 was not substantiated by clinical data.[76] A body of evidence

debunked AZM's claimed effectiveness against COVID-19 including a randomized clinical trial found that outpatients with COVID-19 treated with a single dose of AZM did not result in greater likelihood of being symptom free at day 14 compared to placebo.[77]

Many consider the discovery of AZM to be a breakthrough in the macrolide antibiotic era, and has become one of the best-selling branded antibiotics worldwide.[14] In 2000 the team of researchers involved in the discovery of AZM were awarded the medal of highest honor, "Heroes of Chemistry," by the American Chemical Society for their outstanding contribution to the field.[14] The discovery of AZM represents an atypical drug discovery success story. Unfortunately, as the presented literature illustrates, AZM is often prescribed inappropriately. This is a concern for both the spread of antibiotic resistance and for patient safety. Jump to Chapter 3.1.3 for more information about AZM and cardiac safety.

3.1.2 Clinical Background- Myocardial Infarction

Acute myocardial infarction (MI) is the most severe manifestation of coronary artery disease, and causes more than 2.4 million deaths in the U.S. annually with estimated direct costs of $450 billion USD per year.[78] MI is divided into two categories for management decisions: ST-segment elevation MI (STEMI) and non-STEMI (NSTEMI).[78] STEMI results from complete and prolonged occlusion of an epicardial coronary blood vessel and is defined based on electrocardiographic (ECG) criteria, where NSTEMI typically results from severe coronary artery narrowing, transient occlusion, or microembolization of thrombus and/or atheromatous material.[79] It is estimated that NSTEMI comprises 60-75% of all myocardial infarctions.

In most cases, the cause of MI is disruption of a vulnerable atherosclerotic plaque or erosion of the coronary artery endothelium (type I).[78] Symptoms of MI include chest pain traveling from left arm to neck, shortness of breath, sweating, nausea, vomiting, abnormal heart beating, anxiety, fatigue, weakness, stress, depression, and others.[80] A diagnosis of MI requires biomarker evidence of myocyte necrosis, and either ECG criteria of ishaemia or infarction, or ischaemic symptoms, or both.[78] MI results in irreversible damage to the heart muscle due to lack of oxygen, and may lead to impairment in diastolic and systolic function causing proneness to arrythmia.[81] Reperfusion of the heart occurring less than 6 hours from symptom onset results in an improved prognosis.[82] Most deaths from MI occur prior to hospital arrival, an estimated 5-10%.[81] All patients with STEMI and NSTEMI require chewed aspirin 160 mg to 325 mg as soon as possible.[81] If oxygen saturation is <91%, the patient should have intravenous access and oxygen supplementation.[81] Treatment for STEMI includes immediate reperfusion, preferably emergent percutaneous coronary intervention (PCI), before which patients should receive dual antiplatelet agents, including intravenous heparin infusion and adenosine diphosphate inhibitor receptor (P2Y2 inhibitor).[81] Additionally, glycoprotein IIb/IIIa inhibitor or direct thrombin inhinbitor may be given at the time of intervention.[81] Stable, asymptomatic NSTEMI patients may not benefit from emergent PCI, and should be managed with antiplatelet agents with PCI done within 48 hours of admission[81]. However, NSTEMI patients with refractory ischemia or ischemia with hemodynamic or electrical instability should have PCI emergently[81].

A study examining Medicare fee-for-service beneficiaries who survived MI from 1995 to 2019 found a ten-year mortality rate of 73%, and a recurrent MI rate of 27%; with rates improving consistently throughout the study period (patients hospitalized 2008-2009 had 13.9% lower 10-year mortality risk and 22.5% lower recurrent MI risk than those hospitalized 1995 to 1997)[83]. Additionally, this study found that the hazards of mortality and MI recurrence were increased in men vs. women, Black vs. White patients, and dual Medicare-Medicaid eligible vs. non-dual Medicare-Medicaid eligible patients[83]. MI case fatality rate (the proportion of people diagnosed with MI who end up dying of it) is considered a measure of acute care quality because it is a reflection of processes of care such as medical interventions, early therapeutic treatment, and timely transport of the patient; and has been used for hospital benchmarking in many countries worldwide[84]. It was reported by the Organisation for Economic Co-operation and Development (OECD) that MI case fatality rates decreased substantially between 2009 and 2019.[85] Between 2019 and 2020, however, MI case fatality rates increased in some countries and remained stable in others. This trend between 2019 and 2020 are reflective of challenges faced by health systems during the COVID-19 pandemic.[85]

The contribution of external factors in the development of MI has been proven by epidemiological studies.[81,86] The INTERHEART study published in 2004 used a case-control study design to examine the effect of risk factors on MI across 52 countries, and found that abnormal lipids, smoking, hypertension, diabetes, abdominal obesity, psychosocial factors, consumption of fruits, vegetables, and alcohol, and regular physical activity were the most important risk factors for MI worldwide in all sexes, ages, and regions.[87] The need remains for a greater understanding of the genetic risk for MI, as

several genetic variants delineating disease pathways have been identified, but their translation to prevention has not been executed.[82] In addition to modifiable risk factors, there are nonmodifiable risk factors for MI including: sex, age, family history of MI, and male pattern baldness.[81] Other risk factors MI include: trauma, vasculitis, cocaine use, coronary artery anomalies, coronary artery emboli, aortic dissection, and excess demand on the heart due to hyperthyroidism or anemia.[81] The SWEDEHEART observational study conducted from 1998 to 2013 used a retrospective study design on a Swedish coronary care unit registry to examine major national events as risk factors for MI. The authors concluded that Christmas and Midsummer holidays were associated with a higher risk of MI, particularly in older and sicker patients; suggesting a role of external triggers especially in vulnerable patients.[86]

3.1.3 Azithromycin and Cardiac Safety

AZM has demonstrated its ability to polarize macrophages towards the anti-inflammatory M2 phenotype in several models of inflammation and tissue damage i.e. spinal cord injury, lung infection, and acute stroke.[88–90] Most recently, a study of AZM in a mouse model of heart attack concluded that mice treated with AZM around the time of their MI had preserved cardiac function (higher ejection fractions) and lower rates of mortality compared to those mice that did not receive AZM.[91]

In human medicine, there are conflicting findings about AZM and cardiac safety.[92] In 2012, a study by Ray et. al. reported 2.9 times the risk of cardiac deaths within 5 days of AZM dispensing compared with amoxicillin.[93] Consequently, the U.S. Food and Drug Administration (FDA) released a warning that AZM can cause potentially fatal irregular

heart rhythm, particularly patients with known cardiac risk factors.[16] Since that time, more studies have examined AZM's association with cardiac outcomes, many of which have shown differing findings. For example, one study on a Danish population found no association of AZM with increased risk of death from cardiovascular causes in a general population of young and middle-aged adults[94]. A study using U.S. Department of Veterans Affairs administrative data including patients ≥65 years old hospitalized with pneumonia and received antibiotic therapy concordant with clinical guidelines[95]. Among the AZM versus control group, there was a significant decrease in the odds of 90-day mortality, but a significant increase in the odds of MIs[95]. Another study using data from 7 European countries reported an association of AZM with increased risk of ventricular arrhythmia when compared to nonuse of antibiotics, but not when compared to current use of amoxicillin[96]. A study using a large U.S. claims database found that there was no association of cardiac events with AZM compared with amoxicillin, with the exception of patients with evidence of concomitant use of QT-prolonging drugs[15]. A study using the U.S. FDA Adverse Event Reporting System to examine the risk of serious cardiovascular adverse events with the use of hydroxychloroquine or chloroquine (HCQ/CQ) or HCQ/CQ + AZM for the treatment of COVID-19 found that patients treated with HCQ/CQ monotherapy or HCQ/CQ + AZM may be at increased risk for serious cardiovascular adverse events, TdP/QTc prolongation, and ventricular arrhythmia compared to comparable therapeutic control groups[97]. A new user cohort design was used to study the safety of hydroxychloroquine alone and in combination with AZM to treat COVID-19. It was observed that AZM in combination with hydroxychloroquine resulted in increased risk of 30-day cardiovascular mortality, chest pain/angina, and heart failure. These findings

suggested that the addition of AZM to hydroxychloroquine treatment may induce heart failure and cardiovascular mortality potentially due to synergistic effects on QT length, and the authors call for caution for this combination use in COVID-19 patients[98]. A meta-analysis of clinical trials and observational studies evaluating the efficacy and safety of pharmacological interventions for COVID-19 found that the combination of HCQ and AZM was shown to be associated with increased QT prolongation incidence and fatal cardiac complications in cardiac-impaired populations[99]. Lastly, a meta-analysis evaluating 12 randomized controlled trials reported no increased risks for mortality or cardiovascular events associated with AZM compared to placebo or standard of care[100].

3.1.4 Filling Gaps in the Literature

The literature presented demonstrates some uncertainty regarding the exposure-outcome relationship of AZM and cardiac outcomes, particularly in regard to differing patient populations. Although the FDA released a warning in 2012, a study found that the prevalence of cardiac risk factors among AZM users remained similar before and after the FDA warning. The lack of change after the FDA warning was hypothesized to be due to the inconsistency in results in the literature, indicating a need to continue to evaluate this potential association[15,101].

The Danish study by Svanstrom et. al. that found no association of AZM use and increased risk of death from cardiovascular causes was done on a young and relatively healthy population[94]. This study captured all individuals with episodes of AZM or penicillin V from 1997 to 2010[94]. Some of the studies described above, however, examine outcomes associated with AZM exposure in a population (or subpopulation) of patients

with heightened severity or risk (i.e., patients ≥65 hospitalized with pneumonia, patients with concomitant use of QT-prolonging drugs, rheumatoid arthritis patients, cardiac-impaired patients)[15,95,98,99]. Among the studies examining populations of more severe patients, there were findings showing that AZM was associated with increased risk of respective events. Among these studies, patients were followed up from 5 to 90 days from AZM exposure[15,95,98,99].

Although there are some studies that examined outcomes among medically severe patients exposed to AZM, none to our knowledge examine the timing of AZM exposure around the time of an MI and resulting long-term outcomes up to 5 years. Furthermore, none of the aforementioned studies examine patients beyond 90 days from the AZM exposure. The work described in this Chapter and Chapter 4 fills a gap in the literature because there is conflicting evidence regarding AZM and cardiac safety, and no studies have examined AZM exposure around the time of and MI.

3.2 Association between AZM exposure long-term cardiac outcomes among myocardial infarction patients

3.2.1 Abstract

Importance: There is clinical concern regarding the potential increased risk of cardiac events with exposure to azithromycin (AZM). Myocardial infarction (MI) results in irreversible damage to the heart muscle due to lack of oxygen, and may lead to subsequent cardiac complications.

Objective: This study aimed to compare long-term subsequent MI and incident HF among MI patients who were exposed and unexposed to AZM around the time of their MI.

Design, Setting, and Participants: This was a retrospective cohort study using Merative™ MarketScan® databases examining adult inpatients admitted with MI from January 1, 2010 to December 31, 2017. Propensity score matching was used to ensure that the exposed and unexposed groups were balanced in baseline characteristics. Two matched cohorts were identified: 1) all eligible patients, and 2) patients free of heart failure at baseline.

Exposure: Evidence of AZM receipt during a window of 7 days pre- to 3 days post-MI admission date compared with unexposed controls.

Main Outcomes and Measures: Time to subsequent MI and incident heart failure (HF) were examined up to five years after the initial MI using Cox proportional hazards regression.

Results: The full analysis cohort included 18,066 patients (AZM N=3,011), and the HF-free analysis cohort included 9,180 patients (AZM N=1,530). The probability of having a subsequent MI up to five years following the initial MI was 15.3% in the AZM group versus 9.7% in the control group (HR [95% CI]=1.39 [1.09, 1.79], p=0.009). The probability of having incident HF was 39.8% in the AZM group versus 35.5% in the control group (HR [95% CI]=1.14 [0.93, 1.41], P=0.215).

Conclusions and Relevance: This study found an increased risk of long-term subsequent MI among MI patients with AZM exposure compared to controls. When needed, alternative antibiotics to AZM should be considered for patients with a history of or at risk for MI.

3.2.2 Introduction

Azithromycin (AZM) is an antibiotic used for the treatment of respiratory infections, cancers, auto-immune diseases, and inflammatory diseases[12–14]. Because of immunomodulator properties of the drug, AZM is also used off-label for the treatment of bronchiectasis, bronchiolitis obliterans syndrome, and pulmonary inflammation due to cystic fibrosis[102,103,104]. It is estimated that AZM is prescribed to more than 30 million patients annually in the United States[15]. There is evidence that AZM prescribing may be frequently inappropriate in certain patients given its safety concerns[92,105]. In 2012, Ray et. al. reported 2.9 times the risk of cardiac deaths within five days of AZM dispensing compared with amoxicillin[93]. Later that year, the U.S. Food and Drug Administration (FDA) released a warning that AZM can cause potentially fatal irregular heart rhythm, particularly in patients with known cardiac risk factors. Subsequently, studies were published with contradicting findings, showing no increased likelihood of cardiac outcomes as a result of AZM[15,94]. Despite the FDA warning, AZM prescribing practices in at-risk patients remained unchanged, which was hypothesized to be due to the inconsistent evidence in the literature[16,105,106].

Myocardial infarction (MI) causes more than 2.4 million deaths in the U.S. annually with estimated direct costs of $450 billion per year[78]. MI results in irreversible damage to the heart muscle due to lack of oxygen, and may lead to subsequent cardiac complications including recurrent MI. Among patients who have an MI, it is estimated that 6.9% experience a recurrent MI at 3 years[107]. MI is the most common cause of heart failure (HF) (a chronic progressive condition in which the heart cannot pump enough blood and oxygen

to support other organs)[81,108,109]. It is estimated that 13% of MI patients are diagnosed with HF at 30 days, and 20-30% at 1 year post-MI[108,109].

AZM remains so commonly prescribed that some patients in the real world are likely to be on a course of AZM close to the time of an MI. There are no studies to our knowledge that examine long-term outcomes associated with AZM exposure near the time of a myocardial infarction (MI). This study aims to examine the exposure of AZM in a 10-day window around MI and its association with long-term outcomes compared to unexposed controls.

3.2.3 Methods

3.2.3.1 Study Population

This was a retrospective cohort study using Merative™ MarketScan® databases, a nationally representative U.S. claims database of commercially insured patients. Adult (≥18 years old) inpatients admitted with MI as the primary diagnosis and length of stay of 1—30 days occurring from January 1, 2010 to December 31, 2017 were eligible for inclusion in this study (Appendix 3.1). Patients were required to have continuous pharmacy and medical enrollment during the one year prior to and including their date of admission ("baseline period"). The "index date" was defined as the date of admission for MI.

Exposure to AZM was defined as any receipt of AZM during a window of 7 days pre- to 3 days post-index date (Appendix 3.1). Patients with evidence of AZM prescription overlapping with at least 1 day of the exposure window were deemed exposed to AZM, and otherwise patients were deemed controls.

3.2.3.2 Outcomes

Long-term outcomes examined up to five years post index were: time to subsequent MI (defined as MI in the primary position on the claim[110]) and time to incident HF (defined as evidence of first HF diagnosis in any position on the claim) (Appendix 3.1).

3.2.3.3 Statistical Analysis

To ensure that the exposed and unexposed groups were balanced in baseline demographics and comorbidities, propensity score matching was used to select control patients using propensity score matching. Variables used for propensity score matching were selected by reviewing relevant literature to identify factors that could potentially confound the relationship between AZM exposure and outcomes of interest. The selected matching variables were evaluated on the index date (age, sex, region, Charlson Comorbidity Index (CCI) score), during the index MI visit (length of stay, NSTEMI vs. STEMI, index year, renal failure, septic shock, blood transfusion, ventilator, cardiogenic shock, intra aortic balloon pump), or during the baseline period (chronic obstructive pulmonary disease (COPD), glucocorticoid therapy, hypertension, diabetes, carotid artery disease, HF (omitted for analyses of incident HF)). An exact match was required for sex, region, and MI year.

Two matched cohorts were identified: 1) using all eligible patients, and 2) using only patients free of HF at baseline in order to examine incident HF outcomes. Match quality was optimized by executing a number of match iterations including modification of the distance, caliper, matching ratio, and method. The match iterations were scrutinized using standardized mean differences and visual inspection of baseline characteristics by exposure group. First, the optimal matching distance was selected by examining matches using both the logit of the propensity score and the Mahalanobis distance. Both distances

were performed using no caliper and a caliper of 0.2 * standard deviation of propensity score. The optimal matching ratio was examined by performing propensity score matches with a ratio of 1 to 1, 2, 3, 5, 10, 20, and 30. Lastly, greedy nearest neighbor and optimal matching methods were compared. After conducting all the iterations to ensure match quality, matches were performed using a 1:5 greedy nearest neighbor algorithm (i.e., matching without replacement), with no caliper.

Patient characteristics (demographics, comorbidities, and index MI information) were summarized overall and stratified by exposure group (AZM vs. control). Subsequent MI and incident HF were assessed for up to five years from the discharge date of index MI. Patients were censored at five years post-index MI, or disenrollment; whichever came first. Information regarding disenrollment due to death was not available in the data. Number of patients with the event per person-year and median time to event were reported by exposure group. Differences in the time to each outcome by exposure group were visualized using Kaplan-Meier curves. Cox proportional hazards modelling was used to include adjustment for residual confounding, and to examine the hazards of long-term outcomes in AZM vs. control. Covariates were included in the Cox model if they met one of two criteria: 1) the standardized mean difference (SMD) between treatment and control after propensity score matching was more than 10%; or 2) the variable had potential to change differentially between cases and controls post-index (such variables were included as time-varying covariates). Violation of the proportional hazards assumption was assessed using Schoenfeld residuals and log-log survival curves.

Both 1:5 matched populations had a subgroup of patients with continuous enrollment 30 days post-index in order to observe 30-day outcomes. Differences in 30-day

outcomes between groups were examined using chi-squared tests, and additional adjustments for residual confounding were included using logistic regression. Variables were included for adjustment if the standardized mean difference (SMD) between AZM and control after propensity score matching was >10%. Analyses were performed using SAS v. 9.4.

3.2.4 Results

3.2.4.1 Baseline Characteristics

424,515 patients met the inclusion/exclusion criteria for the study, among which 267,832 had no HF at baseline. After implementing 1:5 propensity score matching, the full analysis cohort included 18,066 patients (Table 3.2.1), and the HF-free analysis cohort included 9,180 patients.

The full cohort contained 3,011 patients exposed to AZM and 15,055 controls. Variables that were included in the propensity score matching algorithm were well-balanced between the AZM and control groups, including: age (mean±SD = 67.4±14.4; sex (54.7% male); region (33.7% North Central); CCI score (mean±SD = 6.3±3.2); index MI length of stay (days, mean±SD = 5.7±5.1); NSTEMI (51.2%); index MI year(18.3% in 2011); renal failure (22.6%); septic shock (4.1%); blood transfusion (0.2%); ventilator (0.7%); cardiogenic shock (5.1%); intra-aortic balloon pump (2.0%); COPD (37.2%); glucocorticoid therapy (41.7%); hypertension (78.6%); diabetes (40.4%); carotid artery disease (10.3%); and HF (49.1%) (Table 3.2.1).

The HF-free cohort contained 1,530 patients exposed to AZM and 7,650 controls. Variables that were included in the propensity score matching algorithm were well-

balanced between the AZM and control groups, including: (mean±SD = 63.4±14.4); sex (55.3% male); region; CCI score (mean±SD = 5.2±3.0); index MI length of stay (days, mean±SD = 4.5±4.3); NSTEMI (48.9%); index MI year (18.2% in 2011); renal failure (14.0%); septic shock (3.4%); blood transfusion (0.2%); ventilator (0.3%); cardiogenic shock (2.5%); intra-aortic balloon pump (1.4%); COPD (31.8%); glucocorticoid therapy (42.9%); hypertension (73.2%); diabetes (34.6%); and carotid artery disease (7.4%) (Table 3.2.2).

3.2.4.2 Long-Term Outcomes

A total of 978 patients experienced a subsequent MI (244 exposed to AZM vs. 734 controls). In the AZM group, a rate of 4.1 subsequent MIs per 100 person-years was observed compared to 2.5 subsequent MIs per 100 person-years in the control group. As seen in Figure 3.2.1, the time to subsequent MI was lower in the AZM group vs. the control group starting within the first six months post-index MI through the 5 years post-index. At five years, the probability of having a subsequent MI is 15.3% in control compared to 9.7% in the AZM group (Figure 3.2.1). The rate of subsequent MI was significantly higher in the AZM group vs. control (HR [95%CI]=1.39 [1.09, 1.79], p=0.009) (Table 3.2.3).

A total of 2,210 patients were diagnosed with incident HF (418 exposed to AZM vs. 1,792 controls). In the AZM group, a rate of 14.8 incident HF diagnoses per 100 person-years were observed compared to 12.6 incident HF diagnoses per 100 person-years in the control group. As seen in Figure 3.2.2, the probability of incident HF is lower in the AZM group vs. control starting less than one year following index MI. At five years, the probability of incident HF was 35.5% in the control group compared to 39.8% in the AZM

group (Figure 3.2.2). This increased rate of incident HF was not statistically significant in the AZM group vs. control (HR [95%CI]=1.14 [0.93, 1.41], P=0.215) (Table 3.2.3).

3.2.5 Discussion

This study shows that patients exposed to AZM within a 10-day window of an MI have an increased risk of subsequent MI within five years compared to those unexposed to AZM in that window. This is the first study to our knowledge to examine long-term outcomes following the receipt of AZM around the time of an MI using a large claims database.

This filled a unique gap because the existing literature demonstrated some inconsistency regarding the exposure-outcome relationship of AZM and cardiac outcomes, particularly in patient populations with differing severity; and no studies have followed patients up to 5 years[15,94–96]. An FDA warning was released in 2012 that AZM can cause potentially fatal irregular heart rhythm, especially in patients with known cardiac risk factors[16]; however AZM prescribing practices in said at-risk patients remained unchanged[101]. This was hypothesized to be due to inconsistent findings in the literature, indicating the need to continue to evaluate the potential association[101].

Studies by Svanstrom et. al.(2012) and Patel et. al.(2020) contradicted the FDA warning, showing no increased risk of cardiac events associated with AZM. These and others created ambiguity on the safety of AZM and cardiac outcomes[15,94–96]. The Svanstrom et. al. study examined a Danish population of young (<65 years old) and healthy (no hospitalizations in the past month) adults. On top of the generalizability issues with a Danish cohort, this study does not examine a cardiac-impaired or at-risk population.

The study's large control group sample size and the use of a well-defined patient population with a concurrent MI are notable strengths. This approach allowed for a robust analysis of the association between AZM and subsequent MI and incident HF in a high-risk patient group due to MI. Additionally, the study adjusted for potential confounding factors by using propensity score matching, which enhanced the validity of the findings. As such, the study's findings have significant implications for clinical practice, suggesting that caution should be exercised when prescribing AZM to patients with a history of MI. Alternative antibiotics should be considered when feasible to minimize the potential risk of subsequent MI. However, additional research is needed to corroborate these findings and investigate the underlying mechanisms of the observed association. For example, AZM has documented inflammation modulatory effects, which reduce infarct expansion and the development of heart failure after a large myocardial infarction in animal models; an effect that was not observed in this retrospective human study. Therefore, prospective trials would bolster the evidence shown in the present study to guide clinical decision-making in this context.

There are some limitations of this study. First, this study uses Merative™ MarketScan® claims databases, which is primarily used for billing and not research purposes. Due to the nature of this data source, we do not have information on the reason for death, and for that reason the study findings should be interpreted in the context of the outcomes described and not death. Additionally, the severity of the MI is not directly available; however we aimed to adjust for this by matching on the variables examined during the index MI event (length of stay, NSTEMI vs. STEMI, index year, renal failure, septic shock, blood transfusion, ventilator, cardiogenic shock, intra aortic balloon pump)

as a proxy for MI severity. Merative™ MarketScan® claims databases does not contain patient race/ethnicity information, which could be a confounder that we were not able to adjust for. A future direction of this work is to reproduce the study in another data source to confirm the findings are generalizable in other populations outside of commercially insured U.S. patients, and to mitigate some of the limitations of the Merative™ MarketScan® database. Additionally, AZM exposure was identified using NDC and HCPCS codes, and any other receipt of AZM was not accounted for, as it is not available in claims data. This study spans the transition from ICD-9-CM to ICD-10-CM, which were both used in this study. However, it should be noted that Panozzo et. al. found that the incidence and prevalence of MI was similar across the two coding eras.[111] Next, this study did not examine the dose of AZM. Examining the dose-response of AZM on the outcomes is important to elucidate its true influence and is a future direction of this work.

Given this study examines time-to-event outcomes the findings may be subject to immortal time bias, meaning during the period of observation there is some interval during which the outcome cannot occur, leading to over- or underestimation of the outcome. However, there were several study design attributes that helped avoid this bias. Firstly, this study was designed with a one-year washout period leading up to the index MI, and all patients were discharged from that index MI event. Therefore, we have ensured that all time intervals in which the study participants may have experienced subsequent MI were captured. Additionally, for all incident HF outcomes we examined this in a population of patients that were free of HF at baseline. Lastly, we required patients to be continuously enrolled in the one year leading up to index MI, ensuring we had reliable information on the patients prior to the possible AZM exposure and index MI event.

The AZM group in the full matched cohort had a higher proportion of patients with evidence of pneumonia diagnosis at index than control (35.3% vs. 16.0%). Suspected or confirmed pneumonia likely drove some of the AZM exposure, as AZM is a first-line therapy for the treatment of community-acquired pneumonia. It is possible that the existence of an active infection at the time of MI could impact both outcomes including cardiac remodeling quality and extent of ischemic injury. One study found that patients hospitalized for MI who developed infections during the course of a hospitalization for STEMI (median time to diagnosis was 3 days) was associated with significantly higher rates of death and death or MI at 90 days[112]. However, we opted not to match on pneumonia at index in this study to avoid the unintended consequence of selecting control subjects with AZM exposure undocumented by NDC or HCPCS codes in the claims data set. Additionally, there are known limitations of the validity and accuracy of ICD codes to identify pneumonia[113]. To assure that the results of the Cox proportional hazards model for time to subsequent MI were not confounded by patients with evidence of pneumonia at index in the AZM group, we ran a sensitivity analysis excluding patients with pneumonia at index from both AZM and control, and the results were sustained (HR [95% CI]=1.46[1.10, 1.93], P=0.009) (Appendix 3.2).

While the study has limitations, its findings highlight the importance of careful consideration when prescribing AZM to high-risk patients. Because this is the first study to examine the long-term outcomes associated with AZM receipt around the time of an MI, more research is needed to examine this hypothesis.

3.2.6 Conclusion

In this cohort study, we found increased risk of subsequent MI within five years among patients exposed to AZM around the time of their first MI compared to unexposed controls. When needed, alternative antibiotics to AZM should be considered for patients with a history of or at risk for MI. More research is warranted to examine the outcomes associated with AZM exposure around the time of an MI.

3.2.7 Tables and Figures

Table 3.2.1 Baseline characteristics in matched full cohort

	Overall (N=18,066)	**AZM (N=3,011)**	**Control (N=15,055)**
Total Observation years (sum)	35753.0	6022.8	29730.2
Age	67.4±14.4	67.5±14.9	67.3±14.3
Male	9852 (54.5%)	1642 (54.5%)	8210 (54.5%)
Region			
Northeast	3522 (19.5%)	587 (19.5%)	2935 (19.5%)
North Central	6084 (33.7%)	1014 (33.7%)	5070 (33.7%)
South	6024 (33.3%)	1004 (33.3%)	5020 (33.3%)
West	2286 (12.7%)	381 (12.7%)	1905 (12.7%)
Unknown	150 (0.8%)	25 (0.8%)	125 (0.8%)
Baseline Comorbidities			
CCI (mean±SD)	6.3±3.2	6.3±3.0	6.3±3.2
Cancer	5246 (29.0%)	904 (30.0%)	4342 (28.8%)
Chronic Kidney Disease	3353 (18.6%)	540 (17.9%)	2813 (18.7%)
Diabetes	7293 (40.4%)	1219 (40.5%)	6074 (40.3%)

End Stage Renal Disease	788 (4.4%)	106 (3.5%)	682 (4.5%)
Heart Failure	8867 (49.1%)	1481 (49.2%)	7386 (49.1%)
Hypertension	14198 (78.6%)	2357 (78.3%)	11841 (78.7%)
Hyperlipidemia	1962 (10.9%)	299 (9.9%)	1663 (11.0%)
Stroke	1210 (6.7%)	605 (20.1%)	605 (4.0%)
Peripheral Artery Disease	2191 (12.1%)	314 (10.4%)	1877 (12.5%)
Glucocorticoid Therapy	7537 (41.7%)	1251 (41.5%)	6286 (41.8%)
IBD	269 (1.5%)	41 (1.4%)	228 (1.5%)
Neuromuscular Disease	5 (0.0%)	3 (0.1%)	2 (0.0%)
COPD	6726 (37.2%)	1133 (37.6%)	5593 (37.2%)
Cartoid Artery Disease	1865 (10.3%)	309 (10.3%)	1556 (10.3%)
Index Event Variables			
Index MI Year			
2010	2448 (13.6%)	408(13.6%)	2040 (13.6%)
2011	3300 (18.3%)	550 (18.3%)	2750 (18.3%)
2012	2904 (16.1%)	484 (16.1%)	2420 (16.1%)
2013	2394 (13.3%)	399 (13.3%)	1995 (13.3%)

2014	2340 (13.0%)	390 (13.0%)	1950 (13.0%)
2015	1776 (9.8%)	296 (9.8%)	1480 (9.8%)
2016	1500 (8.3%)	250 (8.3%)	1250 (8.3%)
2017	1404 (7.8%)	234 (7.8%)	1170 (7.8%)
Index event length of stay, days (mean±SD)	5.7±5.1	5.7±4.9	5.6±5.2
NSTEMI	9257 (51.2%)	1531 (50.8%)	7726 (51.3%)
Renal failure**	4082 (22.6%)	678 (22.5%)	3404 (22.6%)
Septic Shock	738 (4.1%)	135 (4.5%)	603 (4.0%)
Cardiogenic Shock	926 (5.1%)	149 (4.9%)	777 (5.2%)
Intra Aortic Balloon Pump	369 (2.0%)	58 (1.9%)	311 (2.1%)
Blood Transfusion	33 (0.2%)	7 (0.2%)	26 (0.2%)
Ventilator	124 (0.7%)	28 (0.9%)	96 (0.6%)
Pneumonia at Index	3469 (19.2%)	1062 (35.3%)	2407 (16.0%)

Table 3.2.2 Baseline characteristics in matched heart failure-free cohort

	Overall (N=9,180)	**AZM (N=1,530)**	**Control (N=7,650)**
Total Observation years (sum)	17021.1	2819.8	14201.3
Age (mean±SD)	63.4±14.4	63.7±14.6	63.6±13.9
Male	5076 (55.3%)	846 (55.3%)	4230 (55.3%)
Region			
Northeast	1734 (18.9%)	289 (18.9%)	1445 (18.9%)
North Central	3000 (32.7%)	500 (32.7%)	2500 (32.7%)
South	3330 (36.3%)	555 (36.3%)	2775 (36.3%)
West	1056 (11.5%)	176 (11.5%)	880 (11.5%)
Unknown	60 (0.7%)	10 (0.7%)	50 (0.7%)
Baseline Comorbidities			
CCI	5.2±3.0	5.2±2.8	5.2±3.0
Cancer	2630 (28.6%)	464 (30.3%)	2166 (28.3%)
Chronic Kidney Disease	942 (10.3%)	161 (10.5%)	781 (10.2%)
Diabetes	3172 (34.6%)	529 (34.6%)	2643 (34.5%)
End Stage Renal Disease	181 (2.0%)	23 (1.5%)	158 (2.1%)
Hypertension	6720 (73.2%)	1110 (72.5%)	5610 (73.3%)

Hyperlipidemia	1215 (13.2%)	180 (11.8%)	1035 (13.5%)
Stroke	1511 (16.5%)	221 (14.4%)	1290 (16.9%)
Peripheral Artery Disease	699 (7.6%)	103 (6.7%)	596 (7.8%)
Glucocorticoid Therapy	3942 (42.9%)	658 (43.0%)	3284 (42.9%)
IBD	160 (1.7%)	23 (1.5%)	137 (1.8%)
Neuromuscular Disease	2 (0.0%)	1 (0.1%)	1 (0.0%)
COPD	2923 (31.8%)	482 (31.5%)	2441 (31.9%)
Cartoid Artery Disease	680 (7.4%)	109 (7.1%)	571 (7.5%)
Index Event Variables			
Index MI Year			
2010	1326 (14.4%)	221 (14.4%)	1105 (14.4%)
2011	1674 (18.2%)	279 (18.2%)	1395 (18.2%)
2012	1404 (15.3%)	234 (15.3%)	1170 (15.3%)
2013	1092 (11.9%)	182 (11.9%)	910 (11.9%)
2014	1086 (11.8%)	181 (11.8%)	905 (11.8%)
2015	780 (8.5%)	130 (8.5%)	650 (8.5%)
2016	930 (10.1%)	155 (10.1%)	775 (10.1%)

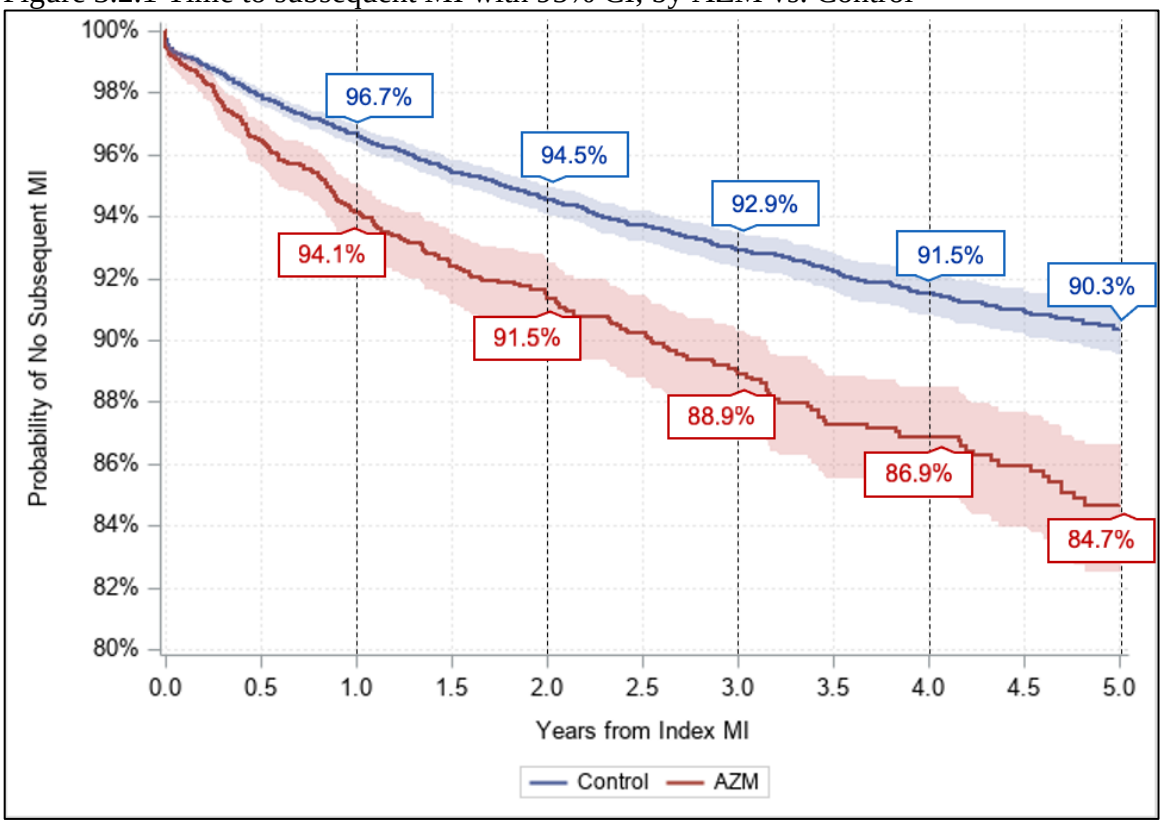
2017	888 (9.7%)	148 (9.7%)	740 (9.7%)
Index event length of stay (mean±SD)	4.5±4.3	4.5±4.3	4.4±4.3
Renal Failure**	1284 (14.0%)	216 (14.1%)	1068 (14.0%)
Septic Shock	316 (3.4%)	56 (3.7%)	260 (3.4%)
Cardiogenic Shock	231 (2.5%)	41 (2.7%)	190 (2.5%)
Intra Aortic Balloon Pump	126 (1.4%)	24 (1.6%)	102 (1.3%)
Blood Transfusion	17 (0.2%)	4 (0.3%)	13 (0.2%)
Ventilator	24 (0.3%)	7 (0.5%)	17 (0.2%)
NSTEMI	4485 (48.9%)	748 (48.9%)	3737 (48.8%)
Pneumonia at Index	1232 (13.4%)	406 (26.5%)	826 (10.8%)

Table 3.2.3 Results from Cox Proportional Hazards Model

	Subsequent MI (N=18,066)		**Incident HF (N=9,180)**	
	HR (95% CI)	**P-value**	**HR (95% CI)**	**P-value**
AZM vs. no AZM	1.39 (1.09, 1.79)	0.009	1.14 (0.93, 1.41)	0.215
CCI score (time-varying)	1.14 (1.11, 1.18)	<0.001	1.21 (1.18, 1.24)	<0.001

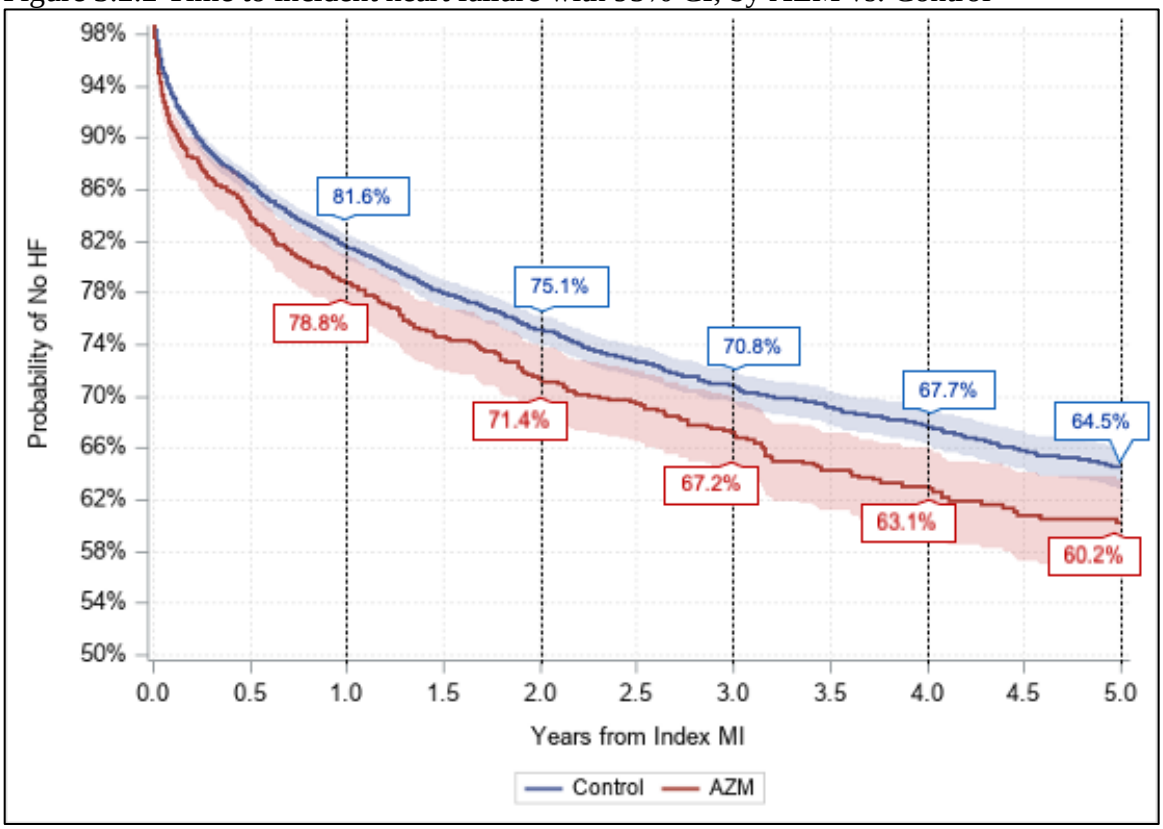
MI=myocardial infarction; HF=heart failure; HR=hazard ratio; CI=confidence interval; AZM=azithromycin

Figure 3.2.1 Time to subsequent MI with 95% CI, by AZM vs. Control



MI=myocardial infarction; CI=confidence interval; AZM=azithromycin

Figure 3.2.2 Time to incident heart failure with 95% CI, by AZM vs. Control



HF=heart failure; CI=confidence interval; AZM=azithromycin

CHAPTER 4. AZITHROMYCIN EXPOSURE AND SHORT-TERM OUTCOMES

4.1 Association between AZM exposure short-term cardiac outcomes among myocardial infarction patients

4.1.1 Abstract

Importance: There is clinical concern regarding the potential increased risk of cardiac events with exposure to azithromycin (AZM). Myocardial infarction (MI) results in irreversible damage to the heart muscle due to lack of oxygen and may lead to subsequent hospital utilization and cardiac complications.

Objective: This study aimed to compare short-term hospital utilization and incident heart failure among MI patients who were exposed and unexposed to AZM around the time of their MI.

Design, Setting, and Participants: This was a retrospective cohort study using Merative™ MarketScan® databases examining adult inpatients admitted with MI from January 1, 2010 to December 31, 2017. Propensity score matching was used to ensure that the exposed and unexposed groups were balanced in baseline characteristics. Two matched cohorts were identified: 1) all eligible patients, and 2) patients free of heart failure at baseline. Patients were required to have 30 days of continuous enrollment post-MI.

Exposure: Evidence of AZM receipt during a window of 7 days pre- to 3 days post-MI admission date compared with unexposed controls.

Main Outcomes and Measures: All-cause hospitalization, MI-related hospitalization, MI-sequelae-related hospitalization and incident HF were examined 30 days post-MI using logistic regression.

Results: The full analysis cohort included 16,266 patients (AZM N=2,718), and the HF-free analysis cohort included 8,512 patients (AZM N=1,411). The odds of all 30-day outcomes were significantly higher in the AZM group vs. control (OR [95% CI] for all-cause readmission: 1.34 [1.17, 1.55], P<0.001; MI-related readmission: 1.68 [1.35, 2.08], P<0.001; MI-sequelae-related readmission: 1.42 [1.20, 1.69], P<0.001; and incident HF: 1.64 [1.36, 1.97], P<0.001).

Conclusions and Relevance: This study found an increased odds of 30-day hospital readmissions and incident HF among MI patients with AZM exposure compared to controls. When needed, alternative antibiotics to AZM should be considered for patients with a history of or at risk for MI.

4.1.2 Introduction

As mentioned in Chapter 3, Azithromycin (AZM) is a commonly used antibiotic used for the treatment of respiratory infections, cancers, auto-immune diseases, and inflammatory diseases[12–14]. Because of immunomodulator properties of the drug, AZM is also used off-label for the treatment of bronchiectasis, bronchiolitis obliterans syndrome, and pulmonary inflammation due to cystic fibrosis[102,103,104]. In 2012, the U.S. Food and Drug Administration (FDA) released a warning that AZM can cause potentially fatal irregular heart rhythm, particularly in patients with known cardiac risk factors. Subsequently, studies were published with contradicting findings, showing no increased likelihood of cardiac outcomes as a result of AZM[15,94]. Despite the FDA warning, AZM prescribing practices in at-risk patients remained unchanged, which was hypothesized to be due to the inconsistent evidence in the literature[16,105,106].

Myocardial infarction (MI) causes more than 2.4 million deaths in the U.S. annually with estimated direct costs of $450 billion per year[78]. It is estimated that 13% of MI patients are diagnosed with HF at 30 days, and 20-30% at 1 year post-MI[108,109].

AZM remains so commonly prescribed that some patients in the real world are likely to be on a course of AZM close to the time of an MI. There are no studies to our knowledge that examine outcomes associated with AZM exposure near the time of a myocardial infarction (MI). This study aims to examine the exposure of AZM in a 10-day window around MI and its association with long-term outcomes compared to unexposed controls.

4.1.3 Methods

4.1.3.1 Study Population

This was a retrospective cohort study using Merative™ MarketScan® databases, a nationally representative U.S. claims database of commercially insured patients. Adult (≥18 years old) inpatients admitted with MI as the primary diagnosis and length of stay of 1—30 days occurring from January 1, 2010 to December 31, 2017 were eligible for inclusion in this study (Appendix 3.1). Patients were required to have continuous pharmacy and medical enrollment during the one year prior to and including their date of admission ("baseline period"). The "index date" was defined as the date of admission for MI.

Exposure to AZM was defined as any receipt of AZM during a window of 7 days pre- to 3 days post-index date (Appendix 3.1). Patients with evidence of AZM prescription overlapping with at least 1 day of the exposure window were deemed exposed to AZM, and otherwise patients were deemed controls.

The methods of propensity score matching used to ensure that the exposed and unexposed groups were balanced in baseline demographics and comorbidities are described in Chapter 3.2.3.3. Two matched cohorts were identified: 1) using all eligible patients, and 2) using only patients free of HF at baseline in order to examine incident HF outcomes. The analyses described in this chapter include patients from the two matched cohorts in Chapter 3 with the additional requirement of continuous enrollment 30 days post-index.

4.1.3.2 Outcomes

Outcomes were examined 30-days post-MI and were: all-cause hospitalization, MI-related hospitalization (inpatient admission with diagnosis of MI/unstable angina, chest pain, ischemic heart disease in any position on the claim), MI-sequelae-related hospitalization (inpatient admission with diagnosis of HF, arrythmia, carditis, stroke, or cardiac arrest in any position on the claim), and incident HF (Appendix 3.1).

4.1.3.3 Statistical Analysis

Differences in 30-day outcomes between groups were examined using chi-squared tests, and additional adjustments for residual confounding were included using logistic regression. Variables were included for adjustment if the standardized mean difference (SMD) between AZM and control after propensity score matching was >10%. Analyses were performed using SAS v. 9.4.

4.1.4 Results

4.1.4.1 Baseline Characteristics

The full cohort contained 2,718 patients exposed to AZM and 13,548 controls. Variables that were included in the propensity score matching algorithm were well-balanced between the AZM and control groups, including: age (mean±SD = 66.7±14.3; sex (54.7% male); region (33.8% South); CCI score (mean±SD = 6.1±3.1); index MI length of stay (days, mean±SD = 5.5±5.0); NSTEMI (51.0%); index MI year(18.4% in 2011); renal failure (20.5%); septic shock (3.0%); blood transfusion (0.2%); ventilator (0.6%); cardiogenic shock (4.2%); intra-aortic balloon pump (2.0%); COPD (36.2%); glucocorticoid therapy (41.7%); hypertension (78.4%); diabetes (40.1%); carotid artery disease (10.3%); and HF (47.5%) (Table 4.1.1).

The HF-free cohort contained 1,411 patients exposed to AZM and 7,101 controls. Variables that were included in the propensity score matching algorithm were well-balanced between the AZM and control groups, including: (mean±SD = 63.2±13.9); sex (55.6% male); region; CCI score (mean±SD = 5.0±2.8); index MI length of stay (days, mean±SD = 4.3±4.1); NSTEMI (48.7%); index MI year (18.2% in 2011); renal failure (12.3%); septic shock (2.5%); blood transfusion (0.2%); ventilator (0.2%); cardiogenic shock (2.1%); intra-aortic balloon pump (1.4%); COPD (30.9%); glucocorticoid therapy (43.0%); hypertension (73.2%); diabetes (34.6%); and carotid artery disease (7.3%) (Table 4.1.2).

4.1.4.2 Short-Term Outcomes

Those exposed to AZM experienced a higher probability of all-cause readmission (10.0% in AZM vs. 7.6% in control), MI-related readmission (4.3% in AZM vs. 2.6% in control), and MI-sequelae-related readmission (6.8% in AZM vs. 4.9% in control). After adjustment, the odds of each outcome were significantly higher in the AZM group vs. control (OR [95% CI] for all-cause readmission: 1.34 [1.17, 1.55], P<0.001; MI-related readmission: 1.68 [1.35, 2.08], P<0.001; and MI-sequelae-related readmission: 1.42 [1.20, 1.69], P<0.001 (Table 4.1.3).

Among the HF-free cohort, patients exposed to AZM had a higher proportion of 30-day incident HF (11.9% in AZM vs. 7.5% in control), and the odds of 30-day incident HF were significantly higher in the AZM group vs. control (OR [95% CI]: 1.64 [1.36, 1.97], P<0.001) (Table 4.1.3).

4.1.5 Discussion

This study shows that patients exposed to AZM within a 10-day window of an MI have an increased odds of 30-day incident HF and hospital utilization compared to those unexposed to AZM in that window. This is the first study to our knowledge to examine outcomes following the receipt of AZM around the time of an MI using a large claims database. This filled a unique gap because the existing literature demonstrated some inconsistency regarding the exposure-outcome relationship of AZM and cardiac outcomes[15,94–96], and no studies examined AZM exposure around the time of an MI and its association with short-term outcomes. An FDA warning was released in 2012 that AZM can cause potentially fatal irregular heart rhythm, especially in patients with known cardiac risk factors[16]; however AZM prescribing practices in said at-risk patients remained unchanged[101]. This was hypothesized to be due to inconsistent findings in the literature, indicating the need to continue to evaluate the potential association[101].

Studies by Svanstrom et. al.(2012) and Patel et. al.(2020) contradicted the FDA warning, showing no increased risk of cardiac events associated with AZM. These and others created ambiguity on the safety of AZM and cardiac outcomes[15,94–96]. The Svanstrom et. al. study examined a Danish population of young (<65 years old) and healthy (no hospitalizations in the past month) adults. On top of the generalizability issues with a Danish cohort, this study does not examine a cardiac-impaired or at-risk population.

The Patel et. al. study uses the same data source as the present study (Merative™ MarketScan® databases); however, the population is defined by AZM or amoxicillin prescriptions. Because of the broadness of these therapies to treat acute respiratory infections, which are common among otherwise healthy individuals, the Patel et. al. study

captured many healthy patients. The study did include analyses of some higher-risk subgroups, finding that among patients with history of syncope/cardiac dysrhythmias/nonspecific chest pain or with baseline cardiovascular disease, those exposed to AZM did not have significantly higher odds of short-term cardiac events compared to amoxicillin[15]. This finding provides important context to better interpret the results of the work presented. What distinguishes the present study from Patel et. al. is the timing of AZM receipt within a 10-day window of experiencing an MI. The findings of the present study showed increased odds of hospital utilization and incident heart failure 30 days post index in AZM compared to control, contrasting the Patel et. al. findings. Being that a difference between these two studies was the timing requirement of AZM receipt around an MI event, we hypothesize the timing of AZM receipt around the time of an MI could be the attributable cause. Because this is the first study to examine the outcomes associated with AZM receipt around the time of an MI, more research is needed to examine this hypothesis. In particular, there was no adjustment or consideration for the dose of AZM. Examining the dose-response of AZM on the outcomes is important to elucidate its true influence and is a future direction of this work. Lastly, this study could be reproduced in another data source to confirm the findings are generalizable in other populations outside of commercially insured U.S. patients.

There are some limitations of this study. First, this study uses Merative™ MarketScan® claims databases, which is primarily used for billing and not research purposes. Due to the nature of this data source, we do not have information on the reason for death, and for that reason the study findings should be interpreted in the context of the outcomes described and not death. Additionally, the severity of the MI is not directly

available; however we aimed to adjust for this by matching on the variables examined during the index MI event (length of stay, NSTEMI vs. STEMI, index year, renal failure, septic shock, blood transfusion, ventilator, cardiogenic shock, intra aortic balloon pump) as a proxy for MI severity. Merative™ MarketScan® claims databases does not contain patient race/ethnicity information, which could be a confounder that we were not able to adjust for. Additionally, AZM exposure was identified using NDC and HCPCS codes, and any other receipt of AZM was not accounted for, as it is not available in claims data. This study spans the transition from ICD-9-CM to ICD-10-CM, which were both used in this study. However, it should be noted that Panozzo et. al. found that the incidence and prevalence of MI was similar across the two coding eras.[111]

4.1.6 Conclusion

In this cohort study, we found increased odds of incident HF and hospital utilization among patients exposed to AZM in a 10-day window of an MI. When needed, alternative antibiotics to AZM should be considered for patients with a history of or at risk for MI. More research is warranted to examine the outcomes associated with AZM exposure around the time of an MI.

4.1.7 Tables and Figures

Table 4.1.1 Baseline characteristics of full cohort with 30 days continuous enrollment post MI

	Overall (N=16,266)	**AZM (N=2,718)**	**Control (N=13,548)**
Age (mean±SD)	66.7±14.3	67.0±14.8	66.7±14.2

Male	8905 (54.7%)	1480 (54.5%)	7425 (54.8%)
Region	(0.0%)	(0.0%)	(0.0%)
Northeast	3153 (19.4%)	529 (19.5%)	2624 (19.4%)
North Central	5421 (33.3%)	910 (33.5%)	4511 (33.3%)
South	5498 (33.8%)	911 (33.5%)	4587 (33.9%)
West	2055 (12.6%)	345 (12.7%)	1710 (12.6%)
Unknown	139 (0.9%)	23 (0.8%)	116 (0.9%)
Baseline Comorbidities			
CCI (mean±SD)	6.1±3.1	6.2±3.0	6.1±3.1
Cancer	4597 (28.3%)	814 (29.9%)	3783 (27.9%)
Chronic Kidney Disease	2905 (17.9%)	481 (17.7%)	2424 (17.9%)
Diabetes	6521 (40.1%)	1093 (40.2%)	5428 (40.1%)
End Stage Renal Disease	660 (4.1%)	93 (3.4%)	567 (4.2%)
Heart Failure	7719 (47.5%)	1307 (48.1%)	6412 (47.3%)
Hypertension	12754 (78.4%)	2122 (78.1%)	10632 (78.5%)
Hyperlipidemia	1769 (10.9%)	272 (10.0%)	1497 (11.0%)
Stroke	3478 (21.4%)	522 (19.2%)	2956 (21.8%)

Peripheral Artery Disease	1907 (11.7%)	276 (10.2%)	1631 (12.0%)
Glucocorticoid Therapy	6784 (41.7%)	1153 (42.4%)	5631 (41.6%)
IBD	248 (1.5%)	39 (1.4%)	209 (1.5%)
Neuromuscular Disease	4 (0.0%)	3 (0.1%)	1 (0.0%)
COPD	5883 (36.2%)	1010 (37.2%)	4873 (36.0%)
Cartoid Artery Disease	1668 (10.3%)	270 (9.9%)	1398 (10.3%)
Index Event Variables			
Index MI Year			
2010	2235 (13.7%)	375 (13.8%)	1860 (13.7%)
2011	2995 (18.4%)	500 (18.4%)	2495 (18.4%)
2012	2613 (16.1%)	437 (16.1%)	2176 (16.1%)
2013	2174 (13.4%)	362 (13.3%)	1812 (13.4%)
2014	2079 (12.8%)	344 (12.7%)	1735 (12.8%)
2015	1576 (9.7%)	265 (9.7%)	1311 (9.7%)
2016	1337 (8.2%)	223 (8.2%)	1114 (8.2%)
2017	1257 (7.7%)	212 (7.8%)	1045 (7.7%)
Index event length of stay (mean±SD)	5.5±5.0	5.6±4.8	5.4±5.0

NSTEMI	8295 (51.0%)	1388 (51.1%)	6907 (51.0%)
Renal failure	3320 (20.4%)	553 (20.3%)	2767 (20.4%)
Septic Shock	487 (3.0%)	91 (3.3%)	396 (2.9%)
Cardiogenic Shock	681 (4.2%)	565 (20.8%)	116 (0.9%)
Intra Aortic Balloon Pump	319 (2.0%)	52 (1.9%)	267 (2.0%)
Blood Transfusion	27 (0.2%)	6 (0.2%)	21 (0.2%)
Ventilator	102 (0.6%)	21 (0.8%)	81 (0.6%)
Pneumonia at Index	2806 (17.3%)	910 (33.5%)	1896 (14.0%)

Table 4.1.2 Baseline characteristics of heart failure-free cohort with 30 days continuous enrollment post MI

	Overall (N=8,512)	**AZM (N=1,411)**	**Control (N=7,101)**
Age (mean±SD)	63.2±13.9	63.2±14.5	63.2±13.7
Male	4733 (55.6%)	784 (55.6%)	3949 (55.6%)
Region			
Northeast	1617 (19.0%)	274 (19.4%)	1343 (18.9%)
North Central	2762 (32.4%)	460 (32.6%)	2302 (32.4%)
South	3100 (36.4%)	508 (36.0%)	2592 (36.5%)
West	976 (11.5%)	159 (11.3%)	817 (11.5%)
Unknown	57 (0.7%)	10 (0.7%)	47 (0.7%)
Baseline Comorbidities			
CCI (mean±SD)	5.0±2.8	5.1±2.7	5.0±2.9
Cancer	2364 (27.8%)	426 (30.2%)	1938 (27.3%)
Chronic Kidney Disease	854 (10.0%)	144 (10.2%)	710 (10.0%)
Diabetes	2945 (34.6%)	486 (34.4%)	2459 (34.6%)
End Stage Renal Disease	162 (1.9%)	21 (1.5%)	141 (2.0%)
Hypertension	6235 (73.2%)	1021 (72.4%)	5214 (73.4%)

Hyperlipidemia	1132 (13.3%)	164 (11.6%)	968 (13.6%)
Stroke	1345 (15.8%)	195 (13.8%)	1150 (16.2%)
Peripheral Artery Disease	634 (7.4%)	93 (6.6%)	541 (7.6%)
Glucocorticoid Therapy	3658 (43.0%)	619 (43.9%)	3039 (42.8%)
IBD	145 (1.7%)	22 (1.6%)	123 (1.7%)
Neuromuscular Disease	1 (0.0%)	1 (0.1%)	0 (0.0%)
COPD	2632 (30.9%)	434 (30.8%)	2198 (31.0%)
Cartoid Artery Disease	618 (7.3%)	95 (6.7%)	523 (7.4%)
Index Event Variables			
Index MI Year			
2010	1245 (14.6%)	207 (14.7%)	1038 (14.6%)
2011	1548 (18.2%)	254 (18.0%)	1294 (18.2%)
2012	1313 (15.4%)	220 (15.6%)	1093 (15.4%)
2013	1010 (11.9%)	165 (11.7%)	845 (11.9%)
2014	1001 (11.8%)	170 (12.0%)	831 (11.7%)
2015	723 (8.5%)	123 (8.7%)	600 (8.4%)
2016	852 (10.0%)	138 (9.8%)	714 (10.1%)

2017	820 (9.6%)	134 (9.5%)	686 (9.7%)
Index event length of stay (mean±SD)	4.3±4.1	4.4±4.1	4.3±4.1
Renal failure	1051 (12.3%)	179 (12.7%)	872 (12.3%)
Septic Shock	215 (2.5%)	41 (2.9%)	174 (2.5%)
Cardiogenic Shock	176 (2.1%)	32 (2.3%)	144 (2.0%)
Intra Aortic Balloon Pump	115 (1.4%)	22 (1.6%)	93 (1.3%)
Blood Transfusion	15 (0.2%)	3 (0.2%)	12 (0.2%)
Ventilator	20 (0.2%)	5 (0.4%)	15 (0.2%)
NSTEMI	4145 (48.7%)	692 (49.0%)	3453 (48.6%)
Pneumonia at Index	1005 (11.8%)	358 (25.4%)	647 (9.1%)

Table 4.1.3 Results from logistic regression models for 30-day outcomes

	All-cause Readmission (N=16,376)		**MI-Related Readmission (N=16,376)**		**MI-Sequelae-Related Readmission (N=16,376)**		**Incident HF (N=8,512)**	
	OR (95% CI)	**P-value**	**OR (95% CI)**	**P-value**	**OR (95% CI)**	**P-value**	**OR (95% CI)**	**P-value**
AZM vs. Control	1.34 (1.17, 1.55)	<0.001	1.68 (1.35, 2.08)	<0.001	1.42 (1.20, 1.69)	<0.001	1.64 (1.36, 1.97)	<0.001

No covariates were included in any of the models.

CHAPTER 5. IMPLICATIONS AND RECOMMENDATIONS

5.1 Introduction

The U.S. Centers for Disease Control and Prevention (CDC) defines appropriate antibiotic use as the "the right antibiotic, at the right dose, for the right duration, at the right time, and reduce unnecessary antibiotic use"[5]. To achieve this flawlessly in practice is a utopian, and perhaps unattainable, expectation. Nonetheless, the effort to critically examine current practices of antibiotic use and move towards a greater extent of appropriate antibiotic use is critical for preserving the use of antibiotics for the future and protecting patient safety in the present. The aspects of CDC's appropriate antibiotic use definition covered in this dissertation are antibiotic duration and reducing unnecessary antibiotic use in the procalcitonin (PCT) research, and the right antibiotic at the right time in the azithromycin (AZM) research. Furthermore, there is a need to examine the right dose of AZM. The projects described have filled distinct gaps in the literature in regard to appropriate antibiotic use. This chapter expands on the implications to appropriate antibiotic use, future directions, and recommendations for the work described in this dissertation.

5.2 Procalcitonin Implications

Chapter 2 addresses two aspects of the CDC definition of appropriate antibiotic use: antibiotic duration and reducing antibiotic use. The gap in the literature discussed in Chapter 2.1.7 was observation of PCT and antibiotic use among LRTI patients under ordinary conditions in a hospital where PCT testing is available in-house. This gap was addressed by the novel case study of adopting PRO-GAP at UKHC. The overarching goal of PRO-GAP was to improve the meaningful interpretation of PCT for antibiotic decision-

making at our institution by implementing an algorithmically driven protocol designed for guidance of rapid real-time decision-making. In order to examine whether the PRO-GAP protocol was successful in achieving this goal, we designed studies examining antibiotic duration among LRTI patients at UKHC, patients that would be impacted by the PRO-GAP protocol, during 2019 and 2020 (prior to PRO-GAP) and 2021 (after PRO-GAP). Two studies were executed: the first examining data from 2019 and 2020; and the second combining the 2019 and 2020 data into one group and comparing it to 2021. The findings of these studies revealed that there was no association of PCT ordering and antibiotic duration prior to PRO-GAP; and after PRO-GAP there was a significant association of >1 PCT with reduced antibiotic duration, supporting our hypothesis that the adoption of PRO-GAP would contribute to meaningful interpretation of PCT for antibiotic-decision making. Given the limitations of pre-post study designs, the difference in antibiotic duration may not be fully attributable to PRO-GAP. The findings are, however, supportive of PCT initiatives in hospitals to adopt protocols or guidelines suggesting the use of PCT for antibiotic decision-making.

5.2.1 Future Directions

There is a need for additional research beyond the scope of the two studies examining PCT and antibiotic duration in Chapter 2. Although it was valuable to examine whether PCT and antibiotic use was changed after adopting a hospital protocol as a case study, the sample size was small (N=751). A study using a larger, more representative electronic health records data source (i.e., Merative Marketscan EMR, Optum EHR data) examining differences in antibiotic duration between those with 0, 1, or >1 PCT among similar cohort of patients (adult LRTI patients hospitalized with ≥1 antibiotic prescription) would likely

produce a larger sample size. This proposed study would reveal whether PCT ordering is broadly associated with reduced antibiotic duration across multiple institutions. Also, this would enable a contrast for the work done at UKHC, shedding light on how the institution compares to others.

Additionally, it should be noted that the PCT work described in this dissertation does not consider the lab value of PCT. The association of PCT and antibiotic use is estimated by exploring an association of the number of PCT orders (0, 1, or >1) and days of antibiotic duration (with offset for length of stay). To more specifically explore whether providers utilize PCT to guide antibiotic decision-making, the association of the PCT lab value and its corresponding antibiotic prescription (or lack thereof) must be examined. A study examining PCT lab values and the resulting antibiotic decision among a similar cohort of patients (adult LRTI patients hospitalized with ≥1 antibiotic prescription) could be done using UKHC electronic health records. This proposed study would further elucidate PCT and antibiotic use at UKHC, and expand upon our knowledge of provider decision-making in this area.

Lastly, as discussed in Chapter 2.1.6, there remains a controversy amongst clinicians on the utility of PCT for this purpose. One of the reasons for the controversy is the results of the PCT Antibiotic Consensus Trial (ProACT) showed that PCT-guided antibiotic prescribing did not result in less antibiotic exposure than usual care. However, this trial was conducted in 14 hospitals with high adherence to quality measures for the treatment of pneumonia, and the authors hypothesize there were few opportunities for PCT guidance to change antibiotic decisions antibiotics were already being used judiciously at these hospitals[40]. Among the 14 hospitals included all but one were located in urban areas,

and none were located in Kentucky. If the trial were run in hospitals with a larger need for improvement of appropriate antibiotic use, there may have been a greater chance for PCT to move the needle on antibiotic use. For these reasons, the ProACT trial results may not be generalizable to all hospital systems, particularly in areas more vulnerable to inappropriate antibiotic use, i.e. states with higher antibiotic prescribing rates than the national average. There were no studies done on a single hospital in Kentucky examining the use of PCT and antibiotic prescribing before and after the institutional adoption of PCT guidance.

The two studies described in this chapter contribute to the body of literature demonstrating the and utility of PCT-guided antibiotic prescribing. However, provider attitudes towards PCT for antibiotic decision-making were not examined in the work described here. This is very important to consider, which could be quantified and examined via institutional surveys.

5.2.2 Procalcitonin Recommendations

The findings of the work in Chapter 2 are supportive of PCT-guided antibiotic prescribing protocol adoption; particularly in institutions where the PCT testing is available with the absence of a formal protocol recommending it for antibiotic decision-making. The work done at UKHC demonstrates that a PCT protocol may contribute to improved antibiotic duration and reducing antibiotic use at one institution. The PRO-GAP protocol adopted at UKHC can be found in Appendix 2.3.

5.3 Azithromycin Implications

The work described in Chapters 3 and 4 are the first studies to examine outcomes following the receipt of AZM around the time of a myocardial infarction using a large claims database. This filled a unique gap because the existing literature demonstrated some inconsistency regarding the exposure-outcome relationship of AZM and cardiac outcomes, particularly in patient populations with differing severity[15,94–96]. An FDA warning was released in 2012 that AZM can cause potentially fatal irregular heart rhythm, especially in patients with known cardiac risk factors[16]; however AZM prescribing practices in said at-risk patients remained unchanged[101]. This was hypothesized to be due to inconsistent findings in the literature, indicating the need to continue to evaluate the potential association[101]. Furthermore, there were no studies that explored the timing of AZM receipt around a major cardiac event.

The studies by Svanstrom et. al.(2012) and Patel et. al.(2020) contradict the FDA warning, showing no increased risk of cardiac events associated with AZM. These and others created ambiguity on the safety of AZM and cardiac outcomes[15,94–96]. The Svanstrom et. al. paper examined a Danish population of young (<65 years old) and healthy (no hospitalizations in the past month) adults. On top of the generalizability issues with a Danish cohort, this study does not examine a cardiac-impaired or at-risk population.

The Patel et. al. paper uses the same data source as the present work (Merative™ MarketScan®); however, the population includes patients dispensed AZM or amoxicillin prescriptions. As mentioned in Chapter 3.1.1, Zithromax® (branded AZM) has been one of the best-selling antibiotic products worldwide, and more than 40 million patients are prescribed AZM annually[14,70]. Because of the broadness of AZM prescribing to treat acute

respiratory infections, which are common among otherwise healthy individuals, the Patel et. al. study captured many healthy patients. The study did include analyses of some higher-risk subgroups (age ≥65; history of syncope/cardiac dysrhythmias/nonspecific chest pain, concurrent use of QT-prolonging medicines, cardiovascular disease), however the only group with significantly higher odds of short-term cardiac events was the subgroup with concurrent use of QT-prolonging medicines. Among subgroups with history of syncope/cardiac dysrhythmias/nonspecific chest pain or with baseline cardiovascular disease, those exposed to AZM did not have significantly higher odds of short-term cardiac events compared to amoxicillin. This finding is very important context when interpreting the results of the work presented. What distinguishes the studies described in Chapters 3 and 4 from the existing literature is the timing of AZM receipt within a 10-day window of experiencing an MI. The findings of the short-term outcomes presented in Chapter 4 showed increased odds of hospitalizations and incident heart failure 30 days post index in AZM compared to control, opposing the findings from the Patel et. al. paper. Being that the key difference between these two studies was the timing requirement of AZM receipt around and MI event, we hypothesize the timing of AZM receipt around the time of an MI is the attributable cause. Because these are the first studies to examine the outcomes associated with AZM receipt around the time of an MI, more research is needed to confirm the validity of this hypothesis.

The work described in Chapters 3 and 4 address aspects of the CDC definition of antibiotic use including the right antibiotic at the right time. The contrasting evidence in the literature regarding AZM and cardiac outcomes has called into question whether AZM is the “right” antibiotic for cardiac-impaired or at-risk patients. The window of exposure

being a 10-day period surrounding an MI event addresses whether the timing of AZM around an MI has an impact on cardiac outcomes. These studies are the first to examine outcomes associated with AZM exposure near the time of an MI event. More research is warranted to further examine the timing of AZM exposure and MI.

5.3.1 Future Directions

These findings certainly present opportunities for additional research. Firstly, although it was novel to examine patients unexposed to AZM in the 10-day window as controls, in order to provide a better comparison to the findings of Patel et. al., the studies could be reproduced with patients exposed to other antibiotics (i.e., amoxicillin) in the same time range (10-day window around MI) as an active comparator group. Secondly, since the hypothesized reason for the effect is the timing of AZM around the MI, sensitivity analyses examining AZM exposure timing (1-day gap before/after MI, 5 -day gap before/after MI, etc.) are necessary. Next, there was no adjustment or consideration for the dose of AZM. According to the CDC definition of appropriate antibiotic use, the right dose must be considered, and is a future direction of this work. Examining the dose-response of AZM on the outcomes is important to elucidate the true influence. Lastly, this study could be reproduced in another data source to confirm the findings are generalizable in other populations outside of commercially insured U.S. patients.

5.3.2 Azithromycin Recommendations

These are the first studies examining the impact of AZM exposure around the time of a major cardiac event compared to unexposed controls on both short- and long-term outcomes. This work contributes to the body of evidence supporting that AZM may be

harmful in patients with known cardiac risk factors, and in AZM should be avoided around the time of an MI. However, more research is needed to elucidate the dose-response of AZM around an MI and cardiac outcomes, and the specific timing of AZM with the MI that causes the most harm.

5.4 Conclusion

This dissertation examined appropriate antibiotic use in two distinct disease states and for distinct rationales. More specifically, this dissertation explored a biomarker initiative to improve antibiotic use, and the consequences of the timing of an antibiotic exposure with another major medical event. What is consistent across these projects is leveraging real world data to answer questions about appropriate antibiotic use with the goal of informing clinical practice.

Chapter 2 discusses PCT and how it was used to guide antibiotic use with the goal of improving antibiotic use; addressing reducing unnecessary antibiotic use and the right duration from the CDC definition of appropriate antibiotic use. Chapters 3 and 4 present AZM exposure around the time of an MI and its association with long- and short-term outcomes, which addresses the right antibiotic and the right time from the CDC definition of appropriate antibiotic use. Across these two projects, the only aspect of the CDC definition of appropriate antibiotic use that was not addressed in this dissertation is the right dose. This is, however, a future direction of Chapters 3 and 4, where the dose-response of AZM and cardiac outcomes will be examined in future work. Appropriate antibiotic use is a complex topic in healthcare, but an increasingly important one as antibiotic resistance is spreading its threat to healthcare is growing. Leveraging real world data is an

increasingly essential means to answer questions about appropriate antibiotic use, and thereby preserving the use of antibiotics for the future and protecting patient safety in the present.

APPENDICES

APPENDIX 2.1. ICD-10 codes for lower respiratory tract infection (LRTI) and exclusion criteria

LRTI	ICD-10 Code(s)
Pneumonia	J13.X, J15.X, J18.X
COPD with acute bronchitis	J44.0
COPD with acute exacerbation	J44.1
Exclusion criteria	
Asthma	J45.909
Emphysema	J43.9
Bacterial infection	A15.X, A31.X, A49.X, B90.X, B95.X, B96.X, B99.X
Neutropenia	D70.X
Active Immunosuppression	D84.9

APPENDIX 2.2 Baseline characteristics of LRTI patients stratified by year.

	Mar-Sept 2019 (N=275)	Mar-Sept 2020 (N=154)	Unadjusted P-value

Age, years	62.4 (13.3)	59.5 (14.1)	0.03
Sex			0.93
Female	131 (47.6)	74 (48.1)	
Male	144 (52.4)	80 (52.0)	
Race			0.80
White	235 (85.5)	134 (87.0)	
Black/African American	39 (14.2)	19 (12.3)	
Asian	1(0.4)	1(0.7)	
Qualifying diagnosis			0.97
COPD with complication	112 (40.7)	63 (40.9)	
Pneumonia	163 (59.27)	91 (59.1)	
Length of stay, days*	4.0 [2.0, 6.0]	5.0 [3.0, 6.0]	0.18
Number of PCT orders			
0	200 (72.7)	103 (66.9)	0.06
1	67 (24.4)	39 (25.3)	
>1	8 (2.9)	12 (7.8)	

Days of antibiotic therapy*	4.0 [3.0, 6.0]	4.0 [3.0, 6.0]	0.34

Characteristics are summarized as mean (SD) for continuous variables and n (%) for categorical variables unless otherwise noted. P-values represent t-tests for continuous variables and chi-squared tests for categorical variables unless otherwise noted.
**Summarized as median [Q1, Q3]; differences analyzed using a Kruskal-Wallis test.*

APPENDIX 2.3 Procalcitonin-guided antibiotic prescribing protocol (PRO-GAP)

Background

Each year in the U.S., at least 2.8 million people are infected with antibiotic-resistant bacteria, and more than 35,000 people die as a result[3]. Antibiotics are needed to treat life-threatening conditions caused by bacteria, however any time antibiotics are used they can contribute to antibiotic resistance[3]. The most important preventable risk factor for antibiotic resistance is inappropriate and unnecessary antibiotic use[3]. For that reason, antibiotic stewardship, the effort to measure and improve how antibiotics are prescribed, is critically important.

Lower respiratory tract infections (LRTI) and sepsis often have bacterial causes, but viruses and non-infectious diseases can cause similar symptoms. Patients suspected for LRTI and sepsis often have an unclear clinical picture and are thus prescribed fixed antibiotic regimens. This may result in unnecessarily long treatment durations or unnecessary antibiotics altogether.

Procalcitonin (PCT) is a precursor hormone of calcitonin, that is not detectable in healthy individuals[31]. However, the production of PCT is upregulated in response to some bacterial infections and can decrease rapidly during recovery[31]. Thus, PCT provides important additional information, which can supplement clinical and diagnostic parameters. PCT has good discriminatory properties for the differentiation between bacterial and viral infections with rapidly available results[41]. PCT *per se* cannot isolate or detect specific pathogens, but the level of PCT may be useful to estimate the probability of a severe bacterial infection. However, the PCT levels should always be interpreted in a

context with clinical presentation, medical history, physical examination and if available microbiological assessment of the patients.

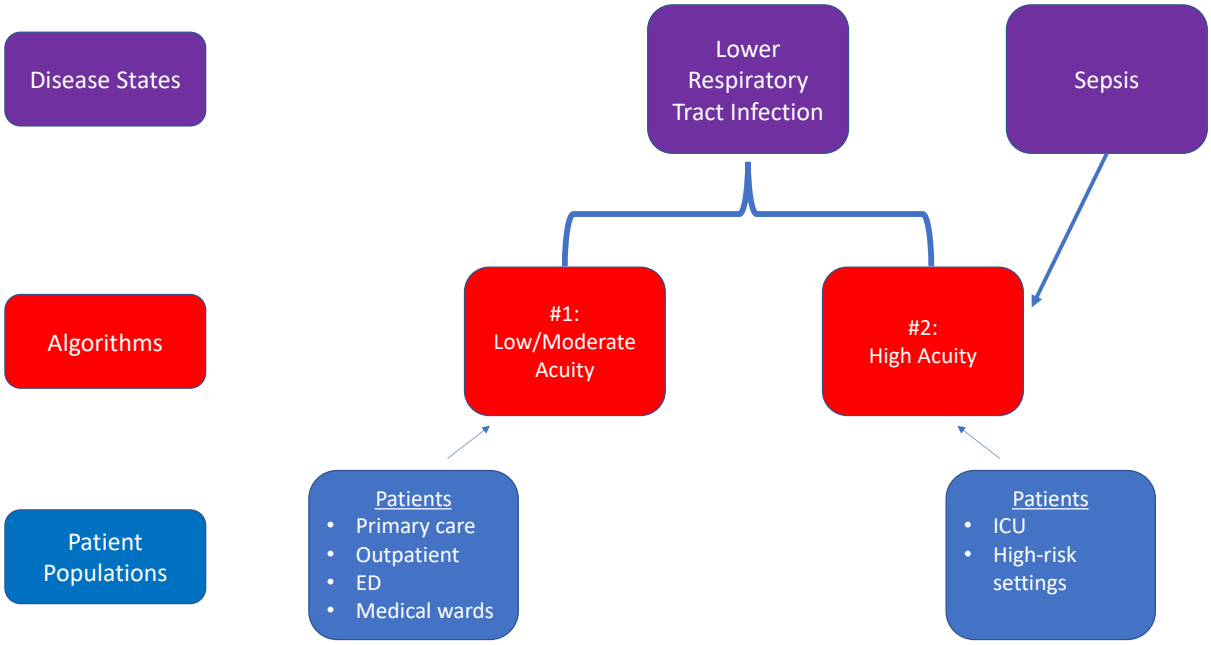
In recent years, there has been great interest in biomarkers that are able to indicate the risk for bacterial infection in a short time after admission and thus, can help to reduce antibiotic overuse and potentially diminish antibiotic associated side effects, mortality and treatment failure. The use of PCT for this propose was approved by the US Food and Drug Administration (FDA)[30]. This decision was based on several randomized controlled trials which have analyzed infections of different severity in various clinical settings ranging from primary care to ICU and have investigated and demonstrated the efficacy and safety of PCT-guided decision-making with regard to antibiotics. Several academic hospitals across the U.S. have adopted protocols for procalcitonin-guided antibiotic prescribing including (but not limited to): University of Nebraska, University of Michigan, University of California- LA, University of California-SF, and University of Wisconsin.

The proposed protocol for PCT-guided antibiotic prescribing for LRTI and sepsis patients was created with the specific characteristics and needs of the patient population at UKHC.

Algorithm Summary and Definitions

The protocol proposed consists of two algorithms for decision-making. The algorithms were split up by patient acuity (low and moderate, high). As seen in Figure 1, LRTI is split into low/moderate acuity and high acuity, and sepsis falls into the high acuity algorithm.

Figure 1. Algorithm Summary



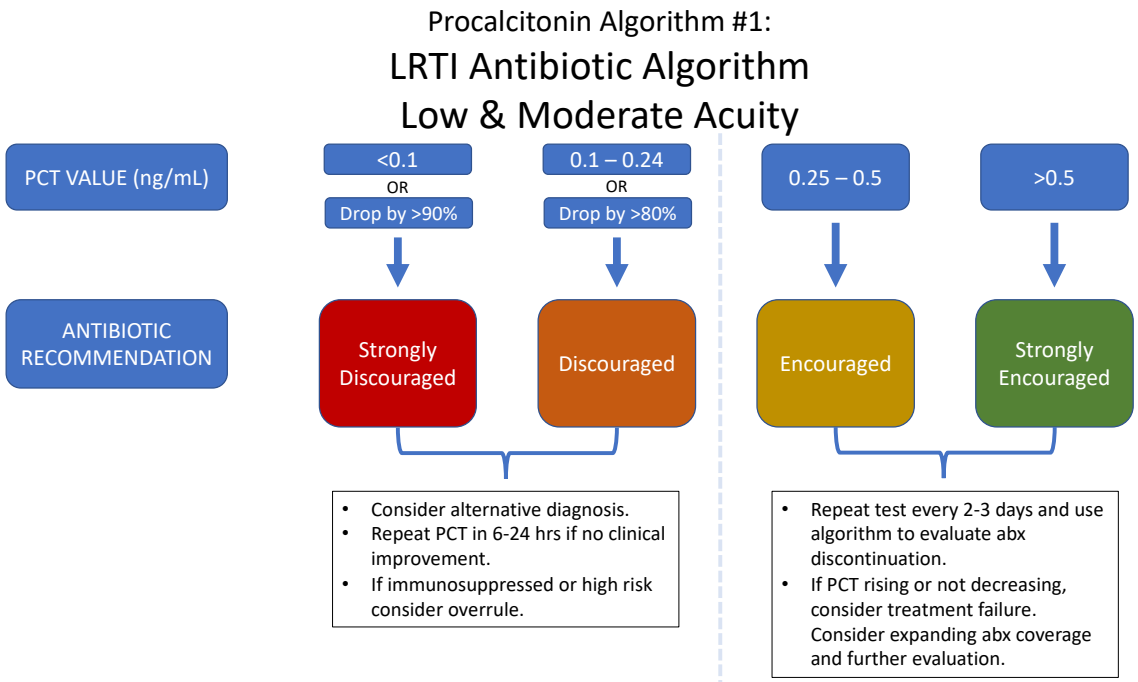
There are several important definitions for the algorithms in this protocol. Firstly, we have definitions for the two disease states. We define LRTI as any of the following disease states: pneumonia, bronchitis, bronchiolitis, unspecified acute LRTI, COPD with exacerbation or acute LRTI, bronchiectasis with exacerbation or acute LRTI. Sepsis is life-threatening organ dysfunction caused by a dysregulated host response to infection, and is defined by "The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)," published in the *Journal for the American Medical Association*.

Secondly, we have definitions for the separated acuity levels based on hospital location. "Low and moderate acuity" includes patients in primary care, outpatient, emergency department, and medical wards. "High acuity" includes patients in higher risk settings including ICU.

Algorithms

Algorithm #1 (Figure 2) applies to low and moderate acuity LRTI patients. The ranges of values for PCT are each associated with an antibiotic recommendation: <0.1 ng/ml indicates antibiotics are strongly discouraged, 0.1—0.24 ng/ml indicates antibiotics are discouraged, 0.25—0.5 ng/ml indicates antibiotics are encouraged, and >0.5 indicates antibiotics are strongly encouraged. Additionally, if there is a drop of >90% since a previous PCT test antibiotics are strongly discouraged and if there is a drop by <80% antibiotics are discouraged. Below the antibiotic recommendations are additional notes for the clinician. If the PCT value indicates that antibiotics are strongly discouraged or discouraged, the clinician should consider alternative diagnosis, repeat PCT test in 6-24 hours if no clinical improvement, and consider overruling the antibiotic recommendation if the patient is immunosuppressed or otherwise high risk. If the PCT value indicates that antibiotics are strongly encouraged or encouraged, the clinician should repeat the PCT test every 2 to 3 days to guide early antibiotic discontinuation.

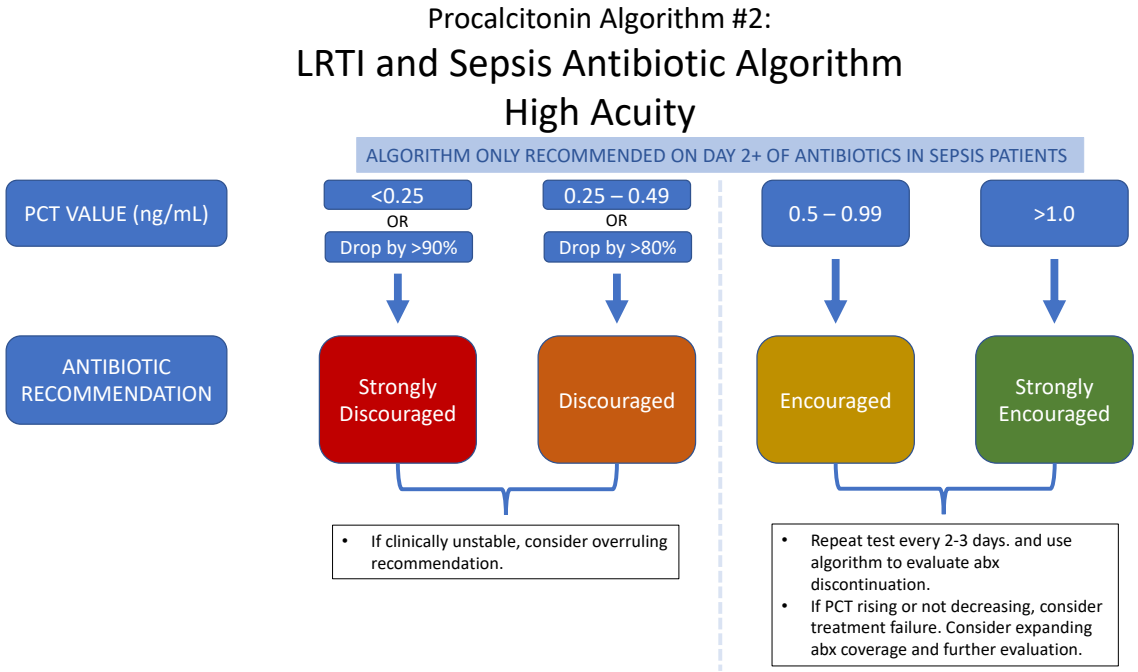
Figure 2. Antibiotic Initiation for Low/Moderate Acuity Patients with LRTI



Algorithm #2 (Figure 3) applies to high acuity LRTI and Sepsis patients. This algorithm is only recommended for sepsis patients if they have been on two or more days of antibiotics. The ranges of values for PCT are each associated with an antibiotic recommendation: <0.25 ng/ml indicates antibiotics are strongly discouraged, 0.25—0.49 ng/ml indicates antibiotics are discouraged, 0.5—0.99 ng/ml indicates antibiotics are encouraged, and >1.0 indicates antibiotics are strongly encouraged. Additionally, if there is a drop of >90% since a previous PCT test antibiotics are strongly discouraged and if there is a drop by <80% antibiotics are discouraged. Below the antibiotic recommendations are additional notes for the clinician. If the PCT value indicates that antibiotics are strongly discouraged or discouraged, the clinician should consider overruling the antibiotic recommendation if the patient is clinically unstable. If the PCT value indicates that antibiotics are strongly encouraged or encouraged, the clinician should repeat the PCT test

every 2 to 3 days to guide early antibiotic discontinuation. If the PCT level is rising or not decreasing, the clinician should consider it a treatment failure, consider expanding antibiotic coverage, and evaluate further.

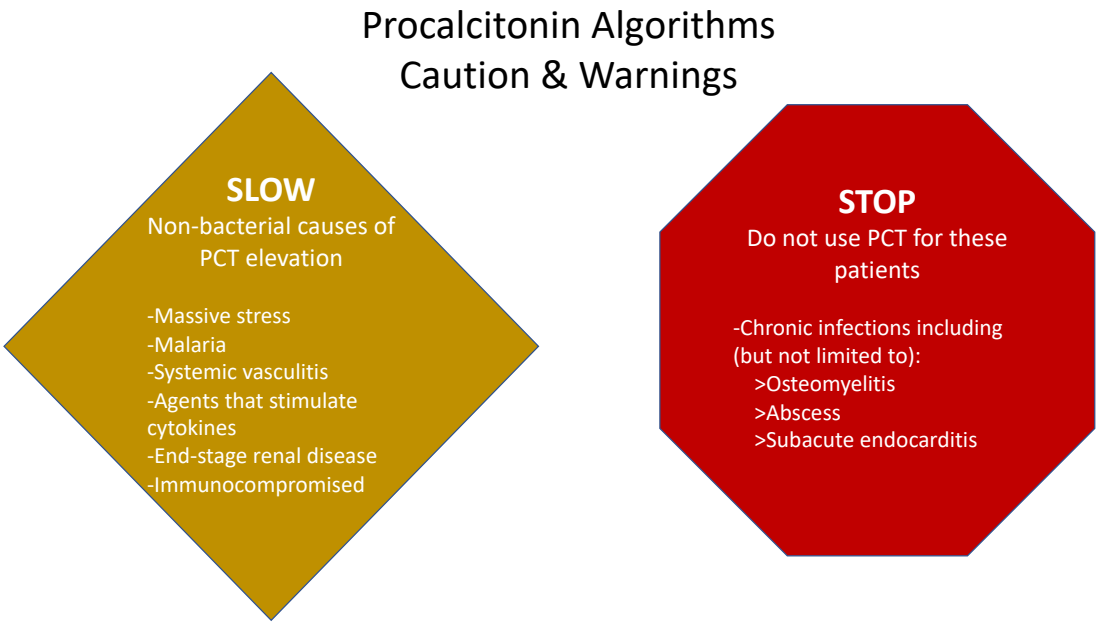
Figure 3. Antibiotic Initiation for High Acuity Patients with LRTI



Caution and Warnings

Procalcitonin is meant to be one piece of the puzzle for antibiotic decision-making. There are some cases where clinicians should proceed with caution when interpreting procalcitonin values, and other cases where procalcitonin is not appropriate to use as a guide for antibiotic prescribing. Figure 7 shows non-bacterial causes of potential procalcitonin elevation, and patients where procalcitonin should not be used to guide prescribing at all.

Figure 7. Caution and Warnings



APPENDIX 3.1 Diagnosis, Drug, and Procedure Codes used in Chapter 3 and 4

Variable	**Coding system**	**Codes**
Myocardial Infarction	ICD-9	410.x
	ICD-10	I21.xx, I22.x
AZM	NDC	00069305034', '00069305050', '00069305107', '00069305175', '00069306030', '00069306075', '00069306086', '00069307030', '00069307075', '00069307086', '00069308030', '00069311019', '00069312019', '00069313019', '00069314019', '00069315014', '00069315083', '00069406101', '00069417002', '00069417021', '00069417034', '00093202623', '00093202631', '00093202694', '00093202723', '00093714609', '00093714618', '00093714619', '00093714656', '00093714693', '00093714756', '00093714823', '00093714923', '00093714931', '00093714994', '00093716919', '00093716933', '00093716956', '00093716990', '00093716993',

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Heart Failure	ICD-9	402.0x, 402.1x, 402.9x, 404.0x, 404.1x, 404.9x, 428.x
	ICD-10	I50.9x
Myocardial Infarction-Related Hospitalization	ICD-9	410.x, 411.x, 410.9, 786.5, 414.8, 414.9
	ICD-10	I21.xx, I22.x, I20.0, I24.x, R07.9, I25.9
Myocardial Infarction -sequelae-related Hospitalization	ICD-9	402.0x, 402.1x, 402.9x, 404.0x, 404.1x, 404.9x, 428.x, 427.x, 421.x, 422.x, 43x.x, 427.5
	ICD-10	I50.9x, I49.x, I48.9x, R00.1, I40.x, I51.4, H34.1x, G45.x, I6x.x, I46.9
Cancer	ICD-9	14x.x, 15x.x, 16x.x, 17x.x, 19x.x, 20x.x, 21x.x, 23x.x
	ICD-10	D0x.x, D1x.x, D3x.x, D4x.x, Cxx.x
Chronic Kidney Disease	ICD-9	585.9, 403.0, 403.1, 403.9
	ICD-10	I12.9, N18.3, N18.9
Diabetes	ICD-9	250.x1, 250.x3, 250.x0, 250.x2
	ICD-10	E10.x, E11.x
	ICD-9	585.6

End Stage Renal Disease	ICD-10	N18.6
Hypertension	ICD-9	401.x, 402.x, 403.x, 404.x, 405.x
	ICD-10	I10.x, I11.0
Hyperlipidemia	ICD-9	272.x
	ICD-10	E78.2, E78.5
Stroke	ICD-9	430.x, 431.x, 432.x, 433.x, 434.x, 435.x, 436.x, 437.x, 438.x
	ICD-10	H34.1x, G45.x, I60.x, I61.x, I63.x, I64.x
Peripheral Artery Disease	ICD-9	443.9
	ICD-10	I73.9
IBD	ICD-9	564.1
	ICD-10	K58.x
Neuromuscular Disease	ICD-9	335.29
	ICD-10	G12.20
COPD	ICD-9	491.x, 492.x, 496.x
	ICD-10	J44.9
Cartoid Artery Disease	ICD-9	433.1x
	ICD-10	I65.2x
NSTEMI	ICD-9	410.71
	ICD-10	I21.4, I22.2
Acute renal failure	ICD 10	N17, N17.9
	ICD 9	5849

Dialysis for renal failure	ICD 10	Z99.2
	ICD 9	V45.11
Renal replacement therapy	CPT	90945, 90947, 90999
Septic shock	ICD 10	R65.21
	ICD 9	785.52
Blood transfusion	CPT	36430, 36440, 36450, 36455, 36456, 36460
Ventilation	CPT	94002
Cardiogenic shock	ICD 10	R57.0
	ICD 9	785.51
Intra aortic balloon pump	CPT	33967, 33968, 33970, 33971
Pneumonia	ICD-9	486.x
	ICD-10	J18.9x

Glucocorticoid Therapy	NDC	00603389919',	'00555030102',	'00603459321',	'00054474131',
		'11980018010',	'00054418025',	'00054472825',	'00591544205',
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APPENDIX 3.2 Results from Cox Proportional Hazards Model for Subsequent MI, sensitivity analysis excluding patients with pneumonia at index

	Subsequent MI (N=14,597)	
	HR (95% CI)	**P-value**
AZM vs. no AZM	1.46 (1.10, 1.93)	0.009
CCI score (time-varying)	1.14 (1.10, 1.18)	<0.001

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VITA

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Education

PhD, Pharmaceutical Sciences August 2019-May 2023
Concentration: Pharmaceutical Outcomes and Policy
Dissertation Title: "Striving for Appropriate Antibiotic Use: a Biomarker Initiative, and Outcomes Associated with Azithromycin Exposure"
University of Kentucky College of Pharmacy; Lexington, KY
Mentor: Chris Delcher, PhD

Master of Public Health, Health Policy and Management
May 2017
Emory University Rollins School of Public Health; Atlanta, GA

Bachelor of Science; Public Health, Spanish
May 2015
Tulane University; New Orleans, LA

Industry Experience

Health Economics and Outcomes Research Contractor September 2021-Current
AbbVie

- Part-time contract worker as an extension of the work during the Experiential Internship (see below)
- Led a real-world evidence study using Merative™ MarketScan Databases regarding treatment patterns of branded prophylactic chronic migraine treatments. Main responsibilities included: hypothesis generation, designing and drafting study protocol and clearing through AbbVie Protocol Review Committee, conducting all data analyses in SAS, writing and clearing an abstract and manuscript, summarizing and presenting findings internally.

Health Economics and Outcomes Research Experiential Internship
Summer 2021
AbbVie

- Wrote a study protocol and executed a claims analysis using Optum Clinformatics® Data Mart database to compare healthcare resource and prescription drug utilization of chronic migraine patients treated with varying preventative therapies.

Teaching Experience

Teaching Assistant: Leadership in Pharmacy
Spring 2021

University of Kentucky College of Pharmacy; Lexington, KY

Teaching Assistant: Scholarship I & II, Introduction to Research Methods Fall 2019, Fall 2020
University of Kentucky College of Pharmacy; Lexington, KY

Teaching Assistant: GI & Nutrition
Spring 2020
University of Kentucky College of Pharmacy; Lexington, KY

Awards and Honors

Lyman T. Johnson Fellowship recipient August 2019-August 2021

- Competitive $15,000 fellowship for students from diverse backgrounds

Reily Center Award for Outstanding Customer Service
2015

- Recognition for exceptional work as a membership services representative

Peer-reviewed Manuscripts

- Flannery, A.H., Venn, C.M., **Gusovsky, A.,** Henderson, S., Kiser, A.S., Prescott, H.C., Rhee, C., Delcher, C., Morris, P.E., 2022. Frequency and Types of Healthcare Encounters in the Week Preceding a Sepsis Hospitalization: A Systematic Review. Critical Care Explorations 4, e0635. https://doi.org/10.1097/CCE.0000000000000635
- Delcher, C., Wang, Y., **Gusovsky, A.,** Benitez, J. Balancing Data Provision and Data Protection: A Natural Experiment with HIV and Syphilis Surveillance Data in the United States. Sexually Transmitted Diseases. (In press).

Abstracts & Posters

- **Gusovsky, A.,** Burgess, D., Burgess, D., Slade, E., Delcher, C., Woodworth, A., Chael, J., & Osborne, T. (2021). Diagnostic Stewardship in Lower Respiratory Tract Infections Using Procalcitonin. Antimicrobial Stewardship & Healthcare Epidemiology, 1(S1), s31–s32. Society for Healthcare Epidemiology of America (SHEA), virtual conference, Spring 2020.
- Forrest JM, **Gusovsky A**, Venditto VJ, Delcher C, Feola DJ. Impact of azithromycin on 30-day readmission rates after acute myocardial infarction: A retrospective analysis of a US insurance claims database. 36th Annual Great Lakes Pharmacy Resident Conference 2022.
- **Gusovsky, A.,** Dong, Y., Zhao, C., Park, T., & Shah, D. (2023). Real-world adherence to subsequent Prophylactic Therapy Among Chronic Migraine (CM) Patients Initially Treated with a Calcitonin Gene-related Peptide Monoclonal Antibody (CGRP mAb). Association of Managed Care Pharmacy National Meeting, San Antonio, TX, March 2023.
- **Gusovsky, A.,** Dong, Y., Zhao, C., Park, T., & Shah, D. (2023). Real-world adherence to subsequent Prophylactic Therapy Among Chronic Migraine (CM) Patients Initially Treated with a Calcitonin Gene-related Peptide Monoclonal Antibody (CGRP mAb). Encore. American Academy of Neurology 75th Annual Meeting, Boston, MA, April 2023.

- Dong, Y., **Gusovsky, A.,** Park, T., Shah, D., & Zhao, C. (2023). Real-world adherence to Subsequent CGRP mAb Treatment Among Chronic Migraine (CM) Patients Initially treated with Onabotulinumtoxin A. Association of Managed Care Pharmacy National Meeting, San Antonio, TX, March 2023.
- Shah, D., Zanardo, E., Urosevic, A., MacKnight, S., **Gusovsky, A.,** Laliberte, F. (2023). A Comparison of Persistence, Adherence, and Healthcare Costs Among Patients with Chronic Migraine treated with OnabotulinumtoxinA or CGRP Monoclonal Antibodies. Association of Managed Care Pharmacy National Meeting, San Antonio, TX, March 2023.

Peer Review

Centers for Disease Control and Prevention, Preventing Chronic Disease (PCD)
November 2022

- Peer reviewer

Invited Presentations

- "AZM exposure and short- & long-term cardiac outcomes among myocardial infarction patients: a real-world analysis," University of Kentucky Pharmaceutical Outcomes and Policy Seminar, February 2023
- "Procalcitonin-Guided Antibiotic Prescribing (PRO-GAP): Retrospective Data Analysis," University of Kentucky Pharmaceutical Outcomes and Policy Seminar, March 2020
- "Procalcitonin-Guided Antibiotic Prescribing: Preliminary Research Plan," University of Kentucky Pharmaceutical Outcomes and Policy Seminar, October 2020
- "Procalcitonin-Guided Antibiotic Prescribing (PRO-GAP): Policy Case Study," Pharmaceutical Outcomes, Policy, and Public Health, University Course, University of Kentucky College of Pharmacy, September 2021
- "Strategic use of real-world evidence: snapshot of a health economics and outcomes research summer internship," University of Kentucky Pharmaceutical Outcomes and Policy Seminar, November 2021
- "Spanning the Pharm Sci Spectrum – Immunotherapy," University of Kentucky College of Pharmacy Graduate Student Retreat Research Panel, August 2022

Government Experience

U.S. Centers for Disease Control and Prevention, Health Policy Analyst
2017-2019
Antimicrobial Resistance Coordination and Strategy Unit, Policy/Communications
Northrop Grumman Corporation Contractor, Atlanta, GA

- Provided support for advanced planning and partner outreach regarding congressional relations related to antibiotic resistance.
- Reviewed current research publications regarding new antibiotic development, antibiotic stewardship, and antimicrobial resistance domestically and globally; and created a weekly newsletter shared internally at CDC.
- Evaluated success by analyzing quantitative metrics from various team efforts, creating a report, and dispersing internally at CDC.

Junior Policy Analyst
2017

The Global Bridge Group, LLC, Virtual Consulting

- Continued CDC systematic review as a consultant regarding costs of surveillance for vaccine preventable diseases.
- Data extraction, management, and analysis; prepared a manuscript to be submitted to WHO for publication.

Graduate Economics Research Assistant; Global Immunization Division
2016-2017
Centers for Disease Control and Prevention, Atlanta, GA

- Evaluated and analyzed costs of global immunization programs as a part of the Economics Unit.
- Conducted a systematic review on the costs of surveillance for vaccine preventable diseases.

Graduate Policy Research Assistant; Division of Parasitic Diseases and Malaria
2016-2017
Centers for Disease Control and Prevention, Atlanta, GA

- Wrote a policy brief on Chagas Disease by interviewing experts at CDC and researching existing literature.

Other Experience

Mectizan Donation Program Graduate Assistant
2015-2016
The Task Force for Global Health, Decatur, GA

- Researched policy history regarding the elimination of Onchocerciasis and Lymphatic Filariasis
- Managed and analyzed data from international applications for Ivermectin donated by Merck & Co.

Political Affairs Intern
Summer 2015
The Borgen Project, Virtual

- Fundraised for global hunger and poverty in developing countries
- Political advocacy for U.S. foreign affairs
- Called senators and congressmen to get support for bills for foreign aid

Undergraduate Chagas Disease Intern
2014-2015
Tulane University School of Public Health and Tropical Medicine, New Orleans, LA

- Worked under Dr. Claudia Herrera to review literature for Chagas Disease policy
- Oral and written translation from English to Spanish

Undergraduate Intern
2014-2015
Trop-G, New Orleans, LA

- Assisted with the formation of the international collaboration among Tulane University, Baylor College of Medicine, and Universidad Autónoma de Yucatán for Neglected Tropical Diseases research
- Created website content in English and Spanish

Summer Intern
Summer 2013
Instituto de Efectividad Clínica y Sanitaria, Buenos Aires, Argentina

- Researched and drafted a white paper on international funding for research on Chagas Disease
- Met with senior leadership to brainstorm and incorporate changes to the document

Skills

Research

-Secondary data analysis
-Biostatistical and epidemiological methods
-Retrospective and prospective study design
-Research proposal
-Real world data management and analysis
-Grant writing
-Hypothesis generation
-Cost studies
-Outcomes research
-Project management
-Statistical programming (SAS, R, SPSS)

Languages

-Fluent in Spanish

Software

-Microsoft Office -Adobe

Leadership & Service

COVID-19 Vaccine Registration in Hispanic Community Volunteer
April 2021
UK College of Pharmacy Graduate Program Working Group 2020-Current
UK American Association for Pharmaceutical Scientists Outcomes and Policy Rep.
2019-2020
Rollins School of Public Health Student Ambassador
2015-2016
Rollins Student Government Activities Coordinator
2015-2016
Emory Student Government Legislator
2015
Tulane Public Health Student Government Peer Advisor Chair
2013
Sigma Delta Tau Sorority Alumna

International Education Experience

Public Health Study Abroad Program
Summer 2013
Fudan University; Shanghai, China

Trainings

University of Connecticut Statistics Biopharmaceutical Summer Academy
Summer 2020

- Two-week intensive for students planning to pursue a career as a statistician in pharmaceutics and health analytics
- Sponsored by: Boehringer-Ingelheim, Vertex, Pfizer, Biogen, and Servier