REAL-WORLD UTILIZATION OF DRUG X IN THE OUTPATIENT SETTING

CAPSTONE PROJECT REPORT

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CHAPTER I

INTRODUCTION

The first reports of the use of intravenous antibiotic administration in an outpatient setting in the United States were in the 1970s. Outpatient intravenous antibiotic administration has since grown in popularity for a multitude of reasons, including cost cutting measures and shorter length of stay for healthcare systems, the increased availability of outpatient care, and increased acceptance of this form of treatment by providers, patients, and insurance companies (Bowling, Lewis, & Owens, 2013). In addition, treatment in the hospital can cause undue burden on a patient and their family. Patients treated in an outpatient setting are not faced with unfamiliar surroundings, potential isolation from family and friends, lack of privacy, and the increased risk of hospital-acquired infections (Petrak & Allison, 2016). Furthermore, the transition from being sick back to the patient's normal functioning state can be expedited and recovery can be achieved at a quicker pace (Petrak & Allison, 2016).

Treatment in an outpatient setting can occur in various facilities, such as, outpatient hospital clinics, doctors' offices, free standing infusion centers, or in the home or facility in which the patient resides. For the purpose of this study, when referencing intravenous antibiotic therapy, outpatient setting refers to treatment provided in the patient's home or in an outpatient infusion center. In addition, for the purpose of this study, there are two ways in which treatment can be administered in the home setting. A home health agency can provide a visiting nurse to go to the patient's home to administer the medication or the patient can administer the medication themselves, or with the help of a trained family member or friend. Both treatment options come with advantages and disadvantages. A visiting nurse can evaluate the patient's home to ensure that the environment is conducive to medication administration. A visiting nurse also provides

skilled medication administration and support. Using a visiting nurse can be costly to the patient, and therefore, self-administration may be a better option for some patients. Self-administration can lead to lack of compliance to medication therapies and requires extensive training to ensure the patient or caregiver administering the medication understands how to appropriately administer the medication (Bowling, Lewis, & Owens, 2014).

In addition to ensuring the patient is eligible to receive intravenous antibiotic therapy in the outpatient setting based on ability to self-administer and living in an environment that allows for safe medication administration, the patient must also have an infection that can be effectively treated in the outpatient setting. The patient also needs to be in stable enough condition that they do not require care in the hospital setting. Infections amenable to intravenous antibiotic therapy in an outpatient setting frequently include osteomyelitis, cellulitis, intra-abdominal infections, urinary tract infections, and skin and soft tissue infections (Tice, 2000; Bowling, Lewis, & Owens, 2014). These infections are frequently caused by *Pseudomonas* species, *Enterobacter* species, *Escherichia coli*, and methicillin-resistant *Staphylococcus aureus* (Shrestha & Mathur, 2016). The aforementioned infections and their causative pathogens pose major clinical problems as antibiotic resistance continues to increase (Lwin & Bannan, 2020; Roux et al., 2021).

As more and more infections continue to become multi-drug resistant, it is imperative that there be development in the field of antibiotics. Drug X is a synthetic tetracycline class antibiotic used to treat complicated intra-abdominal infections. The clinical use and efficacy of Drug X in the outpatient setting is being studied through a multi-site phase IV post-market retrospective chart analysis. The data presented is representative of data collected at Home Infusion Pharmacy X during the duration of this study. Since the beginning of this study, electronic health records from thirty-seven patients receiving treatment with intravenous Drug X

have been evaluated. Mid-line data for this study was presented at the Making a Difference in Infectious Diseases (MAD-ID) 2020 Annual Meeting and showed that clinicians are using Drug X off-label to treat multi-drug resistant infections outside of the abdomen. These data showed that Drug X has been used to treat and has resulted in clinical cure in complicated intra-abdominal infections (FDA-approved indication), skin, skin structure, and soft tissue infections, and less frequently, sepsis and infections categorized as "other" (Hwang et al., 2020). The infections were caused by several organisms including various *Enterococcus* species, methicillin-resistant *Staphylococcus aureus, Escherichia coli*, and *Acinetobacter baumannii* (Hwang et al., 2020).

CHAPTER II

BACKGROUND AND LITERATURE REVIEW

As antibiotic resistance continues to climb to dangerously high levels all over the world, more and more infections are becoming harder, and sometimes impossible, to effectively treat (World Health Organization, 2020). When compared with their drug susceptible counterparts, antibiotic resistant and more specifically, multi-drug resistant organisms, were associated with increased rates of mortality. Multi-drug resistant organisms carry an economic burden of more than 20 billion dollars a year in the United States alone (Munita & Arias, 2016). Due to the impact that antibiotic resistance and multi-drug resistance have caused, the World Health Organization established that they were among the most important public health threats in the 21st century. If antibiotic resistance and multi-drug resistance were to continue at their current rate, without any reliable interventions, it is estimated that they could be responsible for 300 million deaths and cost the global economy 100 trillion dollars by 2050 (Munita & Arias, 2016). It is important to note that research and development in the field of antimicrobials has significantly declined with regard to pharmaceutical companies because of the challenges faced when trying to identify novel or more effective compounds to treat drug resistant organisms (Munita & Arias, 2016).

There are several mechanisms by which organisms develop resistance to the effects of antibiotics. Organisms can restrict the access of the antibiotic, remove the antibiotic, change or destroy the antibiotic, bypass the effects of the antibiotic, or change the targets of the antibiotic (Centers for Disease Control and Prevention, 2020). Organisms develop resistance through these mechanisms by mutating existing genes or by acquiring new genes. Mutation of existing genes, or vertical evolution, occurs in response to the organism's attempt to neutralize antibiotics.

Ultimately, this mechanism results in organisms with resistance gene mutations, and therefore, results in antibiotic resistance. Acquiring new genes, or horizontal gene transfer, occurs when genetic elements carrying resistance genes randomly insert themselves into bacterial chromosomes, resulting in antibiotic resistance (Sartelli *et al*., 2016).

Alteration or destruction of the antibiotic compound by the resistant organism is one of the most successful means to antibiotic resistance. The alterations made to the antibiotic inhibit its ability to interact with the resistant organism. The resistant organisms produce enzymes that are capable of making chemical changes to the antibiotic through acetylation (changes to the acetyl functional group), phosphorylation (attachment of a phosphoryl group), or adenylation (attachment of adenosine monophosphate molecule to the amino acid side chain). Destruction of an antibiotic is achieved by destroying bonds within the antibiotic. For example, in beta-lactam antibiotics, the amide bond is destroyed, which effectively renders the antibiotic useless (Munita & Arias, 2016). Beta-lactam antibiotics, tetracycline antibiotics, and fluoroquinolone antibiotics are particularly susceptible to changes in their ability to permeate the membrane of the resistant organism. This type of resistance is mediated by a reduction in porins on the resistant organism's surface, thereby, inhibiting the antibiotic's ability to cross the membrane, particularly the aforementioned antibiotics that have intracellular targets (Munita & Arias, 2016). Tetracycline antibiotics and fluoroquinolone antibiotics are frequently inhibited by the resistant organism changing the target site to decrease the antibiotic's affinity or protection of the target, such that the antibiotic is completely avoided. Particularly with fluoroquinolone antibiotics, mutational resistance occurs through inhibition of DNA gyrase and topoisomerase IV. Fluoroquinolone antibiotics interact with both of these enzymes; however, both are also required for the resistant organism to survive. Due to the requirement of DNA gyrase and topoisomerase IV for the

resistant organism's survival, resistance requires a multitude of genetic mutations within the organism over time to attain effective resistance (Munita & Arias, 2016).

Antibiotic resistant Gram-negative organisms are frequently found in hospital-acquired infections, accounting for up to thirty-three percent of hospital-acquired infections overall. Most commonly, these organisms are found in complicated intra-abdominal infections and complicated urinary tract infections. These organisms are often found to be resistant to beta-lactam antibiotics—generally the first line of therapy for these types of infections—fluoroquinolone antibiotics, aminoglycoside antibiotics, and sulfamethoxazole-trimethoprim (Golan, 2015). Furthermore, both Gram-positive and Gram-negative organisms are capable of producing extended-spectrum beta-lactamases (ESBLs), a common resistance mechanism that has quickly become a global health issue. ESBL-producing organisms pose a significant risk of morbidity and mortality, along with increased costs and delayed recovery, if they are not adequately treated from the beginning (Solomkin *et al*., 2017). Inadequate empiric therapy is associated with poor patient outcomes and increases the likelihood of further resistance. Complicated intra-abdominal infections are characterized by infection of the sterile abdominal area, often caused by a multitude of organisms. Complicated intra-abdominal infections are said to be polymicrobial and often involve various enteric microorganisms such as *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Enterobacter* species, and *Bacteroides* species (Scott, 2019; Sartelli *et al*., 2016).

As previously mentioned, complicated intra-abdominal infections are frequently associated with increased morbidity and mortality, especially in high-risk patients. Effective management of complicated intra-abdominal infections requires timely empiric antibacterial

therapy with antibiotics that are broad spectrum and likely to be effective against a multitude of potential infection-causing organisms. In an effort to raise awareness regarding antibiotic resistance among intra-abdominal infection-causing organisms and to improve antibiotic prescribing habits, an organization called Antimicrobials: A Global Alliance for Optimizing their Rational Use in Intra-Abdominal Infections (AGORA) was formed (Sartelli *et al*., 2016). AGORA asserts that improvements and enhancements in infection prevention and control and prescribing the appropriate antibiotics only when truly necessary can aid in maintaining the efficacy of antibiotics. It is important to note that there is an established relationship between antibiotic prescribing practices and the rise in the presence of antibiotic resistant organisms. Antibiotic selective pressure involving bacteria within the intestinal tract is a two-step process comprised of killing susceptible bacteria of the commensal intestinal microbiota, or gut flora, and promoting the overgrowth of multi-drug resistant organisms within the intestinal microbiota. This process increases transmission between patients, and thus, increases the risk of outbreak among antibiotic resistant organisms (Sartelli *et al*., 2016).

Surveillance and epidemiological studies have been conducted to analyze trends associated with organism incidence and antibiotic resistance. The studies that focused on intra-abdominal infections identified ESBL-producing *Enterobacteriaceae* as a primary factor in the presence of antibiotic resistant organisms in intra-abdominal infections (Sartelli *et al*., 2016). This extensive evidence suggested that antibiotic resistant organisms are frequently found in complicated intra-abdominal infections. This likely spurred the research and development of novel antibiotics that are effective against antibiotic resistant organisms that cause the infections. Between 2018 and 2019, the United States Food and Drug Administration approved two new antibiotics for the treatment of complicated intra-abdominal infections. These novel therapies

included Drug X Brand Name and a combination drug called Recarbrio (Andrei, Droc, & Stefan, 2019). Drug X Brand Name, or Drug X, is a fully synthetic fluorocycline and tetracycline-class antibiotic that is effective against Gram-positive and Gram-negative organisms, particularly those with tetracycline resistance mechanisms. Recarbrio is a combination therapy that consists of imipenem (an antibacterial), cilastatin (a renal dehydropeptidase inhibitor), and relebactam (a beta-lactamase inhibitor). Whereas Drug X Brand Name is effective against both Gram-positive and Gram-negative organisms, Recarbrio is only effective against several Gram-negative organisms (Andrei, Droc, & Stefan, 2019).

Tetracycline antibiotics were first discovered in the 1940s. Tetracyclines are a class of antibiotics that prevent the attachment of aminoacyl-tRNA to the ribosomal acceptor site, thereby, inhibiting protein synthesis. Tetracyclines are broad spectrum antibiotics. This means they effective against a wide range of Gram-positive and Gram-negative organisms, along with various other organisms (Chopra & Roberts, 2001). Tetracycline antibiotics were previously broken down into three generations (Janser, 2016); however, with the discovery of Drug X, a fourth generation of tetracyclines has been introduced. Tetracyclines have bactericidal and bacteriostatic properties. Tetracyclines classified as typical are bacteriostatic and prevent protein synthesis by binding to the organism's ribosomal subunits (Tariq, Faheem Askari Rizvi, & Anwar, 2018). Other tetracyclines are classified as atypical and are bactericidal. These tetracyclines disrupt the cell membrane and inhibit cellular processes and synthesis pathways, thereby, preventing the pathogen from reproducing (Tariq, Faheem Askari Rizvi, & Anwar, 2018). In addition to having antibacterial properties, tetracyclines frequently exhibit non-antibiotic properties. They have been found to be useful in treatment of rheumatoid arthritis,

tumor invasion and metastasis, and angiogenesis due to their immunomodulatory and anti-inflammatory properties (Tariq, Faheem Askari Rizvi, & Anwar, 2018).

Drug X is a fourth-generation tetracycline, or a fully synthetic fluorocycline. The unique modifications in the tetracyclic D ring allow Drug X to be effective against organisms that express common tetracycline-specific resistance mechanisms (Scott, 2019). In addition to its effectiveness against many organisms, Drug X is well-tolerated by most patients, with the most common adverse reactions being infusion site reactions and gastrointestinal upset (nausea, vomiting, and diarrhea) (Scott, 2019). Like the other generations of tetracycline antibiotics, Drug X inhibits protein synthesis; however, it achieves this at a fourfold lower drug concentration. While other tetracyclines are either bacteriostatic or bactericidal, Drug X has both properties, making it effective against more organisms (Scott, 2019).

In addition to developing new and effective antibacterial therapies, hospital-based antibiotic stewardship programs can be helpful in mitigating development of further antibiotic resistance. Antibiotic stewardship programs are designed to optimize the treatment of infections through evidence-based strategies such as using antibiotics prophylactically only when clinically indicated and using the fewest number of antibiotics for the least amount of time that has shown to be clinically effective. A Cochran meta-analysis showed that the inclusion of these strategies and interventions in clinical practice decreased the incidence of antibiotic resistance and hospital-acquired infections because the overprescribing and overuse of antibiotics in inpatient units decreased (Sartelli *et al*., 2016).

Significance

Multi-drug resistant organisms are on the rise globally, which poses significant risks to the ability to effectively treat multi-drug resistant organisms (Van Hise *et al*., 2020). Studies suggest that multi-drug resistant organisms including methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococci*, *Enterobacteriaceae* such as *Escherichia coli* and *Klebsiella pneumoniae*, and carbapenem-resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii* found in pneumonia, urinary tract infections, intrabdominal infections, and skin infections may show susceptibility to Drug X (Van Hise *et al*., 2020). In response to these multi-drug resistant infections, some healthcare systems have developed plans to implement antimicrobial stewardship programs. These programs are implemented by using evidence-based interventions and guide principles for promoting, improving, monitoring, and evaluating the appropriate use of antibiotic therapies (Majumder *et al*., 2020). Some antimicrobial stewardship programs have focused on the use of outpatient intravenous antibiotics because it can mitigate the time spent in acute care and emergency department settings. Limiting time spent in acute care and emergency department settings can lessen, or in some cases, eliminate the risk for the spread of infections caused by multi-drug resistant organisms. Furthermore, outpatient intravenous antibiotic administration can improve patient comfort and reduce costs associated with inpatient hospital stays (Le Marechal *et al*., 2018).

Since these multi-drug resistant infections are on the rise, it is imperative that healthcare systems have access to antibiotic therapies that are effective against resistant organisms. Real-world utilization studies are required to understand how infectious disease clinicians are using existing antibiotics in practice. This opens the door to determining novel uses for existing antibiotics. These real-world utilization studies are also vital to finding out if antibiotics are

clinically effective and if they do, in fact, result in microbiological cure. In addition, real-world utilization studies are required to develop evidence-based interventions to support the use of outpatient intravenous antibiotic administration. These studies also have the ability to show whether outpatient treatment actually improves patient comfort, satisfaction, and outcomes.

CHAPTER III

PROBLEM AND HYPOTHESIS

As more and more infections continue to become multi-drug resistant, it is imperative that there be development in the field of antibiotics. Drug X is a fully synthetic fluorocycline tetracycline class antibiotic. Drug X was approved by the United States Food and Drug Administration in 2018 to be used in the treatment of complicated intra-abdominal infections. Mid-line data in this study has shown that clinicians are using Drug X off-label to treat multi-drug resistant infections that occur outside of the abdomen. These data have shown that Drug X has been used to treat and has resulted in clinical cure in complicated intra-abdominal infections (FDA-approved indication), skin, skin structure, and soft tissue infections, and less frequently, sepsis and infections categorized as "other." The infections were caused by several organisms including various *Enterococcus* species, methicillin-resistant *Staphylococcus aureus, Escherichia coli*, and *Acinetobacter baumannii.*

As previously mentioned, there is a need to develop evidence-based practices to promote antibiotic stewardship practices within the healthcare system. Real-world utilization studies, like this one, are required to guide and provide evidence for the development and implementation of antibiotic stewardship programs. It is known that outpatient intravenous antibiotic administration has the ability to promote patient comfort and satisfaction and reduce healthcare costs associated with inpatient hospital stays; however, there is little evidence to guide the implementation of outpatient intravenous antibiotic administration and healthcare systems continue to take varied approaches to implementation.

Hypothesis and Specific Aims

For the purpose of this capstone project report and thesis, I hypothesize that Drug X will be used in infections other than those classified as complicated intra-abdominal infections. In addition to being used in these infections, I hypothesize that Drug X will be clinically effective and result in microbiological cure. I also expect that this retrospective observational clinical study will help provide evidence-based guidelines for the implementation of outpatient intravenous antibiotic administration for providers and clinicians in acute care and emergency department settings. The primary study objective is to describe clinical utilization, treatment, infection type, and organism types in patients treated with Drug X in an outpatient setting. The secondary study objective is to describe clinical efficacy in patients treated with Drug X and to describe the infecting organism(s) and the microbiological outcome post-Drug X treatment.

Hypothesis: Drug X can effectively treat infections other than those classified as complicated intra-abdominal infections.

Aim 1: Evaluate the outpatient utilization of Drug X, the infection types, and the organism types that it is being used to treat.

Aim 2: Analyze the clinical efficacy of Drug X in the infections and organisms it is being used to treat.

Aim 3: Categorize adverse events, if any, associated with the use of Drug X.

CHAPTER IV

RESEARCH DESIGN AND METHODOLOGY

The Real-World Utilization of Drug X in the Outpatient Setting study is an on-going retrospective observational analysis of adult patients over 18 years of age who have been prescribed Drug X and received one or more doses of Drug X in the outpatient setting as part of outpatient intravenous antibiotic therapy. All patients prescribed Drug X were followed by an infectious disease practitioner. Once therapy concluded, all information relevant to the study of Drug X administration was collected from the electronic patient records. This study was approved by the WCG Institutional Review Board.

Patients were identified via a routine report for Drug X dispensation. The report to identify patients consisted of information regarding the patient and dispense date of Drug X. This report was generated on a biweekly basis. After the patients receiving intravenous antibiotic Drug X had been identified, electronic patient records were reviewed and relevant medical information, hospitalization history, Drug X orders and infectious disease practitioner notes were abstracted, if available. Electronic patient record review was completed by me, Sofia Alcasey, the Clinical Research Coordinator, and confirmed as necessary by my supervisor at Home Infusion Pharmacy X, Pablo Saenz, PharmD.

Baseline demographic information collected included patient age, gender, race, height, weight, basal metabolic index (BMI), presence of comorbidities (particularly, alcohol/substance addiction, asthma, autoimmune diseases, cancer, chronic obstructive pulmonary disease (COPD), diabetes, gastrointestinal disease, genitourinary disease, heart disease, chronic infectious disease, and liver disease), Charlson Comorbidity Index, liver function, and renal function.

Charlson Comorbidity Index provides an estimation of the risk of short-term mortality. The score is determined from a pre-selected number of chronic diseases. Points are obtained if the condition is present in the patient. The higher the score, the higher the risk of short-term mortality. This could be important in determining the prognosis for the patient because comorbidities are known to play an important role in patient mortality and other patient outcomes (Brusselaers & Lagergren, 2017). Liver function is determined by evaluating certain biochemical markers. Liver function can generally be determined from specific laboratory values. Once liver function is calculated, the level of liver disease can be determined (Gowda *et al*., 2009). Bacterial infections are common among patients with liver disease and these infections can have significant repercussions among these patients. Infections are frequently associated with systemic inflammation and significantly increased risk of mortality, particularly in patients with cirrhosis (Bruns, Henning, & Stallmach, 2014). Renal function, like liver function, can be determined by certain biochemical markers in routine laboratory results. Renal function tests allow healthcare professionals to ensure that renal disease, if present, is being managed appropriately (Gounden, Bhatt, & Jialal, 2021). Some studies have shown that patients with chronic kidney disease may not only be at elevated risk of contracting infections caused by multi-drug resistant organisms, but may also harbor, or serve as a reservoir, for these organisms. This is in part due to the fact that these patients have high rates of infection, frequent antibiotic use, frequent hospitalization, and therefore, have more exposure to organisms that are or may become multi-drug resistant (Su *et al*., 2018).

Patient charts were also reviewed to determine if the patient had any risk factors for multi-drug resistant organisms. These risk factors included hospitalization in the 90 days prior to the first dose of Drug X, antibiotic administration (oral or parenteral) in the 90 days prior to the

first dose of Drug X, surgery in the 30 days prior to the first dose of Drug X, prosthetic devices or hardware implants, referral from a skilled nursing facility, long-term acute care or nursing home, chronic hemodialysis, intravenous drug use, or colonization or infection with *Clostridium difficile*, methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcu*s (VRE), carbapenem-resistant *Enterobacteriaceae* (CRE), or any extended spectrum beta-lactamase (ESBL)-producing bacteria. Next, the clinical infectious diagnosis was identified. If the infection was classified as an intra-abdominal infection, the primary source of infection had to be selected from the following: abscess, appendicitis, cholecystitis, diverticulitis, peritonitis, trauma, pelvic inflammatory disease, other, or unknown. If the infection was classified as bacteremia, the primary source had to be selected from the following: catheter-associated urinary tract infection (CAUTI), central line bloodstream infection (CLABSI), endocarditis, intra-abdominal, skin and soft tissue, pneumonia, other, or unknown. Bone and joint infection, cardiac infection, diabetic foot infection, gastrointestinal infection, genitourinary infection, respiratory infection (upper respiratory infection, bronchitis, community acquired pneumonia, and hospital acquired pneumonia), sepsis, and skin and soft tissue infection were possible other clinical infectious diagnoses. If none of the aforementioned diagnoses applied, a free-text entry could be used to classify the infection. If it was available, microbiology associated with the primary clinical infectious diagnosis was collected. The cultured organism genus and species, along with the source of the culture (abscess, blood, CNS fluid, tissue, sputum, urine, other, or unknown), date of collection, the Drug X minimum inhibitory concentration (MIC), or the lowest amount of the antibiotic that will inhibit visible growth of the organism overnight, and the Drug X susceptibility or resistance of the organism.

In addition to data about the organism being treated, systemic antibiotics used for any infection in the 30 days prior to the first dose of Drug X were reported, if the pharmacy data was available in the patient's electronic medical record. If this data was available, the start and end dates, the name of the antibiotic, the stage of treatment (prophylactic, empiric, definitive, add-on combination therapy, de-escalation, switch to oral, Drug X replacement therapy, other, or unknown), the dose, frequency, and route of administration (intravenous infusion bag, intravenous elastomeric pump, oral, other, or unknown) were collected. Stage of treatment is important because it can determine if the organism is susceptible to the drug it is being treated with. Most commonly, the terms empiric and definitive are used to describe stage of treatment. Empiric therapies are therapies that are initiated in critically ill patients at the same time that cultures or specimens are collected. These therapies are generally broad-spectrum and are intended to cover many organisms that could be causing the infection. Definitive therapies are therapies used after the culture or specimen results have come back. These therapies are based on susceptibility data and are generally more narrow spectrum therapies that target the specific organism found in the culture (Leekha, Terrell, & Edson, 2011). The same information was collected for the antibiotics prescribed specifically to treat the clinical infectious diagnosis, including Drug X. The care setting that Drug X therapy had been initiated in and completed or discontinued in was also collected from the patient's electronic health record. If available, the source control measures taken prior to or at the time of initiation of Drug X therapy were collected.

Lastly, information regarding the outcomes after completion or discontinuation of Drug X therapy were collected. This information included data regarding the clinical outcome—whether Drug X resulted in clinical cure, clinical improvement, or clinical failure. Clinical cure

was defined as complete resolution of clinical signs and symptoms of infection, with no additional antibiotic therapy required at the end of Drug X therapy. Clinical improvement was defined as improved clinical signs and symptoms of infection at the end of Drug X therapy with a switch to a narrower spectrum antibiotic at the end of Drug X therapy or a switch to an oral antibiotic at the end of Drug X therapy. Clinical failure was defined as persistent or worsening signs and symptoms of infection and/or new signs and symptoms of infections, with Drug X therapy being stopped and a rescue antibiotic required, or Drug X being discontinued prematurely due to an adverse event.

Microbiological outcomes—microbiological cure or microbiological failure—were also collected. Microbiological cure was defined as complete eradication of the causative organism. Microbiological failure was defined as persistence of the causative organism, persistence with decreased susceptibility, presumed persistence, or the development of a new or super-infection. The following were considered to be adverse events if they occurred during Drug X therapy and were documented as such, if the information was available in the patient's electronic health record: 1. *Clostridium difficile* infection while receiving Drug X treatment, 2. discontinuation of Drug X due to an adverse event, 3. patient death in the 30 days following the last dose of Drug X, and 4. hospital admission or readmission attributable to the treated infection and in the 30 days following the initiation of Drug X treatment. Any other adverse events that did not fall into the aforementioned categories were also reported as necessary.

Patient electronic health records were reviewed on a weekly to biweekly basis. A report was generated for patients who received Drug X from Home Infusion Pharmacy X's home infusion pharmacy within the given timeframe. Once these patients were identified, all records including, but not limited to, chart notes, medication orders, and laboratory results, were printed

out and reviewed for necessary data. Necessary data from the patient's electronic health record was extracted and reported to the electronic case report form that was embedded into the REDCap database. REDCap is an electronic data capture software developed by Vanderbilt University for designing clinical and translational research databases.

The population of this study included all patients 18-years-old or older that had been prescribed and received at least one dose of Drug X in an outpatient setting. The inclusion criteria allowed for any adult patient treated with one or more doses of Drug X in an outpatient setting to be included; however, the population for this specific site was limited to patients that received Drug X from Home Infusion Pharmacy X's home infusion pharmacy. If insufficient electronic health records existed for the patient, they were excluded from the analysis. For example, a patient lacking chart notes or laboratory results would be excluded, as the necessary data is unavailable.

In the analysis of the collected data, descriptive statistics were used to assess the primary and secondary outcomes of this study. Categorical variables are summarized as frequencies and percentages. Continuous variables are summarized with the number of observations (number of patients included in this site's analysis), mean, standard deviation, median, minimum, and maximum. Patients receiving systemic antibiotics in the 30 days prior to initiation of Drug X therapy will be summarized overall, by antibiotic, and by stage of treatment. Summaries for demographic information (age, gender, race), baseline information (height, weight, BMI, comorbidities, Charlson comorbidity index, liver function, and renal function), patient risk factors for multi-drug resistant organisms, primary source of infection, causative organisms, Drug X susceptibility of the organisms, number of Drug X doses per day, duration of Drug X

therapy, care setting where Drug X therapy was initiated and completed, safety of Drug X, clinical outcomes, and microbiological outcomes are also presented.

CHAPTER V

RESULTS AND DISCUSSION

In this retrospective observational study, data from a total of thirty-seven patients receiving outpatient intravenous antibiotic treatment with Drug X from Home Infusion Pharmacy X's home infusion pharmacy were used to understand the real-world clinical utilization of Drug X. Drug X was approved by the United States Food and Drug Administration in 2018 and is marketed by Pharmaceutical Company X. It is currently only approved for use in complicated intra-abdominal infections. However, the data provided throughout this study may pave the way for further approval by the United States Food and Drug Administration.

TABLE 1. Patient Baseline Demographics

	Age (years)	**Height (inches)**	**Weight (pounds)**	**BMI**
Number of Observations	37	37	37	37
Mean	55.405	67.351	192.865	29.654
Standard Deviation	+/- 15.143	+/- 3.924	+/- 75.473	+/- 10.642
Median	57	67	178	28.4
Minimum	31	61	97	17.2
Maximum	86	75	476	68.3

As shown in TABLE 1, the data from the thirty-seven patients who were treated with outpatient intravenous Drug X therapy showed the average patient age to be about 55 years of age (M = 55.405, SD = +/- 15.143). The average patient height was about 67 inches (M = 67.351, SD = +/- 3.924). The average patient weight was about 193 pounds (M = 192.865, SD = +/- 75.473), with an average BMI of about 30 (M = 29.654, SD = +/- 10.642).

TABLE 2. Gender

Gender		
	Percentage	**Frequency**
Male	54%	20
Female	46%	17

TABLE 3. Race

Race		
	Percentage	**Frequency**
White	24%	9
Black/African	11%	4
Hispanic/Latino	16%	6
Not Available	49%	18

TABLE 2 and TABLE 3 show the gender and race breakdown of each patient whose data was collected. A little more than half of the evaluated patients were male (54%) and 46% of the patients were female. Data regarding patient race was unavailable for about half of the patients (49%), with the remaining patients being White (24%), Black or African (11%), or Hispanic or Latino (16%).

TABLE 4. Liver Function

Liver Function		
	Percentage	**Frequency**
Child-Pugh Class A	32%	12
Child-Pugh Class B	22%	8
Child-Pugh Class C	0%	0
Not Available	46%	17

TABLE 5. Renal Function

Renal Function		
	Percentage	**Frequency**
Normal	30%	11
Mild	16%	6
Moderate	8%	3
End Stage	3%	1
Not Available	43%	16

Data regarding liver function and renal function in the 24 hours prior to Drug X therapy initiation were collected, if it was available. These data are summarized in TABLE 4 and TABLE 5. Liver function was evaluated based on Child-Pugh class, with Class A being least severe liver disease and Class C being most severe liver disease. Liver function data was not available for about half (46%) of the evaluated patients. The remaining patients were classified as Class A (32%) or Class B (22%). None of the patients had a Child-Pugh score of Class C. Renal function was evaluated based on estimated glomerular filtration rate (eGFR). eGFR values describe the stage of kidney disease, if kidney disease is present. Renal function data was not available for 43% of the patients. The remaining patients had normal renal function (30%), mild kidney disease (16%), moderate kidney disease (8%), or end stage kidney disease (3%).

FIGURE 1. Comorbidities Present Among Patients

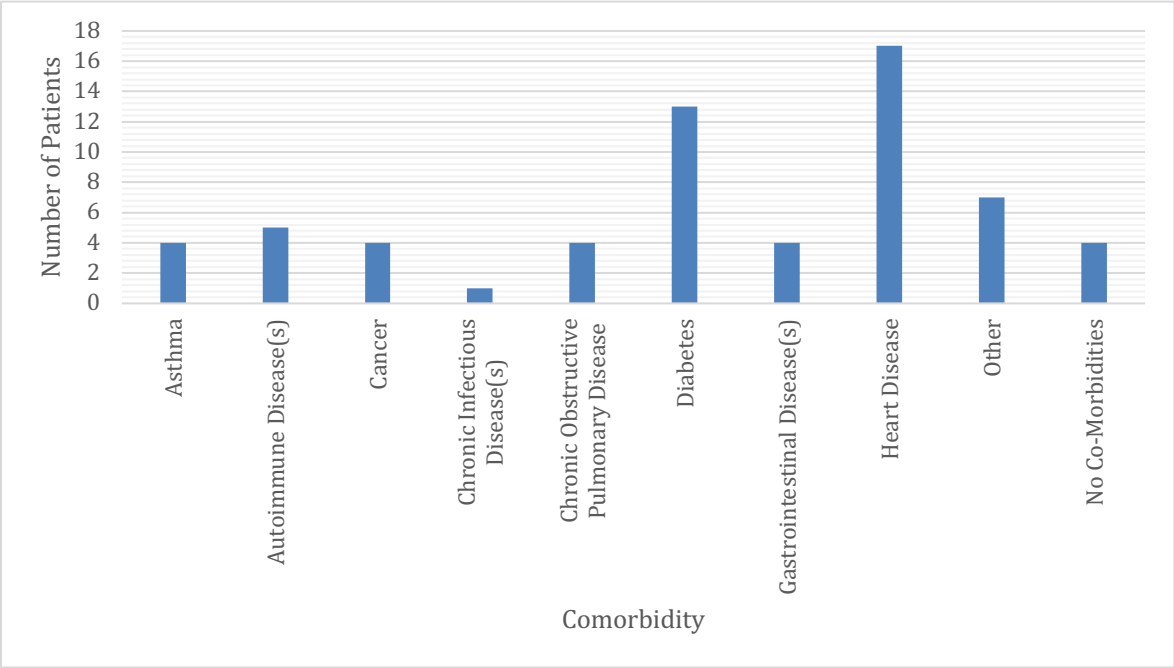


FIGURE 1 shows the breakdown of comorbidities among the patients. Of the thirty-seven patients that were evaluated, four of the patients (11%) had no comorbidities present. The two most common comorbidities seen among the patients were diabetes, which was seen in 13 of the patients (35%), and heart disease(s), which were seen in 17 of the patients, or 46% of the evaluated patients. Other comorbidities seen in these patients were asthma (four patients or 11%), autoimmune disease(s) (five patients or 14%), cancer (four patients or 11%), chronic infectious disease (one patient or 3%), chronic obstructive pulmonary disease (four patients or 11%), gastrointestinal disease(s) (four patients or 11%), and comorbidities classified as “other” (seven patients or 19%).

TABLE 6. Charlson Comorbidity Index

Charlson Comorbidity Index		
	Percentage	**Frequency**
Score of 0	22%	8
Score of 1-2	11%	4
Score of 3-4	41%	15
Score >/= 5	24%	9
Not Available	3%	1

TABLE 6 contains Charlson Comorbidity Index scores for the evaluated patients. The data regarding comorbidities, in turn, helped determine the patient's Charlson Comorbidity Index score. Sufficient data to calculate Charlson Comorbidity Index score was unavailable for one patient. Of the remaining thirty-six patients, 22% had a score of zero, 11% had a score of one to two, 41% had a score of three to four, and 24% had a score greater than or equal to five.

FIGURE 2. Presence of Multi-Drug Resistant Organism Risk Factors

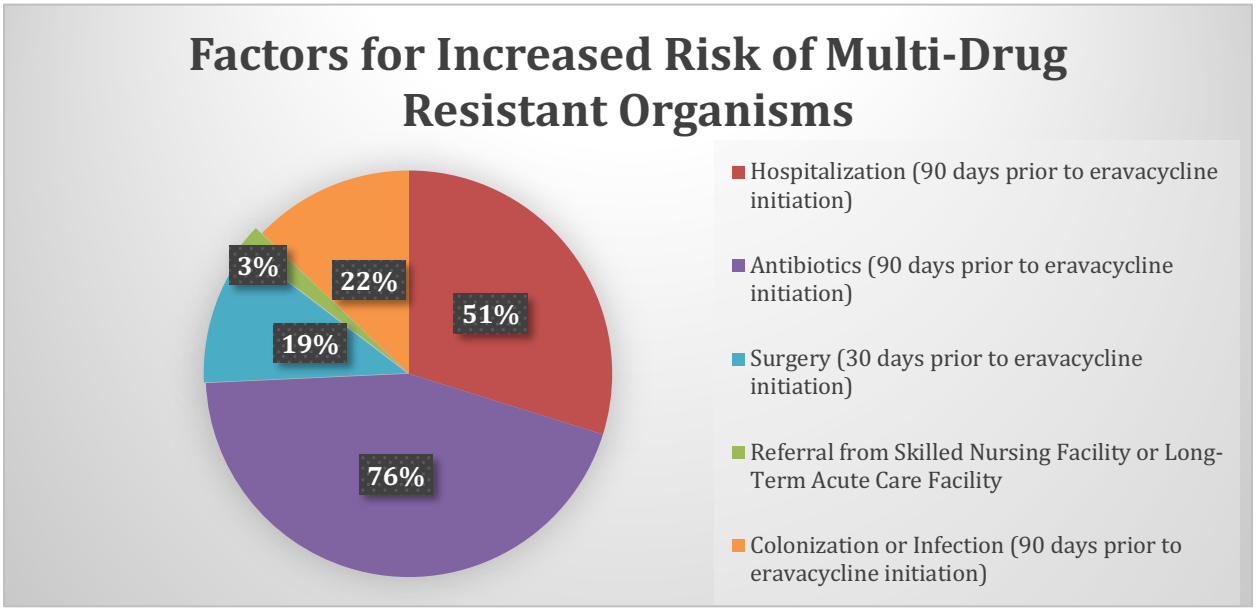


FIGURE 2 summarizes the presence of factors that increase a patient's risk for contracting an infection caused by a multi-drug resistant organism. Prosthetic devices or

hardware implants, chronic hemodialysis, and intravenous drug use were not seen in any of the patients. The most common risk factors present among these patients were hospitalization within the 90 days prior to initiation of Drug X therapy, which was seen in 51% of the patients, and antibiotic use within the 90 days prior to initiation of Drug X therapy, which was seen in 76% of the patients. Surgery within the 30 days prior to initiation of Drug X therapy was a risk factor that was present in 19% of the patients. Colonization or infection within the 90 days prior to initiation of Drug X therapy was present in 22% of the patients. Lastly, referral from a skilled nursing facility or long-term acute care facility was present in 3% of the evaluated patients.

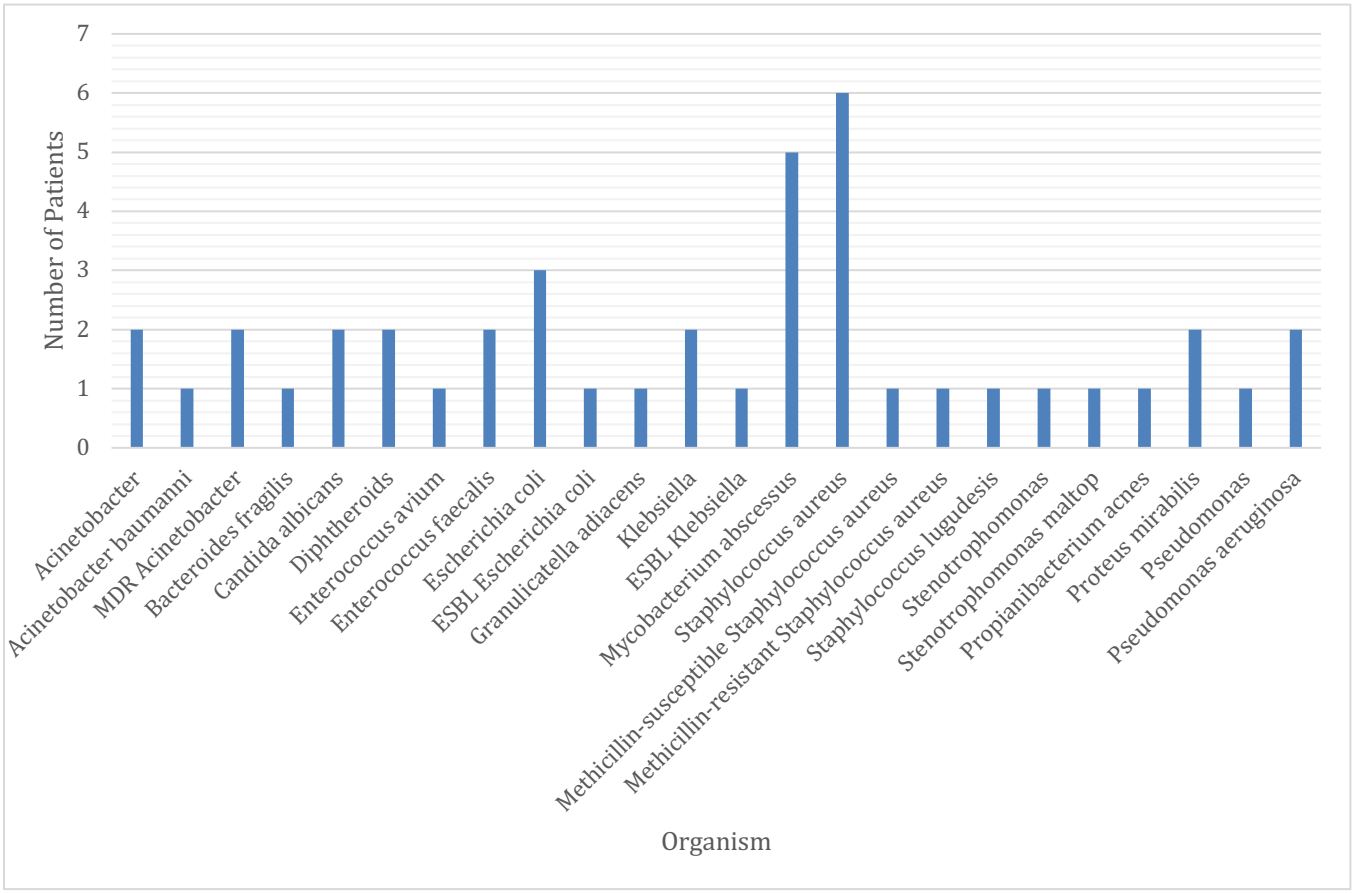
TABLE 7. Clinical Infectious Diagnosis

Clinical Infectious Diagnosis		
	Percentage	**Frequency**
Bone and Joint Infection	19%	7
Bacteremia	0%	0
Cardiac Infection	3%	1
Diabetic Foot Infection	8%	3
Gastrointestinal Infection	3%	1
Genitourinary Infection	3%	1
Intra-Abdominal Infection	8%	3
Respiratory Infection	16%	6
Sepsis	5%	2
Skin and Soft Tissue Infection	24%	9
Other	11%	4

TABLE 7 contains a summary of the infections that Drug X was being used to treat. The most common infection that clinicians were using Drug X in were skin and soft tissue infections. Nine patients (24%) had documented skin and soft tissue infections. Bone and joint infections accounted for 19% (or seven patients) of the infections among these patients. Respiratory infections were seen in 16% of the patients (or six patients). Three patients (8%) with intra-abdominal infections and three patients (8%) with diabetic foot infections were treated with Drug

X. Two patients (5%) were treated with Drug X for sepsis. Lastly, one patient (3%) with a cardiac infection, one patient (3%) with a gastrointestinal infection, and one patient (3%) with a genitourinary infection were also treated with Drug X. None of the evaluated patients were being treated for bacteremia.

FIGURE 3. Microbiology Associated with the Primary Clinical Infectious Diagnosis



Microbiology data was not available for twelve patients. FIGURE 3 summarizes the microbiology results for the 25 patients that had microbiology data available. Of the 25 patients with available microbiology data, two had samples collected that produced no growth. The remaining 23 patients had one or more organisms present in the microbiology sample. The most commonly found organisms were *Escherichia coli*, *Mycobacterium abscessus*, and

Staphylococcus aureus. *Acinetobacter* species, *Enterococcus* species, *Klebsiella* species, *Stenotrophomonas* species, and *Pseudomonas* species were found in the cultures of multiple patients, as well. Drug X MIC was only available for one of the patients. The Drug X MIC was 4, which indicates the lowest amount of the drug required to inhibit visible growth of the microorganism. This patient had cultures positive for *Enterococcus faecalis*, *Klebsiella*, and *Staphylococcus aureus*. Drug X resulted in clinical improvement in this patient.

TABLE 8. Systemic Antibiotic Therapies Used to Treat the Primary Clinical Infectious Diagnosis—Not Including Drug X

Systemic Antibiotics Used to Treat Primary Clinical Infectious Diagnosis	
Antibiotic	**Stage of Treatment**
Vancomycin	Empiric, unknown
Ceftriaxone	Empiric, definitive, unknown
Levofloxacin	Empiric, unknown
Daptomycin	Empiric, definitive, add-on/combination, unknown
Ertapenem	Definitive, add-on/combination, empiric, unknown
Piperacillin-tazobactam	Empiric, unknown
Metronidazole	Empiric, unknown
Meropenem	Definitive, empiric, add-on/combination, unknown
Ciprofloxacin	Definitive, empiric, unknown
Cefepime	Empiric, unknown
Amoxicillin	Definitive, empiric, unknown
Clindamycin	Add-on/combination, unknown
Amikacin	Definitive, empiric, unknown
Imipenem-cilastatin	Add-on/combination, unknown
Linezolid	Add-on/combination, definitive, unknown
Telavancin	Definitive, empiric, unknown
Tigecycline	Empiric, definitive, unknown
Imipenem-cilastatin/relebactam	Definitive, unknown
Ceftaroline	Add-on/combination, unknown
Doxycycline	Prophylactic, empiric, unknown
Ceftolozane/tazobactam	Empiric, definitive, unknown
Aztreonam	Empiric, unknown
Micafungin	Add-on/combination, unknown
Ceftazidime	Definitive, unknown
Minocycline	Definitive, unknown
Sulfamethoxazole-trimethoprim	Unknown

TABLE 8 provides a summary of the systemic antibiotic therapies that were used prior to initiation of treatment with Drug X. It is important to note that the data regarding stage of treatment was frequently missing from the patient chart notes and was recorded as "unknown." However, if an inference about the stage of treatment could be made based on chart notes, laboratory results, or susceptibility reports, then it was recorded as empiric, definitive,

prophylactic, de-escalation, or add-on/combination therapy based on the information available at the time of data collection. It is also important to note that many patients were prescribed and given more than one antibiotic in an effort to treat the primary clinical infectious diagnosis prior to initiation of Drug X therapy. In addition to information on stage of treatment, many patient charts lacked pharmacy data, particularly, those who were seen in a clinic versus being seen in the hospital with therapy initiated by an infectious disease specialist from the hospital.

TABLE 9. Drug X Treatment Summary

Drug X Stage of Treatment	
Stage of Treatment	**Number of Patients**
De-escalation	4
Add-on/combination	4
Empiric	4
Definitive	16
Replacement	1
Unknown	8
Drug X Dosing Frequency	
Dosing Frequency	**Number of Patients**
Every 12 hours	23
Every 24 hours	14
Drug X Therapy Initiation Setting	
Start Setting	**Number of Patients**
Hospital	12
Home care	16
Clinic	8
Long-term acute care facility	1
Drug X Therapy Completion Setting	
Stop Setting	**Number of Patients**
Hospital	1
Home care	25
Clinic	9
Long-term acute care facility	2

Stage of treatment, dosing frequency, therapy initiation setting, and therapy completion setting for treatment with Drug X are summarized in TABLE 9. Most often, Drug X was prescribed as definitive treatment. Sixteen of the 37 patients were given Drug X as definitive treatment. Four patients received Drug X as de-escalation therapy. Four patients received Drug X as add-on or combination therapy. Four patients received Drug X as empiric therapy. One patient received Drug X as replacement therapy. Lastly, stage of treatment was unknown for eight of the patients. More than half (23 patients) received Drug X every 12 hours, or twice a day, for the

duration of therapy. The remaining 14 patients were prescribed Drug X every 24 hours for the duration of therapy. Most often, therapy was initiated in the hospital and concluded in the patient's home or initiated in the patient's home upon hospital discharge and concluded in the patient's home. If therapy could not be safely concluded in the patient's home, post-initiation in the hospital, therapy concluded in a clinic or in a long-term acute care facility.

TABLE 10. Summary of Clinical Outcome

Clinical Outcome Post-Treatment with Drug X	
Clinical Outcome	**Number of Patients**
Clinical cure	22
Clinical improvement	6
Clinical failure	5
Unknown	4

Clinical outcomes post-treatment with Drug X are displayed in TABLE 10. Clinical cure was found in 22 of the 37 patients evaluated at this site. Clinical improvement was seen in six of the 37 patients. Treatment resulted in clinical failure in five of the 37 patients and outcome was unknown for four of the 37 patients. Based on the clinical outcomes, Drug X may not be effective against ESBL *Escherichia coli*, methicillin-resistant *Staphylococcus aureus* (MRSA), and some *Stenotrophomonas* species. Drug X resulted in clinical cure for some patients with cultures positive for multi-drug resistant (MDR) *Acinetobacter*, *Klebsiella*, some *Staphylococcus aureus* organisms, and *Pseudomonas aeruginosa.* However, because microbiology outcomes data was unavailable for all of the patients at this site, it was difficult to determine specifically

which organisms expressed intermediate susceptibility or were not susceptible to Drug X in the patients that resulted in clinical improvement or clinical failure, particularly in those with cultures positive for more than one organism. In patients with cultures positive for multiple organisms it was also difficult to definitively determine which organisms were truly susceptible to Drug X.

In addition to the information presented above, there were several other items that were evaluated during patient chart review for this study. Data was collected regarding source control; however, this data was present for very few patients. In the patients that had chart notes that documented these measures, source control typically consisted of removing whatever was thought to be the source of the infection or causing exacerbation of the infection. Dressing changes, wound irrigation, wound packing, and antibiotic bead placement were several other source control measures that were observed during chart review. Outcomes data was hard to come by for most patients because after therapy completed, there were no updated notes or laboratory reports. Microbiological cure was impossible to determine for any of the 37 patients because data for microbiology post-treatment was unavailable for every patient. This also hindered the ability to collect information regarding mortality in the 30 days following conclusion of treatment with Drug X and information about hospital admission or readmission in the 30 days following conclusion or termination of treatment with Drug X. Two of the five patients with documented clinical failure were readmitted to the hospital—one patient was readmitted due to progression of the infection and data regarding the hospital readmission was unavailable for the other patient. A third patient with documented clinical failure was admitted to the hospital for a PICC line infection. Lastly, none of the patients evaluated at this site had a diagnosis of *Clostridium difficile* while receiving treatment with Drug X and none of the patients

experienced any other adverse events while receiving treatment with Drug X or in the 30 days following conclusion of treatment.

Due to the fact that Drug X is still a relatively new drug, there are very few studies that evaluate its use in the treatment of other infections, particularly those that are not classified or sourced from a complicated intraabdominal infection. The studies that are available are mostly comparison studies that evaluate Drug X efficacy against the efficacy of other therapies in the same class of antibiotics. A major group of clinical trials, the Investigating Gram-Negative Infections Treated with Drug X (IGNITE) 1 to 4 clinical trials, demonstrate that Drug X has effectively treated infections caused by various *Enterobacteriaceae* organisms including *Pseudomonas aeruginosa* (Solomkin *et al*., 2018) and *Klebsiella pneumoniae* (Solomkin *et al.,* 2017). This confirms the finding that *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* may be susceptible to Drug X. However, the IGNITE4 clinical trial also indicated that patients with *Pseudomonas aeruginosa* as the predominant organism or are at high risk for poor outcomes should be treated with therapy specific to *Pseudomonas aeruginosa*. This suggests that *Pseudomonas aeruginosa* susceptibility may vary based on the infection and that efficacy in infections caused by *Pseudomonas aeruginosa* may result in clinical cure because of inhibition of bacterial synergy, or the inhibition of bacterial growth and proliferation (Solomkin *et al.,* 2018).

CHAPTER VI

SUMMARY AND CONCLUSIONS

Thus far, the study has provided information to confirm the hypothesis that Drug X is being used to treat infections other than the FDA-approved indication of complicated intra-abdominal infections. In addition to being used in the treatment of complicated intra-abdominal infections, the data collected has shown that Drug X has also been used in bone and joint infections, cardiac infections, diabetic foot infections, gastrointestinal infections, genitourinary infections, respiratory infections, sepsis, skin and soft tissue infections, and infections classified as "other." When it was available, microbiology data provided information about what kind of organisms were being treated. The study has also shown that Drug X results in clinical cure in some infections, and therefore, may be effective in treating the organisms that caused the infection. Based on the current data collected, organisms that may be susceptible to Drug X include the following: multi-drug resistant (MDR) *Acinetobacter*, *Klebsiella*, some *Staphylococcus aureus* organisms, and *Pseudomonas aeruginosa*. However, because microbiology data following completion of Drug X therapy or termination of Drug X therapy, definitive determination of susceptible organisms is not possible. More research needs to be done to determine specifically which organisms are susceptible to Drug X and if there are any infections that cannot be treated with Drug X due to an inability to produce clinical cure or clinical improvement. The study has not ruled out the presence of adverse events associated with Drug X; however, no adverse events were observed during chart review of the patients at this site.

Limitations

There are a multitude of limitations associated with retrospective observational chart review studies, and this study was no exception. One of the most prominent limitations in this study was the availability of necessary data. Microbiology laboratory results after completion of Drug X therapy was not available for any of the patients evaluated at this site. Due to the lack of microbiology outcomes data, it was difficult to draw conclusions regarding which organisms are susceptible to Drug X and which organisms are not susceptible to Drug X. In addition to the lack of microbiology outcomes, various other pieces of data were unavailable within the patient's chart. While this may not have affected the outcome of the study, it provided limited data for the interpretation of other aspects of the study. Another fairly significant limitation of the study was the population sample. While this study is being conducted at other sites, the data presented above is only reflective of one particular site. Many of the same infectious disease clinicians were seen among the patients evaluated. It is possible that Drug X was a preferred drug of the clinician and that is why it was used, not because laboratory results indicated that Drug X would be an effective treatment. Lastly, training for the study overall was extremely limited. This could possibly impact the integrity of the data collected, especially if information about an important variable was missed during chart review. Furthermore, there were no site monitoring visits or periodic meetings to ensure that training had been completed or that research staff understood all of the processes.

Future Directions

There are many avenues that future research could take. Future research should try to ensure that researchers have access to all necessary variables through the available patient records or have the ability to reach out to the prescribing clinician for information regarding that variable. If future research is conducted in the outpatient setting, it could be beneficial to inform the infectious disease clinicians that there is research being done, so the more information about the patient and the diagnosis, the better. If the data is initially unavailable, the researchers should be able to reach out to clinicians in order to obtain the necessary information. Another approach that could be taken would be to conduct chart review in the clinic instead of in an outpatient setting or at the pharmacy dispensing the medication. Further research studies should be designed to eliminate chart abstraction errors. One possible way to mitigate errors would be to ensure proper training and a standardized process for abstracting records from patient charts. Periodic meetings with monitors and study lead teams would be beneficial to ensure that the site is conducting the study appropriately.

CHAPTER VII

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CHAPTER VIII

CAPSTONE PROJECT EXPERIENCE

Project Site

My capstone project was conducted through Home Infusion Pharmacy X in Plano, Texas. Home Infusion Pharmacy X takes a multifaceted approach to outpatient treatment. They offer home infusion, infusion clinics, and home delivery for specialty medications.

Journal Summary

During my capstone project, I was the Clinical Research Study Site Coordinator for the study. I was responsible for abstracting all data from patient charts and inputting that data into the electronic data capture system. I was also responsible for ensuring that the appropriate information was provided to the pharmaceutical company for IRB approval renewal. Aside from working on the study itself, I also spent time working on a research proposal for this capstone project and working on this report in order to understand the outcome of the study thus far.