OPTIMIZING MEDICAL RESOURCES FOR THE TREATMENT OF INFECTIOUS DISEASES IN SOUTH AFRICA

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ABSTRACT

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BACKGROUND: Over the past two decades, healthcare expenditures worldwide have increased dramatically. In an era of rising antibiotic resistance, the need for more effective and efficient utilization of healthcare resources could not be more applicable than in the field of infectious diseases. Based on a review of available literature, several interventions targeted at improving antibiotic stewardship have been successful in decreasing healthcare costs in high income countries. Unfortunately, little research has been done in low income countries, including those on the African continent. South Africa in particular lends itself to further study. Despite spending more of its gross domestic product (GDP) per capita on healthcare than most of its neighbors, South Africa is still faced with many of the healthcare issues present in the rest of the continent, including the rise of multidrug-resistant pathogens and an increased Human Immunodeficiency Virus (HIV) seroprevalence.

OBJECTIVE: The objective of this research was to analyze current healthcare practices in the treatment of infectious diseases in South Africa in order to identify areas needing more efficient utilization of resources.

METHODS: The objective was accomplished by conducting two prospective observational cohort studies. In the first study, data related to patients presenting to two emergency departments in Cape Town, South Africa, were collected to evaluate the efficacy of clinical decision rules currently used when drawing blood cultures. The decision to collect a set of blood cultures was made by the physician, who then recorded a set of clinical parameters known at the time of collection.

In the second study, a quality improvement analysis was done to evaluate effectiveness of current intravenous (IV)-to-oral antibiotic switch therapy practices at a tertiary referral center in Cape Town. During the study, all patients receiving IV antibiotic therapy in the internal medicine wards were followed throughout the course of their IV therapy and were evaluated on their eligibility to switch to oral antibiotic therapy based on a list of criteria.

RESULTS: In the first study, 500 blood culture sets were collected from 489 patients. Thirty-nine (7.8%) of these were positive for disease causing pathogens, and 13 (2.6%) contained contaminants. Clinical features that were independently associated with a positive culture result included the presence of diabetes, systolic blood pressure <90 mmHg, diastolic blood pressure <60 mmHg, and a suspected biliary source of infection. Thirty-six (95%) of these positive cultures were found to influence patient management in a significant way.

In the second study, 71 (55%) of the 129 patients receiving IV antibiotic therapy met all the criteria for switching to oral antibiotics and only 4 (5.6%) of those were switched once the patient became eligible. Patients eligible for switching were continued on IV therapy for a mean of 3.1 (+/-1.6) days (median=3, Interquartile range (IQR)= 2-4 days) after meeting the criteria, and the most common indications for therapy within this group were community-acquired pneumonia (58.2%), sepsis of unknown cause (13.4%), and urinary tract infection (11.9%). The most common IV antibiotics used in this group were ceftriaxone 1 g (77.6%) and amoxicillin/clavulanate 1.2 g (13.4%). Fifteen (21.1%) of the patients meeting the criteria for switching did not have a blood culture sample taken prior to initiation of therapy.

CONCLUSIONS: In the end, the stated objective of the project was met: analyzing current healthcare practices in the treatment of infectious diseases in South Africa helped to identify areas needing more efficient utilization of resources. The first study determined that, while blood cultures are an essential aspect of the treatment of infectious diseases, no consistent set of rules exists that allows physicians to predict when to order these studies. Further, when relying on clinical judgment, the vast majority of blood cultures ordered are negative. The second study identified several key mechanisms that led to inappropriately continued IV antibiotic treatment. The results of both studies highlight the need for more research to facilitate targeted interventions.

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PRIOR PUBLICATIONS & PRESENTATIONS

PUBLICATIONS:

Boyles, T. H., Davis, K., Crede, T., Malan, J., Mendelson, M., & Lesosky, M. (2015). Blood cultures taken from patients attending emergency departments in South Africa are an important antibiotic stewardship tool, which directly influences patient management. *BMC Infect Dis, 15*, 410. doi: 10.1186/s12879-015-1127-1

PRESENTATIONS AND POSTERS:

Mendelson, M., Boyles, T., & Davis, K.. (2014). Limiting the Use of Antibiotics in Hospitals Oral Presentation presented at: 17th World Congress of Basic and Clinical Pharmacology Conference; Cape Town, ZAF.

CHAPTER 1: GENERAL INTRODUCTION

Over the past two decades, healthcare expenditures worldwide have increased dramatically. In the United States alone, total healthcare expenditures per capita have increased by roughly $320 per person per year since 1995 (see *Figure 1*). In the same time period, the fraction of its gross domestic product (GDP) spent on healthcare has also increased from 13% in 1995 to over 17% in 2013.[1] This trend is not isolated only to developed countries like the United States, but is also seen in developing nations with fewer resources where rising healthcare costs can be particularly devastating.

In the era of rising antibiotic resistance, the need for more effective and efficient utilization of healthcare resources and better targeted interventions could not be more applicable than in the field of infectious diseases. The Centers for Disease Control and Prevention (CDC) reported that the approximately half of all outpatient antibiotic prescriptions are unnecessary.[2] Unnecessary prescriptions, while increasing healthcare costs directly themselves, also have negative indirect effects. For example, it is estimated that antibiotics cause one out of five emergency department visits for adverse drug events in the United States.[2] Additionally, the inappropriate use of antibiotics has also contributed to the increased prevalence of multidrug-resistant pathogens. As a result, multiple public health organizations have developed programs that emphasize the need for greater antibiotic stewardship. In the United States, the CDC has established an initiative called *Get Smart: Know When Antibiotics Work* that guides physicians on appropriate antibiotic use.[2] On a global scale, the World Health Organization (WHO) has a similar initiative called *The Pursuit of Responsible Use of Medicine*.[3] Antibiotic stewardship initiatives, such as these, have been shown in literature to effectively reduce inappropriate antibiotic use, antibiotic resistance,

and hospital acquired infections, while improving clinical outcomes and decreasing healthcare costs in the process.[4,5]

Unfortunately, little research has been done on reducing healthcare spending in low resource environments, such as the African continent. Understanding the full extent of issues surrounding antimicrobial resistance is limited because surveillance of drug resistant pathogens is restricted to only a few countries, resulting in an incomplete picture. Despite these limitations, available data suggest that the African continent faces similar issues to the Western world with regards to increasing drug resistance. [6] Still, without more information on how antimicrobials are used in these settings, it is impossible to determine which interventions to employ to minimize unnecessary healthcare expenditures and reduce indirect effects.

Among the various nations comprising the African continent, South Africa in particular lends itself to study in greater detail. Despite its relative wealth and advanced healthcare system compared to the majority the continent, South Africa is still plagued by many of the healthcare issues present in its neighbors. South Africa spends approximately 50% more of its GDP per capita on healthcare expenditures than Botswana, a neighboring African country with a similar GDP per capita (see *Figure 2*).[1] Regardless, it is not apparent that this increased healthcare expenditure leads to improved clinical outcomes in the country. For example, South Africa still accounts for 84% of the continent's multidrug-resistant tuberculosis (MDR-TB) and 96.8% of its extensively drug-resistant tuberculosis (XDR-TB).[6] Because of its position as one of Africa's leaders in healthcare spending while still facing health problems present in much poorer countries, in-depth studies on South Africa's use of resources for treating infectious diseases could lead to greater insight into how cost-saving measures can be implemented across the continent. *More generally, analyzing current healthcare practices in the treatment of infectious diseases in South Africa can help to identify areas that need more efficient utilization of resources.*

To accomplish this analysis, two distinct prospective observational cohort studies were performed. In the first study, an analysis of patients presenting to two emergency departments in Cape Town, South Africa, was performed to evaluate the efficacy of clinical decision rules currently used when drawing blood cultures. In the second study, an analysis of hospitalized patients at a tertiary referral center in Cape Town was performed to evaluate effectiveness of current intravenous (IV)-to-oral antibiotic therapy switch practices.

CHAPTER 2: BLOOD CULTURE STUDY

Section 2A: Background

Fever associated with bacteremia is among the leading causes for admission to hospitals worldwide. While rapid treatment with empiric antibiotic therapy is essential to caring for these patients, identifying the causative organism and its resistance pattern allows physicians to tailor the choice of antibiotic to target specifically the pathogen in question. In most cases, this new antibiotic is narrower in spectrum with a more favorable side effect profile. Therefore, obtaining blood cultures during the initial evaluation of patients with suspected bacteremia prior to the initiation of empiric antibiotic treatment is critical to both providing high quality patient care and practicing responsible antibiotic stewardship.

Nevertheless, despite their overt utility in clinical practice, studies performed in high income countries indicate that blood culture results have only influenced patient management in 0.2-2.8% of cases.[7-9] Blood cultures that do not contribute to patient management hinder clinical care as they are expensive, expose healthcare workers unnecessarily to blood-borne pathogens and cause discomfort to patients, while unrecognized contaminants may lead to inappropriate initiation of antimicrobial therapy and associated consequences.[10] Therefore, studying the effectiveness of the current clinical decision rules used when drawing blood cultures in the emergency department setting is paramount to improving the efficiency and effectiveness of healthcare.

While several studies in literature have developed clinical rules to determine when blood cultures should be drawn in high income countries, these rules are not easily translatable to other areas for a number of reasons.[9-11] Aside from basic differences in patient population, such as differing Human Immunodeficiency Virus (HIV) seroprevalence and the presence of other chronic conditions that could complicate the clinical rules, studies done in these areas have shown marked differences in the most common pathogens cultured and even associated clinical features. For example, a systematic review and meta-analysis in high income countries found that the predominant organisms isolated were *Escherichia coli*, *Streptococci* species, and *Staphylococcus aureus*, and infection was associated with fever, tachycardia, tachypnea, and hypotension.[7,9-13] In contrast, a similar analysis of African countries found that the predominant organisms isolated included *Salmonella typhi*, non-typhoidal *Salmonella*, *Brucella* species, and *Streptococcus pneumoniae*, and infection was associated with lethargy restlessness, oral candidiasis, and jaundice.[8]

Understanding healthcare in South Africa with respect to these data is even more complicated, as it shares multiple features with both high income countries and other African countries. While South Africa is relatively more developed and has more advanced healthcare infrastructure than its neighbors, it is still afflicted by many of the issues present in other African countries, including a high HIV seroprevalence (19.1% in 2013) and presence of MDR and XDR organisms.[14] As there have been no published studies of blood stream infections in South Africa, it is impossible to predict whether the clinical rules developed for high income countries should be applied. Therefore, a prospective observational cohort study of patients presenting to two emergency departments in Cape Town, South Africa, was performed to evaluate the efficacy of clinical decision rules currently used when drawing blood cultures.

Section 2B: Methods

A prospective observational cohort study was done on adult patients (age ≥ 16 years) presenting emergency departments in two hospitals in Cape Town, South Africa, between April and December 2013. The two hospitals, Groote Schuur Hospital and Victoria Hospital, each admit approximately 40,000 adult patients per year. Additionally, both primarily treat urban populations in Cape Town.

Written informed consent was obtained from all patients entered into the study. Ethical approval was granted by the Faculty of Health Sciences Human Research Ethics Committee for the University of Cape Town (Reference 172/2013). When the decision to draw blood cultures was made by a patient's physician, he or she was asked to complete a form containing the patient's known clinical details at the time that blood cultures were ordered, including any co-morbidities (HIV, diabetes, or malignancy), use of antibiotics in the past 48 hours, the presence of chills, temperature, pulse, blood pressure, respiratory rate, oxygen saturation, inspired oxygen concentration, presence of confusion, and CRB-65 score (see *Figure 3*). A CRB-65 score, a validated predictor of mortality for community-acquired pneumonia, was calculated by assigning one point for confusion, respiratory rate ≥30 breaths per minute, systolic blood pressure <90 mmHg or diastolic blood pressure <60 mmHg, and age ≥65 years.[10,15] In addition, the physicians were asked to determine the likely source of infection based on their clinical judgment, selecting from lower respiratory tract, urinary tract, endocarditis, skin and soft tissue, biliary tract, gastrointestinal, gynecologic, meningitis, unclear source of infection, and "other."

Each set of blood cultures ordered was comprised of a single aerobic bottle, which was weighed after the sample was drawn to determine the volume added. Organisms and their resistance patterns were identified using standard laboratory procedures established by the

National Health Laboratory Service in South Africa. Positive blood culture results were then reviewed in conjunction with each patient's medical record by two infectious disease specialists to decide whether the organisms identified were contaminants. The results were also reviewed to determine whether they would influence patient management. By evaluating whether the isolate was also grown from another sterile site (*i.e.,* without the use of a blood culture) and the antibiotics initially prescribed were appropriate for the organism's resistance pattern.

Statistical analysis of the data gathered involved calculating frequency (percentage) and median (inter-quartile range [IQR]) for the entire data set in addition to the subsets of true bacteremia, contaminant growth, and no growth. Simple comparisons between groups of discrete variables were conducted using Fisher's exact test, and comparisons between groups of continuous variables were conducted using Wilcoxon rank sum test. To better understand the relationship between potential clinical features and the likelihood of a blood culture yieldereing a clinically significant result, regression models with a single explanatory variable were created. Multivariable regression modeling and classification tree analysis w also performed using randomly selected development sub-samples (50% of data) in an attempt to find a clinical prediction rule. Unfortunately, no models performed well enough (*i.e.,* with a high negative predictive value) on the validation set to consider developing such a set of rules. The full set of details on the statistical methods used in this study are available in the original published article's online supplement.[10]

Section 2C: Results

Four hundred and eighty-nine patient encounters were recorded during the study period, yielding a total of 500 blood culture sets. Of these, 410 cultures were collected from Groote Schuur Hospital, and 90 were collected from Victoria Hospital. Of the total number of blood cultures collected, 39 (7.8%) cultures yielded true pathogens and 13 (2.6%) yielded contaminants. From the cultures growing true pathogens, 43 unique organisms were identified, comprised of 26 gram-negative bacteria, 15 gram-positive bacteria, and two cases of *Cryptococcus neoformans* (see *Table 1*). The most common pathogens identified were *Escherichia coli, Klebsiella pneumoniae,* and *Streptococcus pneumoniae.* The results of the univariate descriptive analysis and the odds ratio (OR) resulting from univariate logistic regression of the complete data can be found in *Table 2.* From the data collected, the median patient age was 48 years old (IQR 31-64). Additionally, 111 (22%) of the patients in the study were diabetic and 96 (19%) were HIV positive.[10]

Based on the univariate analysis of the complete data set, the following factors were found to be predictive of a positive blood culture: presence of diabetes (OR 2.08, 95% CI 1.04-4.01), diastolic blood pressure <60 mmHg (OR 2.48, 95% CI 1.30-4.70), systolic blood pressure <90 mmHg (OR 3.26, 95% CI 1.31-7.34), and suspected biliary source of infection (OR 9.42, 95% CI 3.25-26.83). Of note, HIV infection, temperature, pulse rate, respiratory rate, and presence of chills were not found to be predictive of positive blood cultures in this study.[10]

Figure 4 details how the classification of the 39 blood culture sets that contained true pathogens influenced patient management. Thirty-eight of the blood cultures yielded definitive identification of the organism and its antibiotic resistance pattern. In two of the cases, no change in management was made because the pathogen was also cultured from cerebrospinal fluid. In the remaining 36 cases (95%), the results directly contributed to patient management. In nine of the cases, the pathogen in question was resistant to the empiric therapy chosen by the physician. In 22 of the cases, the physician was able to switch the empiric antibiotic to one with a narrower spectrum.[10]

Section 2D: Discussion

As noted, in the majority of cases in which blood cultures yielded true pathogens, the results directly influenced patient management. Nine (25%) of the organisms cultured were resistant to the chosen empiric antibiotic therapy, and the remainder of the results led to a direct change in the parameters of the therapy chosen, modifying either the duration of treatment or the spectrum of the agent used. As these are all vital components of successful antibiotic stewardship, the use of blood cultures in patients with suspected infections is imperative.

Because this study is the first of its kind in South Africa, it provides important data on how the patient population there differs from others in the region. While the incidence of true bacteremia in this study is near the upper end of the range when compared to those performed in emergency departments in high income countries, it is lower than the majority of other areas in Africa.[7-9, 10, 12, 16-17] This result was expected, given that South Africa is defined by the World Bank as an upper-middle income country.[10] Therefore, it is reasonable to assume that the incidence of infection would fall between that of high income and low income countries.

Interestingly, the results of this study show that South Africa also differs from other African countries in several key ways. First, this study did not show a link between HIV seroprevalence and the presence of bacteremia. It is possible that this lack of an association is secondary to the relatively low incidence of non-typhoidal *Salmonella* infection found in this patient population. Usually, uncontrolled HIV is one of the greatest risk factors for non-typhoidal *Salmonella* in Africa, and consequently, non-typhoidal *Salmonella* is one of the most commonly cultured pathogens in low income countries. However, it is also possible that improved sanitation along with the widespread coverage of antiretroviral therapy in the areas of Cape Town studied, when compared to other African cities, has led to an unusually high prevalence of controlled HIV (*i.e.,* more patients with functionally intact immune systems) and consequently a significantly decreased incidence of this pathogen.[10] Without the predisposition to HIV-associated pathogens that are present in other areas of Africa, the range of pathogens cultured in South Africa more closely resembles that of other, relatively high income countries. Indeed, the most common pathogen identified in this study, *Escherichia coli*, is also the most common pathogen identified in studies examining high income countries.[7,11,12] It is likely that the similar prevalence of diabetes and urinary catheter use in the urban population of Cape Town and other high income countries also contributes to the similarity in pathogens cultured between the two.[10] In contrast, the most common pathogens shown to cause bacteremia in nearby regions of Africa include non-typhoidal *Salmonella*, *Streptococcus pneumoniae*, and *Staphylococcus aureus.*[8]

While a secondary goal of this study was to identify a set of clinical decision rules that could be used with high sensitivity and negative predictive value to calculate the probability of blood culture positivity, the researchers were unable to generate a model because of the small sample size used and the diversity of patients that presented to the two emergency departments studied. Still, several clinical features were identified that could be used as predictors for positive blood cultures. These include the presence of diabetes, diastolic blood pressure <60 mmHg, systolic blood pressure <90 mmHg, and a suspected biliary source of infection. Unfortunately, the wide confidence intervals obtained for these variables limits specific conclusions.[10]

Also of interest, several clinical features that were initially expected to predict bacteremia were found to have no association with positive blood cultures. For example, temperature, pulse rate, respiratory rate, and the presence of chills did not predict the presence of bacteremia, despite having been shown to be predictive in other studies.[9, 11-13] Temperature, pulse rate, and respiratory rate make up a significant portion of the Systemic Inflammatory Response Syndrome (SIRS) criteria, a clinical decision-making tool that is classically used to predict the presence of systemic inflammation. However, numerous studies have shown that the SIRS criteria is neither sensitive nor specific for the diagnosis of infection, as many other conditions can cause a patient to meet the criteria.[18] Additionally, the presence of chills is subjective and also nonspecific, and its connotations may vary in different locations.

This study has a number of limitations. While the gold standard for documenting true bacteremia requires that the same organism be cultured on two consecutive blood cultures, the standard practice of both emergency departments analyzed required that single cultures were used in this study. To minimize the likelihood that some isolates were misidentified as true pathogens, each positive case was examined by two infectious disease specialists who ensured that the organisms identified were consistent with the clinical setting.

Several biases of unknown significance were also present in the study. First, since sample collection was initiated based on physician discretion rather than standardized criteria, it is not possible to determine the risk of bacteremia in patients that were not suspected to have an infection. Additionally, the choice to obtain blood cultures was based on the physician’s clinical suspicion for bacteremia, which is highly dependent on his or her clinical experience and skill. This is especially pertinent to this study, as Groote Schuur Hospital, is a teaching institution where relatively inexperienced physicians may be practicing under supervision. Lastly, it is likely that some physicians obtained blood cultures without filling out the additional paperwork necessary to be included in this study due to time constraints.

CHAPTER 3: INTRAVENOUS-TO-ORAL ANTIBIOTIC SWITCH THERAPY STUDY

Section 3A: Background

In the advent of rising antibiotic resistance, antimicrobial stewardship initiatives are increasingly important in optimizing antibiotic usage and to decreasing potential sequelae of their use. One potential way to accomplish this is through IV-to-oral antibiotic switch therapy use in an inpatient setting, which involves switching from an IV antibiotic to its oral antibiotic equivalent as soon as a patient is determined to be clinically stable.[19] Switch therapy has many benefits including reduced incidences of catheter-related infections, shortened hospital stays, and related benefits such as decreased risk of nosocomial infections, reduced workload and nursing time, and reduced costs.[19-20] These benefits are especially pertinent in a low resource setting that lacks adequate infrastructure to administer IV antibiotics safely in an outpatient setting. To aid in the clinical decision process for implementing switch therapy, several guidelines have been suggested in the literature that have had varying degrees of success.[19-21]

The objective of this study was to evaluate the current execution of IV-to-oral antibiotic switch therapy at a large teaching hospital in South Africa that had recently implemented an antibiotic stewardship program in order to highlight which patients could benefit from early switch therapy and to identify current roadblocks to its successful implementation. Ultimately, the data could then be used as a pre-intervention baseline in a quality improvement project to implement hospital-wide changes with the goal of reducing unnecessary IV antibiotic use and improve the institution's antibiotic stewardship.

Section 3B: Methods

To evaluate and document the current IV-to-oral antibiotic switch therapy practices, a prospective observational cohort study was performed over a one month period (June-July 2013), documenting all IV antibiotic usage in each of the four internal medicine wards in the hospital. Patients not under the care of a medical team were excluded from the study. For each patient on IV antibiotics, the patient's ward and bed number were recorded along with dates the patient was febrile while taking antibiotics, antibiotic dosage, prescription start and end dates, indications for antibiotic therapy, number of days of treatment, and whether the IV regimen was completed, stopped, or changed to an oral alternative.

Each patient on IV antibiotics was then evaluated based on the following criteria to determine the patient's eligibility to switch to an oral alternative[21-22]:

1) The patient met none of the indications requiring long term IV antibiotic use. These included: endocarditis, meningitis, CNS infection, osteomyelitis, prosthetic material infection, *Staphylococcus aureus* bacteraemia, undrained or undrainable abscesses, and neutropenic fever.
2) The patient is able to take oral medication and must lack indications of potential malabsorption.
3) An oral alternative is available for the current IV antibiotic regimen.
4) The patient should have a documented temperature of less than 38˚C for 24 hours.
5) The patient should be clinically improving or remaining stable, as indicated in the patient's medical charts.

If a patient met all five criteria, then the patient's continued IV antibiotic treatment was considered to be inappropriate, and the number of days from the day the criteria was met to the day the patient was taken off of IV antibiotics was documented. Antibiotic charts and prescription charts were checked every weekday, and weekend usage was reviewed retrospectively on the following Monday. If a patient was started on IV antibiotics in the emergency department or observation ward and continued once the patient was moved to the medical ward, the days the patient was in all departments were included. If a patient was switched to oral, even if an IV dose was given on the day of the switch, the day was not counted towards the number of inappropriate days.

Section 3C: Results

Over the 28 days of the study, a total of 129 patients under the care of a medical team received IV antibiotics. These patients were divided into two categories: those who met the criteria for IV-to-oral switch (71 patients) and those that did not meet the criteria for IV-to-oral switch (58 patients), based on whether they met all of the criteria for switching. The former group was then subdivided further into those who did get switched from IV-to-oral appropriately (5.6%) and those who did not (94.4%), based on whether the patient was switched to an oral alternative within 24 hours of all the criteria being met (see *Figure 5*). The data collected in each of these categories is shown in *Table 3*.

Patients in the IV-to-oral Switch Not Made Appropriately Group were continued inappropriately on IV antibiotics for an average of 3.1 (+/-1.6) days (median=3 days, IQR= 2-4 days) after meeting the criteria. The most common indication for therapy within this group was community-acquired pneumonia (58.2%), followed by sepsis (13.4%) and urinary tract infection (11.9%) (see *Figure 6*).

The most common IV antibiotics used within this group were ceftriaxone 1 g (77.6%) and amoxicillin/clavulanate 1.2 g (13.44%). Six patients were on dual IV antibiotic therapy (see *Figure 7*).

Within the Could Switch category, 15 of the 71 patients did not have a blood culture taken prior to the initiation of antibiotic therapy. Of the remaining 56 patients, seven patients had a true positive blood culture, and four had a contaminant blood culture. A urine sample was sent prior to starting empiric antibiotic therapy for all patients with an indication of a urinary tract infection (UTI).

Section 3D: Discussion

Using the criteria to evaluate the current execution of switch therapy, these results show significant areas that need improvement, especially in the treatment of community-acquired pneumonia. The 5.6% of eligible patients who were appropriately switched to oral antibiotics was lower than the 16% (19/119 patients) seen at another teaching hospital in South Africa prior to their initiation of the switch therapy criteria.[19] The same study also had a different breakdown of IV antibiotics used, with ampicillin (21.5%; 134/622) and amoxicillin/clavulanate (14%; 87/622) being the top two antibiotics used compared to ceftriaxone 1 g (77.6%) and amoxicillin/clavulanate 1.2 g (13.44%).[19]

Several mechanisms contribute to these results. With a limited number of medical beds available, most patients that are admitted to the wards have complex medical needs that initially require IV antibiotics, while those who need oral antibiotics are often discharged to receive outpatient therapy. Inherent to this practice is the belief that an oral antibiotic cannot attain the same bioavailability as its IV equivalent. While this may be true in the case of critically ill patients or in patients who are unable to absorb oral medications, newer antibiotics are now able to provide higher serum and tissue concentrations, making many oral antibiotics viable alternatives to IV antibiotic use.[22]

Additionally, the hospital used a paper chart system in which patients had a general medicine chart and a separate medication chart for antibiotics as part of an antimicrobial stewardship initiative. An initial study done at the same hospital showed clinical benefits to having a separate antibiotic medication chart.[4] Unfortunately, their use in practice led to several indirect effects that proved detrimental to this goal. The two medical charts were always not kept together, and there were no indications made on the general medicine chart that the patient also had an antibiotic chart. This could be a potential source of confusion regarding continuity of antibiotic therapy when multiple providers were treating a given patient. This problem was further complicated by the nature of the teaching hospital setting, where multiple students, medical residents, and specialists were all involved in the care of the patient. Because these personnel all needed to use the medical charts, the antibiotic medication chart was sometimes not located with the patient's general medicine chart, which interfered with medication prescribing and management.

The problems associated with the dual-medication chart system were further exacerbated by the fact that the antibiotic charts were only utilized by certain departments within the hospital. Notably, these charts were not used by certain specialty wards or in the emergency department. Therefore, if a patient was initiated on antibiotic therapy in one of these departments prior to being transferred to a medical ward, their initial antibiotic management would be recorded in the general medicine chart instead of the separate antibiotic chart. Once such a patient was transferred to a medical team, an antibiotic chart was started. However, the antibiotic chart would often not account for prior antibiotic therapy recorded in the general chart. Thus, the antibiotic chart would not accurately reflect the total duration of therapy that a patient received, often leading to a misinterpretation of when a patient would be eligible to switch to oral therapy from IV therapy.

Lastly, antibiotic charts frequently lacked adequate indications for why antibiotic therapy was initiated. Since many details of antibiotic therapy such as duration of treatment and when to perform the IV-to-oral switch, are dictated by these indications, the absence of indications for antibiotic therapy in the antibiotic chart interferes with the coordination of care across all healthcare providers involved in the treatment of a patient.

In order to avoid such oversights, the following recommendations can be made based on the results of the study: 1) The antibiotic chart should include the total number of days that a patient has been on antibiotic treatment regardless of where initiated. Great care must be taken to ensure that antibiotics administered and recorded in the general medicine chart are accurately reflected in the antibiotic chart. 2) The general medicine chart must always include an indication of whether an antibiotic chart has been created for a given patient. Including this information in the general medicine chart will reduce confusion regarding whether and when antibiotic treatment of a given patient was initiated. 3) Antibiotic charts must include the indication for treatment. Because many antibiotics have uses in the treatment of a wide variety of illnesses but with different dosages and durations, including the indications for treatment in the antibiotic chart will allow providers to determine when an IV-to-oral switch is indicated.

One limitation of the study was that the investigators were not the primary medical providers for the patient, so the reasons for continued IV antibiotic therapy were not always known or adequately charted. To compensate for this limitation, the investigators reviewed the patient's medical charts and laboratory results to better understand the reasoning behind continued use. The results were also affected by the recent implementation of weekly antibiotic stewardship rounds. During these rounds, infectious diseases faculty would review the medical charts of all patients currently on antibiotics in an effort to decrease the inappropriate use of these medications. The impact of these rounds on the study results is unknown. Lastly, because the prospective nature of this study required continual review of physical medical charts placed near clinical work areas, it is possible that some physicians changed their prescribing behaviors over the course of the study when they perceived that they were being observed by clinical investigators.

Section 3E: Further Studies

At the conclusion of this study, the results were presented to the hospital's Internal Medicine department and a discussion was held on how to correct some of the areas that had been identified as needing improvement. A follow-up study was then conducted from August to October 2015. The study consisted of a pre-intervention follow-up study for one month in August to September 2015 performed only on patients receiving antibiotics for the indication of community-acquired pneumonia. A targeted intervention was then performed over a month that consisting of twitter campaigns, teaching sessions, and stickers added to the antibiotic medication charts with the goal of improving conscientious antibiotic use. Following the intervention, a post-intervention study was performed for another month.

While the majority of the analysis is still pending, several trends can be noted from the initial data (see *Table 4*). First, there was an overall improvement between the initial study to the pre-intervention study in the mean number of days that patients were inappropriately kept on IV antibiotics after meeting switch criteria, and the percent of patients switched appropriately improved. There was further improvement following the intervention, although the post-intervention study was performed immediately following the intervention, and therefore may not reflect a long term effect. Finally, all three studies showed that ceftriaxone remained the most common antibiotic used for patients who were not switched appropriately. One reason for this may be the hospital's current practices of using amoxicillin/clavulanate as the oral alternative to ceftriaxone 1 g daily, which is from a different class of drugs, instead of oral cefixime 400mg daily, an agent from the same drug class that is used by some other institutions. As a result, certain prescribers may not recognize ceftriaxone as having an oral alternative and therefore may not have viewed patients on it as meeting the switch therapy criteria. However, further studies on this subject are needed before definitive interventions can be suggested.

CHAPTER 4: GENERAL CONCLUSION

In the end, the stated objective of the project was met: analyzing current healthcare practices in the treatment of infectious diseases in South Africa helped to identify areas needing more efficient utilization of resources. In the first study, the analysis of patients presenting to two emergency departments in Cape Town, South Africa, for the purpose of evaluating the efficacy of clinical decision rules currently used when drawing blood cultures was able to identify that while blood cultures are an essential aspect of the treatment of infectious diseases, no consistent set of rules exists that allows physicians to predict when to order these studies. As indicated by the data collected, when relying on clinical intuition and judgment alone, the vast majority of the blood cultures ordered are negative and waste healthcare resources unnecessarily. Unfortunately, until further studies can be performed to generate such a set of clinical rules, the current practices must continue in the interest of patient safety.

In the second study, the analysis of hospitalized patients at a tertiary referral center in Cape Town, South Africa, for the purpose of evaluating the effectiveness of current intravenous-to-oral antibiotic therapy switch practices was able to identify several key areas where interventions could dramatically reduce the number of days that IV antibiotics are used inappropriately. These extra days of unnecessary IV antibiotics waste healthcare resources through a variety of mechanisms, including increasing hospital length of stay, increased labor demands from maintaining IV access, and increased risk of nosocomial infections. Preliminary data obtained after study completion indicate that these interventions have great promise in improving the adherence to responsible IV-to-oral antibiotic switch therapy practices and consequently antibiotic stewardship.

These studies, while overtly specific to healthcare practices in South Africa, are nevertheless relevant to healthcare worldwide, as many of the problems and findings identified in this project are translatable to other areas. By continuing to conduct thorough reviews of current healthcare practices in infectious diseases in a variety of settings, great improvements can be made in both reducing unnecessary health expenditures and propagating responsible antibiotic stewardship globally.

LIST OF TABLES

Table 1: Organisms identified from 500 blood culture sets in the blood culture study

Gram Positive Bacteria		Gram Negative Bacteria		Fungi	
Streptococcus pneumoniae	4	*Escherichia coli*	9	*Cryptococcus neoformans*	2
Enterococcus faecalis	3	*Klebsiella pneumoniae*	5		
Enterococcus faecium	3	*Enterobacter sp.*	2		
Staphylococcus aureus	2	*Morganella sp.*	2		
Streptococcus constellatus	1	*Klebsiella oxytoca*	1		
Streptococcus pyogenes	1	*Citrobacter sp.*	1		
Gram positive cocci (un-speciated)	1				

Table 2: Median values for blood culture study variables

Characteristic	All data *n=500*	Blood Culture Negative *n=461*	Blood Culture Positive *n=39*	OR (95% CI)
Age (years)	48	47	51	1.01 (0.99, 1.02)
Temperature (C)	37.4	37.4	37.4	1.14 (0.92, 1.45)
Pulse (bpm)	110	109	117	1.02 (1, 1.04)
Respiratory rate (bpm)	22	22	24	1.02 (0.98, 1.06)
Oxygen Saturations	96	96	96	0.99 (0.94, 1.05)
Chills present	210	190	20	1.57 (0.83, 3)
Diabetic	111	96	15	2.08 (1.04, 4.01)
HIV Infected	96	87	9	1.33 (0.6, 2.72)
Diastolic BP <60 mmHg	138	118	20	2.48 (1.3, 4.7)
Systolic BP <90 mmHg	38	30	8	3.26 (1.31, 7.34)
Biliary Source	19	12	7	9.42 (3.25, 26.83)
LRTI	206	195	11	1 (ref)
Meningitis	28	24	4	2.36 (0.63, 7.24)
Unknown	103	93	10	1.59 (0.66, 3.75)
UTI	56	51	5	1.44 (0.45, 4.02)

Table 3: Breakdown of patient categories in the IV-to-oral antibiotic switch therapy study

Category	# of Patients
Total patients on IV Antibiotics	129
Could Switch	71
IV-to-Oral switch made appropriately	4
IV-to-Oral switch not made appropriately	67
Could Not Switch	58

Table 4: Results of follow up studies on the IV-to-oral antibiotic switch therapy study showing improvements in mean number of days patients continued on IV antibiotics inappropriately and the percentage of patients switched over to oral antibiotics appropriately after meeting switch therapy criteria

Study Group	Mean # of Days Inappropriate	% of Patients Switched Appropriately
Initial Study	2.38 days	7%
Pre-Audit Study	1.58 days	31%
Post-Audit Study	0.47 days	63%

LIST OF FIGURES

Figure 1: Healthcare spending per capita in the United States from 1995 to 2013. Data from World Bank database.[1]

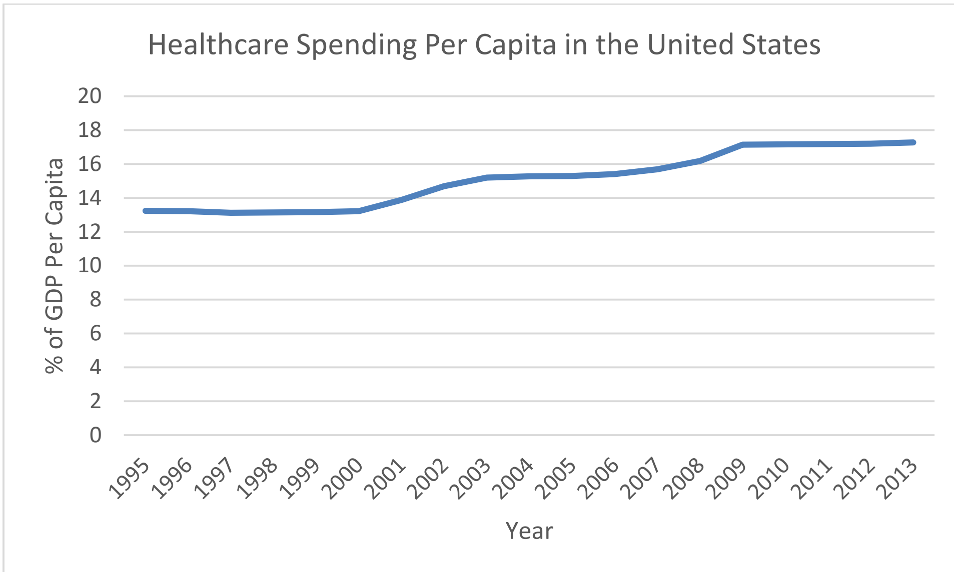


Figure 2: Percent of South Africa's GDP spent on healthcare per capita compared to other countries. Data from World Bank database.[1]

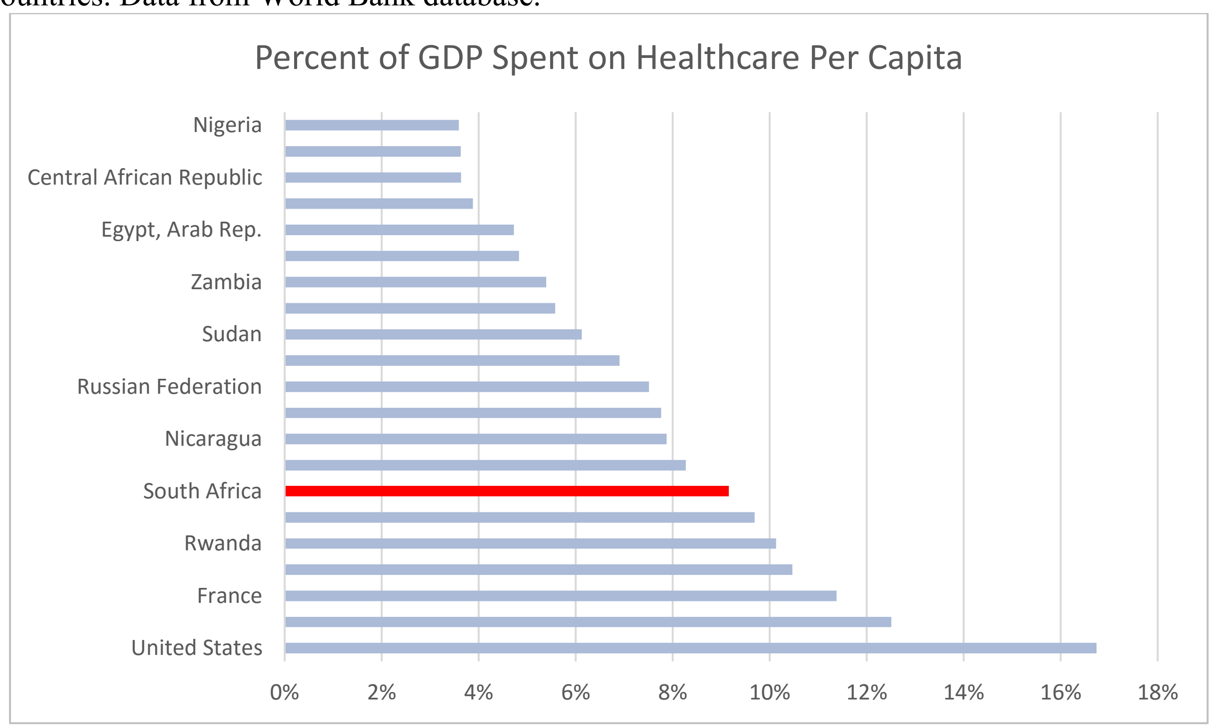


Figure 3: Blood culture data collection form used by emergency department physicians when collecting blood cultures to record clinical data known about patient at time of blood draw

Blood culture data collection form				
Date	Hospital number		Age/DoB	M /F
Presenting complaint				
Antibiotics last 48hrs	Y	N		
Chills present	Y	N		
Most likely source of infection (circle one)				
Lungs	Pneumonia	Bronchitis	AECOPD	
Urinary tract	Lower	Upper		
CVS	Endocarditis			
Skin/soft tissue	Cellulitis	Wet gangrene	Nec. fasciitis	Abscess
Devices	IV line			
Intraabdominal	Bowel	Biliary	Gynae	Unclear
CNS	Meningitis			
Unclear source	Sepsis syndrome			
Other (specify)				
Co-morbid conditions (circle)				
Diabetes I	HIV			
Diabetes II	CCF			
COPD	PVD			
IHD	Other			
Active TB				
Active malignancy				
Chronic renal disease				
Pre-admission				
Urinary catheter	Y	N		
Peripheral IV catheter	Y	N		
Central IV catheter	Y	N		
Residence	Hospital/Long stay facility	Home		
Examination				
Temperature	C			
Blood pressure	mm Hg			
Pulse rate	/min			
Respiratory rate	/min			
Oxygen saturations	%			
Inspired oxygen	RA	% O_2		
Confusion	Y	N		

Figure 4: Categorization of positive blood culture results reflecting the extent of how culture results impacted management

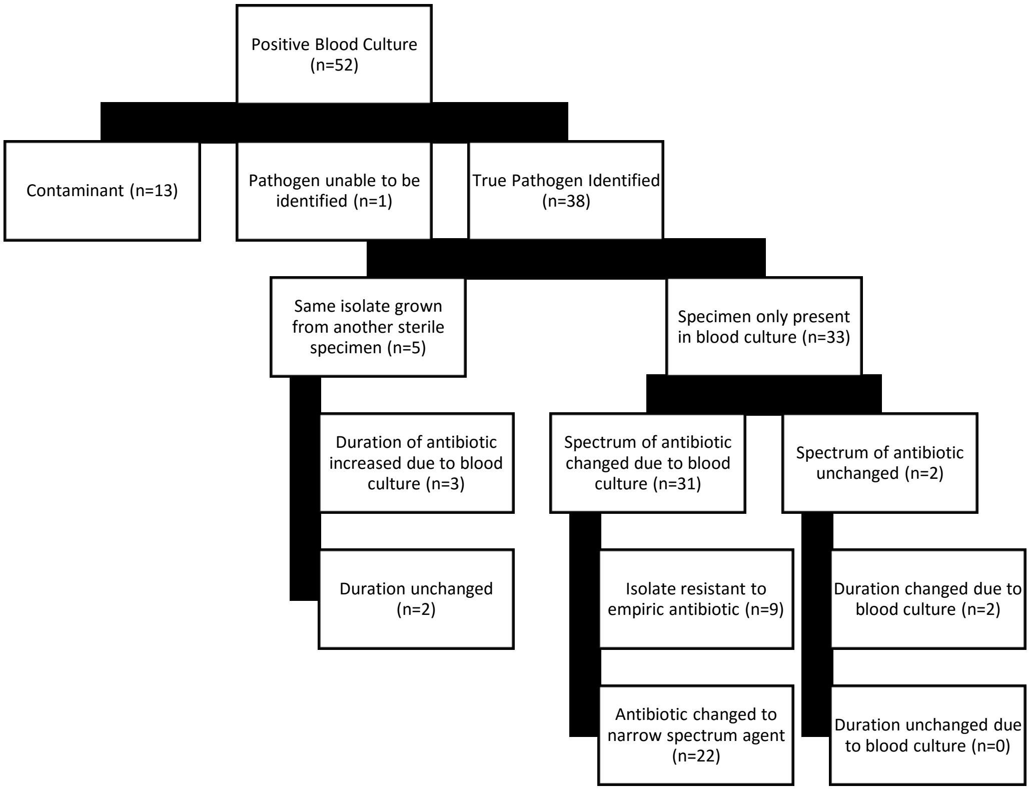


Figure 5: Classification of patient categories based on their eligibility for switch therapy

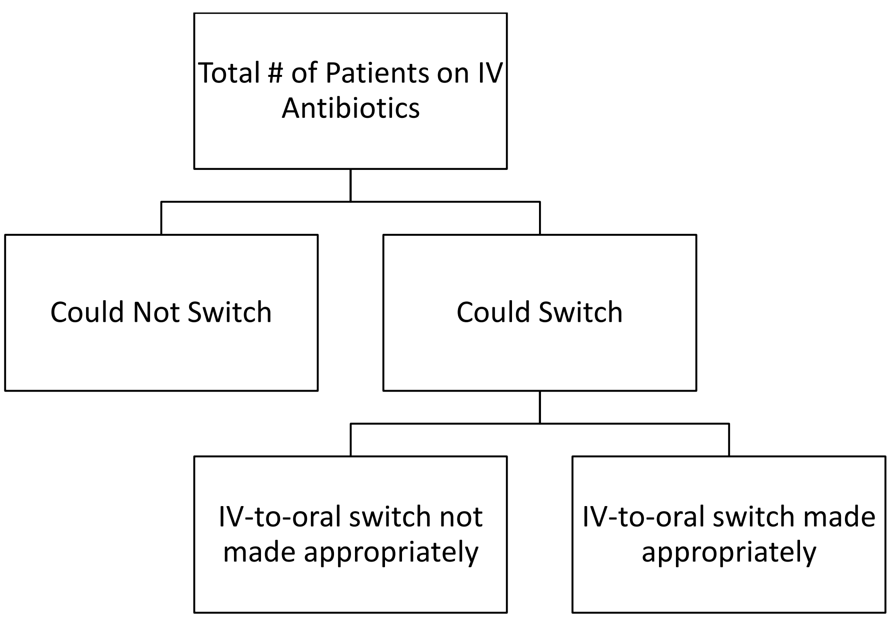


Figure 6: Breakdown of indicated sources of infections for patients in the "Not Switched Appropriately" category

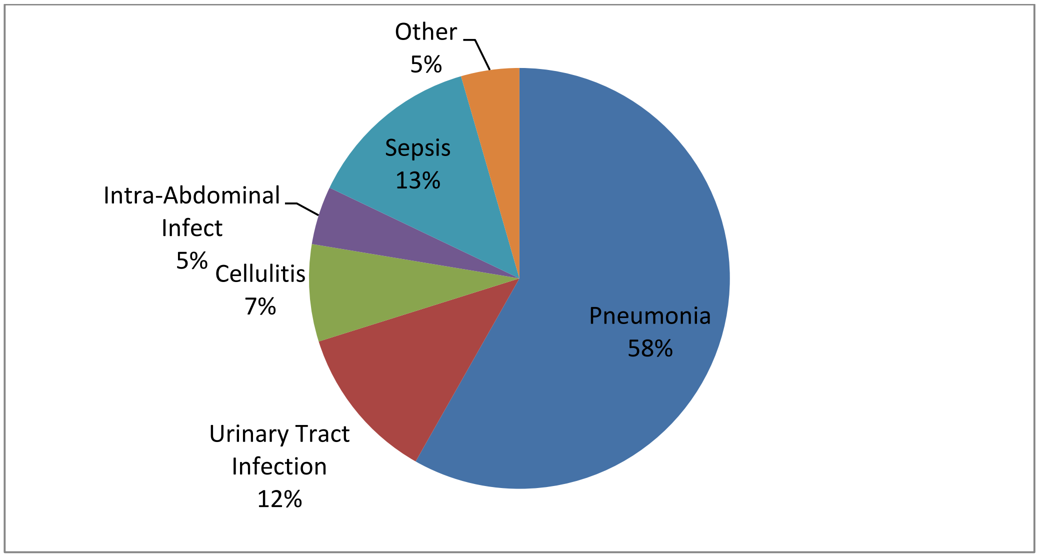
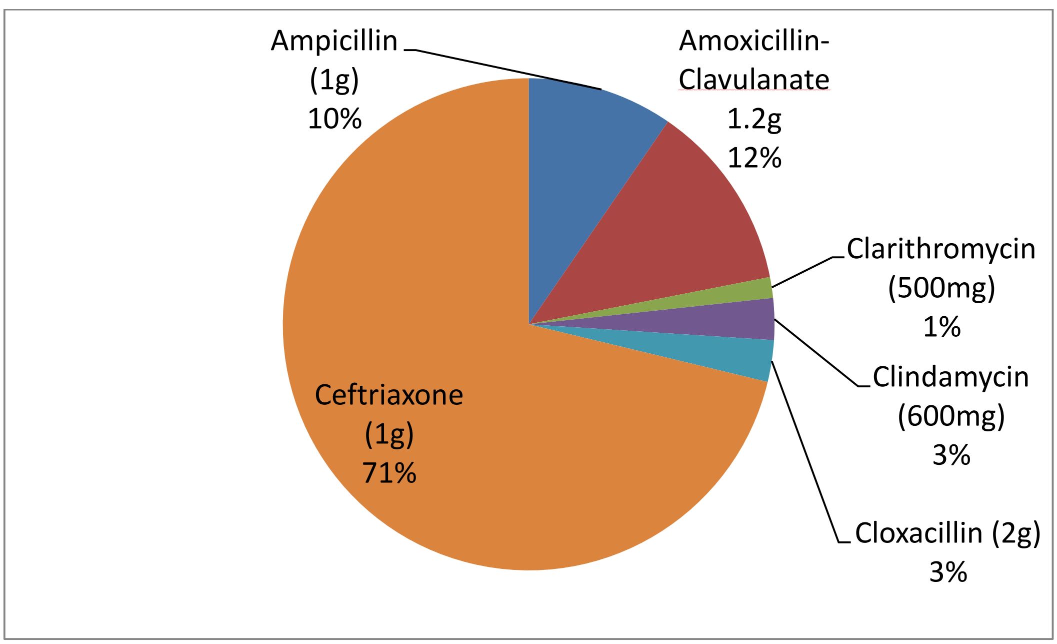


Figure 7: Breakdown of empiric antibiotics used for patients in the "Not Switched Appropriately" category



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