

**ANTIBIOTIC USAGE IN AN INTENSIVE CARE UNIT OF A TERTIARY LEVEL
PUBLIC HOSPITAL**

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DECLARATION

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DEDICATION

This research report is dedicated to my husband, my kids, my parents and my siblings. Your love, prayers and support has made all this come together and I will forever remain grateful.

To my in-laws and my entire family, the immense love, sacrifices and prayers have anchored me through the journey of living. This research report is also dedicated to my colleagues and every staff member of Helen Joseph Hospital. I am elated to be one of you.

“My dad always said that hard work beats talent when talent doesn't work hard enough”.

Katee Sackhoff

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LIST OF DEFINITIONS

Antibiotics: Medications that are used to kill bacterial microorganisms.

Antibiotic containment: The curbed use of antibiotics to reduce antibiotic resistance.

Antibiotic resistance: This occurs when a bacteria changes to adapt to antibiotics rendering the drug not useful.

Antibiogram: This is a summary of cumulative proportion of microorganisms that is susceptible to particular antibiotics

Antibiotic stewardship: A synchronized program which promotes the efficacious use of antibiotics to prolong shelf life.

Concurrent antibiotic use: This is the use of more than one antibiotic simultaneously.

Definitive therapy: Prescription of antibiotics that is guided by a culture result.

Empiric therapy: Use of antibiotics that is not guided by a culture result but through matching the narrowest spectrum antibiotic to the most likely pathogen.

Intensive care unit (ICU): Section of the hospital which provide intensive care to the very ill patients.

Prophylactic therapy: Use of antibiotics that is given once off to protect against infection normally given prior to certain surgical procedures.

LIST OF ANTIBIOTIC ABBREVIATIONS

KEY	ANTIBIOTIC	ANTIBIOTIC GROUP
Am/Cla	Amoxicillin and clavulanic acid	Penicillin with a β -lactamase inhibitor
Amp/Amo	Ampicillin or amoxicillin	Penicillin
Azit	Azithromycin	Macrolide
Cefa	Cefazolin	First-generation cephalosporin
Ceftaz	Ceftazidime	Third-generation cephalosporin
Ceftri	Ceftriaxone	Third-generation cephalosporin
Cipro	Ciprofloxacin	Fluoroquinolone
Clin	Clindamycin	Lincomycin
Clox	Cloxacillin	Penicillinase-resistant penicillin
Colix	Colistin	Polypeptide
Etap	Ertapenem	Carbapenem
Imip	Imipenem/Cilastatin	Carbapenem
Linez	Linezolid	Oxazolidone
Ppt	Piperacillin tazobactam	Penicillin with a β -lactamase inhibitor
Tobra	Tobramycin	Aminoglycoside
Vanco	Vancomycin	Glycopeptide

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ABSTRACT

Introduction: Antibiotic resistance presents a great challenge as the World Health Organization declared antibiotic resistance a global threat. Considering the high disease burden, prescribers are pressured to treat empirically rather than definitively especially in the intensive care units (ICU) where critically ill patients need rapid treatment.

Aim: The aim of this study was to document the utilization of antibiotics in a tertiary level hospital intensive care unit.

Method: This was a retrospective record review and data was collected for a two-month period in 2016 and 2017. Information was transcribed from the ICU charts. Variables included antibiotic chosen, number of antibiotics per patient, duration and frequency of treatment as well as information on the microorganisms involved. Data was analysed quantitatively using mean, median and frequency.

Result: The majority (67% in 2016 and 75% in 2017) of patients admitted to the Helen Joseph Hospital (HJH) ICU during the study period were on antibiotics and the majority were treated empirically. The most frequently used antibiotics were amoxicillin/clavulanic acid followed by piperacillin/tazobactam. The majority of antibiotics stocked in the ICU were started on day zero of admission compared to the restricted antibiotics. The average antibiotic per patient was one and a maximum of three antibiotics was used concurrently. The average length of stay in HJH ICU was two days. *Klebsiella pneumoniae* (17%), *Enterobacter cloacae* (15%), *Staphylococcus aureus* (11%), *Escherichia coli* (9%) and *Pseudomonas aeruginosa* (6%) were the frequently most isolated pathogens.

Conclusion: The study concluded that restriction of antibiotics does improve antibiotic utilization. Also the length of stay in the HJH ICU is short. Concurrent use of antibiotics was low. Furthermore, there were some antibiotics utilization patterns seen which are not

supportive for a successful antibiotic stewardship. If there are no interventions informed by utilization studies, same patterns will continue.

CHAPTER 1: INTRODUCTION

This chapter is structured to understand the impending threat of antibiotic resistance and the impact of utilization of antibiotics in the intensive care unit (ICU). It also highlights the factors which have fuelled the rise in the global microorganism resistance. This chapter concludes with an outline of the problem statement, research question as well as the aim and objectives of the study.

1.1. Background

The rapid development of antibiotics in the past century has meant that infectious diseases that once had high mortality and morbidity rates are treatable with antibiotics with a high success rates (Davies, 2007; Lau *et al.*, 2004; Pignatari and Myake, 2015). In developing countries like South Africa, where levels of poverty are high, antibiotics have effectively been able to reduce the morbidity and mortality of poverty influenced infections (Ventola, 2015).

Globally antibiotic consumption rose by 36% between the years 2000 and 2010 (Meyer and Sibanda, 2016). In South Africa the use of antibiotics increased with population growth between the years 2000 and 2010 (O'Neill, 2014). Also, lack of regulation of antibiotics, convenient availability as well as the ability to cure infections have made antibiotics an easy choice and this have further increased over consumption (Ventola, 2015).

In the last ten years the increase in both the capacity and number value of multiresistant organisms has become a global health issue (Roca *et al.*, 2015). The excessive use of antibiotics which includes over prescribing, long duration of antibiotic use and wrong choice of antibiotics has led to the increase of resistant strains (Edgar *et al.*, 2008; Essack, 2006; Farrell, 2009; Mabila *et al.*, 2016; Messina *et al.*, 2017). Multidrug resistant microorganisms, which are only sensitive to the last-line and older more toxic antibiotics like colistin, are on the rise (O'Neill, 2014).

The ICUs of the hospitals admit the critically sick and the use of multiple antibiotics in these units for fear of not knowing which antibiotics will work has further disadvantaged the fight against antibiotic resistance (Thomas *et al.*, 2015; Paruk *et al.*, 2012). Moreover, in the ICUs, antibiotic stewardship intervention like de-escalation to narrower spectrum antibiotics when culture results are received is not generally practiced. Also, failure to stop previous antibiotics before starting a new one has further led to patients admitted in the ICU receiving multiple antibiotics (Thomas *et al.*, 2015; Paruk *et al.*, 2012).

A study which looked at the use of antibiotics in the ICU of hospitals including the public and private sector in five different provinces noted that antibiotics were prescribed to more than 50% of the patients and in these patients, 72% received it for an inappropriate duration (Paruk *et al.*, 2012). Antibiotics are prescribed to 44-97% of the patients admitted to hospital and are mostly unnecessary in a developing country like South Africa (Hadi *et al.*, 2008). In South Africa, a study showed the prevalence of inappropriate antibiotic prescription practices to be 60% in the private sector and 40% in the public sector (Paruk *et al.*, 2012). Factors that have been noted to pressure the physicians' decision to irrationally prescribe antibiotics include patient demands, uncertainty as to which patients would gain from antimicrobial therapy, daily pressures from clinical practice, patient complaints, physical observation, control of disease, physicians' self-confidence and the daily pressures from varying policies and research discoveries (Sosa and Travers, 2002; Simpson *et al.*, 2007).

The burden of antibiotic resistance impacts widely on certain clinical and economical outcomes of the patients and society. These consequences may include increased length of hospital stay, adverse events, and cost to the hospital, patient and society (Zilahi *et al.*, 2016). Furthermore, failure of an antibiotic leads to the usage of costlier substitutes which places an increased burden on the financial growth of the economy (Essack, 2006). In South Africa, microorganisms especially the Gram-negative microbes which are multi-resistant to

antibiotics are a great health problem and are increasing the toll of human mortality and morbidity (Brink *et al.*, 2012; Davies, 2007; Paruk *et al.*, 2012; Zhang *et al.*, 2006).

The use and abuse of antibiotics have raised antibiotics resistance to one of the greatest health problems. It is envisaged that one in three people will die from a multidrug resistant causing disease by 2050 (O'Neill, 2014). The slide to the pre-antibiotic era where there were no antibiotics will affect new medical progress. New technological improvements like transplants and chemotherapy will be made impossible due to the lack of effective choice of antibiotics (Gillon and Wyncol; 2016, Messina *et al.*, 2017).

Additionally, the rise of antibiotic resistance strains has not been matched by an increase in the discovery of original antibiotics. The past thirty years have seen a decrease in new antibiotics. If antibiotic usage together with the development of resistance is not monitored, this will lead back to the era where there were no antibiotics. Fewer antibiotics in the pipeline and low efficacy due to resistance of available antibiotic are factors burdening the health system (Adeniji, 2017; Lee *et al.*, 2013; Mabila *et al.*, 2016).

Considering the different resistance patterns seen across countries, individual country strategies to improve and continue the therapeutic benefits of antibiotics are necessary (Chaudhry and Prajapat, 2017). The prevalence of infections in the South African (PISA) ICUs reported in the study done by Paruk *et al.*, (2012) affirmed strongly to reduce the emergence of antimicrobial resistance and recommendations were published which included advising prescribers on the correct empirical choice, dosing methods, de-escalation and duration of treatment.

The principles of antibiotic stewardship include the surveillance of antibiotic use, improved antibiotic policies and management as well as antibiotic management programmes. The main aim of antibiotic stewardship is to improve the use of antibiotics through appropriate controls which includes choice of antibiotics, de-escalation, education and continuous antibiotics

usage monitoring (Richards, 2016; Boyles *et al.*, 2013). Pharmacist critical evaluation of prescriptions by checking basic antibiotic stewardship principles for example if cultures was sent before dosing antibiotics, duration of treatment, checking for accurate dosing, double antibiotic coverage, if antibiotic is prescribed empirically, definitively or prophylactically will improve and save the efficacy of antibiotics for the future (Boyles *et al.*, 2013). A study done in South Africa showed a decrease in overall consumption of antibiotics after starting routine ward rounds done by pharmacists. Through the help of antibiotic stewardship programs, global consumption of antibiotics has been reported to be reduced by 22-36% (Vitrat *et al.*, 2014). A stewardship program implemented in a hospital showed that restricting cephalosporin use decreased the development of resistant *Klebsiella* species. Remarkably in the same study, the use of imipenem/cilastatin increased by 141% during the same period which then increased the number of resistant *Pseudomonas aeruginosa* (Vitrat *et al.*, 2014). Even though there are no randomized controlled trials that have measured the clinical impact of antibiotic stewardship intervention like de-escalation in critically ill patients, various antibiotic stewardship programs have decreased antibiotic consumption and improved use of antibiotics by applying basic antibiotic stewardship principles (Boyles, 2013; Vitrat *et al.*, 2014).

To prolong the life span of the antibiotics available, antibiotic stewardship plays an important role. Monitoring antibiotic use and changes in resistance patterns is a key to understanding the underlying mechanisms by which resistance develops, persists and disseminates. If prescribing patterns are not monitored and kept under surveillance, more deadly diseases will arise from multidrug-resistant strains of microorganisms (Mabila *et al.*, 2016; Masterton, 2008; Yeo, 2016). Thus, there is a paramount need for studies to review prescribing practices.

1.2. Problem Statement

The global rise in resistance to antibiotics has made antibiotics, which are some of the most important drugs ever discovered, to be relatively ineffective. To prolong the efficacy of antibiotics, utilization of antibiotics needs to be measured and understood to ensure institutionalised evidence-based systems to curb the global problem of resistance. Resistant pathogens distributions vary greatly (Sulaiman, 2016). To date, there is little information on antibiotic prescription patterns especially in the ICUs of the public and private sector in South Africa (Paruk *et al.*, 2012).

Even with an abundance of research published worldwide on the usage of antibiotic in the ICU, there is a need for antibiotic utilization research in South Africa to monitor specific prescribing patterns. This information will guide local strategies, hence the relevance of this study to generate usage pattern data as per World Health Organization guidelines as an indicator for antimicrobial use.

1.3. Research Question

How were antibiotics used in the ICU at Helen Joseph Hospital across two-time periods without any intervention?

1.4. Aims and Objectives

The aim of this study was to determine the utilization of antibiotics in the ICU at Helen Joseph hospital.

To achieve the above aim, the following objectives were outlined:

1. Document which antibiotics are prescribed, their dosing frequency and duration of use as well as the number of antibiotics used per patient.

2. Record if antibiotics were prescribed empirically, prophylactically or definitively.
3. Document the microorganisms isolated.
4. Compare the utilization of antibiotics in the ICU between the two months (2016 and 2017).

1.5. Summary

The discovery of antibiotics was one of the marvels of medical discoveries, but the misuse of this miracle drug has compromised its place in the treatment of infections and diseases. In South Africa, which is further disadvantaged economically, antibiotic resistance will cause worse health outcomes to patients and the society. Pharmacists and other health professionals can play important roles in the usage of antibiotics and hence can improve prudent use.

Important strategies based on drug utilization studies helps to inform appropriate policies to prolong the life span of antibiotics.

The next chapter is the literature review.

CHAPTER 2 LITERATURE REVIEW

2.1. Introduction

This section draws attention to the utilization of antibiotics and antibiotic resistance as it affects the ICU and the world. This chapter also highlights antibiotic resistance, its prevalence and mechanisms of resistance and dissemination. The different strategies employed globally and in South Africa through surveillance and antibiotic stewardship are further discussed here.

2.2. Infections and infectious disease burden

Infectious diseases cause 57 million annual deaths in a global population of 6.2 billion (Wheelis, 2011). In addition to established infections, developing and re-emerging infections have caused global concern. Presenting a threat presently are not only the new evolving diseases but also diseases thought to have been curbed and these organisms are becoming more virulent. The epidemics of present and previously named infectious diseases that intermittently emerge worsen the global problem of infections (Kombe and Darrow, 2001; Ventola, 2015).

Patients admitted in the ICU possibly develop infection due to the conditions why they are admitted in the ICU, immune compromised health status due to critical illness and invasive procedures which are common in the ICU (Vincent *et al.*, 2016). Health care facilities particularly the ICU remain an important location for the development of antimicrobial resistance (Kollef, 2001).

However, since selective pressure may occur, failure in infection control will allow for dissemination of resistant bacteria. Though the effective use of antibiotics with better infection control strategies informed by adequate utilization and surveillance studies through

antibiotic stewardship can be successful in treating numerous infections (Arbee *et al.*, 2012; Essack *et al.*, 2005; Mabila *et al.*, 2016)

2.2.1. *Diagnosis of infections*

The diagnosis of infection in the critical ill can be challenging due to the impact of the illness on pharmacokinetics and pharmacodynamics parameters, lack of confirmatory result and immunosuppression from critical illness (Vincent *et al.*, 2016). However, a timeous culture result for patients admitted to the ICU is important as this will allow for the correct choice of antibiotic therapy (Vincent *et al.*, 2016).

A raise in temperature and white blood cell counts which are typical signs of infections are not specific and can occur in other condition of people that are critically ill. In the absence of cultures within the first day, clinicians use infection markers to diagnose the presence of an infection (Markanday, 2015; Vincent *et al.*, 2016).

Biomarkers are a group of protein that react to inflammation and injury by increasing or decreasing in concentration. C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), procalcitonin (PCT) are some important biomarkers which are used by clinicians to establish infections in patients (Markanday, 2015). This group of proteins respond to inflammation and injury to different degrees for example the CRP can increase a few thousand fold while the ceruloplasmin levels rise 25%-50% and the fibrinogen levels rise only a small amount (Markanday, 2015).

The CRP levels are better than the ESR levels as it is an improved measure of acute phase response as well being more sensitive to inflammation. The PCT may also be more useful since it more specific for example it does not rise in non-infectious inflammatory conditions e.g. gout and arthritis. However, there have been reports in the literature of transient rises in procalcitonin in massive trauma like burns and surgery. New technologies have also improved

assays where results can be obtained in thirty minutes or less (Gilbert, 2011; Markanday, 2015; Simon *et al.*, 2004).

2.3. Antibiotic usage in the ICU

The ICU accommodates patients who have critical medical problems and are housed in a small restricted area. Dissemination of bacteria and emergence of resistance is exacerbated due to overcrowded nature of the area, reduced nursing staff due to economic burden, increased critically ill patients who are admitted for a longer periods and overuse of antibiotics (Kollef, 2001; Sarin *et al.*, 2013). The widespread use of antibiotics to reduce and cure infection has made antibiotics the most frequently prescribed drug in the ICU (Kolak, 2010; Perekoa *et al.*, 2015). Decisions for prescribing antibiotics are mostly empiric and based on behavioural pressure and experience (Sarin *et al.*, 2013; Williams *et al.*, 2011)

Antibiotic resistance seen in the ICU is increasing the global public health threat by increasing the mortality and morbidity of patients being treated with antibiotics (Chaudhry and Prajapat, 2017). Even though the ICU houses a small number of patients, antibiotics are used in larger numbers as clinicians are pressured to prescribe antibiotics because patients are very ill and often colonized with difficult to treat pathogens (Kollef, 2001). Also, the change in pharmacokinetics of the critically ill patients plays a factor hence monitoring and optimizing antibiotic usage in the ICU is advantageous (Calbo and Garau, 2005).

Therefore, adequate monitoring and regulation of antibiotic usage, regional surveillance which should include the ICU is necessary to contain the growing burden of antibiotic resistance and contain the limited antibiotics available (Chaudhry and Prajapat, 2017; Chunnillall *et al.*, 2015; Gillon and Wyncoll, 2016).

2.4. Antibiotic resistance

Antibiotic resistance is a situation where the microorganism changes in some way to survive the prevailing conditions despite the presence of antibiotics. Resistant pathogens continue to regrow and regenerate in the presence of adequate therapeutic dose of antibiotics (Van Wyk, 2015). The increase in antimicrobial resistance is seen in the ICUs due to the exposure to numerous broad-spectrum antibiotics. Hence the incidence of culturing multidrug resistant strains is usually higher in the ICUs compared to other wards in the hospital and this has created a huge burden (Chastre, 2008; Sarin *et al.*, 2013).

The 20th and the 21st century have experienced treatment failure of antibiotics due to increasing burden of antibiotic resistance all over the world especially in the ICUs (Lee *et al.*, 2013). Today, methicillin-resistant *Staphylococci aureus* (MRSA) is prevalent around the world. MRSA which was once present only in the ICUs of the hospital have moved into communities thereby becoming even more transmissible and hence a reason for concern (Bloomfields, 2006). A study by Lodise *et al.*, (2002) compared the outcome of infections caused by very resistant enterococcus (VRE) to the susceptible strain and demonstrated that VRE affects treatment outcomes negatively.

A primary function of bacteria is to become more complex to ensure survival (Van Wyk, 2015). The use of efflux pumps, production of enzymes, genetic alteration and development of alternative pathways are some mechanisms which microorganisms utilize to become resistant (Van Wyk, 2015).

2.4.1. Risk factors driving antibiotic resistance

A variation in patient characteristics, hospital procedures and environmental setting creates a risk factor in the development of resistant pathogens in the hospital. In the hospital setting, factors such as dialysis, intensive care stay, mechanical ventilation, urinary catheterisation, previous and current antibiotic therapy, venous and peripheral catheters, previous

hospitalization, wounds, immune compromised therapy, comorbidities, severity of illness and surgery have been reported as risk factors for the development of resistant pathogens (Essack, 2006).

2.4.2. Antibiotic use and selection pressure

Selection pressure refers to the condition that allows certain organisms with certain characteristics to survive. When microorganisms are exposed to antibiotics, susceptible populations are eradicated leaving the resistant strain to replicate passing on genetic material to offspring (Essack, 2006). Antibiotic use is the key factor driving selection pressure (Tello *et al.*, 2012)

Evidence in the literature links the inappropriate use of antibiotics to the increase of resistance with resistant strains prevalent in wards where antibiotics are used in large doses such as the intensive care (Perekoa *et al.*, 2015; Zilahi *et al.*, 2016). However, the linkage of the overuse of antibiotics to the increase in antibiotic resistance is complex and controversial. Although it is generally accepted that reducing the use of antibiotics and increasing prudent prescribing would reduce selection pressure which leads to the increase in antibiotic resistant strains (Tello *et al.*, 2012; Zilahi *et al.*, 2016).

2.4.3 Pharmacodynamics, pharmacokinetics and clinical efficacy

Pharmacodynamics refers to the relationship between the quantity of drug in the cell tissue, the toxicity and the effect reached at the site of action (Grau *et al.*, 2007). Pharmacokinetic characteristics refer to the absorption, distribution and elimination of the antibiotics. These properties regulate antibiotics access through different cell barriers, their effect against microorganisms, hepatic and renal clearance and their higher or lower distribution properties which are important in critically ill patients admitted in the ICU (Grau *et al.*, 2007).

The clinical efficacy of antibiotic therapy is achieved in its adequate concentration in the plasma to achieve adequate therapeutic levels. In the clinically ill who are in the ICU, the

recommended therapeutic level may not be adequate due to fluid shifts, including the opening of extracorporeal circuits which alters the volume of distribution. This predisposes further to microorganism resistance due to sub therapeutic levels of antibiotics (Gillon and Wyncoll, 2016; Alexander *et al.*, 2008). Hence knowledge of the pharmacodynamics and pharmacokinetics properties of antibiotics is important to guide adequate antibiotic choice and dosing (Levison and Levison, 2009).

2.5. Antibiotic utilization patterns

Since the rise of antibiotic use is linked to the increase in antibiotic resistance, reviewing antibiotic utilization patterns is important (Meher *et al.*, 2014). The true impact of antibiotic resistance and its effect on the health outcome of the patients is not properly understood hence the prescription pattern of antibiotics needs to be known and compared to data from other parts of the world (Truter, 2015).

The PISA study which looked at the utilization of antibiotics in South African ICUs demonstrated that average antibiotic per prescription was three (Paruk *et al.*, 2012) while another study done in an ICU in India by Anand *et al.*, (2016) demonstrated 1.73 antibiotics per prescription. Comparing the different types of antibiotics utilized, a study done by Ansari, (2001) studied the utilization of antibiotics in the different wards of a teaching hospital in Iran where ampicillin, cefazolin, ceftizoxime, gentamicin, and cephalexin was the most frequently used antibiotics. In a study in another university teaching hospital in Iran by Ebrahimzadeh *et al.*, (2008), the most commonly used antibiotics was cefazolin followed by ampicillin, ceftizoxime and gentamicin. In both the studies, the ICU featured among the wards which used antibiotics the most. An antibiotic utilization study done in South Africa in retail pharmacies across the country reported that beta-lactam antibiotics were the most frequently prescribed antibiotics followed by antivirals and then fluoroquinolones (Truter, 2015). The

different measures of antibiotic use as they relate to antibiotic resistance is important knowledge as it ensures better interventions are made (Schellack *et al.*, 2017).

2.6. Initialisation of antibiotic therapy

Empirical antibiotic treatment is the use of an antibiotic which is not guided by a culture result and based on experience while definitive antibiotic therapy is a therapy guided by a culture result. Prophylactic use of antibiotic is the use of antibiotics to prevent anticipated infection. Culture results from the laboratory are usually not available within 24-48 hours of admission and withholding antibiotics from the critically ill patient raises mortality and morbidity rates. Empiric use and choice of antibiotics which is informed by the hospital antibiogram to cover suspected microorganism offers a safer health outcome in patients (Leekha *et al.*, 2011). Different to this thought, the time for initiation of antibiotics will require a complex consideration if to start antibiotics immediately after cultures are taken (aggressive option) or after infection is confirmed (conservative option). The aggressive route of starting antibiotics as soon as cultures are obtained will lead to unnecessary and long duration of antibiotic use. However, the second more conservative route might lead to harmful delay of antibiotics (Hranjec *et al.*, 2012). Notably, a study done by Hranjec and Sawyer, (2014) found that in normotensive patient with suspected infection, waiting to secure results which confirms infection reduced mortality in comparison with the aggressive way of starting antibiotics on suspicion of an infection (Hranjec *et al.*, 2012). The challenge of treating the very sick patients in the ICU leads to the overuse of antibiotics empirically rather than definitively.

While some diagnoses require immediate use of antibiotics, some diagnoses can await a culture result. Initiating empiric antibiotic choice in certain diagnoses such as sepsis and febrile neutropenia should be immediate. However, in diagnoses such as endocarditis and

osteomyelitis, where the patient may have been ill for many weeks, antibiotic treatment can be withheld until several blood cultures have been received. In these cases, early initiation of antibiotics can suppress microorganism growth and reduce the chances of finding the right diagnosis (Leekha *et al.*, 2011)

2.7. Duration of antibiotic therapy

Duration of antibiotics is important as it is linked to increased emergence of antibiotic resistance, adverse effects and overall cost to the health system (Zilahi *et al.*, 2016). The ideal duration of antibiotic is still not understood adequately as there is no randomized controlled data supporting this view due to ethical reasons (Havey *et al.*, 2013). The length of antibiotics used in the critically ill with bloodstream infections is often different in various scenarios but frequently extended (Havey *et al.*, 2013). A study done by Chin *et al.*, (2010) reported that the duration of antibiotics varied from 1-42 days.

The best way to reduce overuse of antibiotics is to discontinue antibiotics when no longer required using blood cultures with clinical progress, keeping the antibiotic course as short as possible and not starting antibiotics when not essential for example when treating colonization (Zilahi *et al.*, 2016). A microbiological result alone does not justify elongated duration of antibiotics therapy because clinical cure does not necessarily mean microorganism abolition. The use of biomarkers may be used when deciding on the appropriate duration for antibiotics, but they should be interpreted thoughtfully (Zilahi *et al.*, 2016).

A study done by Chastre *et al.*, (2003) compared two durations of antibiotic therapy in the treatment of ventilated acquired pneumonia. When comparing the recurrence of ventilated acquired pneumonia in patients treated with antibiotics for eight days and 15 days, the frequency of recurrence of pulmonary infections by resistant microorganism from patients treated for eight days was less than those patients treated for longer periods. One of the

various advantages of reducing the duration of antibiotics is the decrease in selective pressure for resistant pathogens (Puskarich *et al.*, 2011).

There are certain situations where a long duration of antibiotic therapy is beneficial. There is evidence that long duration of antibiotics is indicated for treatment of infective endocarditis, *Legionella* pneumonia, osteomyelitis and fungal infections however, long duration of treatment with antibiotics predisposes for antibiotic resistance and adverse effect of the medication (Lawrence and Kollef, 2009). There is an increasing indication from the literature that reduction in the duration of the course of antibiotics in the ICU can thus reduce the negative effects of antibiotic overuse (Zilahi *et al.*, 2016).

2.8. Surveillance

Surveillance as defined by Pittet (2005) ‘is an on-going, systematic, collection, analysis and interpretation of data essential for planning, implementation and evaluation of public health practices which is closely integrated with the timeous dissemination of data to the necessary parties’. In recent times it has been more inclusively defined by Meyer and Sibanda (2016) as ‘a multidisciplinary systemic approach to optimising the appropriate use of all antimicrobials to improve patient outcome and limit the development of resistant pathogens while ensuring patient safety’.

Surveillance is fundamental to any antibiotic resistance strategy providing information required through data from drug utilization studies to trace and monitor an antibiotic resistance problem (Meyer and Sibanda, 2016; Smith and Coast, 2002). Thus the objective of surveillance is to facilitate the containment of antibiotic resistance by informing different strategies necessary to improve rational prescribing (rational drug use, reduction in the duration of therapy, dosing regimen using the pharmacodynamics and pharmacokinetics) of the particular population, implementation of infection control policies and procedures and the

amendment to standard treatment guidelines following data collected (Essack, 2006; Johnson, 2015; Pittet, 2005).

Several surveillance programs have been developed for a precise goal, for example, in Germany, the surveillance of antibiotic use and bacterial resistance in ICUs (SARI) has been designed to find a connection between antibiotic use in the ICU and the emergence of antibiotic resistance (Meyer *et al.*, 2006). Even though establishing antibiotic use and the development of resistance is complex, the prudent use of antibiotics in the ICU should be promoted to reduce resistant pathogens (Meyer *et al.*, 2006).

More recently, South Africa has also joined the international call by the WHO to reduce antibiotic resistance with a more national approach with the South African Antibiotic Stewardship Program (SAASP). This program has increased the knowledge of antibiotics use and put in place systems and guidelines to improve appropriate and judicious antibiotic use through harmonization of antibiotic guidelines, education, engaging in economic dialogue with the stakeholders and strengthening antibiotic stewardship in the public and private health sector (Fidssa.co.za, 2018)

In South Africa, a surveillance study was set up in KwaZulu-Natal to appraise the appropriateness of the standard treatment guidelines and the essential drug list in the public health system. Resistance profiles ranged from 14-100% with the district having more susceptible microorganisms than the tertiary hospitals. The study resolved that the standard treatment guidelines are not ideal for adequate therapeutic outcome as the resistance in the different hospitals varies widely (Essack *et al.*, 2005; Essack, 2006). The developed world has shown progress to international surveillance policies which is aimed at improving prudent antibiotic use, however, the developing countries like South Africa are still yet to attain a co-ordinated surveillance system (Chaudhary, 2016).

Furthermore, since resistant pathogen distributions vary differently and following sensitivity pattern from other regions will not be as effective, surveillance studies are needed in South Africa to monitor zone resistance patterns, guide local empirical therapy and to implement timely and adequate countermeasures (Chaudhry and Prajapat, 2017; Roukens *et al.*, 2017).

2.9. Antibiotic Stewardship

The first definition of antibiotic stewardship emanated in the 1997 as a systematic collection of strategies, guidelines, policies and tools to improve the prescribing of antibiotics to reduce resistance and improve rational use (Howard *et al.*, 2015).

The ICU uses antibiotics frequently and hence presents an ideal arena to rollout and monitor antibiotic stewardship strategies (Howard *et al.*, 2015). In South Africa, irrational and lack of cautious prescribing which includes the use of broad-spectrum antibiotics, the use of a combination of antibiotics and prolonged duration of therapy has further driven the emergence and dissemination of multidrug resistant bacteria in the ICU. This is clearly seen in the ICUs where even up to ten antibiotics are given concurrently (Ramsamy *et al.*, 2013, Paruk *et al.*, 2012).

The role of antibiotic stewardship is in the preventing and reducing the emergence of resistant microorganism, the reduction of antibiotic side effect and cost effective antibiotic usage. As new antibiotics that are effective might only be available in the next one to two decades, the onus is on every health practitioner to challenge irrational prescribing practices (Brink *et al.*, 2012; Kaki *et al.*, 2011). The most important ways of curbing antibiotic resistance are the use of policies which are informed by local antibiogram patterns which will then allow the effective choice of an empiric therapy and effective antibiotic stewardship (Ramsamy *et al.*, 2013).

2.9.1 Antibiotic stewardship intervention by pharmacist to improve antibiotic use

Pharmacists are the safe custodian of medicines and have impacted positively on good antibiotic stewardship. Stewardship development plans made by pharmacists can reduce antibiotic consumption, improve surgical site prophylaxis guideline adherence and improve antibiotic rational use and therapeutic monitoring of many antibiotics (Boyles *et al.*, 2013). Antibiotic Stewardship initiative and implementation takes a multidisciplinary team to achieve a positive impact (Boyles *et al.*, 2013; Kubin, 2011). Although in South Africa, clinical pharmacy is still in its early stages and faces various challenges, there is evidence that pharmacist-initiated intervention improves utilization of antibiotics. Pharmacist-initiated intervention to ensure appropriate use of antibiotics are seen in the studies done by Somai *et al.*, (2014), Zhou *et al.*, (2015) and in South Africa by Boyles *et al.*, (2013) were able to reduce antibiotic consumption and improve utilization.

2.10. Summary

The ICU hospitalizes the critically ill and this may lead to the excessive use of antibiotics and often inappropriate. Factors like not knowing how severe the microorganism causing the illness is pressure clinicians to prescribe antibiotics even when not necessary. This has fuelled the growth of antibiotic resistance in the intensive care unit. Information from drug utilization and surveillance studies has been used to successfully improve the utilization of antibiotics in hospitals. Antibiotic resistance shows regional differences so a blanket approach of using another countries antibiogram to choose or decide on the antibiotics usage in this country will be not be effective. South Africa has antibiotic stewardship rolled out in hospitals but synchronized information and strategies for curbing antimicrobial resistance is still a challenge. The interventions made by clinical pharmacist have shown successful improvement

in the compliance to appropriate antibiotic use. The next chapter is the methodology where the process and procedure followed for this study is stipulated.

CHAPTER 3 – METHODOLOGY

3.1. Introduction

This chapter is the methodology and explains the procedure followed in this study. It includes the study design, sampling, data sources, data collection, description of data collection tool, explanation of the process in issuing antibiotics to the wards, statistical analyses and ethical considerations.

3.2. Study design, setting and population

This was a sub study of a larger study to review the usage of antibiotics in the different public hospitals in Gauteng (Appendix 1). It was a retrospective record review which was conducted in the ICU of Helen Joseph Academic Tertiary Hospital (HJH) from 15th January 2016 to 15th of February 2016 and from 15th of January 2017 till the 15th of February 2017. These times was chosen across both years to ascertain if there were similarities with antibiotic utilization without any intervention been implemented.

HJH is a provincial tertiary level hospital in Auckland Park, Johannesburg. The hospital has 616 beds in total. The ICU is a ten-bedded unit and admits approximately ten patients per week.

This study included critically ill patients who were admitted straight to ICU or transferred from other wards to the ICU and who met the inclusion criteria. The ICU charts of patients admitted during the study periods were all analysed.

3.3. Sampling

All the ICU files of patients admitted within the stipulated study period were analysed. The exclusion criteria included:

- Patients below the age of eighteen.
- Patients whose ICU chart was not found
- Patients who had incomplete information on their ICU charts and this missing information could not be tracked on LABTRAK

3.4. Data sources

The ICU charts are used in the unit to document patient information, diagnosis, medications and interventions made by healthcare professionals. The chart contains patient information relating to the antibiotics prescribed, diagnosis, doctors notes and laboratory tests ordered.

Information relating to cultures and infection markers is frequently documented on the ICU chart. When information relating to laboratory tests was not found on the chart, it was accessed on the LABTRAK system. The LABTRAK system is the software which is used by the provincial hospital to receive patient results and communication from the National Health Laboratory services (NHLS).

3.5. Data collection

Data collection was for the two months and included all patients that were admitted in the ICU from the period of 15th January 2016 to 15th of February 2016 and from the 15th January 2017 to the 15th February 2017. All patients' ICU charts admitted in the study periods were pulled from archives in the records and filing department of HJH. Data was then collected and recorded using a modified version of the South African Antibiotic Stewardship Program (SAASP) antibiotic prescription form (Appendix 2).

The NHLS LABTRAK barcode stock on the patient's ICU charts was used to track the microbiology results. Alternatively, the patients' hospital number and/or surname was used to get required information from the software.

3.6. Data collection tool

The ICU chart records all the information that is necessary when prescribing antibiotics.

Using this as a data collection tool allowed the researchers to collect information on antibiotic use from the ICU charts. The South African Stewardship Program Antibiotic (SAASP) form was amended by removing patient names and date of birth to maintain confidentiality. The variables which were documented for each patient are included in Table 1 below.

Table 1: Description of variables

Variables	Description
Study number	Allocated by the researcher to maintain confidentiality.
Demographics	Gender and age
Usage of antibiotics	Doses, strengths, frequency and route of administration of all antibiotics prescribed.
Date of admission and date of discharge	The date of admission and date of discharge from the ICU per patient was used to calculate the average length of stay.
Microorganisms and sensitivities cultured	To ascertain sensitivity patterns of isolated microorganisms
Infection markers ordered	To determine the frequency in which infections markers were ordered
Diagnosis indicated	Diagnosis documented on the ICU chart

3.7. Process of antibiotic issue in Helen Joseph

Figure 1 explains the process followed when stock is ordered from the ICU.

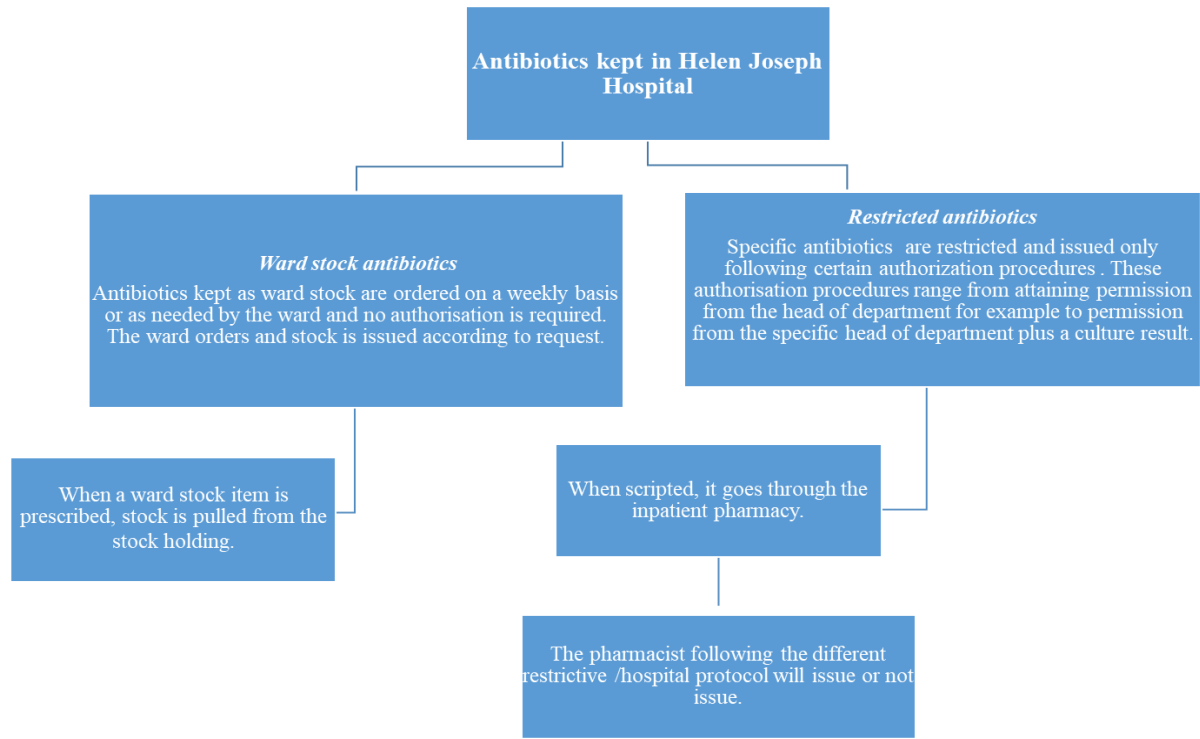


Figure 1: Process followed when antibiotics are issued in HJH

3.8. Statistical Analyses

The variables collected using the data collection tool (Appendix 2) were captured on a Microsoft Excel version 14.0.6112.5000 spread sheet and analysed using Stata/IC version 14.1. Descriptive statistics including means and medians with standard deviations and inter-quartile ranges (IQR) were calculated. The Shapiro-Wilk test was used to determine whether the variables followed a normal distribution. The variables which followed a normal distribution are reported using the mean ($\pm$ SD) and the variable that did not follow a normal distribution are expressed as median (interquartile range) and frequency (Cagan *et al.*, 2017). The Kruskal Wallis test was used to assess the statistical difference in the median number of days and on what decision the choice of antibiotics was based (Dalgaard, 2008).

3.9. Ethical consideration

Hospital approval to conduct this study was attained (Appendix 3). Ethics approval from Human Research Ethics Committee (Medical) of the University of the Witwatersrand was granted (M170395). Study numbers were allocated to patient files. No dates of birth or patient names were recorded on the collection tool. An information data sheet which correlated study number to patient name and birth date was accessible to only the researcher and the supervisors. This information sheet was locked away in a secured cupboard for five years. Anonymity and confidentiality of the patients was maintained throughout the study. Clinicians' details were not recorded.

CHAPTER 4: RESULTS

4.1. Introduction

This chapter analyses the result from the study carried out in the ICU of HJH. Issue of antibiotics to the ICU, files excluded/missing files, demographics, length of stay in the ICU, antibiotic use in the ICU, culture and sensitivity testing, infection markers are headings used to report this chapter.

4.2. Excluded and missing files

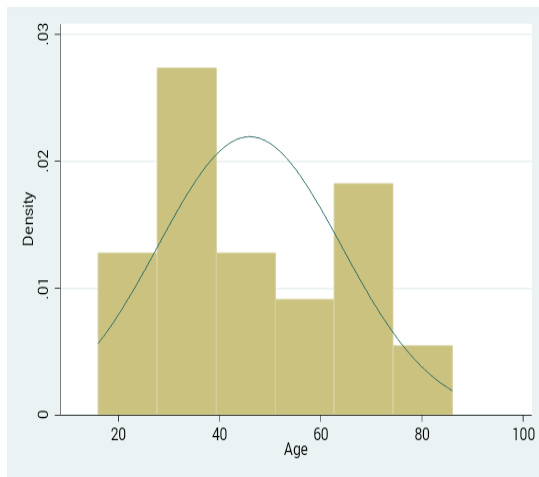
A total of 60 and 61 patients were recorded on the ICU admission book for 2016 and 2017 study periods respectively. There were a few ICU patient files which were excluded in 2016 (n=3) and 2017 (n=2). Files were excluded if the information within the file was incomplete or if the patient was under the age of 18 years. There were eleven files in 2016 and eight files 2017 which could not be located. The total number of files included in the study periods therefore was 46 for 2016 and 51 for 2017.

4.3. Demographics

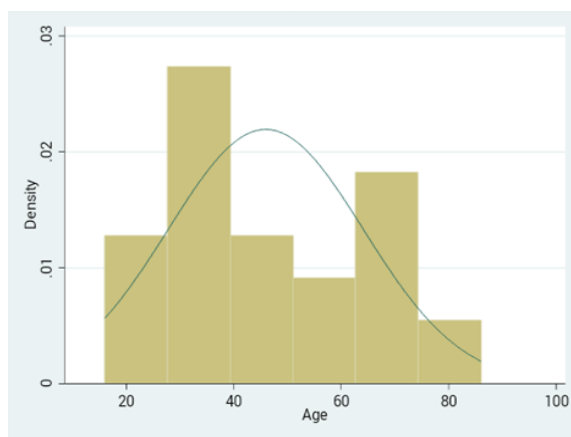
Table 2 summarizes the demographic data of the patients in the ICU for the two years. The age in the two study periods was normally distributed. The average age was 42 years in both 2016 and 2017. However, the biggest single group of patients were between 30 and 39 years (Figure 2). In 2016, the ICU had 8.7% more females admitted than males. In contrast there were 13.7 % more males than females admitted in 2017.

Table 2: Demographic data for the two study periods

Variables	2016 (n=46)	2017 (n=51)
Age, years mean (SD)	41.9 (16.50)	42.9 (18.18)
Female, n (%)	25 (54.3)	22 (43.1)
Male, n (%)	21 (45.75)	29 (56.9)



a. (Histogram of patient age in 2016 study period)



b. (Histogram of patient age in who, study period)

Figure 2: Histogram of patient age in (a) 2016 and (b) 2017 in years

4.4. Diagnosis recorded on the ICU chart

The primary diagnosis necessitating an ICU admission as documented on the ICU chart is summarised in Table 3. The recorded diagnosis on the ICU chart for the majority of the patients was the initial diagnosis for which the patient was admitted into the ICU. These diagnoses most often do not relate to the reason for antibiotics been used in these patients. From this retrospective study carried out in HJH ICU only 20% (n=9) of the charts in 2016 and 12% (n=6) in 2017 recorded diagnosis which were related to the antibiotic use. No diagnosis was recorded in the ICU chart for 9% (n=4) in 2016 and 6% (n=3) in 2017.

Table 3: Primary diagnosis recorded on the ICU charts for 2016

Diagnosis as recorded on the ICU charts	2016 (n=42)	2017 (n=48)
Sepsis	8	4
Post laparotomy and colostomy insertion	7	5
Epilepsy	4	0
Poisoning and overdose	3	1
Poly trauma and Fractures	3	6
Tumour and cancer	3	4
Chronic obstructive pulmonary disease	2	1
Motor vehicle accidents	2	0
Overdose	2	1
Cerebrovascular accident	1	1

Diagnosis as recorded on the ICU charts	2016 (n=42)	2017 (n=48)
Incision drainage	1	3
Meningitis	1	1
Rectal resection	1	0
Renal dysfunction	1	1
Respiratory distress	1	2
Subarachnoid bleed	1	0
Thyroid storm	1	0
Cerebral Oedema	0	1
Congenital heart failure	0	1
Mastectomy	0	1
Allergy	0	1
Gastroenteritis	0	1
Hemiarthroplasty	0	1
Hepatitis syndrome	0	1
Hydrocephalus	0	1
Malaria	0	2
Pneumonia	0	3
Pulmonary Tuberculosis	0	1
Stab wounds	0	2

Diagnosis as recorded on the ICU charts	2016 (n=42)	2017 (n=48)
Temporal burr hole (intracerebral)	0	1
Vertebral fusion	0	1

4.5. Length of stay in ICU

The admitted patients in the two study periods had similar lengths of stay in the ICU. The median number of days in the ICU for both the 2016 and the 2017 study period was two but the interquartile range (IQR) for 2016 was (1-5) and for 2016 was a (1-4) day. Longest stay was 19 days and 22 days in 2016 and 2017 respectively.

4.6. Antibiotic use in the ICU

In reviewing the antibiotics used in the 2016 and 2017 (Figure 3), a greater percentage of patients were on antibiotics in 2017 (74.5%) than 2016 (67.4%). Overall, a total of 52 antibiotics were used in 2016 and 56 in 2017. Out of the total antibiotics administered to the patients in the study period, 60% (n=31) in 2016 and 78% (n=44) in 2017 were kept as routine ward stock. Amoxicillin/clavulanic acid (42% in 2016 and 25% in 2017) and piperacillin/tazobactam (14% in 2016 and 16% in 2017) ranged among the most frequently prescribed antibiotic in the ICU during the 2016 and 2017 study period. Azithromycin (10% in 2016 and 14%) and ceftriaxone (6% in 2016 and 13% in 2017) also kept as ward stock antibiotics were frequently used during the study times.

Colistin (2% in 2016), linezolid (4% in 2016 and 2% in 2017) and meropenem (5% in 2017) which required stricter measures by pharmacy for issue were used less frequently compared to other antibiotics.

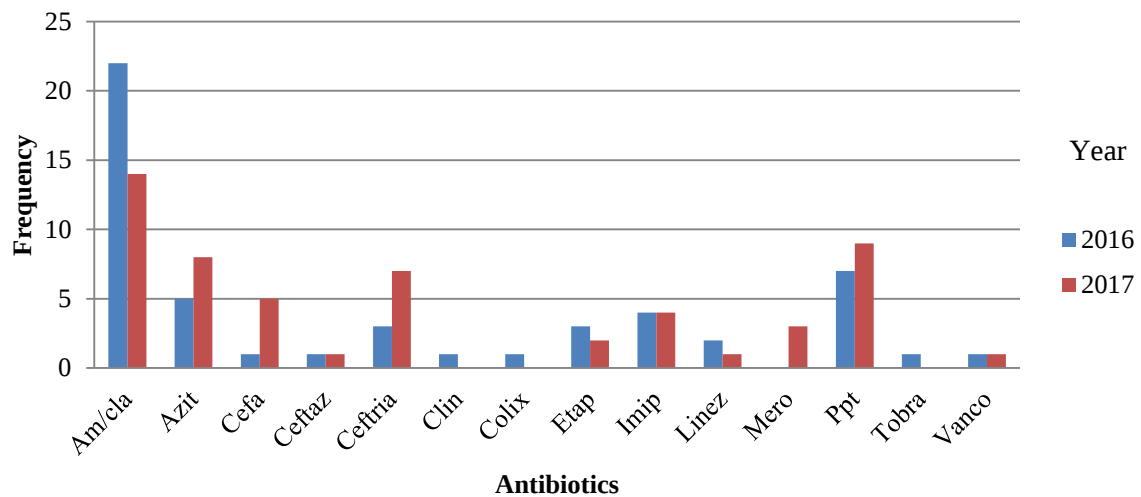


Figure 3: Frequency of antibiotics prescribed in the ICU

4.7. Number of antibiotics used per patient during ICU stay

The number of antibiotics used per patient during their ICU stay is shown in Figure 4. The average antibiotic per patient in 2016 was 1.08 and in 2017 was 1.10. In both study periods no more than a total of four antibiotics were administered to a patient during their ICU stay. Most patients admitted in 2016 (44%) and 2017 (51%) were on one antibiotic during the ICU admission period.

Concurrent use of antibiotics was seen in this study. In 2016, 10% (n=3) of patients on antibiotics were on two antibiotics concurrently and 2% (n=1) was on three antibiotics. In 2017, 11% (n=4) of patients on antibiotics were on two antibiotics simultaneously and none was on three antibiotics. Although there were 7% more patients on antibiotics in the 2017 study period, 8% more patients were on a single antibiotic during their ICU stay compared to the 2016 study time. A higher number of patients used a total of four antibiotics in 2016 (8.7%) than 2017 (3.9%).

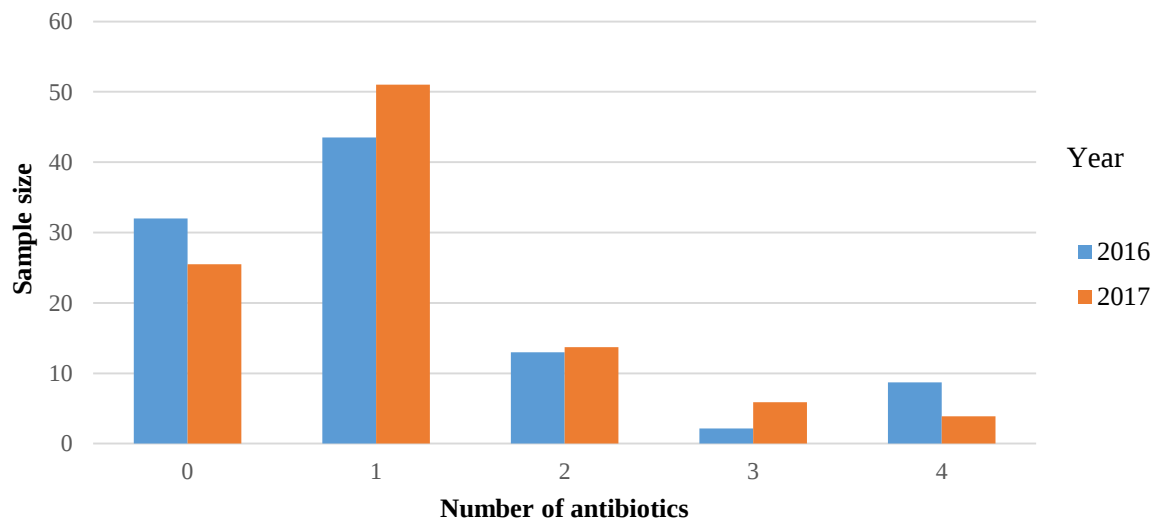


Figure 4: Percentage of antibiotics used per patient during the ICU stay

4.8. Duration of antibiotics use

The average duration of antibiotics used in the two study periods is summarized in Table 4. The days are presented as medians (IQR) because it was not normally distributed.

In both study periods, the duration of antibiotic use varied amongst the antibiotics used.

Piperacillin/tazobactam was used for a median number of four days (IQR 1-11 in 2016 and IQR 4-7 in 2017) while amoxicillin/clavulanic acid was used for a median number of two days in both 2016(IQR 1-4) and 2017(IQR 1-2) study periods.

Ertapenem was used for a longer period in 2016 with a median number of five days (IQR 2-7) while in 2017 all patients received ertapenem for four days. While vancomycin was used for six days for one patient in 2016, vancomycin was used as a once off dose in 2017 for one patient in the ICU.

Table 4: Duration of antibiotic use

	2016		2017	
Antibiotics	Number	Median (IQR)	Number	Median (IQR)
Am/Cla	22	2 (1-4)	14	2 (1-2)
Azit	5	2 (2-3)	8	3 (1.5-3.5)
Cefa	1	1	5	3(1-5)
Ceftaz	1	1	1	4
Ceftri	3	3 (3-18)	7	3 (1-9)
Cipro			1	2
Clin	1	8		
Colix	1	1		
Etap	3	5 (2-7)	2	4
Imip	4	5 (3.5-6)	4	2 (1.5-4)
Linez	2	1.5 (1-2)	1	2
Mero			3	1
Ppt	7	4 (1-11)	9	4 (4-7)
Tobra	1	1		
Vanco	1	6	1	1

** Numbers without (IQR) was for a single patient or uniform range.

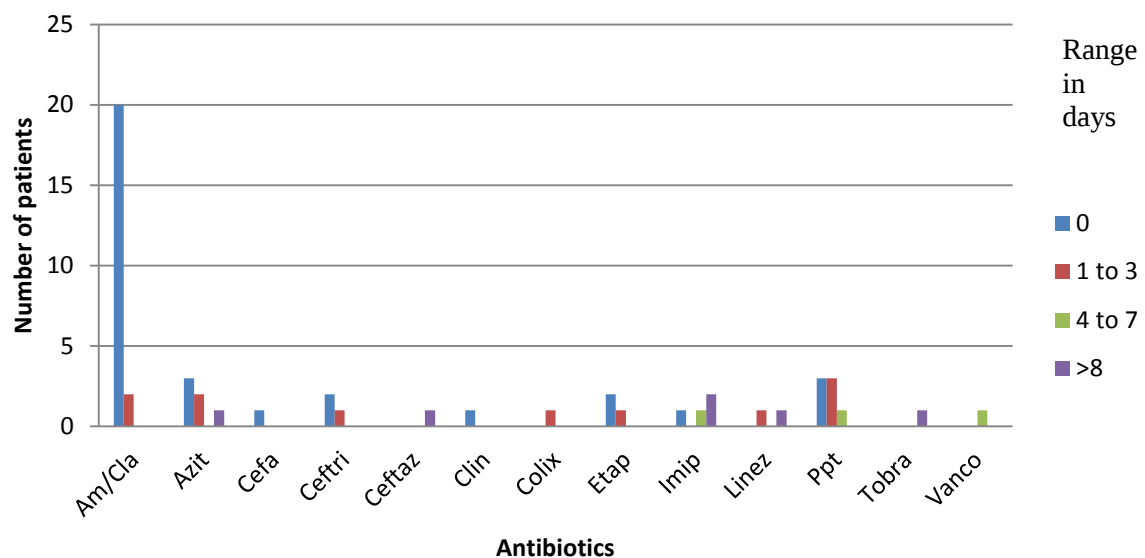
4.9. Day in ICU when an antibiotic was started

The day, according to the patient's stay in ICU, that antibiotic treatment was initiated was documented as seen in Figure 5.

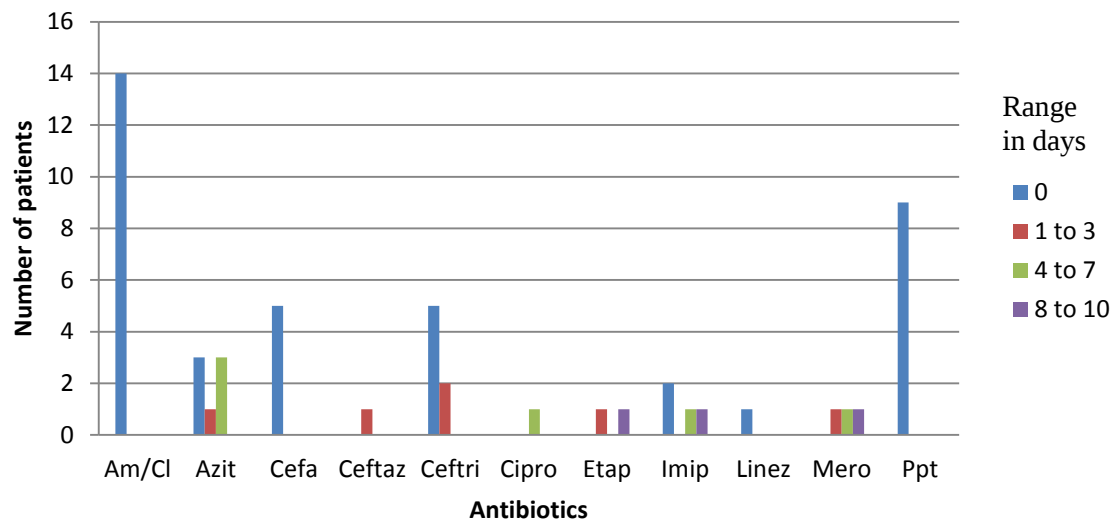
Reviewing all patients file studied, most of the patients, 63% (n=33) and 70% (n=39) admitted in the ICU in 2016 and 2017 respectively, were on antibiotic from day zero of their ICU stay. Amoxicillin/clavulanic acid was prescribed 91% (n=20) of the time from day zero in 2016 and in 2017 100% was started on day zero of ICU stay. Piperacillin/tazobactam was started 43% in 2016 from day zero and in 2017 100% was started on day zero.

Carbapenems are restricted in HJH but 43% (n=3) in 2016 and 22% (n=2) in 2017 was started from day zero of ICU stay. Furthermore, the majority of azithromycin (60% n=3 in 2016 and 43% n=3 in 2017) and ceftriaxone (67% n=2 in 2016 and 71% n=5 in 2017) was started on day zero.

In comparison with other restricted antibiotics like colistin and linezolid which require the infectious disease consultant's signatures and a positive culture result to support pharmacy issue, all were started between days 1-3 of ICU stay.



a. (Day in ICU in which antibiotic was started in 2016)



b. (Day in ICU in which antibiotic was started in 2017)

Figure 5: Day in ICU in which antibiotic was started (a) 2016 and (b) 2017

4.10. Missed doses recorded for all antibiotics used

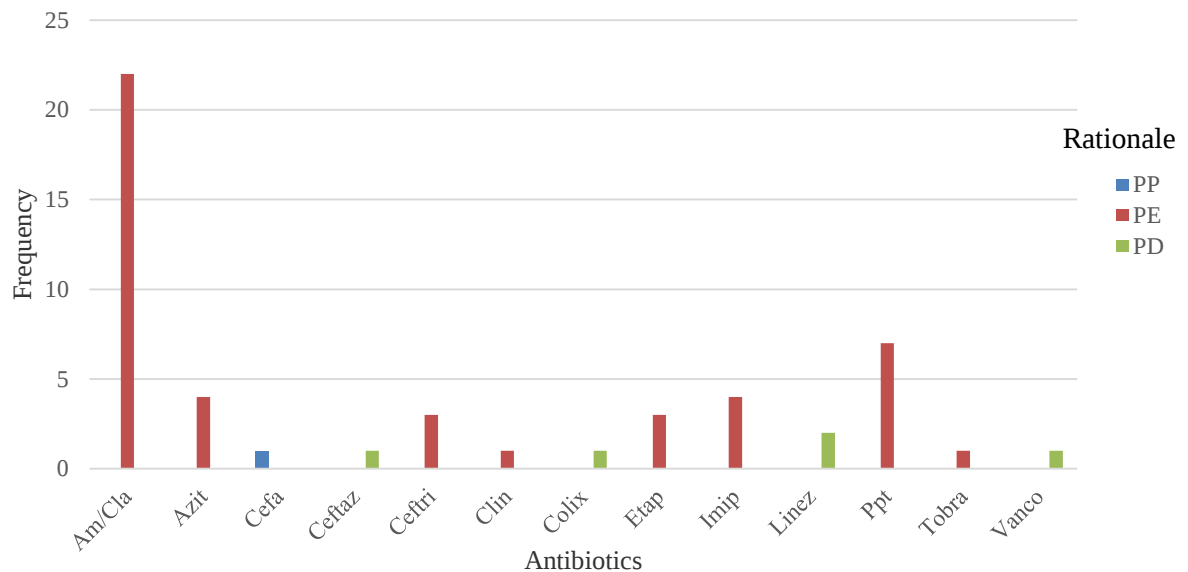
A total of four missed doses were recorded for imipenem/cilastatin in both 2016 and 2017 while in 2016 there was one linezolid dose missed.

4.11. Antibiotic prescribed versus rationale for choice

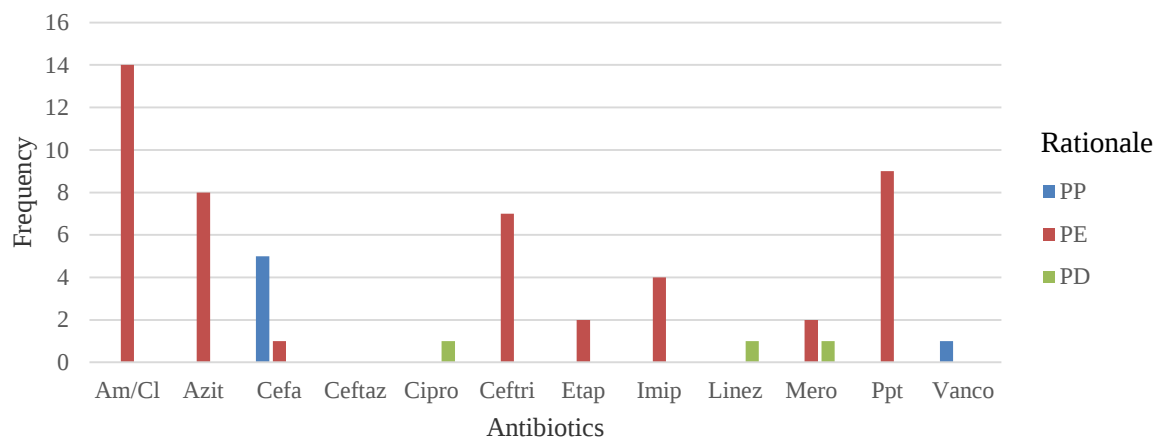
The rationale for prescribing antibiotics (empiric, prophylactic or definitive) was not indicated in all the patient ICU charts. This was determined retrospectively from reviewing the culture result and the day in which antibiotic was started. The terminology “presumed” was used to classify the different rationale because this could not be confirmed with the attending physician.

Figure 6, describes the rational for which the different antibiotics were prescribed. It was noted that amoxicillin/clavulanic acid (100% n=22 in 2016 and 100% n=14 in 2017) and piperacillin/tazobactam (100% in 2016 and 100% in 2017) were presumed to be prescribed

empirically without a definitive culture result. Antibiotics used were considered empiric in 2016 (83% n=43) and (10% n=5) were definitive while in 2017, 84 % (n=47) was considered empiric and 7% (n=4) was definitive. In comparison to the use of linezolid (100%), ciprofloxacin (100%) and colistin (100%) were started definitively following a positive culture result according to hospital formulary.



a. (Rationale for antibiotics prescribed in 2016)



b. (Rationale for antibiotics prescribed in 2017)

Figure 6: Rationale for antibiotics prescribed (a) 2016 and (b) 2017.

*PP = Presumed prophylactic **PE= Presumed empiric *** PD= Presumed definitive

4.11.1. *Rationale for initiation of antibiotic therapy*

Patients' overall antibiotic therapy was reviewed. Rationale of antibiotic therapy based on a culture result, a choice of antibiotics not based on culture and a not applicable group (antibiotic was either used as a once off dose or patients not on antibiotics) was studied and compared (Figure 7). It was noted that of the patients treated with antibiotics (2016: n=31 and 2017: n=38) the majority of the patients were treated empirically (2016: n=19 and 2017: n=26) in 2016 and 2017 respectively.

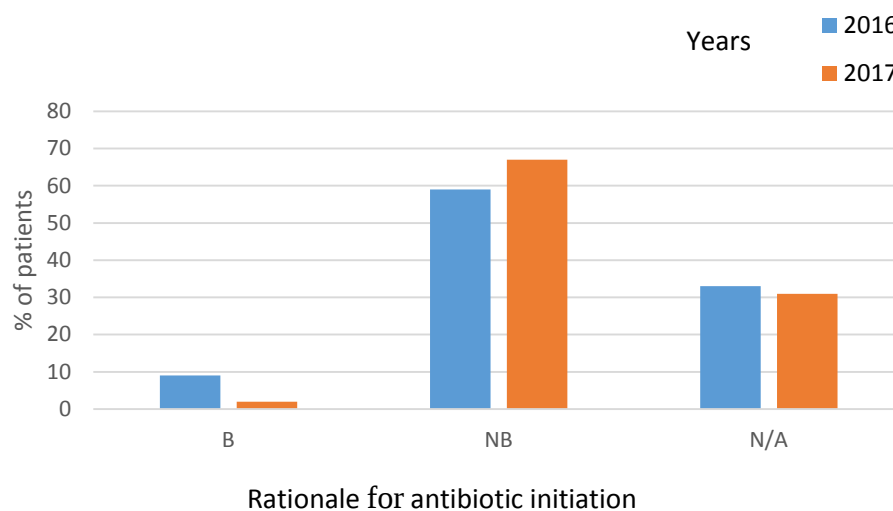


Figure 7: Number of patient compared to decision made regarding antibiotic therapy

****B-** Decision to use antibiotics based on culture

****N/B-** Decision to use antibiotics not based on culture

****N/A-** Patients on a prophylactic dose or not on antibiotics.

4.12. Relationship between rationale for antibiotic choice and mean number of days stayed in the ICU

Figure 8 describes the relationship between the rationale for the choice of antibiotics and the number of days stayed in the ICU. It was seen that most patients in which antibiotics were chosen definitively had the longest stay in the ICU in both 2016 and 2017. Many patients who had a shorter stay in the ICU had empirical antibiotic therapy. The difference between the mean days in ICU across the decision to treat empirically and definitively are statistically different hence statistically significant. (2016: $p = 0.0301$; 2017: $p = 0.0054$).

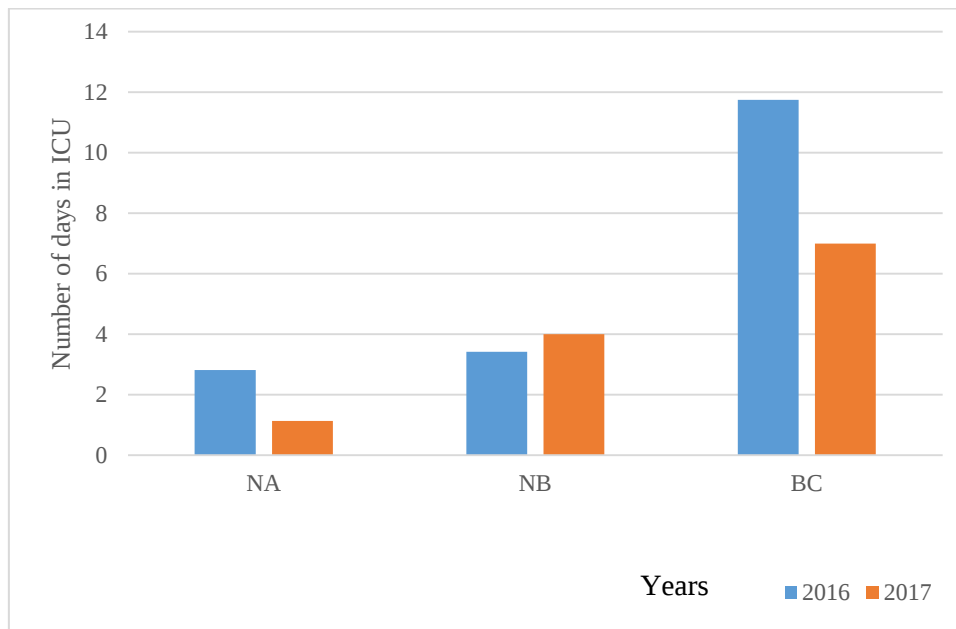


Figure 8: Relationship between rationale for choice of antibiotics compared to mean number of days stayed in the ICU 2016 (a) and (b) 2017

*N/A-Not applicable patient on prophylactic dose or not on antibiotics.

**N/B- Decision to use antibiotics not based on culture

***BC- Decision to use antibiotics based on culture

4.13. Doses of antibiotics used

The total daily doses used in the two periods were similar except for the use of azithromycin, ertapenem and piperacillin/tazobactam. In 2016, azithromycin was prescribed as a daily dose of 500mg while in 2017 it was 500mg twice a day for all patients on azithromycin. Most of the patients were administered piperacillin/tazobactam as an infusion in the two study periods. In 2016, 57% (n=4) received a daily dose of 18g while 43% (n=3) was on a daily dose of 9g while in 2017, all the patients on piperacillin/tazobactam was on a daily dose of 9g. In 2016 and 2017, the prescription of ertapenem followed a 1g dose per day for 60% (n=3) of patients and 40% (n=2) was on 2g per day. It was noted that dose range of 2g-4g a day dose was used for ceftriaxone in both 2016 and 2017.

4.14. Culture and sensitivity pattern shown

A total of 62 culture results and sensitivities were reviewed in 2016 and 43 in 2017. There were more cultures found for the patients receiving antibiotics in 2016 (n=62) compared to 2017 (n=43). The sensitivity patterns of the microorganism that was isolated in the two-study periods are presented in Table 5.

The five most frequently isolated pathogens in the both study period was *Klebsiella pneumoniae* (17%), *Enterobacter cloacae* (15%), *Staphylococcus aureus* (11%), *Escherichia coli* (9%) and *Pseudomonas aeruginosa* (6%). The ESKAPE pathogens which are namely *Enterococcus faecum* (4%), *Staphylococcus aureus* (11%), *Klebsiella pneumoniae* (11%), *Acinetobacter sp* (4%), *Pseudomonas aeruginosa* (6%) and *Enterobacter cloacae* (15%) which are virulent and develop multi resistance were found. Two extended beta lactamases producers which included *Klebsiella pneumoniae* and *Enterobacter cloacae* were isolated in the 2016 study period. There were also more isolates of *Enterobacter cloacae* isolated in the 2016 (13%) study period than in the 2017 (2%).

There were 86% of *Enterobacter cloacae* isolated in both 2016 and the 2017 study period which were sensitive to carbapenems and resistant to co-trimoxazole and ceftriaxone aside one isolate which was resistant to all antibiotics tested for and colistin was suggested by the microbiology laboratory.

Amongst the *Staphylococcus aureus* isolated, 60% in both study periods was sensitive to cloxacillin, 40% was sensitive to only vancomycin. There was 70% *Escherichia coli* isolate which were not sensitive to amoxicillin/clavulanic acid.

Acinetobacter baumannii (n=2) was isolated in both years with the 2016 isolate being resistant to ciprofloxacin, amikacin and sensitive only to colistin but the isolate in 2017 was sensitive to ciprofloxacin and amikacin.

Table 5: Isolates and resistance patterns

Isolates	2016			2017		
	Number of isolates from different patients	Sensitive to	Resistant to	Number of isolates from different patients	Sensitive to	Resistant to
<i>Acinetobacter baumannii</i>	1	Colix	Co-tri,Cipro,PPT, Mero, Imip,amik	1	Cipro, Amik	Amp-pen, PPT, Co-tri, Mero, Cefep
<i>Burkholderia cepacia</i>				1	Co-tri,Ceftri	PPT, Genta, Cefep, Amik, Imip, Colis, cipro
<i>Enterococcus avium</i>	3	Etap Imip	Am/Cla, Co-tri, PPT,Cipro, Ceftri, Cefep			
<i>Enterococcus gallinarum</i>	1	Linez				
<i>Enterococcus faecium</i>	1	Vanco	Amp-Amo	1	Vanco	Amo and Amp
<i>Enterococcus faecalis</i>				1	Amo	

Isolates	2016			2017		
	Number of isolates from different patients	Sensitive to	Resistant to	Number of isolates from different patients	Sensitive to	Resistant to
<i>Enterobacter cloacae</i>	4	Etap, Imip	Co-tri, Amp-cla, Amp-amox, Ceftri cefuroxime	1	Imip, mero	Co-tri, Amox-Amp, Cefep, Ceftri, Cefu cefuroxime
	1	Etap, Cefep, cipro	Co-tri, Amox-cla, Ceftri, cefuroxime			
	1	None (ESBL)	Co-tri, Amp-cla, Amp-amox Ceftri, Cefuroxime, PPT			
<i>Escherichia coli</i>	1	Amox-cla, Etap, Imip	Amp-amox	1	Mero, Imip	Am/Cla, Amp-Pen, Co-tri, Ceftri
	1	Imip	Co-tri, Amp-amox, Cipro			
	1	Imip, ertap	Genta, Co-tri, Amp-amox, Amox-cla, Cipro, Ceftria, cefep			

Isolates	2016			2017		
	Number of isolates from different patients	Sensitive to	Resistant to	Number of isolates from different patients	Sensitive to	Resistant to
<i>Klebsiella pneumoniae</i>	1	Ceftri	PPT, Amp-amo, Co-tri	2	Am/Cla Co-tri, Ceftri	
	1	Am/Cla	Amp-Pen			
	3	Etap Imip	Am/Cla, Co-tri, PPT,Cipro, Ceftri, Cefep			
	1	None	Amp-Amo, Amo-clav, Ceftria Cefep, Tobra, PPT, Mero			

Isolates	2016			2017		
	Number of isolates from different patients	Sensitive to	Resistant To	Number of isolates from different patients	Sensitive to	Resistant to
<i>Haemophilus influenzae</i>				1	Amo-cla	Co-tri
<i>Pseudomonas aeruginosa</i>	1	None	Amp-Amo, Amo-clav, Ceftria Cefep, Tobra, PPT, Mero	1	Ceftri, Imip Cipro	PPT, Tigercycline
	1	None	Amp-Amo, Amo-clav, Ceftria Cefep, Tobra, PPT, Mero			Amp-pen and Clox
<i>Proteus mirabilis</i>	1	Am/Cla, Co-tri				
<i>Proteus vulgaris</i>	1	Etap, imip	Cefazo, Co-tri, Amp-ammo, cefuroxime			

Isolates	2016			2017		
	Number of isolates from different patients	Sensitive to	Resistant To	Number of isolates from different patients	Sensitive to	Resistant to
<i>Staphylococcus aureus</i>	1	Clox	Genta, Co-tri, Amp-Pen, Amocla, Cipro, Ceftria, cefep	2	Clox	PPT, Co-tri, Amp, Pen
				2	Vanco	Amp-pen and Clox
<i>Staphylococcus epidermidis</i>	1	Vanco	Pen-Amp, Clox, Co-tri, Azit, PPT	1	Vanco	Clox, Amp-Pen
<i>Streptococcus pyogenes</i>	3	Pen				
<i>Streptococcus anginosus</i>	1	Pen				
<i>Stenotrophomonas spp</i>				1	Co-tri	

4.15. Infection markers performed

In the two study periods CRP was ordered every day for each patient admitted in the ICU. Procalcitonin on the other hand was only done for one patient in 2016 and for two patients in 2017.

4.16. Summary

From the results, it was seen that amoxicillin/clavulanic acid and piperacillin/tazobactam were the most used antibiotics in the two-periods studied. Antibiotics kept in the ward as routine ward stock were started mostly from day zero of patient's admission compared to restricted antibiotics. Restricted antibiotics were used infrequently in comparison to non-restricted antibiotics. It was also noted that the average length of stay in the HJH ICU was two days. Duration of antibiotic varied widely. Furthermore, the rationale for antibiotic use was based mostly empirical rather than definitive in the two periods studied. Decisions which were based definitively were seen more in patients with longer length of stay in the ICU.

The next chapter is the discussion.

CHAPTER 5: DISCUSSION

5.1. Introduction

Although drug utilization studies have been done in South Africa (Paruk *et al.*, 2012) to investigate the usage pattern of antibiotic in the various ICUs, however there have been no studies such as this in HJH ICU. Operational research such as this will make an important contribution to this hospital.

Clinicians are pressured to prescribe antibiotic for the critically ill in the ICU even when not necessary (Labuschagne *et al.*, 2016; Sarin *et al.*, 2013; Williams *et al.*, 2011). To monitor judicious use of antibiotics, individual hospital antibiotic prescription monitoring is advantageous (Suryawanshi *et al.*, 2015).

Although antibiotic therapy needs to be given without delay in the ICU, considering inconclusive radiological findings and delay in microbiology results leaves the treating clinicians no confirmation hence broad-spectrum antibiotic is chosen frequently and most often inappropriately (Broyles, 2017). Notwithstanding critical care and immediate need for decision, antibiotic stewardship principles should be adhered to before starting antibiotic therapy (Kolak, 2010; Zhang and Singh, 2015).

5.2. Utilization pattern of Antibiotic in the ICU

The ICU is known for high antibiotics use (Williams *et al.*, 2011; Sarin *et al.*, 2013). In this study, 67.4% in 2016 and 74.5% in 2017 of patients admitted in the ICU received antibiotics. Similar range to this HJH study, a range of 76% was reported by Hanssens *et al.* (2005). However, higher values ranging from 80% - 95% were seen in the studies by Anand *et al.* (2016), John *et al.* (2011), Williams *et al.* (2011) and Patanaik *et al.* (2015). This is suggestive that antibiotics are frequently used in the ICU.

Furthermore, lower ranges compared to the result achieved in this study between 30-57.5% were reported in studies by Shankar *et al.* (2005) and Usluer *et al.* (2005). The difference could be due to the different population studied as well as the type and speciality of hospitals where the studies were performed. Antibiotic prescription pattern differs from hospital to hospital and from one ward to another.

Piperacillin/tazobactam and amoxicillin/clavulanic acid which are penicillin antibiotics were the most common antibiotics prescribed in the HJ ICU. This is similar to a study done by Anand *et al.* (2016) in India where piperacillin/tazobactam and amoxicillin/clavulanic acid were amongst the five most prescribed antibiotics in the ICU. Likewise, penicillin antibiotics was the most used antibiotics in a study by Shankar *et al.* (2005) in Nepal. The antibiotic usage trend in HJH could be attributed to penicillin antibiotics being one of the first line antibiotics on the hospital formulary. In contrast to this study Williams *et al.*, (2011) reported the 3rd generation cephalosporins, meropenem and levofloxacin, John *et al* (2011) was cephalosporins and aminoglycosides and Badar and Navale (2012) reported cefotaxime as the most prescribed antibiotics in the ICU.

In this study, lesser utilization of linezolid, colistin, meropenem, and vancomycin was documented, and this was comparable to results found by Anand *et al.* (2016) and Molayi *et al.* (2018). Restrictive protocols have been used to reduce antibiotic consumption (Vitrat *et al.*, 2014). In this study, restricted antibiotics were used to a lesser extent than those kept in the ward as routine ward stock.

Additionally, the duration of antibiotics as seen in this study varied widely from one day to 18 days. This is in line with a study by Chin *et al.* (2010) which reported a wide range of 1-42 days.

Missed doses were not infrequently noted in this study. Missing of antibiotic doses could lead to sub therapeutic levels increasing the emergence of resistant pathogens (Alexander *et al.*, 2008).

An average of one antibiotic was used per patient in this study. Similar range of 1.73-1.74 was seen in the studies by Amit (2013) and Anand *et al.* (2016). Higher number of 2.5-2.74 of antibiotics per person was seen in the studies done by Patel *et al.* (2013) and Khan *et al.* (2013). Even a higher average of three was reported in a study done in South Africa ICUs by Paruk *et al.* (2012).

At most three antibiotics were used concurrently. In both years, an average of 11% (n=7) of two antibiotics and 2 % (n=1) of three antibiotics were concurrently used. In comparison with the study done by Paruk *et al.*, (2012), concurrent use of antibiotics ranged from 2-10 antibiotics.

5.3. Empiric, definitive and prophylactic use of antibiotics

Clinicians face challenges in finding the balance between adequate empiric cover and at the same time reducing selection pressure for resistant strain (Eliopoulos *et al.*, 2003; Zilahi *et al.*, 2016). The overuse of empiric antibiotic coverage is linked to the emergence of antibiotic resistance, yet optimal empiric cover is linked with reduced mortality of patients with severe sepsis and septic shock (Eliopoulos *et al.*, 2003; Ferrer *et al.*, 2014).

Result from this study showed that the most empiric selected antibiotics in the ICU were amoxicillin/clavulanic acid and piperacillin/tazobactam. In line with this study are studies done by Thomas *et al.* (2015) and Chin *et al.* (2010) which reported piperacillin/tazobactam was one of the frequently used empiric antibiotic.

Although in this study all piperacillin/tazobactam initiation was empirical, in the study done by Chin *et al.*, (2010) 32.1% of piperacillin/tazobactam was empiric. Of note, vancomycin was one of the frequently used antibiotics in a study by Thomas *et al.*, (2015) but in this study, vancomycin was one of the least used antibiotics. Hence broad-spectrum antibiotics are frequently chosen as empiric therapy in the ICU. Further, the HJH hospital guideline suggest the use of broad spectrum antibiotic followed by de-escalation to a narrow spectrum when culture results are received. This important principle of stewardship could not be confirmed in our study as the length of stay was short and broad-spectrum antibiotics was continued mostly.

Total number of patients treated empirically in this study was an average of 63%. Comparable ranges were seen in the studies by Chin *et al.* (2010) which reported 68% and Shrikala *et al.* (2010) who reported 63%. In line with these two studies, the antibiotics prescribed in the HJH ICU are mostly empiric. Therefore, necessitating the monitoring of antibiotics used empirically and implementation of stewardship principles.

An average of 8% (n=8) of patients were treated prophylactically. This is lower than the study done by Malacarne *et al.*, (2004) which reported 31%. The reason for the disparity in the numbers of prophylactic cases seen in the study by Malacarne *et al.*, (2004) and this study could be that HJH has a smaller ICU and also their study was a multi-centre study.

Furthermore, in contrast to this study which used 86% of first-generation cephalosporin (cefazolin) prophylactically, the study done by Malacarne *et al.*, (2004) reported a 42% prophylactic use of a third-generation cephalosporin. Altogether, the reviewed studies confirm more antibiotics are prescribed empirically in the ICU (Chin *et al.*, 2010; Shrikala *et al.*, 2010).

Culture results from the laboratory does not often become available within 24 to 72 hours as supported by Vitrat *et al.*, (2014) and Leekha *et al.*, (2011). This pressures the clinicians to

choose antibiotics empirically. This was also seen in this study at HJH as the majority of definitive antibiotic therapy was seen in patients with longer stay in the ICU.

5.4. Length of stay

The average length of stay reported in this study was two days. Comparable range of 3.3 was seen in the studies by Hunter *et al.* (2014). However, longer ranges of 4.5-5.75 was seen in study by Agrawal *et al.* (2017), Biswal *et al.* (2006) and John *et al.* (2011) and in a local study conducted by Hanekom *et al.* (2006) the length of stay was 6 days. The reason for the variation could be varied diseases seen in the different studied population and also in HJH ICU, there are limited ICU beds available and patients once stable are often moved to general ward.

5.5. Diagnosis

The reason for antibiotic therapy was not indicated on the majority of the ICU chart in both 2016 and 2017 study periods. The diagnosis on admission into the ICU remained the diagnosis on all the patients' ICU chart. One of the core elements of antibiotic stewardship principles as cited by Pollack and Srinivasan (2014) is the documentation of the reason of antibiotic initiation. This will help to monitor and implement better policies to support judicious antibiotic use. Therefore, linking diagnosis to the antibiotics used was not attainable in this retrospective record review study.

5.6. Infection markers utilized

Issuing effective antibiotics is the gold standard within an hour of sepsis to reduce morbidity. Culture takes 24-48 hours and many times more, infection markers are advantageous in the ICU to initiate antibiotics and reduce the risk bad health outcomes (Vitrato, 2014).

In this study, CRP was the most frequently used infection marker which was done every day for the patients as routine and this is in line with a study done by Povoas *et al.* (2006). They concluded that with a sensitivity of 92.1 and a specificity of 82.1, CRP is useful in the prediction of infection in the ICU. The PCT was done rarely in the two periods of study. However, studies comparing the use of PCR and CRP in predicting infection found that the PCR was better in accuracy and in identification of severity of sepsis (Markanday, 2015; Nargis *et al.*, 2014). Furthermore, the PCR assay is more expensive than the CRP and this poses a financial challenge.

5.7. Microorganism isolated and sensitivities

In this study the most isolated microorganisms were *Klebsiella pneumoniae* (17%), *Enterobacter cloacae* (15%), *Staphylococcus aureus* (11%), *Escherichia coli* (9%) and *Pseudomonas aeruginosa* (6.3%). Refer to Table 5, *Enterobacter cloacae*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* and *Escherichia coli* which were amongst the commonly isolated in this study was supported by studies done by Radji *et al.* (2011), Tran *et al.* (2017) and Grootorenx and Oosthuizen (2015).

Comparing this study to a study done in a Canadian ICU by Zhanel *et al.* (2008), *Haemophilus influenzae* (7.9%) was one of the ten frequently isolated pathogens. In this study, *Haemophilus influenzae* was infrequently isolated (2%) and was only present in the 2017 time period. This could be attributed to the timing of the study.

The susceptibility of *Klebsiella pneumoniae* showing resistance to ceftriaxone was reported by Radji *et al.* (2011) to be 75.7%. This was similar to this study which was 75%. Another study done in an ICU in Southern Italy by Agodi *et al.* (2015) reported 87% which was higher than that documented in this study. It is clear from these studies presented that pathogens and their susceptibility in different ICUs vary widely.

Even though there were similarities in sensitivity to antibiotics shown by isolates of the same genre in both study periods, there were antibiotic sensitivity disparities found within similar isolates. For example, 50 % of *Klebsiella pneumoniae* isolated was sensitive to amoxicillin/clavulanic acid, 38% was resistant yet sensitive to carbapenems and 13% was not sensitive to any antibiotics tested. This is supported by literature in articles written by Chaudhry and Prajapat (2017) and Sulaiman (2016).

Overall, it is important to understand clearly the genre and sensitivity of the microorganism in question to enable appropriate choice of antibiotics and improve adequate therapy while reducing antibiotic resistance. Knowledge of the present susceptibility patterns also can be used to ascertain the influence of antibiotic stewardship strategies that have been implemented (Chunnilal *et al.*, 2015; Goff, 2011).

5.8. Summary

Based on the findings of this study, broad spectrum antibiotics were chosen frequently in the ICU and comparable to studies from abroad. More antibiotics are prescribed empirically compared to definitive antibiotic therapy in the ICU and this is in line with the literature. The average number of antibiotics used in this study was below the recorded average of the studies mentioned. The length of stay in the HJH ICU was short in comparison to the studies cited. The measures in place restricting the use of specific antibiotics seem effective. The two

infection markers used in the ICU during this study was the PCR and the CRP. The PCR which is better than the CRP was used less frequently.

There are different patterns of antibiotic utilization seen across the world. Also, the pathogens and their susceptibilities vary from hospital to hospital. Considering the difference, it is paramount that each hospital monitors their individual antibiotic usage to enable an informed antibiotic stewardship intervention.

The next chapter is conclusion.

CHAPTER 6: CONCLUSION

6.1. Introduction

This chapter showcases the conclusion of this study carried out for two months in Helen Joseph intensive care unit. This is then followed by the study limitations and recommendations.

6.2. Conclusion

In conclusion the results obtained from this study shows the importance of documenting the usage of antibiotics especially as the hospital embarks on improving antibiotic stewardship. Notably, the majority of patients admitted in the ICU were on antibiotics and the rationale for choice was mostly empiric. The most frequently used antibiotics were amoxicillin/clavulanic acid and piperacillin/tazobactam. It was also eminent in our study that restriction of antibiotics improves utilization as antibiotics which required lesser authorization to release from the dispensary were used more frequently than antibiotics requiring stricter authorization. This study further found that the length of stay in the HJH ICU is short and also concurrent use of antibiotics was low.

This study concluded that if there are no appropriate interventions, same practices will continue. In both study times, similarities were found in antibiotics prescribed, doses, rationale for antibiotic choice and the day on which the antibiotic was started. Also indicating the reason for antibiotic prescription is not generally practiced. This study likewise revealed the susceptibility pattern of microorganisms isolated in the study period and concluded that susceptibility of the same genre of microorganism can differ.

The ICU has major advantages in the pursuit for antibiotic stewardship. The closely monitored and supervised environment offers the chance to optimize antibiotic delivery, track

the outcome, and make early decisions concerning escalation or stopping of antibiotic therapy.

This study informs on the antibiotic use, the dose and the frequencies of antibiotics used on the patients in the two-study period and as well the rationale for which these antibiotics were chosen. This affords baseline data from the HJH ICU which is available for further studies and developing strategies to improve antibiotic use.

6.3. Study limitation

The following study limitations need to be noted:

1. Missing data

- Missing data on the ICU charts made the data collection more difficult.
- The reason for antibiotic initiation was not regularly documented.

2. No electronic information backup

- All information written on the chart was manual and there was no electronic back up of information should chart not be found. This further reduced the studied population.

3. Time and resources constraint

- Period studied was short and only provides a snapshot to the usage of antibiotics in the HJH ICU ward.

6.4. Recommendation from this study

Following the review of data from this study, the following recommendation emerged which could help in improving antibiotic utilization.

- The reason for antibiotic initiation and all information relating to antibiotic use should be documented on the ICU charts when prescribing antibiotics. It also allows for the pharmacist to advise and hence ensure better antibiotic management.
- The time when antibiotics are prescribed needs to be noted on the ICU chart. This will help ensure that the dose is administered within an hour.
- Improvements need to be made to insure all files are archived. A signing system could be implemented to track when files are received and removed.
- Since the ICU admits very sick patients, a fast track should be created for the patients admitted in the ICU by the laboratory and the pharmacy. This will ensure the ICU gets timely results regarding the patients and this will help to make accurate decisions on antibiotic choice. The scripts coming to the pharmacy from the ICU should be analysed by a clinical pharmacist and dispensed timeously. The clinical pharmacist should be responsible to ensure all the restrictive rules have been adhered to by the clinician and ensure appropriate dose, frequency and duration of the antibiotics. The clinical pharmacist will also need to do ward rounds in the ICU ensuring the doses have been dispensed to the patients according to the clinicians' orders and to make recommendations and interventions to ensure a prudent use of antibiotics and an overall functional antimicrobial stewardship plan.

6.5. Recommendation for future studies

Since this study has shown similarities to the common practice which is not advantageous in curbing antibiotic use, further studies need to be carried out to ascertain the effect of implementing an antibiotic prescribing chart.

6.6. Summary

The core element of antibiotic stewardship is in documentation of information relating to the use of antibiotics. This study provided information regarding the utilization of antibiotics in the HJH ICU for the period studied. Without any intervention implemented, there were more similarities than there were differences in the utilization pattern seen in both time.

Furthermore, to ensure that effective antibiotic stewardship program is implemented, intervention informed by utilization studies is central to its success.

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Appendix 1: Wits HREC Approval certificate for the main study


R14/49 Mrs Deanne Johnston and Mrs Yolande van Deventer

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M141141

NAME: Mrs Deanne Johnston and Mrs Yolande van Deventer
(Principal Investigator)

DEPARTMENT: Pharmacy and Pharmacology
Charlotte Maxeke Johannesburg Academic Hospital

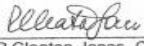
PROJECT TITLE: Situational Analysis of Antibiotic Stewardship in
Gauteng Public Hospitals

DATE CONSIDERED: 28/11/2014

DECISION: Approved unconditionally

CONDITIONS:

SUPERVISOR: Jacqui Miot and Shirra Moch

APPROVED BY: 
Professor P Cleaton-Jones, Chairperson, HREC (Medical)

DATE OF APPROVAL: 30/11/2015
This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS
To be completed in duplicate and **ONE COPY** returned to the Secretary in Room 10004, 10th floor, Senate House, University.
I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated from the research protocol as approved, I/we undertake to resubmit the application to the Committee. I agree to submit a yearly progress report.

 Principal Investigator Signature Date 30-11-15

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix 2: Modified South African Antibiotic Stewardship Program (SAASP) antibiotic prescription form

Appendix D: Modified SAASP Antibiotic Prescription chart. Date of collection :

Study number:				Ward	
Sex:		Age: Years: Months:		Weight	Allergies
				eGFR	

INFECTION EPISODE NUMBER:	Diagnosis				
	☐ Pneumonia	☐ UTI	☐ Meningitis	☐ Line infection	
	☐ Cellulitis	☐ Intra-abdominal infection	☐ Other _____		

Source*	☐ Community acquired	☐ Hospital acquired	Indication	P = Prophylactic E = Empirical D = Definitive
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SEND APPROPRIATE CULTURES BEFORE PRESCRIBING ANTIBIOTICS

Cultures	☐ Sent before antibiotics	☐ Sent after antibiotics	☐ Not Sent
-----------------	--	---	-----------------------------------

*CA = Community acquired: within 5 days of admission
 HA = Hospital acquired: >48h after admission or within 30 days of discharge

Antibiotic Day	1	2	3	4	5	6	7	8	9	10
↓ Time →										

Indication	Medicine Approved Name or GE	Dose	Route	
☐ P	Start Date	Duration	Frequency	
☐ E	Time			
☐ D	Qualification: Designation: (e.g.: Registrar)			

Indication	Medicine Approved Name or GE	Dose	Route	
☐ P	Start Date	Duration	Frequency	
☐ E	Time			
☐ D	Qualification: Designation: (e.g.: Registrar)			

Indication	Medicine Approved Name or GE	Dose	Route	
☐ P	Start Date	Duration	Frequency	
☐ E	Time			
☐ D	Qualification: Designation: (e.g.: Registrar)			

Nursing Codes: 1. Patient away from Ward 2. Nil by Mouth
 3. Patient refused drug 4. Drug not yet obtained
 5. Patient Could not receive drug e.g. vomiting

Once only / Stat dose antibiotics							
Indication	Drug	Dose	Route	Date	Time	Dr's qualification & Designation	Time given
☐ ☐ ☐ P E D							
☐ ☐ ☐ P E D							
☐ ☐ ☐ P E D							

Microscopy & Culture results			
Date	Site*	Pathogen	Sensitivities

*BC= Blood, MSU = Midstream urine, CSU = Catheter specimen urine, CSF = Cerebrospinal fluid, PS = Pus swab, BM= bone marrow, JA = Joint aspirate, TA = Tracheal aspirate

Appendix 3: Helen Joseph Hospital Research Conditional Approval Letter

	GAUTENG PROVINCE REPUBLIC OF SOUTH AFRICA
Helen Joseph Hospital Enquiries: Dr. M. Mukansi Research Committee - Chairperson Tell: 011 489 0306/1087 Fax: 011 489 1038 Email: mirimisi.mukansi@wits.ac.za	
20 March 2017	
To whom it may concern	
SUBJECT: HELEN JOSEPH HOSPITAL RESEARCH COMMITTEE	
PROTOCOL TITLE: Antibiotic usage in the Intensive Care Unit of a Tertiary Level Public Hospital	
Protocol Ref No:	Antoinetta Ejike// MSc. Protocol
Ethics Clearance:	Pending
Principal Investigator:	Antoinetta Ejike
Department:	Pharmacy and Pharmacology
Committee Recommendations	
Conditional access approval has been given subject to the candidate, obtaining and providing the committee with a final clearance certificate issued by HREC.	
Secondly, please ensure that your application has been registered in the NHRD (National Health Research database).	
Thank you in anticipation	
	
Dr. M. Mukansi Chairperson of the HJH Ethics and Research Committee	

Appendix 4: Wits HREC Approval certificate for this study.



R14/49 Ms Ejike Antonietta

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M170395

NAME: Ms Ejike Antonietta
(Principal Investigator)
DEPARTMENT: Pharmacy and Pharmacology
Helen Joseph Hospital

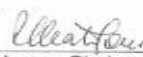
PROJECT TITLE: Antibiotic Usage in an Intensive Care Unit of a Tertiary Level Public Hospital

DATE CONSIDERED: Adhoc

DECISION: Approved unconditionally

CONDITIONS: Sub-Study (M141141)

SUPERVISOR: Mrs Deanne Johnston

APPROVED BY: 
Professor P. Cleaton-Jones, Chairperson, HREC (Medical)

DATE OF APPROVAL: 05/04/2017

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary in Room 10004, 10th floor, Senate House/2nd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand, I/We fully understand the conditions under which I am/we are authorised to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit to the Committee. **I agree to submit a yearly progress report.** The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in March and will therefore be due in the month of March each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature  Date 6/4/17

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix 5: Restricted antibiotics issued per patient in Helen Joseph Hospital ICU

Antibiotics	Route	Hospital Formulary requirement/Restrictions
Amoxicillin/clavulanic acid 1g	PO	None
Ceftazidime 1g	IV	Any consultant signature
Cefepime 1g/2g	IV	Any consultant signature
Ciprofloxacin 400mg/200mg	IV	Sensitivity result + consultants signatures
Clindamycin 600mg	IV	None
Colistin 1mu	IV	Infectious disease consultant signature + sensitivity result
Ertapenem 1g	IV	Any consultant signature
Imipenem 500mg	IV	Any consultant signature
Linezolid 600mg	IV/PO	Infectious disease consultant signature
Meropenem 500mg/1g	IV	Infectious disease consultant signature + sensitivity result + motivation
Vancomycin 0.5g/1g	IV	Any consultant signature

Appendix 6: Antibiotics kept as ward stock in Helen Joseph Hospital ICU

Amoxicillin/clavulanic 375mg	PO
Amoxicillin/clavulanic 1,2g	IV
Azithromycin	IV/PO
Benzathine penicillin	IV
Benzyl penicillin	PO
Benzyl penicillin	IV
Cefazolin 1g	IV
Ceftriaxone 1g	IV
Ciprofloxacin 500mg	PO
Cloxacillin 250mg/500mg	IV
Co-trimoxazole 480mg	IV/PO
Doxycycline 100mg	PO
Gentamicin 80mg	IV
Kanamycin	IV
Phenoxymethypenicillin with vitamin k	PO
Piperacillin/tazobactam 4.5g	IV

Appendix 7: Turnitin similarity report

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12%

SIMILARITY INDEX

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