RETROSPECTIVE DESCRIPTIVE EVALUATION OF EMPIRIC CARBAPENEM-SPARING REGIMENS VERSUS CARBAPENEM USE IN NON-INTENSIVE CARE PATIENTS AT A DISTRICT HOSPITAL IN SOUTH AFRICA

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ABSTRACT

Antimicrobial resistance is a global concern associated with increased morbidity and mortality. It has been estimated that, by 2050, the continuous escalation of antimicrobial resistance, globally, will result in more deaths per year, compared to cancer and diabetes. The direct and indirect impact of ineffective antibiotics, and therefore, antimicrobial resistance, will be hardest felt by low and middle-income countries, as the financial burden will be too great to manage. Carbapenems are considered the last line of antimicrobials to treat multidrug-resistant bacterial infections. They are the preferred choice to treat infections, presenting with extended-spectrum beta-lactamases (ESBL) producing Enterobacteriacea. Various strains of bacteria that have become resistant, due to the selective pressure, as a result of carbapenem over use, are referred to as Carbapenem-resistant Enterobacteriaceae (CRE). The CRE are responsible for serious infections, such as pneumonia, meningitis, bloodstream, urinary tract, and wound infections. Global health systems continuously rely heavily on antimicrobials to treat and prevent both community and hospital acquired infections. Several strategies, through antimicrobial stewardship programmes, have been implemented to curb the spread and development of antimicrobial resistance, globally. One such strategy, which is crucial to limiting carbapenem overuse, is the use of carbapenem-sparing agents first, despite the limited data on this empiric strategy, locally and globally.

This current study, a retrospective and descriptive pilot study, was conducted with the aim of describing and evaluating the use of empiric carbapenem (ertapenem, meropenem and imipenem) versus carbapenem-sparing (piperacillin/tazobactam and or amikacin) regime antibiotics in adult patients (non-intensive care), in terms of specific patient health outcomes, for a period of 6-months (1st March 2018 to 31st of August 2018), at Khayelitsha District Hospital in Cape Town, South Africa. Ethics approval was granted by BMREC-UWC (Reference Number BM18/9/7 on 9 November 2018), and the Department of Health in the Western Cape Province (Reference Number 14 March 2019 WC_201901_011).

An initial all-inclusive list of female and male patients (n=220), who were prescribed either a carbapenem or a carbapenem-sparing regimen, were obtained from the electronic medicine management system for the specified six-month period. A number of patients were excluded (n=130) which included those who: died before receiving either a carbapenem or a

carbapenem-sparing regimen empirically; who had missing clinical data from both electronic record systems; who were transferred to any other health facility for further management; who were initiated treatment (carbapenem or a carbapenem-sparing regimen) at any other health facility; who received both empiric regimens (carbapenem and carbapenem-sparing regimen); who were admitted to ICU; as well as those who were below the age of 18.

The clinical notes were assessed for patients' demographics (age, gender and date of birth), length of stay in hospital, treatment outcomes (demised or discharged), treatment duration, treatment dose, treatment frequency, treatment missed and extra dose(s), immune system status, documentation of past antimicrobial use, type of infection, renal functional, surgical history, site of infection, activity on antimicrobial spectrum (escalation or de-escalation of antimicrobial spectrum), intravenous to oral switch, route of administration, co-morbidities, other treatments co-administered with antimicrobials, allergy documentation and suspected diagnosis prior to initiating empiric study regimens.

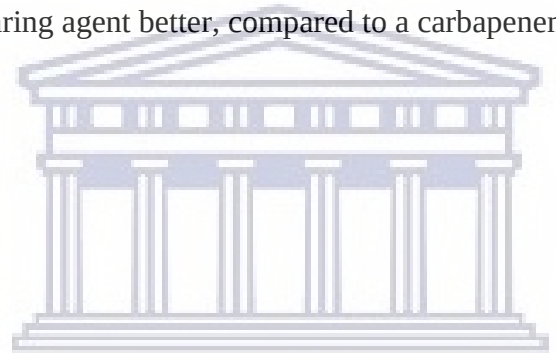
The final number of patients included in this investigation was 90. The patients in the carbapenem group (n = 66) were significantly older ($\rho = 0.01$), with a median (IQR) age of 47 (37–57.3) years, compared to 34 (39.3–52.8) years in the carbapenem-sparing group (n = 24). Risk factors contributing to hospital acquired infections (immune status, ≥ 65 years, prior hospitalisation and surgery or invasive devises) were similar in both groups. Renal failure was significantly ($\rho = 0.00003$) more present in the carbapenem group (n = 41, 45.6%) compared to the carbapenem-sparing group (n=3, 3.3%). Co-administered antibiotics were dispensed to 6 (9.1%) patients receiving the carbapenem regimen and included azithromycin (n = 3); metronidazole (n = 1); vancomycin (n = 1) and trimethoprim/sulfamethoxazole (n = 1). Amoxicillin-clavulanic acid was co-administered with the carbapenem-sparing regimen in two patients (8.3%).

The median (IQR) length of stay in hospital for the carbapenem regimen group was 7 days (3.8-11.3), compared to 6 (3–11) days for the carbapenem-sparing regimen. There was no significant difference in the length of stay in hospital for patients, who had received either a carbapenem or carbapenem-sparing regimen ($\rho = 0.8$).

In the carbapenem study group, the percentage of patients discharged (57.6%), were significantly less ($\rho = 0.02$) than the percentage of patients discharged (83.3%) in the carbapenem-sparing study group. Various factors such as the addition of amikacin which resulted in a synergic effect, younger patients and less renal failure could have contributed to the more positive mortality health outcome in the carbapenem-sparing group compared to the carbapenem group.

This pilot study concluded that there was no significant difference in the length of stay in hospital, among patients treated with either a carbapenem, or a carbapenem-sparing regime at this hospital. Secondly, the use of a carbapenem-sparing regimen was associated with a significant higher percentage of patients, who were discharged. The occurrence of antibiotic spectrum overlap in this current study suggests poor adherence to standard treatment guidelines.

We recommend that an official internal antibiotic stewardship committee be formed to function routinely to actively promote rational use of antibiotics by reinforcing antimicrobial stewardship principles. In addition, we also recommend for the further expansion of this study into other health facilities in the Cape Town metropole to also assess any development of multidrug resistant organisms post carbapenem-sparing agent use, to understand the benefits of using a carbapenem-sparing agent better, compared to a carbapenem.



KEYWORDS

Antimicrobial Resistance

Antimicrobial Stewardship

Carbapenem

Carbapenem-resistant Enterobacteriaceae

Carbapenem-sparing regimen

Health outcomes

LIST OF ABBREVIATIONS AND ACRONYMS

AIDS	Acquired immunodeficiency syndrome
AMS	Antimicrobial stewardship
AMR	Antimicrobial resistance
BC	Blood culture
BLBLI	β-lactam/β-lactam inhibitor
BSI	Blood stream infection
BMREC	Biomedical Research Ethics Committee
CRE	Carbapenem-resistant Enterobacteriaceae
CRP	C-reactive proteins
CAI	Community associated infection
CSF	Cerebrospinal fluid
DM	Diabetes mellitus
DNA	Deoxyribonucleic acid
ECM	Enterprise Content Management
ESBL	Extended-spectrum beta-lactamase
ESBL-E	Extended-spectrum beta-lactamase–producing Enterobacteriaceae
ESBL-EC	Extended-spectrum beta-lactamase–producing Escherichia coli
FDA	Food and Drug Administration
HAI	Healthcare-associated infection / hospital associated infection
HIV	Human immunodeficiency virus

ICH-GCP	International Conference for Harmonisation Good Clinical Practice
ICU	Intensive care unit
ID	Infectious disease
IQR	Interquartile range
IV	Intravenous
IM	Intramuscular
KDH	Khayelitsha District Hospital
KPC	Klebsiella pneumoniae carbapenemase
MAC-AMR	Ministerial Advisory Committee on Antimicrobial resistance
MRSA	Methicillin-resistant Staphylococcus aureus
mRNA	Messenger ribonucleic acids
MDR	Multidrug resistant
NDoH	National Department of Health
NHLS	National Health Laboratory Services
NHRD	National Health Research Database
PBPs	Penicillin-binding proteins
SAMF	South Africa Medicine Formulary
SAASP	South African Antibiotic Stewardship Programme
SAHPRA	South African Health Products Regulatory Agency
SPSS	Statistical Package for the Social Sciences
TB	Tuberculosis

UTI	Urinary tract infection
USA	United States of America
WHO	World Health Organisation
Cmax	Maximum (peak) serum concentration
$t_{1/2}$	Half-life
mg	Milligram
kg	Kilogram
L	Litre
mg/kg	Milligrams per kilogram
mg/L	Milligrams per litre
sd	Standard deviation

DECLARATION

I declare that this research study, entitled, *Retrospective descriptive evaluation of empiric carbapenem-sparing regimens versus carbapenem use in non-intensive care patients at a district hospital in South Africa*, is my own work that has not been submitted for any degree, or examination, at any other university, and that all the sources I have used, or quoted, have been indicated and acknowledged by complete references.

Full name: Isaac Mugoya

Date: 30 January 2021

Signature.....

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DEDICATION

I dedicate this work to God Almighty,
and, my late beloved mother, Naduga Blandina.

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CHAPTER ONE

INTRODUCTION

In this chapter, the researcher provides the background and rationale of the study. In addition, the aim, objectives, and significance of the study are included.

1.1. Background of the study

Antimicrobial resistance is a global concern associated with increased morbidity and mortality (Goff et al., 2017). The development of multidrug resistant patterns in gram-positive, as well as negative bacteria (*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa,* and Enterobacter species) has resulted in difficult-to-treat, or even impossible-to-cure infections, with currently available antimicrobials (Wozniak, Bailey, & Graves, 2019). There is a global escalation in antimicrobial resistance (O'Neill, 2016) as well as infection control challenges (Nguyen et al., 2016), together with the increased speed and volume of the intercontinental migration of people and animals (Rohde & McNamara, 2018), resistant bacteria could spread around the globe with ease.

If this escalated rate of antimicrobial resistance is not addressed successfully, within the next 30 years, an estimated death toll of 10 million people every year could be expected, which would be 1.2 times the mortalities due to cancer, and 6 times those due to diabetes, per year, globally. The financial global cost could be as much as 100 trillion US dollars every year (Neill, 2016).

The greatest concern about the increased antimicrobial resistance is that modern health systems continuously rely heavily on antimicrobials, to treat and prevent community, as well as hospital acquired infections (Zinner, 2007), or to reduce the risk of bacterial infections, post major surgeries (Jocum, 2018). Patients with a compromised immune system such as cancer, diabetes and AIDS (acquired immunodeficiency syndrome), are more vulnerable to several opportunistic infections and antimicrobial treatments are usually required for prophylaxis, or ultimately, treatment of such infections (Onah, Lateef, & Kaigamma, 2018).

The situation is worsened by the lack of new antimicrobial agents globally, with only a few expected to become available in the near future (Luepke et al., 2017). This is especially a

concern in the South African public healthcare sector, which has limited access to available antimicrobials (Chigome, Matlala, Godman, & Meyer, 2020). Therefore, it is crucial that a greater awareness of the rational use of antimicrobials is required, as well as urgent efforts to preserve the use and efficacy of the current available antimicrobials (Mendelson & Matsoso, 2016).

1.2. Rationale for the study

Carbapenems are the antimicrobials of choice to treat infections, presenting with extended-spectrum beta-lactamases-producing (ESBL) Enterobacteriaceae (Vubil et al., 2017). Carbapenem-resistant Enterobacteriaceae bacteria (CRE) are on the increase (Kotb et al., 2020), due to the selective pressure, as a result of carbapenem over-use (Wong et al., 2019). Subsequently, several multidrug resistant organisms have been isolated at public health sector laboratories in South Africa (Perovic et al., 2018).

In response to the World Health Organisation's (WHO) global action plan calling for a collaborative effort from all nations to tackle the increasing burden of antimicrobial resistance (WHO, 2015), South Africa has responded by developing a national antimicrobial resistance strategy framework, as well as an implementation plan to bring antimicrobial resistance under control (NDoH, 2017). This plan is a *one health* approach, where different national departments, such as National Department of Health, Department of Agriculture, Forestry and Fisheries, Department of Environmental Affairs, Department of Science & Technology, National Treasury, Department of Trade & Industry, Department of Basic Education, and Department of Higher Education & Learning, have come together with a common goal of minimising antimicrobial resistance. The Ministerial Advisory Committee on Antimicrobial resistance (MAC-AMR), with representatives from several national departments, collect information on antimicrobial resistance, and use such information to advise the Minister of Health on the progress of the implemented plan (NDoH, 2017).

The South African NDoH collects data on antimicrobial use and resistance, retrospectively, at the hospital and clinic level. Antimicrobial stewardship practice variables, such as taking a culture specimen before initiating of antibiotics, indication for antibiotics, review of antibiotic with culture results, change in regimens of antibiotic (stopping/de-escalation/substitution/addition of agents), IV to oral switch, and duration of therapy, are

among the data that is collected, and reported to the district and provincial antimicrobial resistance committee on a six-monthly basis, to assist with accessing the plan's progress. The provincial antimicrobial resistance committee then report such information to the MAC-AMR (NDoH, 2017).

One of the crucial antimicrobial stewardship (AMS) strategies, implemented locally and globally, to overcome CRE, is to reduce and preserve the use of carbapenem, as well as use carbapenem-sparing agents, initially (Wilson, 2017). However, the data on this empiric strategy is very limited; therefore, several investigations of this kind are paramount to evaluate the usage and health outcomes of these regimens. Consequently, this current retrospective pilot study is an endeavour to contribute to the local body of knowledge in this field.

1.3. Research aim

This current pilot study was aimed at describing and evaluating the use of empiric carbapenem versus carbapenem-sparing antibiotic regimes in adult patients (non-intensive care), in terms of patient health outcomes for a period of 6-months (1st March 2018 to 31st of August 2018), at Khayelitsha District Hospital in Cape Town, South Africa.

1.4. Research objectives

1.4.1. Primary objectives:

- To review current literature-based evidence on carbapenem and carbapenem-sparing regimens in South Africa, as well as globally;
- To describe patient health outcomes (length of stay in hospital and in-hospital mortality);

1.4.2. Secondary objectives:

- To determine which antimicrobial stewardship approaches were implemented;
- To report the findings of this study and make recommendations.

1.5. Significance of the study

The results from this current pilot study could be valuable baseline data for expansion into other district hospitals. In addition, it could contribute to propose recommendations on how to improve existing AMS measures and awareness. Information acquired on the prescribing patterns and use of carbapenem and carbapenem-sparing antibiotics could be used to implement the necessary policy changes, as well as assist guideline developers, to ensure the appropriate use of these antimicrobials within district level hospitals in South Africa.

1.6. Structure of the thesis

The chapters in this thesis are arranged as follows

Chapter 1: Introduction.

Chapter 2: Literature review.

Chapter 3: Study methodology

Chapter 4: Results

Chapter 5: Discussion

Chapter 6: Conclusion, limitations and recommendations

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Appendices

CHAPTER TWO

LITERATURE REVIEW

In this chapter, the researcher explores the brief history of antimicrobial resistance (AMR), the mechanisms of resistance, antimicrobial stewardship, the extended-spectrum beta-lactamases, and the chemistry of carbapenems. In addition, the researcher discusses pharmacodynamics and pharmacokinetics of both carbapenem and carbapenem-sparing agents, as well as clinical studies published in the past decade, comparing the efficacy of carbapenem-sparing regimens (piperacillin/tazobactam) verses carbapenem agents, against infections with ESBL.

2.1. Antimicrobial resistance

The World Health Organisation declared AMR, one of the three most vital public health challenges of the 21st century (WHO, 2014). The estimated impact of growing antimicrobial resistance, on the economies of the world, however, may be negligible, compared to the consequences of a world without active antimicrobials. The greatest concern, regarding increased antimicrobial resistance, lies with the modern health systems that rely heavily on antibiotics to treat community and hospital acquired bacterial infections, reduce the risk of bacterial infections after major surgeries, and prevent infections during the use of immunosuppressive cancer therapies (Neill, 2016).

Antimicrobial resistance is a natural phenomenon that occurs via natural selection, leading to several modifications in the genetic composition of a micro-organism (Prestinaci, Pezzotti, & Pantosti, 2015). Antimicrobial resistance existed before the first discovery of an antibiotic agent (penicillin), by Alexander Fleming, in 1928 (Stekel, 2018), and has been continuously documented, as more antibiotic agents are discovered and used to prevent, or cure infections (Davies, 1996; Ventola, 2015; Meletis, 2016).

2.1.1. Mechanisms of antibiotic resistance

Bacterial pathogens use two strategies to develop resistance to antimicrobial agents, namely, gene mutation, or horizontal gene transfer, when faced with any changes in the environment that threaten their proliferation (Munita & Arias, 2016).

In gene mutation, micro-organisms transform genetically to:
(i) decrease the concentration of an antibiotic at their site of action, through efflux mechanisms;
(ii) decrease cell membrane permeability (McMurry, Petrucci, & Levy, 1980);
(iii) neutralize their activity through structural modifications, or modify the target site, to hinder antibiotic-target site binding (Walsh, 2000).

Micro-organisms use enzymatic reactions to modify antimicrobial agents, through chemical reactions, such as acetylation, phosphorylation, and adenylation (Munita & Arias, 2016). When these functional group(s) are added to the chemical structure of the antibiotic agent, they are inactivated, by destroying the active site. The addition of functional group(s) is better documented in aminoglycosides resistance, by aminoglycoside modifying enzymes that covalently modify the aminol, or hydroxyl groups, to decrease their activity (Ramirez & Tolmasky, 2010). While inactivation, through antibiotic active site destruction, is often seen in β -lactam antibiotics, where β-lactamases destroy the amide bond of the β-lactam ring (Paterson & Bonomo, 2005; Bush, 2013).

Horizontal gene transfer is the acquisition of foreign deoxyribonucleic acid (DNA), through which micro-organisms share genetically transformed material, by transformation (the incorporation of naked DNA), transduction (phage mediated), or conjugation (bacterial "sex") among themselves, irrespective of their species (Thomas & Nielsen, 2005; Munita & Arias, 2016).

2.1.2. Risk factors associated with antimicrobial resistance

Prior antimicrobial use, recent hospitalization and residing at nursing home facilities among others, are key risk factors associated with multidrug resistant micro-organism(s) (Wolfe, Cohen and Larson, 2014). Other risk factors that have been studied and concluded to also contribute to antimicrobial resistance include comorbidities (cancer, renal and liver dysfunction), invasive surgical procedures, intubation and catheterization (Safdar and Maki, 2002).

The presence of kidney failure in patients could increase the risk of acquiring an infection and these patients often require the use of broad spectrum antimicrobial agents (McDonald, Thomas and Nitsch, 2014). It was concluded in a Chinese observational study that patients with poor renal function at the time of hospital admission, had a higher

probability of presenting with infections due to multidrug resistant micro-organisms (Su et al., 2018). Patients with chronic kidney disease were linked with more frequent hospitalization, and can contribute to increased exposure to MDR organisms (James et al., 2009).

Acute kidney failure is when the rate of glomerular filtration falls rapidly and clinically manifests with a sustained increase in the serum levels of urea and creatinine (Hilton, 2011), and chronic kidney failure is defined when the glomerular filtration rate is persistently reduced below 60 ml/min/1.73 m^2 for a period of three months or more (Levin, 2013).

2.2. Antimicrobial stewardship

Antimicrobial stewardship (AMS) is a coordinated multidisciplinary team at work with various activities involving healthcare providers at all levels (Dyar, Huttner, Schouten, & Pulcini, 2017). Consultants, microbiologist, infectious disease (ID) specialists, antimicrobial stewardship pharmacists, and infection control practitioners, often form the core of the antimicrobial stewardship committee, depending on the amount of resources available (Pulcini et al., 2019). The purpose of AMS is not to stop the use of antibiotics, but to promote the rational use, by reinforcing AMS principles, to improve individual patient care, outcomes, and reduce hospital costs, with reduced spread of antimicrobial resistance. Some of these AMS principles include: to use antimicrobial agents only when indicated; collect culture samples prior to initiating therapy; use an appropriate route of administration; ensure the correct dose, frequency and duration of the treatment; select appropriate antimicrobial agent/s, and de-escalate the spectrum, if possible; minimise missed and extra doses; and conduct safety monitoring of treatment (Mendelson, Morris, Thursky, & Pulcini, 2019).

Promoting the rational use of antimicrobial agents, is an effective approach to addressing the ever increasing AMR challenge (Boyles et al., 2017). Antimicrobial stewardship programmes promote the rational use of antimicrobial agents, and could be achieved by designing prescription guidelines that support prescribers to select the correct antimicrobial agent(s), dose, and duration for a specific diagnosis, when a patient is suspected of having an infection (Boyles et al., 2017). Initiating educational programmes and developing strategies are crucial interventions, which an AMS programme could use to promote and implement the rational use of antimicrobial agents (Boyles et al., 2017).

The implementation of AMS programmes, at various healthcare facilities, has been observed to reduce the cost of maintaining patients at hospitals, by encouraging prescribers to use alternative, cheaper, and effective antimicrobial agents available, especially, when treatment becomes definitive, and de-escalation is possible, without negatively impacting the patients' health. This phenomenon was observed in various departments at a Tel Aviv Medical centre, in a study conducted in Israel (Saiag, Khatib, Deby-Lev, Ben-Ami, & Shapiro, 2014). In a study conducted in the United Kingdom, reduced incidences of catheter infections, and the decreased duration of hospital stay was achieved, by promoting the early switch from intravenous to oral therapy, whenever the patient was able to take oral treatment, and when a suitable oral antibiotic agent was available (Laing, Mackenzie, Shaw, Gould, & Douglas, 1998). A decrease in the incidences of *Clostridium difficile* infection, associated with the use of broad spectrum antibiotics among patients was observed, after the implementation and encouragement efforts that resulted from the antibiotic stewardship programme in Northern Ireland (Aldeyab et al., 2012).

2.3. Extended-spectrum β-lactamases (ESBL)

Extended-spectrum β-lactamases (ESBL) are enzymes capable of hydrolysing extended spectrum cephalosporin (ceftazidime, ceftriaxone and cefotaxime) and oxyimino-monobactam (Ghafourian, Sadeghifard, Soheili, & Sekawi, 2015). Beta-lactamase inhibitors such as clavulanic acid and tazobactam, inhibit ESBL, (Rodríguez-Baño et al., 2011). In general, ESBL are produced by gram-negative bacteria, commonly by *Enterobacteriaceae* and *Pseudomonas aeruginosa* (Nordmann & Guibert, 1998).

Three types of ESBL are of clinical significance, namely: TEM-1 ß-lactamases, first discovered in *Klebsiella pneumoniae* in France, in 1984; SHV ß-lactamases, which is the most prevalent among ESBL; and CTX-M type ß-lactamases, first described in 2000, by Tzouvelekis (Shaikh, Fatima, Shakil, Rizvi, & Kamal, 2015). Infections by ESBL-producing micro-organisms are a global threat, due their prevalence in both community and hospital care settings, as well as their association with poor treatment outcomes, and increased hospital costs (Bradford, 2001). To date, studies conducted in South Africa, reveal a high prevalence of ESBL-producing *K. pneumoniae* in the country (Cotton et al., 2000; Bell et al., 2002).

Carbapenems are regarded as the antibiotics of choice, to treat infections, presenting with ESBL; however, their efficacy is being impeded by the increasing rates of ESBL-producing organism resistant to carbapenem, globally (Pana & Zaoutis, 2018).

2.4. Carbapenems

In the following sub-sections, the chemistry, pharmacodynamics, and pharmacokinetics of the carbapenems are briefly summarised.

2.4.1. Brief chemistry of carbapenems

Carbapenem antibiotics, namely, imipenem, ertapenem, doripenem, and meropenem, are β-lactam antimicrobial agents, available for clinical use in South Africa (Rossiter, Blockman and Barnes, 2016). They are known for their broad spectrum of activity within the β-lactam class of antibiotics, against several disease causing pathogens, including gram negative, gram positive aerobes and anaerobes (Norrby, 1995). Due to a unique trans-α-1-hydroxyethyl substituent at the C-5 and C-6 position, unlike a cis configuration in penicillins and cephalosporins, carbapenems possess a high stability against most β-lactamase enzymes, including AmpC β-lactamases and extended-spectrum β-lactamases (Basker, Boon, & Hunter, 1980), which hydrolyses the β-lactam ring in the β-lactam antibiotics, making them less effective against disease causing micro-organisms (Todar, 2011). Carbapenems also differ in chemical structure from other β-lactam antibiotics, such as penicillin and cephalosporin (figure 2.1), by having a double bond between C-2 and C-3, in the five-membered ring structure, and a sulphur group replaced with a carbon atom at position 1, as illustrated in figure 2.2 (Moellering Jr, Eliopoulos, & Sentochnik, 1989).

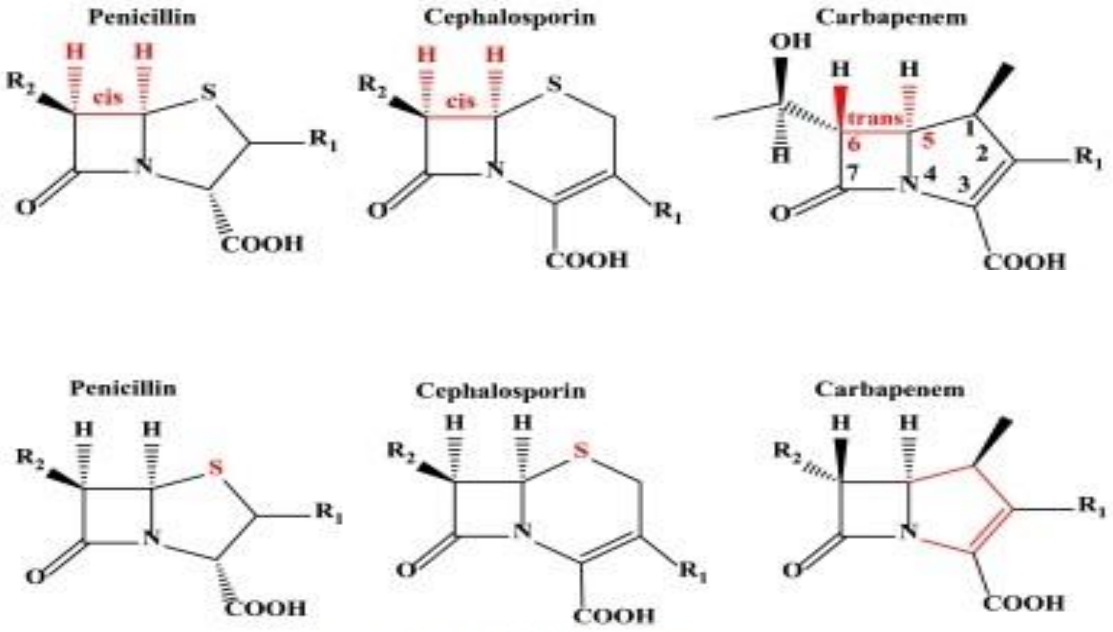


Fig 2.1: Chemical structural differences between carbapenem and other β-lactam antibiotics (Papp-Wallace, Endimiani, Taracila, & Bonomo, 2011).

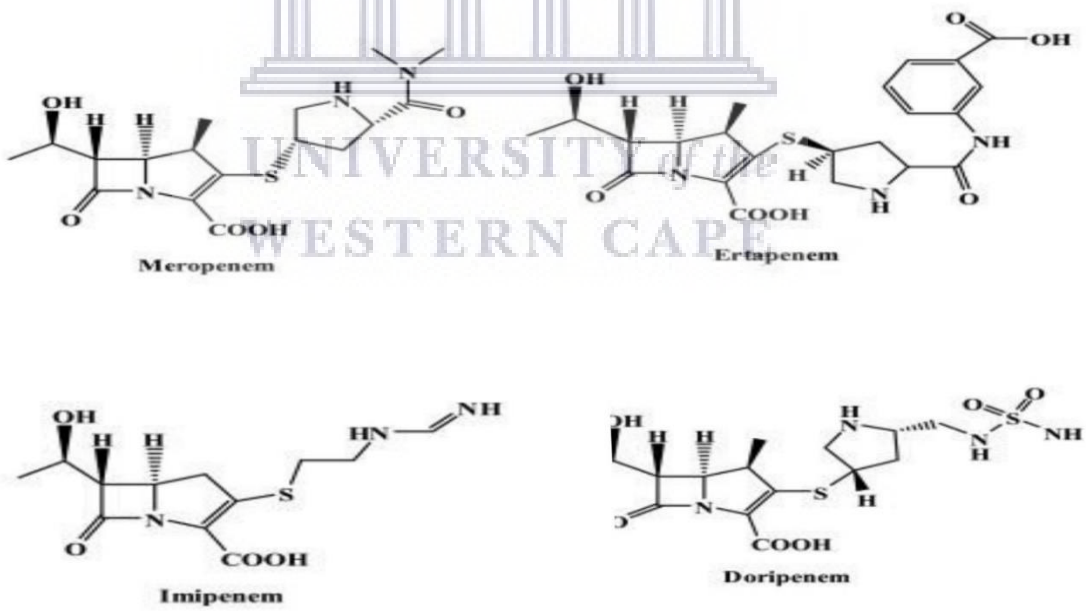


Fig 2.2: Chemical structures of carbapenems (Papp-Wallace et al., 2011).

2.4.2. Pharmacodynamics of carbapenems

2.4.2.1. Mechanism of action

Carbapenems, like other β-lactam antibiotics, kill bacteria (bactericidal), by inhibiting the last step in peptidoglycan synthesis, a heteropolymeric component of the bacterial cell wall, when they bind to, and inactivate penicillin-binding proteins [PBPs] (Papp- Wallace et al., 2011). The variance of potency in various carbapenems is attributed to the difference in their binding affinity for PBPs (Zhanel et al., 2005). Imipenem has a high affinity for PBP2, followed by PBP1a, and PBP1b. However, it has a low affinity for PBP3 (Sumita, Fukasawa, & Okuda, 1990). Meropenem and ertapenem have similar affinity for PBP, as both bind with a high affinity to PBP2, followed by PBP3, PBP1a, and PBP1b (Livermore, Sefton, & Scott, 2003).

Doripenem binding affinity for PBPs vary among the different species of micro-organisms; however, it has strong affinity for PBP3 in *P. aeruginosa*, PBP2 in *Escherichia coli*, and PBP1, PBP2, as well as PBP4 in *Staphylococcus aureus* (Jones, Huynh, & Biedenbach, 2004). Bacteriostatic and bactericidal effects are achieved with carbapenems, when the time above the minimum inhibitory concentration is approximately 20% and 40%, respectively (Nix, Majumdar, & DiNubile, 2004).

A post-antibiotic effect from carbapenems has been reported in gram-negative, as well as gram-positive micro-organisms (Mouton, Touw, Horrevorts, & Vinks, 2000). A post-antibiotic effect of 2 and 4 hours was noted in *E. coli* and *P. aeruginosa* respectively, when exposed to high concentrations of imipenem (a concentration of four times the minimum inhibitory concentration for *E. coli* and *P. aeruginosa*). A post-antibiotic effect of 4 and 5 hours was noted in *E. coli* and *P. aeruginosa* respectively, when being exposed to meropenem. Ertapenem and imipenem showed a post-antibiotic effect of 1.5 and 1.3 hours respectively with *E. coli*, when exposed to a concentration ten times the minimum inhibitory concentration, for a period of 2 hours (Mouton et al., 2000).

2.4.3. Antibiotic spectrum of carbapenems

Carbapenems have a wide-spectrum of activity against gram-negative and gram-positive bacteria, including anaerobes, compared to other beta-lactam antibiotics (Bassetti, Nicolini, Esposito, Righi, & Viscoli, 2009). Imipenem shows a better activity *in vitro,* against gram-positive micro-organisms, and slightly less activity against gram-negative micro-organisms, compared to meropenem (Edwards, Emmas, & Campbell, 2005). Imipenem, as well as meropenem, display great activity against *P. aeruginosa* and *Acinetobacter spp,* but low activity against methicillin-resistant *S. aureus,* which is not clinically significant (Mazzei, 2010). Ertapenem shares its spectrum of activity with imipenem and meropenem, but lack activity against gram-negative, non-fermentative bacteria, which includes *Acinetobacter spp* and *P. aeruginosa*. Doripenem has a superior potency of 2 to 4 times than that of imipenem against gram-positive bacteria, and also shows a slightly greater activity against gram-negative bacteria, including *P. aeruginosa,* than meropenem (Mazzei, 2010).

2.4.4. Mechanism of antibiotic resistance to carbapenems

Resistance to carbapenems could occur, firstly, as a result of the production of β-lactamases, known as carbapenemases, which hydrolyse the carbapenem β-lactam ring, and prevent it from binding to the PBP site of action (Queenan & Bush, 2007). Secondly, resistance could also occur through efflux pumps that prevent the accumulation of carbapenem reaching lethal concentrations inside the micro-organism cell cytoplasm (Meletis, Exindari, Vavatsi, Sofianou, & Diza, 2012). Thirdly, resistance could occur through mutations that alter the expression/ function of porins in the cell membrane, or PBP composition, to compromise the binding of an antibiotic with PBP, or the entry into the micro-organism cell (Doumith, Ellington, Livermore, & Woodford, 2009).

A combination of these mechanisms have been associated with high levels of resistance to carbapenems in several species of micro-organisms, such as *K. pneumoniae, A. baumannii* and *P. aeruginosa* (Limansky, Mussi, & Viale, 2002; Mena et al., 2006; Rodríguez-Martínez, Poirel, & Nordmann, 2009). Gram-positive cocci, typically, become resistant to carbapenems by having substitutions in amino acid sequences of PBPs (Matsumoto et al., 2007; Doumith et al., 2009), while gram-negative rods rely on several mechanisms of resistance, such as the expression of β-lactamases, efflux pumps,

and loss/alternation in PBP, to become resistant to carbapenems (Pearson, Van Delden, & Iglewski, 1999; Wareham & Bean, 2006; Nordmann et al., 2011). This could explain why gram-negative rods present with a high level of resistance to carbapenems, compared to gram-positive cocci.

2.4.5. Pharmacokinetics of carbapenems

2.4.5.1. Imipenem/cilastatin

Imipenem older carbapenem is not absorbed after oral administration. It is co-administered with a dehydropeptidase-1 (DHP-1) inhibitor, such as cilastatin, to minimise the formation of neurotoxic metabolites, due to degradation of imipenem by the DHP-1 enzyme located in the renal tubule (Papp-Wallace et al., 2011). Imipenem/ cilastatin is only available in an intravenous dose form, with a protein binding of 20%. The maximum plasma concentration (C_{max}) of 30-35 mg/L is reached when 500 mg is administered, and a C_{max} of 60-70 mg/L, when 1000 mg is administered as a single dose. It has a half-life ($t_{½}$) of 1 hour, and an area under the curve of 42.4 mg.h/L from a 500 mg administration, and 186 mg.h/L, when the strength is doubled to 1000mg (Papp-Wallace et al., 2011).

Imipenem/cilastatin penetrates well into the different body compartments, with concentrations of 1.6 mg/L in sputum, 2.2 mg/kg in tonsillar tissue, 5.3 mg/kg in prostatic tissue, approximately 2.2 to 3.8 mg/kg in female reproductive organs, and 16 to 79 mg/kg in the renal cortex, with up to 102 mg/kg in the renal medulla after 1 to 2 hours of administering a 500 mg dose (Buckley, Brogden, Barradell, & Goa, 1992). Concentrations of 0.5 to 0.9 mg/L, and 1.1 to 2.3 mg/L are attained in the cerebrospinal fluid after 1 to 8 hours of administering 1000 mg of imipenem/cilastatin intravenously, to non-inflamed and inflamed meninges, respectively (Buckley et al., 1992). After an hour of intravenous infusion of 1000 mg, imipenem/cilastatin penetrates lung tissue and reaches a concentration of 5 to 9 mg/L (Wise, Donovan, Lockley, Drumm, J., & Andrews, 1986). Approximately 70% of imipenem is excreted, unchanged, in the urine after administration (Rogers et al., 1985).

2.4.5.2. Meropenem

Meropenem is a thienamycin derivative that does not require co-administration with cilastatin, due to its insensitivity to renal degradation by dipeptidase (Papp-Wallace et al., 2011).

Meropenem has a half-life ($t_{½}$) of 1 hour, protein binding of 2% and is only available in intravenous form. Meropenem is readily and quickly distributed into the interstitial fluids, to reach concentrations of 1.43 to 8.23 mg/kg in the lungs, 0.65 to 4.52 mg/kg in the colon, 4.21 to 5.95 mg/kg in the skin, and 3.93 mg/kg in the gallbladder, 1.5 to 2.5 hours after 1000 mg intravenous infusion. It reaches concentrations of 1.05 mg/kg in the endometrium, 0.6 mg/kg in the ovary, and 1.21 mg/kg in the uterus, 1 to 1.5 hours after a 500 mg intravenous infusion (Hutchison et al., 1995).

Meropenem penetrates inflamed meninges to reach concentration levels of 0.1 to 2.8 mg/L, and 0.3–6.5 mg/L after administering 20 and 40 mg/kg, respectively. Up to 70% of meropenem is excreted through the kidneys, as the parent drug compound (Zhanel, Simor, Vercaigne, Mandell, & Canadian Carbapenem Discussion Group, 1998).

2.4.5.3. Ertapenem

Ertapenem is known for its longer half-life ($t_{½}$), compared to imipenem/cilastatin, doripenem, and meropenem, although, with a narrower antibiotic spectrum compared to other carbapenems (Keating & Perry, 2005).

Ertapenem is only available in intravenous form and has a half-life ($t_{½}$) of 3.8 hours, with a high protein binding of 92-95% (Majumdar et al., 2002). It has a mean C_{max} of 24.4 mg/L, approximately 8 hours after administration, and a mean concentration of 7.8 mg/L at 24 hours after the last administered dose of 1g in adults (Nix, Majumdar, & DiNubile, 2004). Ertapenem penetrates lung tissue to a concentration of 7.6 mg/kg (±4.85 mg/kg), approximately 3 hours after an intravenous infusion of 1g, as a single dose for 30 minutes (Burkhardt et al., 2005). Approximately 80% of ertapenem is excreted, unchanged, through the kidneys (Livermore, Sefton, & Scott, 2003).

2.4.5.4. Doripenem

Doripenem is a newer and potent carbapenem, with an extended infusion time of more than 4 hours, due its high stability in solutions at a temperature of 25°C, unlike imipenem, meropenem, and ertapenem (Mazzei, 2010). Doripenem has low oral availability and is administered intravenously, with a half-life of 0.93 hours, and protein binding of 8.9%. It reaches a C_{max} of 20.2 mg/L, with an area under the curve of 44.1 mg·h/L after the administration of a single intravenous dose of 500 mg (Nandy, Samtani, & Lin, 2010). Since doripenem is completely excreted renally, doses administered to patients with renal impairment, should be adjusted according to their renal function (Matthews & Lancaster, 2009).

2.5. Carbapenem-sparing regimens

In the following sub-sections, the pharmacodynamics and pharmacokinetics of certain carbapenem-sparing regimens are briefly summarised. Carbapenem-sparing regimens are antibiotic agents that include non-carbapenem beta (β)-lactams (piperacillin/tazobactam, ceftazidime/avibactam, ceftolozane/tazobactam, temocillin, cefepime and cephamycins), and non-β-lactam antibiotics (aminoglycosides, quinolones, tigecycline, fosfomycin and eravacycline). They could be used either in combination, or as single agents, to treat infection due to extended-spectrum β-lactamase–producing enterobacteriaceae (ESBL-E), as a strategy to decrease carbapenem usage (Karaiskos & Giamarellou, 2020). This, in turn, could reduce the increasing numbers of carbapenem resistant enterobacteriaceae, due to the selective pressure from carbapenem overuse (Yang et al., 2018).

The focus of this literature review is on piperacillin/tazobactam and aminoglycosides, which are the carbapenem-sparing agents present in the formulary for the public hospital sector in South Africa.

2.5.1. Piperacillin/tazobactam

2.5.1.1. Piperacillin spectrum and mechanism of action

Piperacillin has a similar mechanism of action to other β-lactam antibiotics (Hilal-Dandan & Brunton, 2016), but with an extended spectrum of activity, due to its higher affinity for PBP3 compared to other penicillin antibiotics (Essack, 2001). Piperacillin is a semisynthetic ureidopenicillin, with an extended spectrum of

activity beyond ampicillin, including most strains of *P. aeruginosa*, *E. faecalis*, several bacteroides species, and enterobacteriaceae (Culver & Martens, 1996). It is combined with tazobactam, a β-lactamase inhibitor, which broadens the spectrum beyond every other penicillin agent, by including methicillin-susceptible *S. aureus* (MSSA), *Haemophilus influenzae*, *B. fragilis*, most *E. coli*, and *Klebsiella* (Hayashi *et al.*, 2010). Tazobactam is a penicillinate sulfone, with no significant antibacterial activity on its own, and only increases piperacillin's spectrum of activity, by inhibiting its hydrolysis from several class A serine-β-lactamases commonly produced by *S. aureus*, *Moraxella catarrhalis*, *H. influenzae*, enterobacteriaceae, and bacteroides species (Drawz & Bonomo, 2010).

Piperacillin/tazobactam is designated for the treatment of moderate to severe infections, which includes, hospital-acquired pneumonia (ventilator-associated pneumonia and healthcare-associated pneumonia), community-acquired pneumonia (presenting with a high risk for *P. aeruginosa*), complicated urinary tract infections, catheter related blood stream infection, complicated skin and soft tissue infections (diabetic foot and necrotizing fasciitis), complicated intra-abdominal infection, neutropenic fever, severe sepsis and septic shock (Hayashi et al., 2010).

2.5.1.2. Pharmacokinetics of piperacillin/tazobactam

Piperacillin/tazobactam is only available in parenteral dosage form. Piperacillin and tazobactam have protein binding capacities of 20 to 30%, and 20 to 23%, respectively, and both agents are highly soluble in water (Sörgel & Kinzig, 1993). The elimination $t_{1/2}$ of piperacillin and tazobactam is 0.88 and 0.78 hours, respectively (Hayashi et al., 2010), which could increase in patients with deteriorating renal function (Sörgel & Kinzig, 1993), or those being treated for major burns (Bourget et al., 1996), and significantly decrease in pregnancy (Bourget et al., 1998). The volume of distribution for piperacillin, as well as tazobactam is relatively small, specifically 12.3 and 12.7 L respectively, and penetrates 90% into the skin and lungs (Sörgel & Kinzig, 1993). However, penetration into fatty tissue, muscle, cancellous bone, and cortical bone is less than 30% (Kinzig et al., 1992; Incavo et al., 1994). Small percentages of piperacillin (5%) and tazobactam (17%) are found in the cerebrospinal fluid (CSF) of non-

inflamed meninges, post IV administration (Nau et al., 1997). The combination is ineffective in the treatment of meningitis, due to the inadequate concentrations found in inflamed meninges (Rochon, Moussa, & Autmizguine, 2019). Both agents are excreted in the urine and bile (Hayashi et al., 2010).

2.5.1.3. Mechanism of resistance to piperacillin/tazobactam

Piperacillin, as with other β-lactam antibiotics, faces resistance through the mutation at PBPs, which decreases piperacillin affinity for PBPs; changes in the cell membrane of micro-organisms, which reduce the entry of piperacillin to the site of action; and activation of efflux pumps that continuously lower piperacillin concentration in the cytoplasm of the organism (Fernández & Hancock, 2012). In addition, piperacillin is prone to β-lactamase cleavage, although its combination with tazobactam minimises this threat from most β-lactamases (MacDougall, 2017b). However, this strategy is challenged with an inoculum effect from different types of infections, which decreases the efficacy of tazobactam (Bonfiglio & Livermore, 1994; Thomson & Moland, 2001).

2.5.2. Aminoglycosides

2.5.2.1. Aminoglycosides spectrum and mechanism of action

Aminoglycosides are either natural or semisynthetic derivatives of compounds originating from different soil actinomycetes (MacDougall, 2017a). Most aminoglycosides are utilised primarily to treat infections, due to aerobic gram-negative bacteria (Mingeot-Leclercq, Glupczynski, & Tulkens, 1999). However, some still find use in the treatment of mycobacterial infections (kanamycin, amikacin and streptomycin), as well as in intestinal amebiasis (paromomycin) (MacDougall, 2017a). Aminoglycosides display little activity against anaerobic micro-organisms and limited activity against gram-positive bacteria. Hence they are not recommended for use as sole agents, to treat infections due to these organisms. A synergistic bactericidal effect is attained *in vitro*, when aminoglycosides are used in combination with other antibiotics, such as penicillin, or vancomycin (cell wall active agents), in the treatment of such infections (MacDougall, 2017a).

Aminoglycosides bind irreversibly to 30S ribosomal subunits, inhibiting the synthesis of bacterial proteins and eventually leads to the death of a bacteria cell. This occurs by prematurely terminating mRNA translation that leads to incomplete protein synthesis and or the production of non-functional proteins as incorrect amino acids are incorporation during the synthesis process. (Davis, Chen, & Tai, 1986; Davis, 1987). They are bactericidal and concentration-dependent antibiotics, with an extended post antibiotic effect, particularly against gram-negative bacteria, which makes them ideal for a single-dose, daily administration (MacDougall, 2017a).

Amikacin, gentamicin, kanamycin, tobramycin and streptomycin are aminoglycoside antibiotics available in both IV and IM dosage forms for use in the South Africa. Gentamicin and amikacin are often reserved for use in suspected hospital acquired infection. Amikacin is the most commonly used aminoglycoside to treat hospital acquired infections due to a remarkably low resistance by many gram negative bacilli. Aminoglycosides are recommended for use in combination with bacterial cell wall synthesis inhibitor such as penicillins in infections where multidrug resistant organisms are suspected (Rossiter, Blockman, and Barnes, 2016).

Addition of amikacin to piperacillin/tazobactam, forms an alternative regimen to carbapenem, to treat patients suspected with a hospital acquired infections empirically, in the public sector of South Africa (NDoH, 2019).

2.5.2.2. Mechanism of resistance to aminoglycosides

Resistance to aminoglycosides could occur through enzymatic drug modification, during which process aminoglycosides are modified by aminoglycoside-modifying enzymes (Ramirez & Tolmasky, 2010). These enzymes include aminoglycoside acetyltransferases, phosphotransferases, and nucleotidyltransferases, assumed to have originated from actinomycetes, and acquired via horizontal gene transfer. This leads to loss of aminoglycoside potency, by decreasing their affinity for a target site (Ramirez & Tolmasky, 2010). Amikacin has a high level of resistance to aminoglycoside enzyme modification, and consequently retains a broader spectrum of activity compared to other aminoglycosides (MacDougall, 2017a). Intrinsic aminoglycoside resistance also occurs through the efflux pump mechanism, which continuously forces aminoglycosides out of the bacteria cell, keeping their

concentrations below minimum bactericidal concentrations at the site of action (Aires et al., 1999; Rosenberg, Ma, & Nikaido, 2000).

2.5.2.3. Pharmacokinetics of aminoglycosides

Aminoglycosides are poorly absorbed through the gastro-intestinal tract, and consequently, are only administered parenterally, for systemic use (Craig, 2011). The t½ of aminoglycosides in plasma is 2 to 3 hours in patients with normal renal function, and may be increased in new born babies, or reduced in patients presenting with cystic fibrosis (Mann et al., 1985; MacDougall, 2017a). After an intramuscular administration, all aminoglycosides reach maximum concentration in the plasma, within 30 to 90 minutes. Aminoglycosides have large volume distribution in the lungs, but poor distribution in fatty tissue, as well as little penetration to the eyes, and the central nervous system, except in cases of significant injury (inflammation). High concentrations of aminoglycosides end up in the renal cortex, as well as the endolymph and perilymph of the inner ear, which could contribute to nephrotoxicity and ototoxicity (Simon, Mösinger, & Malerczy, 1973; MacDougall, 2017a). Therefore, aminoglycosides should not be used as the first-line treatment of infections in late pregnancy, as they may accumulate in foetal plasma and amniotic fluid. In addition, aminoglycosides could react with various penicillin antibiotics, *in vitro*, to form an inactive complex; therefore, admixing these two classes of agents should be avoided. It is suggested that aminoglycoside inactivation by penicillin, may still occur at the *in vivo* level, especially in end-stage renal failure. Amikacin is the aminoglycoside that appears to be least affected by this interaction. Piperacillin, similar to amikacin, is also less prone to cause this kind of interaction *in vivo* (Blair, Duggan, & Schroeder, 1982; MacDougall, 2017a).

2.6. Efficacy of carbapenem-sparing regimens versus carbapenems against infections with ESBL-producing bacteria

In this sub-section, the researcher reviews studies to compare the efficacy of carbapenem-sparing regimens versus carbapenems, in the treatment of infections caused by ESBL-producing micro-organisms. Studies that included piperacillin/tazobactam as a carbapenem-sparing regimen in the empiric, or definitive phases, are listed below.

2.6.1. Empiric phase

A multi-centre, post-hoc analysis of six prospective cohort studies was conducted in Spain, to compare the health outcomes (mortality rate at day 30, and duration of hospital stay) of patients, who were being treated with either β-Lactam/β-lactam inhibitor combinations (amoxicillin-clavulanic acid or piperacillin-tazobactam), or carbapenems, for community and hospital acquired blood stream infections that presented with ESBL–producing *E. coli* (ESBL-EC). One-hundred-and-ninety-two patients (>17 years of age), who presented with ESBL-EC in blood cultures were included, and received either a β-lactam/β-lactam inhibitor combination, or a carbapenem, for a duration of more than 48 hours. In the empiric phase analysis, 103 patients received a β-lactam/β-lactam inhibitor combination, or a carbapenem. Seventy-two patients (n = 72) received a β-lactam/β-lactam inhibitor combination (amoxicillin-clavulanic acid [n=37] plus piperacillin-tazobactam [n=35]), while the rest received a carbapenem. The source of infection for 52 (72.2%) and 18 (58.1%) of the patients from the two groups, respectively, was the urinary, or biliary tract (ρ=0.1). The patients presented with community, as well as hospital acquired infections. More patients in the β-lactam/β-lactam inhibitor combination group suffered severe sepsis, or shock. (ρ=0.2), as 9 patients from the β-lactam/β-lactam inhibitor combination group were admitted to ICU, while only 2 patients from the carbapenem group (ρ=0.7) were affected.

The mortality rates were not statistically different, at 9.7% and 19.4% (ρ=0.1), for patients, who were treated with either a β-lactam/β-lactam inhibitor combination or a carbapenem, respectively. The median duration of hospital stay was 12 (8-28) and 13 (9-25) days respectively, also indicating no statistically significant difference (ρ=0.7) among the patients, who were treated with a β-lactam/β-lactam inhibitor combination, or a carbapenem, in the empiric phase. Additionally, no significant statistical (ρ=0.4) difference was evident in the mortality rates of patients, who were treated with amoxicillin-clavulanic acid, or piperacillin-tazobactam (Rodríguez-Baño et al., 2011).

In contrast to the above study, a retrospective study conducted in the USA included 213 patients, who were treated empirically with piperacillin-tazobactam (n=103), or a carbapenem (n=110) for ESBL bacteraemia. Seventeen (17) and eight (8) percent of the patients from piperacillin/tazobactam and carbapenem group respectively, died by the fourteenth day (ρ<0.05). The patients in the piperacillin/tazobactam group were observed

to be associated with a higher mortality rate, than those in the carbapenem group, at day 14 and day 30 (Tamma et al., 2015).

In this American study, firstly, 34% of the patients were admitted to ICU, unlike 8.7% in the Rodríguez-Baño et al. (2011) analysis. Secondly, up to 61% of the patients in the piperacillin-tazobactam group received a lower dose of 3.375 g every 6 hours, instead of 4.5g every 6 hours. Thirdly, the patients in the American study acquired ESBL that were produced by multiple micro-organisms (*K. pneumoniae*, *E. coli* and *Proteus mirabilis*), whereas in the Spanish study, a single micro-organism (*E. coli*) was responsible. Fourthly, in the American study, the patients suffered infections from multiple sources, such as urinary, intra-abdominal, respiratory tract, biliary and catheter inserted sites, unlike those in the Spanish study, who suffered only urinary and biliary infections, which could have influenced the outcomes of this study (Tamma et al., 2015).

Subsequently, a multicentre, multinational, retrospective study, with a large number of participants (n=365) in the empiric treatment phase, involving blood stream infections, due to ESBL-producing *E. coli* (73%) and *K. pneumoniae* (19%) that originated from UTIs (45%) and biliary diseases (12%), revealed similar results to those of the Spanish study, at 30-day mortality. The piperacillin/tazobactam dose was 4.5 gram 6 hourly for 83% of the patients and 11% were admitted to ICU (Gutiérrez-Gutiérrez et al., 2016).

More retrospective observational studies that compare empiric piperacillin-tazobactam versus carbapenems, with variable sites of infections, different environmental settings, number of micro-organisms, and sample sizes, are briefly summarised below.

- A retrospective, multicentre cohort study was conducted in Singapore comparing the 30-day mortality and duration of hospital stay of patients, who were administered, empirically, with piperacillin-tazobactam versus a carbapenem (ertapenem, imipenem and meropenem) to treat blood stream infections due to ESBL from *E. coli* and *K. pneumoniae*. The study included 151 patients, of which, 94 received piperacillin-tazobactam and the rest, a carbapenem. Thirteen (13) of all the included patients were admitted to ICU. More patients presented with a urinary infection in the carbapenem group. The median duration of hospital stay was 18 (10–30) days in the piperacillin/tazobactam group, and 16 (8–24) days in the carbapenem group. The difference in the duration of hospital stay was not statistically significant (ρ=0.15). The thirty-day mortality was 30.9% (n=29) and

29.8% (n=17) for the piperacillin/tazobactam and carbapenem group, respectively [ρ=0.89] (Ng et al., 2016).

- A retrospective study, conducted in Korea, revealed similar results to the study conducted by Rodríguez-Baño et al. (2011). One-hundred-and-fourteen (114) patients, who were diagnosed with blood stream infection (BSI), were included in the study, and received either a piperacillin/tazobactam (n=36), or a carbapenem (n=78), with ESBL isolation from *E. coli or K. pneumoniae*. There was no significant difference in the severity of the illness, between those, who were treated with either a piperacillin/tazobactam, or a carbapenem. Diabetes mellitus was associated with a high number of patients from the piperacillin/tazobactam group (ρ=0.052). The 30-day mortality was 22.2% and 26.9% from the piperacillin/tazobactam and carbapenem group, respectively, with no significant difference in the mortality rate between the two groups [ρ = 0.592] (Kang et al., 2012).
- A multi-centre, multinational, retrospective study, comparing the efficacy of β-lactam/β-lactamase inhibitors to carbapenems, in haematological neutropenic adult patients with ESBL bloodstream infections, included 174 patients in the empiric treatment phase analysis. One-hundred-twenty-six (126) patients received a carbapenem, and forty-eight (48) received a β-lactam/β-lactamase inhibitor (91.7% received piperacillin/tazobactam). The sources of the infections were catheter-related, complicated intra-abdominal infections, and UTIs. Approximately 21.3% of the included patients were admitted to ICU. The mortality rate at day 30 was not significantly different (ρ=0.33), being 13.4% (n=17) in the carbapenem group, and 20.8% (n=10) in the β-lactam/β-lactamase inhibitor group (Gudiol et al., 2017).
- A single-centre, retrospective, cohort study compared carbapenem versus cefepime or piperacillin/tazobactam for the empiric treatment of adult patients, diagnosed with bacteraemia, due to ESBL-producing *E coli*, as a sole micro-organism in patients with hematologic malignancy. Additional sources of infection were catheter-related infections, skin and soft tissue infections, complicated intra-abdominal infection, pneumonia, and UTIs. With a higher percentage of ICU admission (30%), the results of this study were similar to those

of a study conducted by Gudiol et al. (2017), at a day 14 mortality rate (Benanti et al., 2019).

- In a multicentre retrospective cohort study in Korea, the efficacy of empirical non-carbapenem antibiotics was compared with carbapenem for ESBL-producing *E. coli or K. pneumoniae* in adult patients. Patients were either treated with a non-carbapenem, or a carbapenem for longer than 48 hours. Of the 232 patients included, 49 patients were treated with a non carbapenem antibiotic, and 183 with a carbapenem. Forty-one patients in the non-carbapenem group received piperacillin/tazobactam, while the rest received fluoroquinolones. The 30-day mortality rates were determined as 6.3% and 11.4% for the non-carbapenem group and carbapenem groups, respectively. There was no significant difference in the 30-day mortality rate between the two groups [ρ=0.42] (Ko et al., 2018).
- In a multicentre retrospective analysis, conducted in USA, a total of 117 patients, included in the study, received piperacillin/tazobactam (n=66) or a carbapenem (n=51) empirically. The patients were included in the study provided they cultured a positive ESBL-producing bacteria from *E. coli* or *K. pneumonia*, identified by rapid molecular assay. The piperacillin/tazobactam group had 25 patients admitted to ICU, while the carbapenem group had 20 patients (ρ=0.99). In hospital, mortality was 3% and 7.8% for the piperacillin/tazobactam and carbapenem groups, respectively, with no significant difference (ρ=0.4). The mean duration of hospital stay was determined as 7.9 and 7.1 days for piperacillin/tazobactam and carbapenem groups, respectively. No significant difference was evident in the duration of hospital stay between the two groups [ρ=0.88] (John, Colley, Nguyen, & Berhe, 2019).

2.6.2. Definitive phase

- A retrospective observational study was conducted in Singapore with 47 adult patients, who presented with BSI due to *E. coli or K. pneumoniae* that was cefotaxime non-susceptible, but piperacillin-tazobactam and meropenem susceptible *in vitro*. The median age was 75 years (23–100). The patients were administered definitively with either a carbapenem (meropenem, imipenem and ertapenem), or BLBLI (amoxicillin-clavulanate and piperacillin-tazobactam) as a carbapenem-sparing regimen. Twenty-four patients received BLBLI (4.2%

received amoxicillin-clavulanate) and 23 received a carbapenem. Two patients in BLBLI group, and 5 from the carbapenem group, were admitted to ICU, with urinary and biliary tract infections. The 30-day mortality was 8%, and 17% from the BLBLI and carbapenem groups, respectively, with no significant difference (ρ=0.92) in the mortality, between the two groups (Harris et al., 2015).

- A single centre retrospective observational study was conducted in Korea, with adult patients, presenting with acute pyelonephritis caused by ESBL-*E. coli*, susceptible to piperacillin/tazobactam. One hundred and fifty elderly patients participated in the study. The piperacillin/tazobactam group had 68 patients while the carbapenem (ertapenem) group only had 82 patients. The measured treatment outcomes were in-hospital mortality, change of initial antibiotic regimen, or microbiological eradication failure. There was no significant difference in the treatment outcomes between the two groups, at ρ=0.059, 0.257 and 1.0, respectively (Yoon et al., 2017).
- In a randomised controlled trial, conducted in Korea, 66 adult patients were assigned evenly to the piperacillin/tazobactam and ertapenem treatment groups, in which E. coli was a sole ESBL organism isolated. All infections were from the urinary tract source. A twenty-eight-day mortality rate (6.1%) was similar in both treatment groups [ρ=0.1] (Seo et al., 2017).
- A randomised clinical trial that included 378 adult patients, from 9 countries, and 26 sites, was conducted. The patients had at least one positive blood culture with *E. coli or K. pneumoniae* that was resistant to ceftriaxone, but susceptible to piperacillin/tazobactam. These patients were assigned, in a ratio of 1:1, to intravenous piperacillin-tazobactam (n = 188), or meropenem (n = 191), for a minimum of 4 days, and a maximum of 14 days. The total duration of treatment was determined by the clinician, who was treating the patient. The mortality rate at day 30 was 12.3% and 3.7% in the piperacillin/tazobactam and carbapenem groups, respectively (ρ=0.90). Definitive treatment with piperacillin/tazobactam, compared to meropenem, is not supported in this study (Harris et al., 2018).

In conclusion, in the past decade, most of these studies indicated no significant difference in mortality among patients treated empirically with piperacillin/tazobactam, or a carbapenem for infections due to ESBL from *E. coli, K. pneumoniae, Enterobacter cloaca, Klebsiella oxytoca,*

or Proteus mirabilis. The sources of infections included catheter-related, skin and soft tissue, complicated intra-abdominal, pneumonia, and urinary tract. These studies included patients with different severities of infections, number of micro-organisms isolated, and variable sites of infection, which could have had an impact on treatment outcomes, and cause a comparison challenge. A gap in knowledge exists about other micro-organisms that are capable of producing ESBL enzymes and infections from several other sites, not included in the studies above, as well as the role of carbapenem-sparing regimen agent combinations in treating suspected ESBL-producing infections. We are unaware of any studies conducted in South Africa that investigated the specific health outcomes (length of stay in hospital and in-hospital mortality) of carbapenem vs carbapenem-sparing regimens in adults. This study will contribute to that local body of knowledge.

CHAPTER THREE

STUDY METHODOLOGY

This chapter addresses, clarifications of the terms used in data collection process, study design, study site and population, inclusion and exclusion criteria, data collection process, statistical analysis and ethics of this study.

3.1. Clarifications of terms or descriptors used in the data collection process

All terms and descriptors below are defined and described in the researcher's own words to ensure for a consistent data collection process.

Total population sample: All patients, who were electronically issued with, either a carbapenem, or a carbapenem-sparing regimen (piperacillin/tazobactam – PiP/Taz and amikacin) during the period of this current study between 1 March 2018 and 31 August 2018.

Under age of 18: All patients, who were dispensed with either a carbapenem, or a carbapenem-sparing regimen, and below the age of 18 years.

Transferred patients: All patients, who received either a carbapenem, or a carbapenem-sparing regimen, and transferred to a tertiary hospital during the course of the treatment, or after completing the treatment.

Patient demised before treatment: All patients, who were dispensed with either a carbapenem or a carbapenem-sparing regimen, but was demised before receiving any dose.

Patients with missing data: All patients, who were prescribed either a carbapenem, or a carbapenem-sparing regimen, which were dispensed to them, while other electronic data could not be accessed on the ECM.

Treatment initiated at another hospital: All patients, who had either a carbapenem, or a carbapenem-sparing regimen initiated outside of the Khayelitsha District hospital (KDH), before being referred to the KDH for further management.

Length of stay in hospital: The number in days from the instant a patient was initiated on either a carbapenem, or a carbapenem-sparing regimen, to the moment of discharge from, or demise in the hospital.

Suspected diagnosis: The diagnosis documented prior to initiating either a carbapenem, or a carbapenem-sparing regimen.

Immune compromised patients: All patients, who were diagnosed with HIV/AIDS, diabetes, or treated with medicines that are known to supress the immune system (steroids or chemotherapy), before initiating either a carbapenem, or a carbapenem-sparing regimen.

Duration of culture sensitivity: The number of days from the moment culture samples are collected from patients, to the instant that final results of culture growth and sensitivity to antimicrobial agents become available on the electronic data system.

Total sample included: All patients, who meet the inclusion criteria of the study.

Total sample excluded: All patients, who do not meet the inclusion criteria of the study.

Extra dose: Any medicine dose that exceeds the prescribed number of doses per day, or course duration.

Missed dose: The total number of medicine doses that were not administered to the patient, as prescribed.

3.2. Study design

This current study was a pilot investigation. It was a retrospective and descriptive study that evaluated health outcomes in non-intensive care adult patients on either carbapenems, or carbapenem-sparing regimens, in a district hospital in the Western Cape, South Africa.

3.3. Study site

The study site was the Khayelitsha District Hospital (KDH), located in the Khayelitsha Health District of the Metro Region. The KDH is a secondary hospital, with a capacity of 300 beds, admitting males, females, and children. It offers district level care, including a 24-hour emergency centre, with medical, surgical, obstetrics, gynaecology, and paediatric wards, as well as a nursery. The patients visiting this hospital are either down-referred from tertiary

institutions, or up-referred from community health centres within the Khayelitsha district (Western Cape Government [WCG], 2012).

Fig 3.1: Map indicating the location of the Khayelitsha District Hospital, Western Cape Province (https://www.google.com/maps/search/kdh+hospital/@-0.2412701,11.910255,3z/data=!3m1!4b1)

3.4. Population sample

For the purpose of this pilot study all adult patients who were initiated on empiric treatment of a carbapenem, or a carbapenem-sparing regimen, at the KDH, during 1 March to 31 August 2018 were included after applying the stated inclusion and exclusion criteria.

A sample size justification and sample size calculation will only be conducted once this investigation is expanded into other district hospitals in the Cape metropole area.

3.5. Inclusion and exclusion criteria

3.5.1. Inclusion

All female and male patients, older than 18 years, who were admitted in non- ICU wards, and received either a carbapenem, or a carbapenem-sparing regimen empirically, in a 6-month study period between 1 March 2018 and 31 August 2018.

3.5.2. Exclusion

This study excluded all patients, who were younger than 18 years, or patients older than 18 years who:

i. Had been dispensed with either a carbapenem, or a carbapenem-sparing regimen, but died before receiving treatment;

ii. Had deficient clinical data from both electronic record systems;

iii. Had been transferred to any other health facility for further management;

iv. Had initiated treatment (carbapenem, or a carbapenem-sparing regimen) at any other health facility;

v. Had received both empiric regimens (carbapenem and carbapenem-sparing regimen);

vi. Had been admitted to ICU.

3.6. Electronic systems used to collect data

Electronic systems are often used to perform medicine transactions (dispensing, supply chain management), as well as storage of clinical data collected during a patients' hospital stay. The following section describes how retrospective data was acquired to accomplish the aims and objectives of this current study, from different electronic systems utilised by the Western Cape Department of Health.

3.6.1. JAC Medicine Administration System

The JAC Pharmacy System is a medicine management programme that integrates various medicine management processes. It is an access-controlled electronic system that requires login credentials, used at government hospital/clinic facilities, to monitor all medicine transactions in the pharmacy at all times. The JAC Pharmacy System provides its operator with an option to execute a transaction report of any drug of choice, for a given period of time, at a particular set location (facility). This report contains the location (facility name), as well as the patient details, including folder numbers, names of those, and the particulars of the drugs that were dispensed. In addition, it displays the times and dates of the dispensing of drugs to specific patients. The dispensed medicine details, such as name of medicine, strength, quantity and specific pack sizes, are some of the particulars recorded in the transaction report (Wellsky, 2014).

3.6.2. Enterprise Content Management (ECM) system.

The Enterprise Content Management (ECM) is an access-controlled electronic system that requires login credentials. In this system, the patients' clinical records, such as physician notes, nursing staff notes, prescriptions, as well as any other documented records of the patient's stay at the hospital, are scanned and saved, electronically, in pdf files, according to their episode dates.

3.6.3. National Health Laboratory Service (NHLS) system.

The NHLS is a public health laboratory with its own access controlled electronic system that requires login credentials to access medical laboratory results from collected samples. The results are stored according to the dates that the sample was collected and received in the laboratory. The results stored includes the patient's name, folder number, date of birth, the types of samples collected, the time such samples were collected and received, type of test done, time such results became available, and a guide to assist with the possible interpretation of results.

3.7. Data collection process

After permission was granted by the KDH and NHLS to access electronic systems, the JAC was the first electronic data system accessed for transaction reports of carbapenems (imipenem, meropenem and ertapenem), as well as carbapenem-sparing regimens (PiP/Taz and Amikacin), which were extracted for a period of 6-months (from 1 March 2018 to 31 August 2018). Subsequently, the patients' folder numbers from the medicine transaction report (as issued by the pharmacy) of the JAC were used in the ECM system to access the patients' profiles for their detailed demographics and clinical records. The inclusion/exclusion criteria were applied, and only patients, who met the criteria, received unique study numbers, for their retrospective data to be collected.

Several clinical records, such as clinical notes (doctors clinical notes and prescriptions with pharmacists notes), were used to determine the patients' duration of hospital stay, treatment outcomes (demised or discharged), treatment duration, treatment dose, treatment frequency, treatment/s missed, as well as extra dose(s), and immune system status. In addition, the documentation of past antimicrobial use, type of infection, renal functionality, surgical history, site of infection, activity on antimicrobial spectrum (escalation or de-escalation of

antimicrobial spectrum), intravenous to oral switch, route of administration, co-morbidities, other treatments co-administered with antimicrobials, allergy documentation and suspected diagnosis prior to initiating empiric study regimens, were accessed. Nursing notes and administration notes were used, mostly, to access the patients' demographics, such as age, gender, date of birth, weight, date of discharge (where it was not clear in the doctor's clinical notes), as well as temperature readings of the included population sample. All data were recorded onto a study specific data collection form (Appendix A).

The same patient folder numbers, from the medicine transaction reports of those included in this current study, were used in the NHLS system to collect specific laboratory records, such as the period of culture collection, in relation to initiating treatment, type of cultures collected, duration of culture sensitivity availability, type of organism(s) grown, and their sensitivity profiles to available antimicrobial agents, serum creatinine levels, full blood cell count, and C-reactive proteins levels. The recorded information from the data collection form was captured onto an electronic Microsoft Office Excel spreadsheet. Subsequently, this electronic data base was cleaned and the data transferred to the Statistical Package for the Social Sciences [SPSS] (IBM, 2015). All the variables that were recorded in words, were coded, by assigning unique numerical figures to them, before data analysis commenced in the SPSS programme.

3.7.1 Reliability, Validity and Bias

The quality of this quantitative pilot project was ensured to produce consistent accuracy and reliability by incorporating a data collection form (Appendix A) which was specifically developed for this study. The validity was maintained by ensuring accuracy and consistency of the data being captured onto the data collection form (Heale & Twycross, 2015). The study specific data collection form was developed in collaboration with the study supervisors in consultation with two collaborators, Dr GL Muntingh (Tygerberg hospital pharmacy) and Dr J Taljaard (infectious disease specialist from the Faculty of Medicine and Health Sciences, Stellenbosch University). By implementing the same data collection form to capture data from patient health records ensured that the data was collected consistently and accurately.

To ensure content validity (Heale & Twycross, 2015), the data collection form was first tested out by completing the form using two real-life patient health records that were similar to what the study would include. Minor changes were made and the final study specific data collection was finalised and used for all the data collection of this pilot

study. The actual data collection process and recording of the data onto the study data collection form was further only performed by one person and that was the master student.

Researchers should mitigate to limit bias in research by outlining all possible sources of bias (Smith and Noble, 2014). Research bias was limited by ensuring that this study design including the aims and methods were scientific based. The master student and study supervisors worked in close collaboration with expert collaborators in the field to limit design bias. This study limited selection and inclusion bias by including all adult patients who received the specified antimicrobial regimens within the specified time period and it was further mitigated by applying the set inclusion and exclusion criteria. Data collection and measurement bias were limited by using the validated study specific data collection form.

3.8. Statistical analysis

The coded data were analysed with the IBM SPSS statistical software package, version 23 (IBM, 2015). Descriptive statistics, namely, the mean, median, range, frequencies, interquartile range (IQR) and standard deviation (± sd), were used to determine the distribution of several variables, such as demographics, laboratory results, and some antimicrobial stewardship measurable variables (Sarantakos, 2013; Altman & Bland, 2005). The Shapiro-Wilk test for normality (Razali & Wah, 2011), including the histogram and normal Q-Q plots, were used to determine the distribution of the duration of hospital stay, and the duration of the availability of culture sensitivity results.

In addition, the chi-square test (Agresti, 2018) was used to determine whether the distribution of categorical variables (in-hospital mortality) in a population were different from, or related to, each other. The Mann-Whitney U test (non-parametric) was used to compare groups where variables (length of stay in hospital) were not normally distributed (Hollander, Wolfe, & Chicken, 2013). The unpaired t-test (parametric) was used for comparisons between two groups, when the data was, approximately, normally distributed (Geisser & Johnson, 2006). A significance testing level of $p<0.05$ was used.

3.9. Ethical considerations

The Biomedical Research Ethics Committee at the University of the Western Cape (BMREC-UWC) approved a waiver of patient informed consent for this investigation, in terms of the

Ethics in Health Research 2nd edition (Republic of South Africa [RSA], National Department of Health [NDoH], 2015), based on the fact that this current study was a retrospective investigation type. Ethics approval was granted by BMREC-UWC (Reference Number BM18/9/7 on 9 November 2018), with minor amendments, and renewal approved again in September 2019 (Appendix B). The study was extended from 3 to 6 months (1 March 2018 and 31 August 2018) due to electronic record capturing problems experienced by KDH towards the end of 2018.

The proposal and application to conduct this current study was submitted via the National Health Research Database [NHRD] (https://nhrd.hst.org.za/). The NHRD serves as a repository of health-related research that has been, and is being conducted in the public health sector in South Africa. It is a tool for the monitoring and managing of health research for National Health Research Committee, Provincial Health Research Committees, and Research Ethics Committees, across South Africa. Approval was granted by the Department of Health in the Western Cape Province (Appendix C), and access to the study site was granted after presenting the study proposal to the research representatives at the KDH (21 February 2019). The study was approved on 14 March 2019 (WC_201901_011), and access to the NHLS system for laboratory measurements and diagnostics was granted on the 21 June 2019 (Appendix D).

3.9.1. Anonymity

Numeric study numbers were allocated to all the included patients, with a format of P (denoting participant) followed by a number, for example, P001, P002, P003, P004, P005. In addition to the P-number, the researcher recorded the patient's admission folder number on the data collection form, in pencil, as a guide to the patients' identification, as well as for quality assurance, data checking, and monitoring. Subsequently, these patient folder numbers were erased from every data collection form, before data analysis was finalised, to avoid linking data back to a particular patient folder.

3.9.2. Confidentiality

The confidentiality of patients was maintained during the collection and analysis of data, as only the researcher and study supervisors had direct access to the collected data. All collected data were kept in a locked location, at the School of Pharmacy of the University of the Western Cape, and the electronically stored data were password protected, with a password known only to the researcher and study supervisors at all times.

CHAPTER FOUR

RESULTS

In this chapter, the results of this retrospective study, which include descriptive and inferential statistics are presented in tables, figures, and graphs. The total number of patients, who were initially screened from the electronic medicine management system for inclusion into the 6-month study period (1 March 2018 to 31 August 2018) was 220. When the inclusion and exclusion criteria were applied (see methodology), only 90 patients were eligible to be included into this current study. A carbapenem regimen was used in 66 patients, while 24 received a carbapenem-sparing (PiP/Taz and Amikacin) regimen (see Figure 4.1).

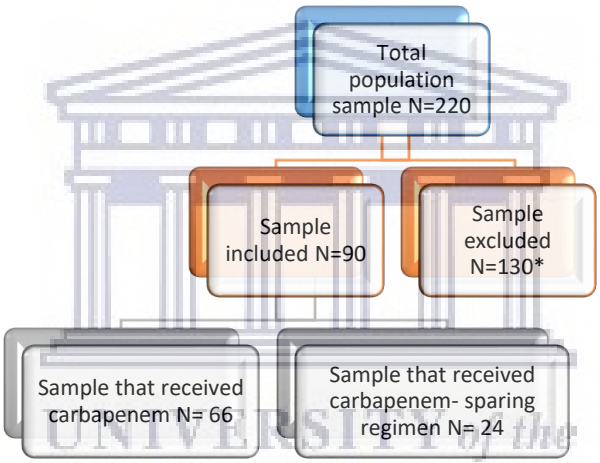


Figure 4.1: Schematic breakdown of included sample over 6-month period (1 March 2018 to 31 August 2018)

*** Majority reasons for excluding were age below 18 years and deficient clinical data from both electronic systems.**

In the following sections, the demographic results are presented first, followed by risk factors for acquiring a hospital infection, laboratory results, measurable antimicrobial stewardship variables, and the health outcomes measured.

4.1. Demographics

The average (standard deviation) and median (interquartile range) results on age (years), weight (kg) gender, immune system status, allergy documentation and comorbidities of this study population are reflected in Table 4.1.

Of the 90 patients, included in this current study, the females constituted 51.1% (n=46). The carbapenem study group had a median age of 47 (37 - 57.3) years, and the carbapenem-sparing study group had a median age of 34 (29.3 - 52.8) years. The median age of the carbapenem study group was significantly higher, compared to the carbapenem-sparing group (ρ=0.01). Only 21.1% (n=19) of this study sample had recorded weights in their clinical notes, at the time of the specific hospitalisation period.

The immune system status of the study population sample was determined as 71.1% (n=64) immunocompromised, 25.6% (n=23) immunocompetent, and 3.3% (n=3) with unknown immune status. No known allergies were recorded for 78.9% (n=71), while 21.1% (n=19) had no recorded allergies. The following comorbidities were recorded for the included sample: 57.8% (n=52) were infected with HIV, 41.1% (n=37) with TB, 18.9% (n=17) had DM (Type II), 31.1% (n=28) had hypertension, 28.9% (n=26) were co-infected with both HIV and TB, and 14.4% (n=13) presented with other diseases. Several patients in the included sample presented with more than two comorbidities.

Table 4.1: Demographic and health variables for study groups

	Carbapenem regimen (n=66)	Carbapenem-sparing regimen (n=24)	ρ-value	Combined
Gender (female/male)	35 / 31	11 / 13	0.55###	46 / 44
Median age (IQR), years	**47** (37 - 57.3)	**34** (29.3 - 52.8)	**0.01**#	46 (33 – 56)
Mean weight (±SD), kg	65.6 (±17.5)	70.7 (±29.7)	0.68##	66.4 (±18.9)*
Immune status				**N (%)**
Compromised	49	15	0.29###	64 (71.1)
Competent	15	8	0.34###	23 (25.6)
Unknown	2	1	0.80###	3 (3.3)
Comorbidities				**N (%)**
HIV	39	13	0.81###	52 (57.8)
TB	27	10	0.68###	37 (41.1)
HIV+TB	19	7	0.98###	26 (28.9)
DM (Type II)	14	3	0.38###	17 (18.9)
Hypertension	20	8	0.10###	28 (31.1)
Other**	11	2	0.50###	13 (14.4)
Allergies				**N (%)**
No known allergy	53	18	0.59###	71 (78.9)
No allergies recorded	13	6	0.35###	19 (21.1)

#Mann-Whitney U test (non-parametric distribution of data) ## Unpaired t-test (parametric distribution of data for independent groups) ###Chi-square test performed on categorical data. * n=19, rest of information not recorded **Psychosis, asthma, epilepsy, gout and COPD.

4.2. Medication history at initiating empiric study regimens

All the different co-administered classes of chronic medicines and acute medications applicable to this current study population are presented in Figure 4.2. Analgesics (n=50), anticoagulants (n=45), anti-tuberculosis (n=36), antiretroviral (n=21), and antihypertensive agents (n=19), accounted for the highest numbers of co-administered classes to this current study population. Co-administered antibiotics were dispensed to 8 patients including: azithromycin (n=3); metronidazole (n=1); vancomycin (n=1); trimethoprim/sulfamethoxazole (n=1), co-administered with a carbapenem; and amoxicillin-clavulanic acid (n=2) that was co-administered with a carbapenem-sparing regimen.

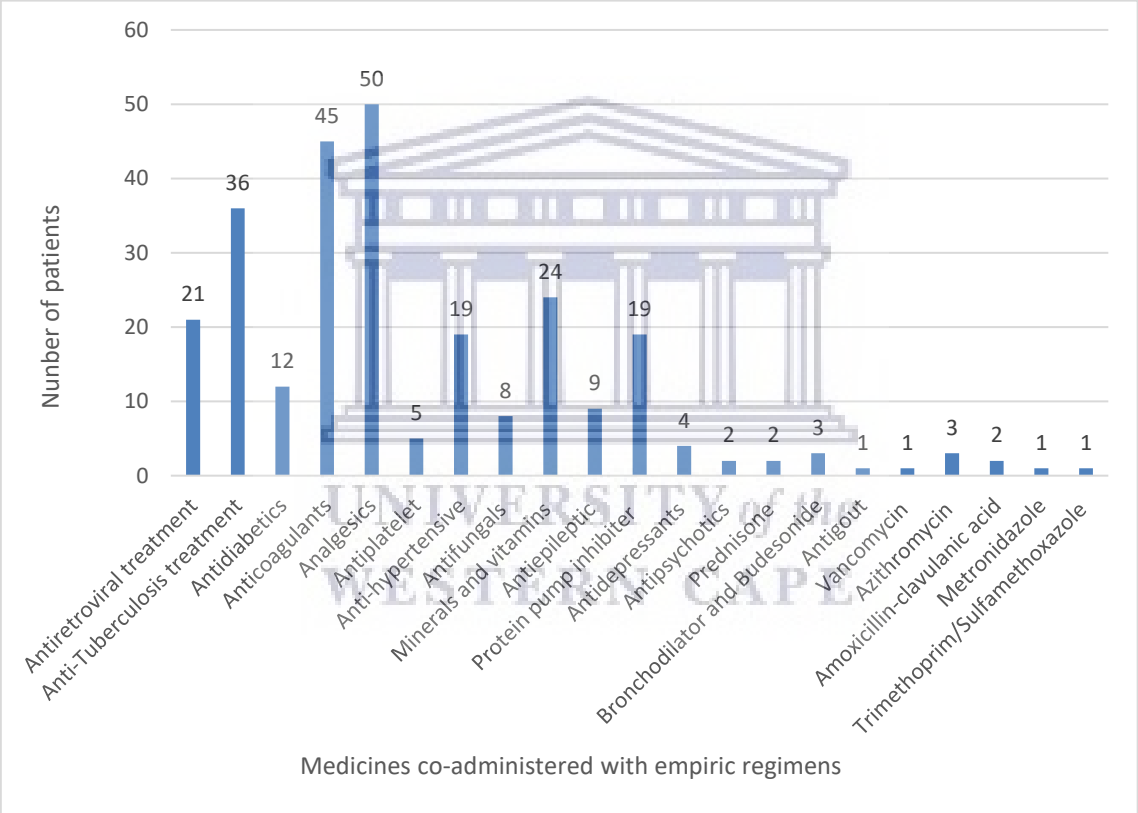


Figure 4.2: Medicines co-administered with empiric study regimens

4.3. Risk factors for acquiring hospital infections or antimicrobial resistance (AMR)

In this current study, patients were assessed retrospectively for the risk of acquiring an infection while in hospital, based on four risk factors, namely, immune system status, age, duration of hospital stay, and the occurrence of any surgical procedure during hospital stay, prior to the current infection. The three risk factors for AMR that were assessed retrospectively, were renal

function, past antimicrobial use (prior to current hospital admission), and living conditions prior to the current infection.

In Table 4.2, in the carbapenem group, 54.4% (n=49) were immunocompromised prior to their current infection, compared to 16.7% (n=15) in the carbapenem-sparing group. The difference in the immune status of the study groups, was not statistically significant (ρ=0.3). In the carbapenem group, 45.6% (n=41) had renal failure prior to current infection, compared to 3.3% (n=3) from the carbapenem-sparing group. The carbapenem group, therefore, was significantly more associated with a high number of kidney failure patients, compared to the carbapenem-sparing group (ρ=0.00003). The total study population (n=90) comprised: 7.7% (n=7) patients above the age of 65 years; 81% (n=73) stayed in the hospital for longer than two days in the previous 3 months prior to the current infection; 14.4% (n=13) had a surgery prior to the current infection while in hospital; while 93% (n=83) had at least a single invasive device procedure prior to the current infection while in hospital.

Table 4.2: Risk factors for acquiring hospital infection and or antimicrobial resistance

Risk factors associated with acquiring a hospital infection	Carbapenem regimen study population N (%)	Carbapenem-sparing regimen study population N (%)	p-values
Immune compromised	49 (54.4)	15 (16.7)	0.3##
≥ 65 years	6 (6.7)	1 (1.1)	
Prior hospital duration: ≥ 2 days prior to current infection	52 (57.8)	21 (23.3)	0.9#
Prior surgery to current infection (while in hospital)	7 (7.8)	6 (6.7)	0.1##
Used invasive device prior to current infection (while in hospital)	61 (67.8)	23 (25.6)	0.3##
Risk factors for acquiring AMR			
Acute renal failure (at diagnosis of current infection)	**41** (45.6)	**3** (3.3)	**0.00003**##
Antibiotic use prior to current infection (within past 3 months)	45 (50)	17 (18.9)	0.8##
Living conditions prior to current infection			
Hospital environment	55 (61.1)	16 (17.8)	0.9##
Nursing home	0 (0.0)	1 (1.1)	
Unknown / not specified	11 (12.2)	7 (7.8)	0.6##

AMR = antimicrobial resistance
# Mann-Whitney U test (non-parametric distribution of data) ## Chi-square test performed on categorical data.

4.4. Laboratory results

Table 4.3, illustrates descriptive statistics of some of the clinically relevant tests (CRP, SrCr and WBC) and temperature readings that were recorded. These tests results were combined as either within 24hrs or less than 36hrs, as they were not routinely ordered by attending physicians, or required at all times in individual cases.

Table 4.3: Laboratory measurement taken during treatment course of empiric study regimens

Type of treatment regimen used	Laboratory tests performed	No. of patients (N)	Minimum	Maximum	Mean	Median (Interquartile range)	Std. Deviation (±)
Carbapenem study population (N=66)	CRP within 24hrs of initiating empiric treatment (mg/L)	28	14.0	417.0	177.7	-	106.8
	CRP less than 36hrs But ›24hrs of initiating treatment (mg/L)	1	31.0	31.0	31.0	-	-
	Serum creatinine within 24hrs of initiating empiric treatment (umol/L)	58	36.0	1543.0	233.4	135 (3.8 - 11.3)	
	Serum creatinine less than 36hrs But ›24hrs of initiating empiric treatment (umol/L)	3	151.0	503.0	313.3		177.6
	WBC within 24hrs of initiating of initiating treatment (x 10^9/L)	47	2.71	37.60	13.2	10.2 (8.2 - 16.4)	7.8
	WBC less than 36hrs But ›24hrs of initiating empiric treatment (x 10^9/L)	4	6.26	36.40	16.2		13.8
	Temperature within 24hrs of initiating empiric treatment (^{0}C)	39	33.50	39.40	36.7	36.8 (36 - 37.1)	1.3
	Temperature less than 36 hrs But ›24hrs initiating empiric treatment (^{0}C)	10	36.2	37.5	36.9		0.4
Carbapenem-sparing regimen study population (N=24)	CRP within 24hrs of initiating empiric treatment (mg/L)	12	29.0	452.0	204.3		144.2
	CRP less than 36hrs But ›24hrs of initiating empiric treatment (mg/L)	1	196.0	196.0	196.0	-.	
	Serum creatinine within 24hrs of initiating empiric treatment (umol/L)	19	18.0	91.0	62.7		20.9
	Serum creatinine less than 36hrs But ›24hrs of initiating empiric treatment (umol/L)	1	86.0	86.0	86.0		-
	WBC within 24hrs of initiating empiric treatment (x 10^9/L)	19	3.59	39.89	14.8	11.8 (5.8 – 19.2)	10.6
	(WBC less than 36hrs But ›24hrs of initiating empiric treatment (x 10^9/L)	1	23.80	23.80	23.8		-
	Temperature within 24 of initiating empiric treatment (^{0}C)	19	28.80	39.60	37.1	37.3 (36.5 - 38.3)	2.2
	Temperature less than36hrs But ›24hrs of initiating empiric treatment (^{0}C)	5	36.1	38.9	37.0		1.1

CRP = C-reactive proteins WBC= white blood cell

The majority of the tests in Table 4.3 were done within twenty-four hours of initiating empiric treatment, for clinical and diagnostic purposes. The tests were less ordered during the course of treatment.

All the laboratory results were performed by the National Health Laboratory Services (NHLS), in accordance with their in-house procedures, under the auspices of the National Department of Health.

4.5. Health outcomes measured

The two main clinical health outcomes that were investigated retrospectively in this study were: length of stay in hospital (in days); and in-hospital mortality (discharged from, or demised in hospital).

4.5.1. Length of stay in hospital

The length of stay in hospital was determined as time in days, from the day that the patient was initiated on the empiric study regimen, until the patient was discharged from, or demised in hospital. Table 4.4 indicates that the carbapenem regimen study group's duration of hospital stay was a median of 7 days (3.8 - 11.3), compared to the carbapenem-sparing regimen study group's median of 6 (3 - 11) days. There was no significant difference in the duration of hospital stay of patients, who received, either a carbapenem, or carbapenem-sparing regimen (ρ=0.8).

Table 4.4: Length of stay in hospital

Variable	Carbapenem regimen study population	Carbapenem-sparing regimen study population	*p-value**
Median number of days (hospital stay)	7	6.0	0.8*
Interquartile Range (IQR)	[3.8 - 11.3]	[4.3 - 11]	
Minimum number of days (hospital stay)	1	1	
Maximum number of days (hospital stay)	41	30	

*Mann-Whitney U test for non-parametric distributed data

4.5.2. In-hospital mortality

The second measurable health outcome of this study was assessed based on whether the patient was discharged from, or demised in hospital. Figure 4.3, indicates that 57.6% (n=38) of the carbapenem study population, and 83.3% (n=20) of the carbapenem-sparing regimen study population were discharged. In the carbapenem study group, the number of patients discharged were significantly less (ρ=0.02) than the number of patients discharged in the carbapenem-sparing study group. Only four patients (16.67%) in the carbapenem-sparing group died compared to twenty-eight (42.42%) in the carbapenem group.

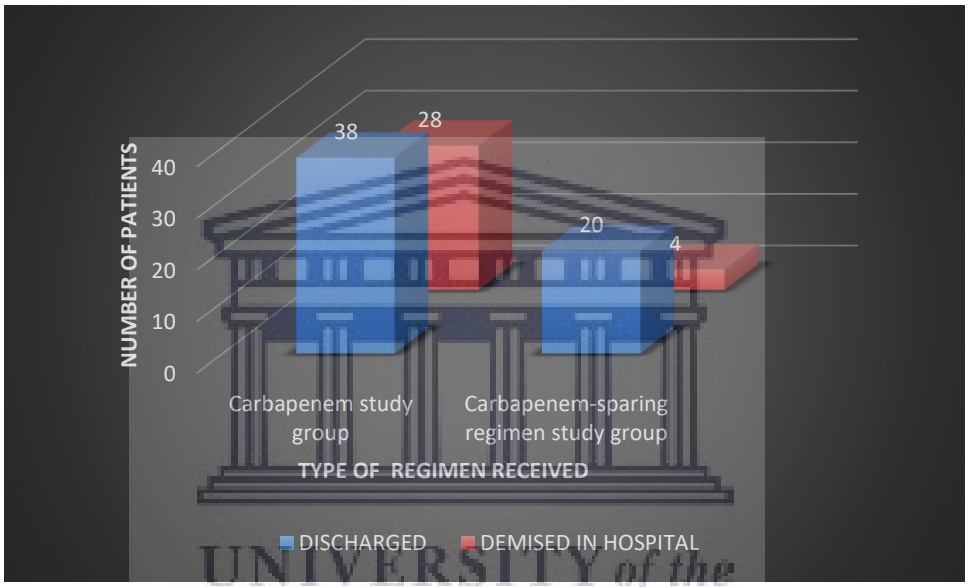


Figure 4.3: In-hospital mortality (discharged or demised)

4.6. Antimicrobial stewardship variables

4.6.1. Study groups and antimicrobial agents administered

The carbapenem group received ertapenem, meropenem, and imipenem, while the carbapenem-sparing group received piperacillin/tazobactam (Pip/Taz) with, or without amikacin. In Figure 4.4, the carbapenem regimen group (n=66) is presented, with ertapenem having been administered more frequently, 83.3% (n=55). Four patients received two different carbapenems each, with one carbapenem being administered, after the discontinuation of the other. In the carbapenem-sparing group, most (n=23) received Pip/Taz plus amikacin, and one patient received only Pip/Taz.

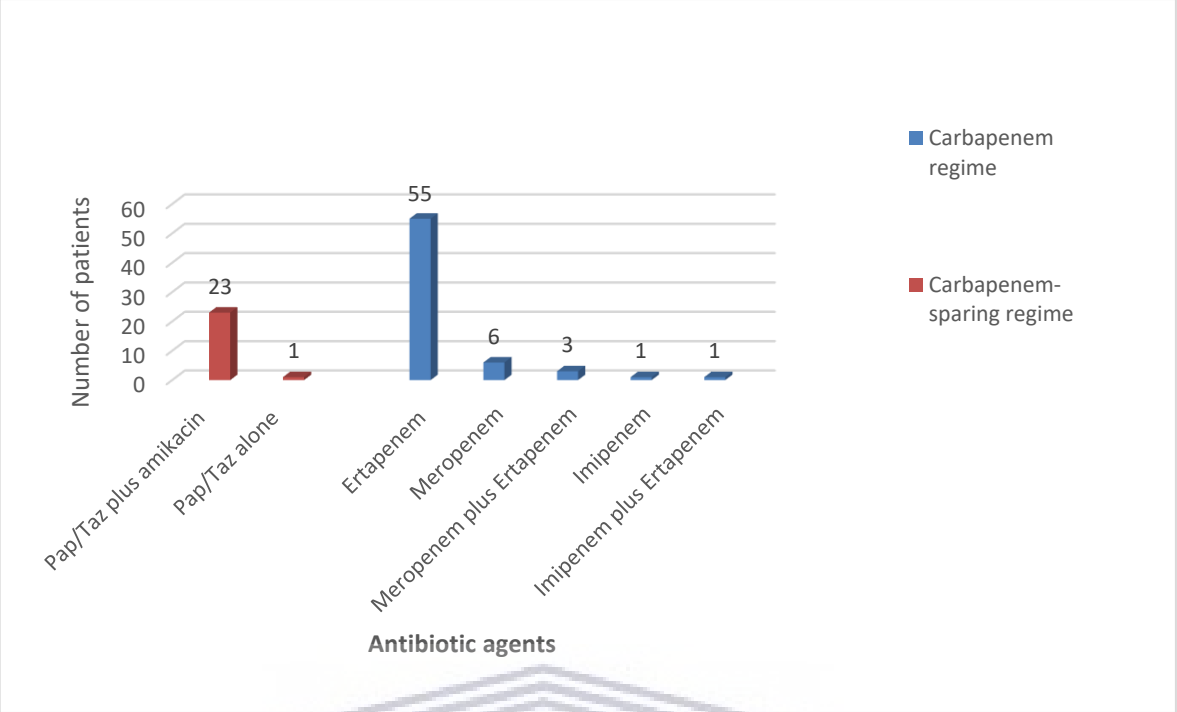


Figure 4.4: Number of patients administered with antimicrobial agents (n=90)

4.6.2. Suspected diagnosis at initiation of empiric regimens

Several suspected diagnoses were made by the prescribers prior to initiating the empiric study regimens. Figures 4.5 and 4.6 reflect the diagnoses made for the carbapenem and carbapenem-sparing regimen groups respectively, which totals seventeen (17) different disease conditions diagnosed during this 6-month retrospective study period. Hospital acquired pneumonia diagnoses were greatest for both the carbapenem group (n=34) and carbapenem-sparing group (n=14). Hospital acquired sepsis (n=17 and n=5 respectively) followed secondly, while patients diagnosed with two disease conditions, prior to the initiation of the study, totalled n=3 and n=2, respectively.

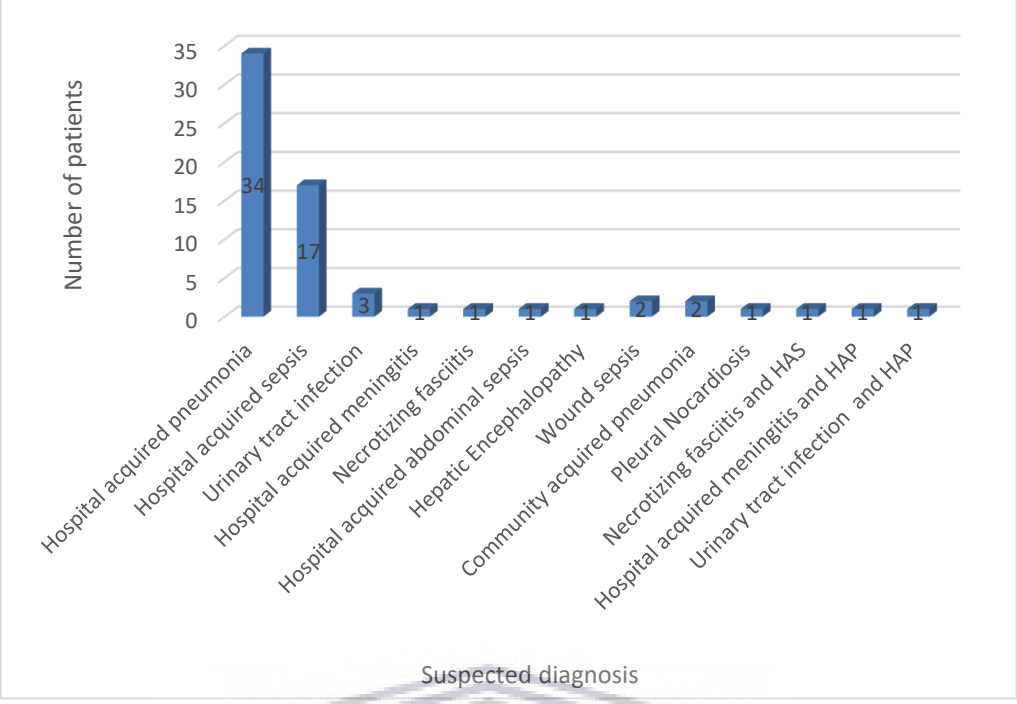
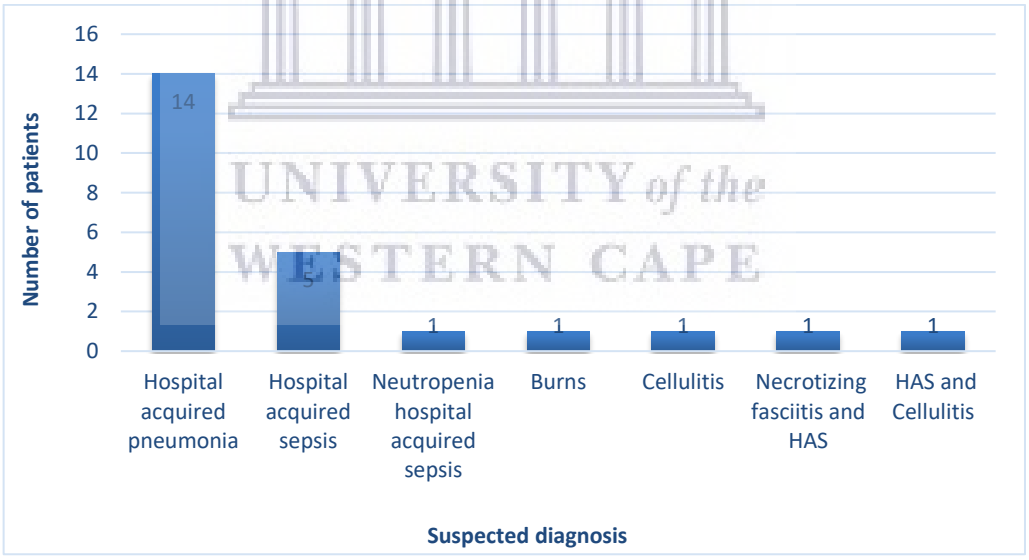


Figure 4.5: Suspected diagnosis on initiating empiric carbapenems

HAP= Hospital acquired pneumonia HAS=Hospital acquired sepsis



HAP= Hospital acquired pneumonia HAS=Hospital acquired sepsis

Figure 4.6: Suspected diagnosis on initiating carbapenem-sparing regimen

4.6.3. Culture sample collection, lead time of culture sensitivity results and micro-organism growth

This study evaluated whether culture samples were collected prior to, or post the initiation of the empiric treatment, lead time of the culture sensitivity results, and the growth of micro-organisms from the collected samples.

4.6.3.1. Culture sample collection

Figure 4.7, indicates that 98.5% (n=65) of the patients in the carbapenem study group had their culture samples collected; 73.8% (n=48) of this total were collected prior to the initiation of the study regimen, 7.6% (n=5) post the initiation, and 18.5% (n=12) did not indicate the time of collection in the clinical notes. In the carbapenem-sparing study group 95.8% (n=23) of the patients had their culture samples collected; 87% (n=20) were collected prior to the initiation of the study regimen and 8.7% (n=2) were collected post the initiation, and one sample was collected without recording the collection time.

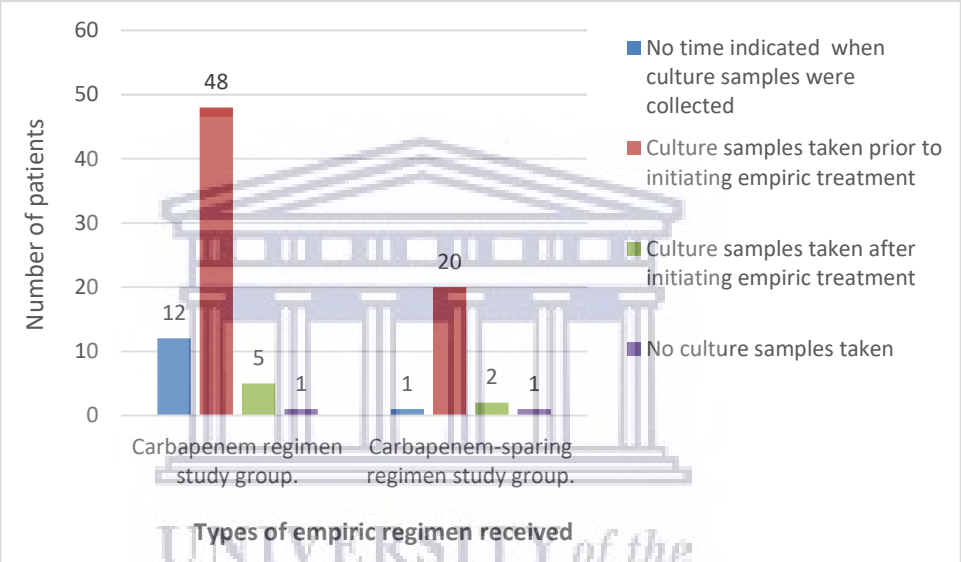


Figure 4.7: Collection of culture samples

4.6.3.2. Lead time of culture sensitivity results

The lead time of culture sensitivity results was determined as the period from the time of culture sample collection, to the availability of the culture sensitivity results, measured in days. As recorded in Table 4.5, the culture samples from the carbapenem study group had median of 5.0 (3.0 – 6.0) days, while carbapenem-sparing study group had a median of 6.0 (3.0 – 6.0) days, before culture sensitivity results were available. Mann-Whitney U test indicated no significant difference in the lead time of culture sensitivity results between the two study groups (ρ=0.58).

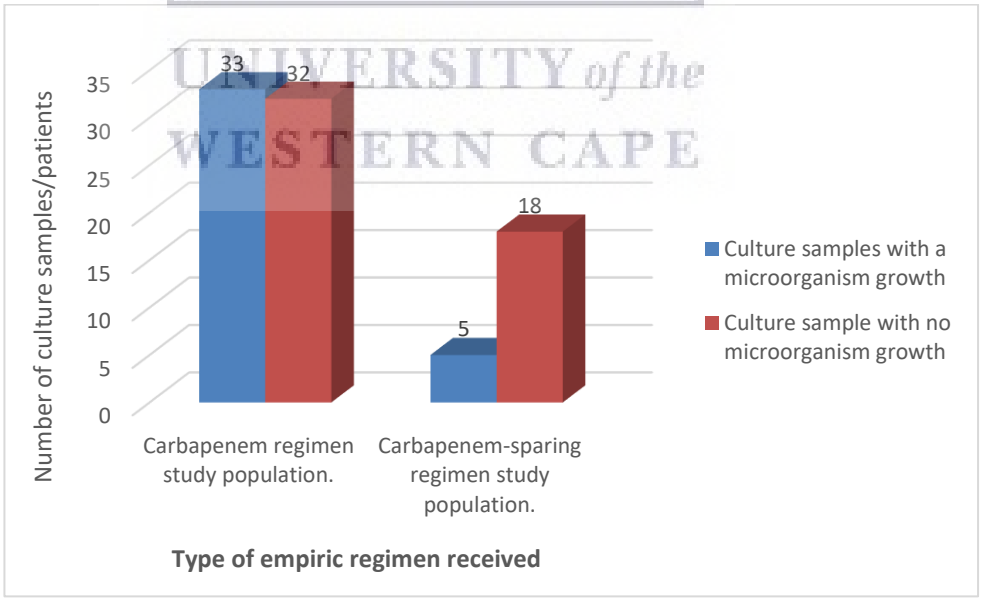
Table 4.5: Duration of availability of culture results

Type of treatment regimen study population.	No. of samples	Minimum no. of days	Maximum no. of days	Median (IQR)
Carbapenem (N=65)	65	2.0	7.0	5.0 (3.0 – 6.0)
Carbapenem-sparing regimen (N=23)	23	2.0	7.0	6.0 (3.0 – 6.0)

*n=2 missing information (time) on when the culture results were collected. IQR, Interquartile range

4.6.3.3. Micro-organism growth

This current study investigated a number of samples that did, or did not, indicate any micro-organism growth. As indicated in Figure 4.8, of the 65 samples that were collected in the carbapenem study group, 50.8% (n=33) showed growth, while in the carbapenem-sparing study group, 21.7% (n=5) of the 23 collected samples showed growth. The Chi-square test showed that samples from the carbapenem study group were significantly associated (ρ=0.02) with a high number of samples, which indicated micro-organism growth, compared to the carbapenem-sparing study group.



n=2 missing information

Figure 4.8: Micro-organism growth from the initial samples collected

The actual micro-organisms that were grown are reflected in Figure 4.9. Of the 38 cultured samples, 18 different species and 1 mixed growth of micro-organisms were recorded. *E. coli* was the most cultured organism (n=8 different samples), followed by *K. pneumonia* (n=6 different samples), *S.aureus* (n=4 different samples), coagulase-negative staphylococci (n= 3 different samples), Methicillin-resistant Staphylococcus aureus (n=2 different samples), *Enterococcus faecium* (n=2 different samples), and the rest of the micro-organisms (*Pseudomonas putida*, *Providencia stuartii*, *Proteus mirabilis*, *Streptococcus pyogenes*, *Cryptococcus neoformans*, *Micrococcus species*, *Nocardia species*, *Candida albicans*, Corynebacterium species, *P.aeruginosa*, *Bacillus cereus* and *Enterobacter cloacae*) were all cultured once, from 12 different samples.

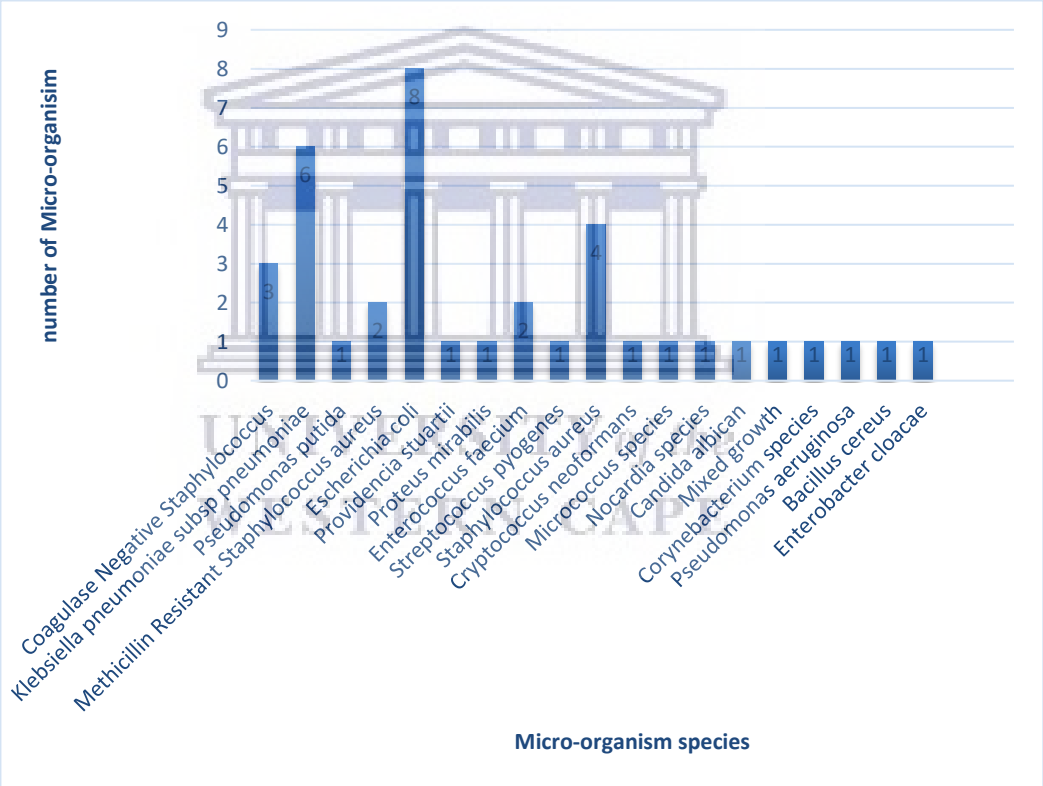


Figure 4.9: Micro-organism grown from collected samples (n=38)

4.6.4. Sensitivity of micro-organisms to available antimicrobial agents

The drug sensitivity results for the samples cultured are reflected in Table 4.6 and indicates the sensitivity of cultured micro-organisms against available antimicrobial agents tested by the NHLS.

Table 4.6: Sensitivity of micro-organisms to available antimicrobial agents

Antimicrobial agents	Total no. of micro-organism	No. of micro-organism resistant	No. of micro-organism intermediate	No. of micro-organism sensitive
Carbapenem-sparing agents				
Piperacillin/Tazobactam	19	4	3	12
Amikacin	12	2	2	8
Gentamicin	25	13		12
Carbapenem agents				
Ertapenem	13	1	1	11
Imipenem	13	2		11
Meropenem	14	1	1	12
Penicillin				
Penicillin / Ampicillin	7	5		2
Cloxacillin	8	4		4
Ampicillin / Amoxicillin	24	22		2
Other ß-lactase inhibitor plus penicillin agent				
Amoxicillin-clavulanic	29	20	2	7
Cephalosporins				
Cefuroxime (IV)	20	10		10
Cefuroxime (Oral)	21	12		9
Cefotaxime / Ceftriaxone	22	12		10
Ceftazidime	17	12	1	4
Cefepime	16	12		4
Cefazolin	3			3
Other aminoglycosides				
Tobramycin	2	1		1
Streptomycin	1			1
Fluoroquinolones				
Ciprofloxacin	28	13		15
Levofloxacin	1			1
Moxifloxacin	1			1
Macrolides				
Erythromycin / Azithromycin	4			4
Antifungal agents				
Amphotericin B	1			1
Other antimicrobial agents				
Trimethoprim-sulfamethoxazole	29	19		10
Clindamycin	6			6
Tetracycline	1			1
Vancomycin	6			6
Rifampicin	3	2		1
Fusidic acid	2			2
Nitrofurantoin	5	3	1	1
Tigecycline	1	1		
Fosfomycin	4			4

4.6.5. Functionality of oral route, IV to oral conversion, and de-escalation or escalation of antimicrobial spectrum

4.6.5.1. Functionality of oral route and IV to oral step down

The patients, who were able to swallow, and those who had the route of administration switched (IV to oral) during treatment, are indicated in Table 4.7. Of the 90 patients, 98.9% (n=89) had fully functional oral routes, while 1 (0.1%) had an unknown/unrecorded functional route. The route of administration was switched (IV to oral) for 2 patients during treatment, after 12 hours of IV treatment.

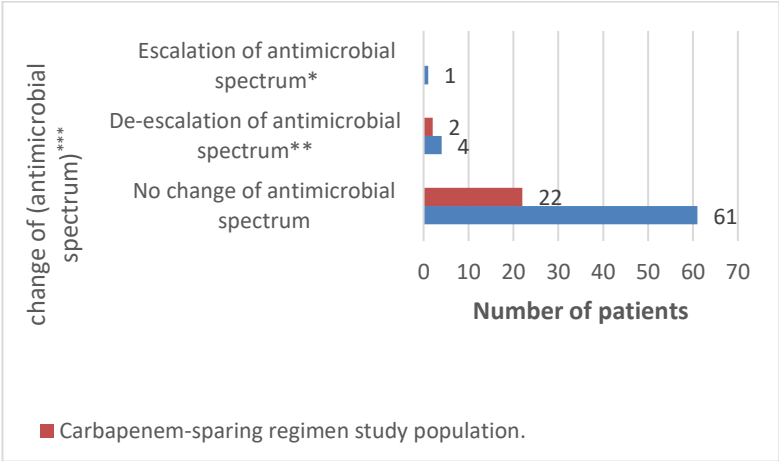
Table 4.7: Functionality of oral route and IV to oral step down

Functionality of oral route N=90		
	Functional*	**Unknown**
N (%)	89 (98.9)	1 (1.0)
Step down of IV to oral route of administration N=90		
Time (hours)	After 12 hours	
N (%)	2 (2.2)	

*Ability to swallow

4.6.5.2. De-escalation or escalation of antimicrobial spectrum

In Figure 4.10, 92.4% (n=61) in the carbapenem group, and 91.7% (n=22) in the carbapenem-sparing group, exhibited no change on the antimicrobial spectrum, during treatment. Six patients in this current study sample exhibited a de-escalation, and one, an escalation, in the antimicrobial spectrum.



*Using a broader spectrum antimicrobial agent ** Using a narrower spectrum antimicrobial agent
***antimicrobial spectrum is the range of micro-organisms that an antimicrobial agent affects (inhibits or kills)

Figure 4.10: De-escalation or escalation of antimicrobial spectrum

4.6.6. Missed doses, extra doses, and duration of administered carbapenem and carbapenem-sparing agents.

The individual breakdown of the missed doses, extra doses administered, and duration (days) of administration of the different carbapenems and carbapenem-sparing agents are reflected in Table 4.8.

Table 4.8: Missed doses, extra doses, and duration of administered carbapenem and carbapenem-sparing agents

Missed doses, extra doses and duration of treatment	Total number of doses	Minimum	Maximum	Mean (SD)	Median (IQR)
Piperacillin/Tazobactam (n=24)					
Missed doses (n=13)	51	1.0	11.0		3.0 (1.0 - 6.0)
Extra doses (n=3)	5	1.0	3.0		1.0 (1.0 - 2.0)
Duration of treatment (days)		1.0	9.0		5.0 (5.0 - 6.0)
Amikacin (n=23)					
Missed doses (n=4)	5	1.0	2.0		1.0 (1.0 – 1.8)
Extra doses (n=1)	1	1.0	1.0		
Duration of treatment (days)		1.0	9.0		5.0 (5.0 – 5.0)
Meropenem (n=9)					
Missed doses (n=3)	4	1.0	2.0		1.0 (1.0 – 1.5)
Extra doses (n=1)	1	1.0	1.0		
Duration of treatment (days)		1.0	10.0	5.0 (3.0)	
Imipenem (n=2)					
Number of missed doses (n=2)	9	3.0	6.0	4.5 (2.1)	
Number of extra doses (n=0)					
Duration of treatment (days)		6.0	14.0	10.0 (5.7)	
Ertapenem (n=59)					
Number of missed doses (n=4)	5	1.0	2.0		1.0 (1.0 – 1.8)
Number of extra doses (n=3)	4	1.0	2.0		1.0 (1.0 – 1.5)
Duration of treatment (days)		1.0	8.0		5.0 (2.0 – 5.0)

The n-values indicated for the antibiotics will be > 90 as some patients received more than one antibiotic agents.

Extra and missed doses were recorded in both carbapenem and carbapenem sparing regimen as shown in table 4.8. This could be due to shortage of medicine stock, movement of patients with in the hospital to attend other medical procedures or misinterpretation of medicine frequencies by the nursing staff.

In this study, the carbapenem group had a significantly higher age and renal failure at empiric initiation and this could have contributed to the significantly lower number of patients that were discharged compared to the carbapenem-sparing group. There was no significant difference in the length of stay among the two groups. A discussion of results follows in the next chapter.

CHAPTER FIVE

DISCUSSION

The findings of this current study, presented in Chapter 4, are interpreted in this chapter, commencing with the demographics, patient health outcomes, and antimicrobial stewardship variables

5.1. Demographics of the population sample included in this current study

The patients in the carbapenem group were significantly older (ρ=0.01), with a median age of 47 (37 – 57.3) years, compared to 34 (39.3 – 52.8) years in the carbapenem-sparing group. Advanced age increases the risk of renal failure, as it is associated with decreased glomerular filtration rate (Douville et al., 2009). Therefore, in this current study, significantly more patients in the carbapenem group were diagnosed with renal failure (ρ<0.00003), and consequently, were not administered the carbapenem-sparing regimen (piperacillin/tazobactam and or amikacin), which is contraindicated in renal failure (Humes, 1988). Evidently, carbapenems were the more appropriate choice for the elderly patients, as well as those with existing renal failure, compared with the carbapenem-sparing group. In several other multinational studies (non-African countries), the median age ranges were lower for the patients receiving the carbapenem-sparing regimen, compared to carbapenem receiving patients (Rodríguez-Baño et al., 2011; Gutiérrez-Gutiérrez et al., 2016; Gudiol et al., 2017). South Africa is burdened with the HIV/AIDS and tuberculosis (TB) pandemics (Satoh & Boyer, 2019; WHO, 2019), mostly in a much younger population, unlike hypertension and diabetes in other countries, which is common at an advanced age. HIV/AIDS and TB often require the use of antimicrobial agents, and could lead to a prolonged hospital stay, which is the key risk factor for acquiring multidrug resistant infections. These type of infections require broader spectrum antibiotics, such as carbapenem or carbapenem-sparing regimens, for treatment. Despite the significant age difference, and associated impaired renal function, which were higher in the carbapenem receiving group, the immune status and underlying conditions of the two treatment groups, were similar, with no significant difference.

Body weight was poorly recorded at the time of hospitalisation (only 21.1% in total), which represents the least recorded variable in this current study. A large prospective cross-sectional study (n= 1012), conducted in western areas of London, explored body weight recording in patients, who were prescribed and administered with narrow therapeutic index antimicrobial agents. They concluded that less than half (46%) of the patients had their body weight recorded (Charani et al., 2015). The reasons for not recording the body weights were not investigated; however, as this was a retrospective study, it could be that these patients had been ill, and possibly unable to stand for weighing.

In addition, allergy was also poorly recorded for this current study population. Knowledge about known allergies is key, prior to initiating any treatment (especially antibiotics), to the patient, as the occurrence of such reactions could lead to avoidable deaths (Madea, Musshoff, Preuss, 2009). The benefits of allergy documentation in a patient's clinical notes remain contested, as other studies report negative effects of such a practice on patients' health outcomes (Charneski, Deshpande, & Smith, 2011; MacFadden et al., 2016). Poor allergy documentation could possibly be due to the patients' inability to communicate (not being accompanied by any relatives), and the lack of immediate access to the patients' previous medical records, prior to initiating the treatment, in cases where swift clinical decisions had to be made.

5.2. Co-administered medication

Several antibiotics were co-administered in both the carbapenem (9.1%) and carbapenem-sparing regimen (8.3%) groups. This created an antibiotic spectrum overlap, as most co-administered antibiotics (azithromycin, metronidazole, trimethoprim/sulfamethoxazole and amoxicillin/clavulanic acid) shared a similar, and narrower antibiotic spectrum, compared with this current study's carbapenem or carbapenem-sparing regimens. However, the use of an antibiotic spectrum overlap to treat infections can increase the possibility of antibiotic resistance development and costs, without any proven benefits on health outcomes (Glowacki et al., 2003). Use of an antibiotic spectrum overlap in this current study may suggest poor adherence to standard treatment guidelines.

5.3. Health outcomes

In this current study, the length of stay in hospital was determined as one of the measures of patients' health outcome. There was no significant difference (ρ=0.8) in the median number of days in hospital, between the patients, who received either a carbapenem, or a carbapenem-sparing regimen. Similar outcomes were reported in a post-hoc analysis study that included patients with ESBL-producing monobactam (*E. coli*) bacteremia, where the biliary and urinary tracts were identified as the source of infection (Rodríguez-Baño et al., 2011), as well as the results from a Korean study that included ESBL-producing *E. coli and K. pneumonia* from multiple sources of infection (Ng et al., 2016). Patients, who stay in hospitals for longer periods, are more susceptible to acquiring infections from multidrug resistant micro-organisms (or could even become a source of such organisms), and increased costs of maintaining such patients are usually involved, unlike those, who spend less time in hospitals.

Presence of co-morbidity(s) and occurrence of surgical procedure(s) in patients during admission in the hospital are some of the key risk factors associated with a prolonged length of hospital stay (Marfil-Garza et al., 2018). Co-morbidities such as diabetes, HIV/AIDS, cancer (while on chemotherapy) often suppresses the immune system of the patients, making them more susceptible to acquiring infections that require treatment while in the hospital and could prolong their hospital stay (Berbudi et al., 2019). Surgical procedures in hospital may prolong patients' hospital stay due to an increased risk of acquiring an infection while in hospital through the wounded area, acquiring MDR infections due to inappropriate use of prophylactic antibiotics prior to the surgical procedure and development of post-surgical complications (Chiu et al., 2017; Alkaaki et al., 2019; Peters et al., 2019). In this study, the difference in the presence of co-morbidities and surgical procedures among the carbapenem and carbapenem-sparing group was not significant. This could explain why the length of stay in the hospital was not statistically different among the two groups that were administered with study regimens.

In this current study, in-hospital mortality was assessed in the adult patients, who were treated empirically with either carbapenem, or carbapenem-sparing regimens, for various infections at this district hospital. The carbapenem study group had a statistically significant (ρ=0.02) lower number of patients, who had been discharged, and had demised, compared to the carbapenem-sparing study group. This is contrary to the outcomes of a similar study by Rodríguez-Baño et al. (2011), who conducted a multicenter post hoc analysis of six prospective cohort studies in Spain (n=103 patients), and observed no significant difference (ρ=0.1) in mortality (9.7% and

19.4%) for patients, who were treated with the β-lactam/β-lactam inhibitor combination and carbapenem, respectively. This followed studies by Kang et al. (2012), Gutiérrez-Gutiérrez et al. (2016), Ng et al. (2016), Gudiol et al. (2017), Ko et al. (2018), Benanti et al. (2019), and John et al., (2019), who observed similar results as those of Rodríguez-Baño et al., (2011). In all the studies, the carbapenem-sparing regimen was piperacillin/tazobactam, as a sole agent, unlike the addition of amikacin in this current study. Amikacin may have resulted in a synergic effect, which contributed to improved health outcomes from the carbapenem-sparing regimen, compared to the carbapenem regimen in this current study. Multidrug resistant (MDR) micro-organisms express drug resistance through several mechanisms and are associated with poor health outcomes (Hirsch & Tam, 2010). The use of empiric combination therapy, with *in vitro* or *in vivo* synergic effect, is one of the few strategies introduced to eliminate the emergence of MDR organisms (Tamma, Cosgrove, & Maragakis, 2012). Amikacin demonstrated good activity against gram-negative micro-organisms, including ESBL-producing pathogens (Bouxom et al., 2018). In a study conducted in USA hospitals, the *in vitro* potency of amikacin against *E. coli, K. pneumoniae and P. aeruginosa* was similar to imipenem and meropenem. Samples were collected from both ICU and non-ICU adult patients, who had been diagnosed with hospital acquired pneumonia (Sutherland, Verastegui, & Nicolau, 2016). In a Korean study that evaluated *in vitro* activities of 21 different antimicrobial agents, in isolation, or in combination with aminoglycosides, against ESBL-producing *E. coli* isolates (n=291), amikacin elevated the piperacillin/tazobactam susceptibility rate by 35.8% (Cha et al., 2015).

The patients in this current study were admitted to non-ICU wards, which implies that they may have been presenting with mild infections, with a minimal inoculum effect to piperacillin/tazobactam. An inoculum effect occurs when an increase in the number of inoculated micro-organisms, leads to a significant increase in the minimal inhibitory concentration of an antibiotic, they are tested against (Brook, 1989). Piperacillin-tazobactam was associated with inoculum effects, in tests with strains producing TEM and SHV-derived ESBLs. High inocula occurs in deep seated infections, such as septic arthritis, endocarditis, abscesses, meningitis, and osteomyelitis, which were not commonly diagnosed in the carbapenem-sparing group, as was evident from this study's suspected diagnosis (Fig 4.6). The larger the inoculum effect, the more susceptible the drug becomes to hydrolysis by beta-lactases enzymes (Thomson & Moland, 2001). This decreases the efficiency of the drug to eliminate a pathogen.

In this study the carbapenem group presented with a significantly higher number of patients with acute kidney failure compared to those in the carbapenem-sparing group ($\rho<0.05$) prior to commencing empiric treatment. Acute kidney failure can be a contraindication to some narrower spectrum antimicrobial agent such as aminoglycosides. Therefore, if such patients present with an infection that requires treatment, broad spectrum antimicrobial agents are usually safer in this group of patients. However, the use of broader spectrum antimicrobials increases the risk of developing multidrug resistant organisms that are associated with a higher in-hospital mortality rate (VanEpps, 2018; Peters et al., 2019). It could be speculated that despite not determining MDR occurrence, the carbapenem group may have developed more of MDR organisms while in hospital than the carbapenem-sparing group due to their broader spectrum of protection. In a study conducted in the USA to determine clinical outcome for intracerebral hemorrhage patients, those with pre-existing renal failure as comorbidity had higher rates for in-hospital complications such as myocardial infarction, sepsis, deep venous thrombosis, gastrointestinal bleeding, longer hospital stay, higher mean hospital charges, pneumonia and urinary tract infection that were statistically significant ($\rho<0.05$). The in-hospital mortality was reported to be higher in patients that had pre-existing renal failure (Khatri et al., 2019). Therefore, patients in the current carbapenem group may have developed several complications that were not investigated in this study which could have been associated with their mortality. The mean age of the carbapenem group was significantly older compared to the carbapenem-sparing group. Acute renal failure in elderly patients increases in-hospital mortality (Khadzhynov et al., 2019; Goldstein and Lee, 2020). Hence patients in the carbapenem group may also have been at a higher risk of death due to their higher age and presence of acute renal failure.

Severe cases of infections are highly associated with poor health outcomes in hospitalized patients as they require highly specialized treatment. Hospital acquired pneumonia was the most suspected type of diagnosis made both in carbapenem and carbapenem sparing regimens group. Patients at an age of 65 years or higher diagnosed with pneumonia are at an increased risk of developing more complications and severe cases of the infection compared younger patients (Vazquez Guillamet and Kollef, 2020). The significant higher age factor in this study's carbapenem group could have contributed to these patients experiencing more severe cases and complications of the infection unlike in the carbapenem-sparing group that could have led to more deaths in this respective group.

5.4. Antimicrobial stewardship variables

5.4.1. Micro-organism growth

Samples were collected and sent to the laboratory, with the aim of determining the causative micro-organism in the infection. Samples from the carbapenem study group were significantly associated with a high number of samples that indicated micro-organism growth, compared to the carbapenem-sparing study group (ρ=0.02). This could imply that the carbapenem-sparing study group may have been exposed to other antibiotic regimens prior to collecting culture samples for the empiric treatment initiation, which possibly, could have interfered with the micro-organism growth.

5.4.2. Culture sample collection

Patients from both carbapenem and carbapenem-sparing study groups had culture samples collected and majority (73.8% and 87%) of those were collected before the study regimens were initiated. Culture samples are collected from suspected sites of infection in the empiric phase of treatment with the aim of identifying offending micro-organism(s). This can lead to narrowing antibiotic spectrum to only cover the offending micro-organism(s) hence decreasing the risk of several collateral damages such as acquiring multidrug resistant organisms or causing other infections such as *Clostridium difficile* associated diarrhea. Implementation of antibiotic stewardship is significantly associated with a reduction in infections due to *Clostridium difficile* and colonisation with MDR organisms (Baur et al., 2017). A decrease in costs and shorter length of stay at two ICUs was report in a cross-sectional study performed in Brasilia where intravenous-to-oral antibiotic switch therapy was done (Gasparetto et al., 2019). All these collective actions performed at the start of a definitive phase if feasible can reduce patient's length of hospital stay and costs of maintaining while in the hospital. Culture samples taken after initiating an antibiotic agent significantly affects the growth of micro-organisms as reported in a clinical cohort study performed in a University Hospital Greifswald in Germany (Scheer et al., 2019). Pathogen loss (loss of an infection causing micro-organism(s) prior to identification) from the culture samples may hinder antibiotic stewardship efforts such a de-escalation of antimicrobial spectrum, IV to oral treatment conversions and possibly discontinuing antibiotic use. Commencement of such

stewardship efforts can be affected by the lead time to the availability of sensitivity results. Although the difference in lead time to the availability of sensitivity result among the carbapenem and carbapenem-sparing group in this study was not significant (ρ=0.58)

The comparison between carbapenem-sparing regimen and carbapenem use among hospitalized patients in this pilot study in terms of the two specified health outcomes (length of stay in hospital and in-hospital mortality), indicated that piperacillin/tazobactam plus amikacin combinations did not affect the length of stay in hospital any differently but significantly less patients succumbed in this group compared to the group receiving carbapenem regimens during the empiric phase.

CHAPTER SIX

CONCLUSION, LIMITATIONS AND RECOMMENDATIONS

In this chapter, the researcher provides a clear conclusion, based on the main outcomes of this current study. In addition, recommendations are made on ways of conducting future improved studies of a similar nature, as well as recommendations for in-hospital practise regarding carbapenem use, to minimise antimicrobial resistance. This current pilot study was aimed at describing and assessing the retrospective use of empiric carbapenems versus a carbapenem-sparing regime of antibiotics in adult patients (non-intensive care), in terms of patient health outcomes for a period of 6-months, at the Khayelitsha District Hospital in Cape Town, South Africa

6.1. Conclusion

According to the findings of this current study, it could be concluded that there was no significant difference in the length of stay in hospital, among patients treated with either a carbapenem, or a carbapenem-sparing regime at this hospital. Acute renal failure was significantly high in the carbapenem group and could have contributed to a poorer outcome with respect to in-hospital mortality. In addition, the use of a carbapenem-sparing regimen was significantly associated with a high number of patients, who were discharged. This provides evidence for the use of piperacillin/tazobactam plus amikacin as a carbapenem-sparing regimen, and empiric treatment in suspected multidrug resistance infections, where no contraindication (such as renal failure) exists. This would reserve empiric carbapenem use for patients with contraindications to the carbapenem-sparing regimen, or use in the definitive treatment, where the offending pathogen is resistant to the carbapenem-sparing regimen. Consequently, carbapenem use would be decreased, which in turn, would decrease carbapenem selective pressure to resistance.

6.2. Limitations of the study

- This was a single centre study, in a district hospital; therefore, the outcomes of this current study cannot be generalized to other hospitals.
- This pilot study was retrospective and the sample size was small and lacked statistical power.

- Due to the retrospective nature of this study, clinical results and notes were not always recorded, some were missing or inadequately scanned onto the hospital electronic system (e.g. site of infection and or type of sample taken for culture) and the severity of illness at the initiation of the empiric treatment was not recorded in the patient records.
- Stratified analysis could not be performed.

6.3. Recommendations

6.3.1. Future study recommendations

- The expansion of this pilot study into other district hospitals in the Cape Town metropole should be conducted for a longer study period, to increase the population sample, in order to increase the statistical power. This will also allow for seasonal changes that might occur.
- Future studies should determine the acquisition of multidrug resistant organisms, post treatment, to understand the risk of using combination antibiotic agents better, as a strategy to spare carbapenem use, because combination-antibiotic-agent-use could be associated with antimicrobial resistance (Llor & Bjerrum, 2014).
- Future studies should determine the type of piperacillin/tazobactam dosing, whether it should be extended or standard (Cutro et al., 2014).
- Future studies should record other antibiotics (Non-carbapenem, or non-carbapenems-sparing regimen agents) administered to the patient prior to the initiation of a carbapenem, or carbapenems-sparing regimen. Culture samples collected after the use of such antibiotics, but before initiating carbapenem, or carbapenems-sparing regimen, should be regarded as collected after the initiation of antibiotics.

6.3.2. In-hospital practise recommendations

The hospital should form an official antibiotic stewardship committee, which at least, should comprise members from different departments in the hospital (clinician, nurse, pharmacist, and pharmacist assistant) to serve the following purposes:

- To train other staff members and ensure that culture samples are taken from all patients, prior to the initiation of antibiotic agents.
- To ensure procedures are in place that cultures are delivered to the NHLS as soon as possible. This could effect a reduction in the lead time of culture results availability.
- To ensure that antibiotic prescriptions are correctly written with no unnecessary abbreviations and to minimise the misinterpretation of medicine use directions during administration.
- To ensure that routine AMS rounds are performed to identify patients, who should be reviewed urgently, with an ID specialist and microbiologist.
- To ensure that pharmacists perform daily ward rounds on patients being prescribed antibiotics to ensure correct dosing and to minimise missed and extra doses administered.
- To ensure that nursing stuff are educated and reminded of the harm of incorrect, missed and extra doses of medicines.
- To ensure that there is adequate stock of antibiotics and monitored supply of such antibiotics to the hospital wards.
- To ensure that appropriate antibiograms are developed, and updated at all times for the hospital and specific wards in consultation with a microbiologist.
- To ensure easy and quick access to appropriate electronic health systems that can provide immediate information on possible previous antimicrobial use or prior hospitalisation on patient admission as a way of screening for those at higher risk of presenting with multidrug resistant infections.

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APPENDICES

Appendix A: Study data collection form

UNIVERSITY OF THE WESTERN CAPE

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Appendix I: Data Collection Form

Section A: Demographics, Disease and Medication History

1. Patient Study Number

2. Date of birth (Date/Month /Year)

3. Gender

- ☐ Male
- Female
- ☐ Others: .....

4. Weight (kg)

5. Height (cm)

6. BMI (kg/m²)

7. Age (years)

8. Ethnicity

- ☐ Black
- ☐ White
- ☐ Asian
- ☐ Coloured
- ☐ Others .....

9. Allergies

- ☐ No known drug allergies
- ☐ Unknown
- ☐ Penicillin
- ☐ Sulphonamides
- ☐ Others .....
- ☐ Not documented

10. Co-morbidities

- ☐ Human Immunodeficiency Virus
  - Yes
  - No
  - Not documented

1

- ☐ Tuberculosis (TB), if yes:
  - Pulmonary TB
  - Extra pulmonary TB
  - Multi-drug resistant TB
  - Extreme drug resistant TB
  - Type not specified
- ☐ Diabetes, if yes:
  - Diabetes type 1
  - Diabetes type 2
  - Controlled
  - Uncontrolled
- ☐ Cardiovascular disease, if yes :
  - Hypertension
  - Angina / Myocardial infarction
  - Arrhythmias
  - Heart failure
  - Heart valve disease
  - Congenital heart disease
  - Hyperlipidaemia
  - Other specify.....
- ☐ Central Nervous system:
  - Stroke
  - Dementia
  - Depression
  - Anxiety
  - Seizures
  - Psychosis
- ☐ Asthma
- ☐ COPD
- ☐ Malignancies
- ☐ Cancer
- ☐ Others.....
- ☐ .....
- ☐ .....
- ☐ .....
- ☐ .....
- ☐ .....

11. Other medicines co-administer with antibiotics

- ☐ Antiretroviral treatment
- ☐ Anti –Tuberculosis treatment
- ☐ Antidiabetics (Insulin, oral tablets or both)
- ☐ Antihypertensive (ACE inhibitors, Angiotensin II receptor antagonists, Diuretics, Calcium channel blockers, Alpha blockers and Beta blockers)
- ☐ Antiarrhythmic agents
- ☐ Dyslipidaemia
- ☐ Antiplatelet agents
- ☐ Anticoagulants
- ☐ Others...- Specify.....
- ☐ .....
- ☐ .....
- ☐ .....
- ☐ .....
- ☐ .....
- ☐ .....
- ☐ None

12. Routes of administration used for medicines co-administered with antibiotics

- ☐ Oral
- ☐ Intravenous
- ☐ Intramuscular
- ☐ Subcutaneous
- ☐ Others.....
- ☐ .....

Section B: Timeline, Diagnosis and Empiric Antibiotic Treatment Used.

1. Type of infection

- ☐ Community acquired infection (CAI)
- ☐ Hospital acquired infection (HAI)

2. Date of Admission (day/month/year)

3. Date of Discharge (day/month/year)

4. Duration of hospital stay (days)

5. Patient Deceased (day/month/year)

6. Suspected diagnosis

.....

.....

.....

7. Carbapenem-sparing regimen used

- ☐ Piperacillin/tazobactam
- ☐ Cefepime
- ☐ Piperacillin/tazobactam with Cefepime
- ☐ Piperacillin/tazobactam with Ampicillin
- ☐ Piperacillin/tazobactam with Gentamycin
- ☐ Piperacillin/tazobactam with Amikacin

8. Treatment regimen of carbapenem-sparing regimens

☐ **(I) Piperacillin/ Tazobactam**

Dose.....

Frequency.....

Date started (day/month/year).....

Date stopped (day/month/year).....

Reason for stopping.....

Number of missed doses .....

Duration.....

Hang time.....

☐ **(II) Amikacin**

Dose.....

Frequency.....

Date started (day/month/year).....

Date stopped (day/month/year).....

Reason for stopping.....

Number of missed doses .....

Duration.....

Hang time.....

☐ **(III) Gentamycin**

Dose.....

Frequency.....

Date started
(day/month/year).....

Date stopped
(day/month/year).....

Reason for stopping.....

Number of missed doses .....

Duration.....

Hang time.....

☐ **(IV) Cefepime**

Dose.....

Frequency.....

Date started
(day/month/year).....

Date stopped
(day/month/year).....

Reason for stopping.....

Number of missed doses .....

Duration.....

Hang time.....

☐ **(V) Ampicillin**

Dose.....

Frequency.....

Date started
(day/month/year).....

Date stopped
(day/month/year).....

Reason for stopping.....

Number of missed doses .....

Duration.....

Hang time.....

9. Carbapenem regimens used

☐ **(I) Meropenem**

Dose.....

Frequency.....

Date started
(day/month/year).....

Date stopped
(day/month/year).....

Reason for stopping.....

Number of missed doses .....

Duration.....

Hang time.....

☐ **(II) Imipenem**

Dose.....

Frequency.....

Date started
(day/month/year).....

Date stopped
(day/month/year).....

Reason for stopping.....

Number of missed doses .....

Duration.....

Hang time.....

☐ **(III) Doripenem**

Dose.....

Frequency.....

Date started
(day/month/year).....

Date stopped
(day/month/year).....

Reason for stopping.....

Number of missed doses .....

Duration.....

Hang time.....

☐ **(IV) Ertapenem**

Dose.....

Frequency.....

Date started
(day/month/year).....

Date stopped
(day/month/year).....

Reason for stopping.....

Number of missed doses .....

Duration.....

Hang time.....

10. Other ORAL antibiotics used (excluding anti-TB treatment during empiric treatment phase)

☐ **(I) Oral Antibiotic 1**

Specify Name.....

Dose.....

Frequency.....

Date started
(day/month/year).....

Date stopped
(day/month/year).....

Duration.....

☐ **(II) Oral Antibiotic 2**

Specify Name.....

Dose.....

Frequency.....

Day started
(date/month/year).....

Day stopped
(date/month/year).....

Duration.....

☐ **(III) Oral Antibiotic 3**

Specify Name.....

Dose.....

Frequency.....

Date started
(day/month/year).....

Date stopped
(day/month/year).....

Duration.....

Section C: Risk factors associated with resistance and hospital acquired infections

1. Immune system status

- ☐ Immune competent
- ☐ Immune compromised (e.g. CA,HIV,DM,transplant and steroid treatment)

2. Antibiotic(s) used prior to current infection/admission (in the last three months)

- ☐ Yes
- ☐ None

3. Antimicrobial resistance noted prior to the current infection

- ☐ If yes, state it
  ……
  ……
  ……
- ☐ None

4. Age (year)

☐

5. Duration of hospital stay (days) prior to current infection

☐

6. Any invasive device/indwelling (Catheter, IV line Ventilator, Endotracheal tube) used prior to current infection

- ☐ If Yes, how many different ones ……
- ☐ None

7. Renal failure

- ☐ Yes
- ☐ No

8. Any surgical procedure prior to current infection

- ☐ Yes
- ☐ No

9. Living conditions prior to current infections

- ☐ Own home
- ☐ Nursing home/ rehabilitation facility (step down facilities)
- ☐ Unknown / Not specified

Section D: Antimicrobial Stewardship Measurable Variables

1. Culture sample obtained prior to initiating treatment

- ☐ Yes
- ☐ No
- ☐ Not sure

2. Site of infection

- ☐ Respiratory
- ☐ Intra-abdominal
- ☐ Skin and soft tissue
- ☐ UTI
- ☐ Septicaemia
- ☐ Unknown
- ☐ Others (specify).....

3. Type of sample collected

- ☐ Sputum
- ☐ Urine
- ☐ Blood
- ☐ Cerebrospinal fluid
- ☐ Others (specify).....

4. Date of culture collection (day/month/year) and time

Time: (24hrs):							

5. Date of culture sensitivity availability (day/month/year) and time

Time (24hrs):							

6. Duration from culture collection to culture sensitivity availability (hours/days)

7. Organism(s) grown from cultures

1).....

2).....

3).....

4).....

5).....

6).....

7).....

8).....

8. Grown organisms and their sensitivity profile

Organism 1 sensitivity profile

Sensitive to	Intermediate to	Resistant to
1.	1.	1.
2.	2.	2.
3.	3.	3.
4.	4.	4.
5.	5.	5.
6.	6.	6.
7.	7.	7.

Organism 2 sensitivity profile

Sensitive to	Intermediate to	Resistant to
1.	1.	1.
2.	2.	2.
3.	3.	3.
4.	4.	4.
5.	5.	5.
6.	6.	6.
7.	7.	7.

Organism 3 sensitivity profile

Sensitive to	Intermediate to	Resistant to
1.	1.	1.
2.	2.	2.
3.	3.	3.
4.	4.	4.
5.	5.	5.
6.	6.	6.
7.	7.	7.

Organism 4 sensitivity profile

Sensitive to	Intermediate to	Resistant to
1.	1.	1.
2.	2.	2.
3.	3.	3.
4.	4.	4.
5.	5.	5.
6.	6.	6.
7.	7.	7.

Organism 5 sensitivity profile

Sensitive to	Intermediate to	Resistant to
1.	1.	1.
2.	2.	2.
3.	3.	3.
4.	4.	4.
5.	5.	5.
6.	6.	6.
7.	7.	7.

Organism 6 sensitivity profile

Sensitive to	Intermediate to	Resistant to
1.	1.	1.
2.	2.	2.
3.	3.	3.
4.	4.	4.
5.	5.	5.
6.	6.	6.
7.	7.	7.

Organism 7 sensitivity profile

Sensitive to	Intermediate to	Resistant to
1.	1.	1.
2.	2.	2.
3.	3.	3.
4.	4.	4.
5.	5.	5.
6.	6.	6.
7.	7.	7.

Organism 8 sensitivity profile

Sensitive to	Intermediate to	Resistant to
1.	1.	1.
2.	2.	2.
3.	3.	3.
4.	4.	4.
5.	5.	5.
6.	6.	6.
7.	7.	7.

9. Final diagnosis

……

……

……

……

10. Assessment of EMPIRIC antibiotic treatment according to guidelines

- ☐ Appropriate
- ☐ In-appropriate

11. De-escalation or escalation process performed

- ☐ Escalation of treatment
- ☐ De-escalation of treatment
- ☐ No change in treatment

Date (day/month/year) of change:

Time (24hrs)

12. IV to oral dose switch performed (hours/days)

- ☐ None

Section E: Definitive treatment

1. Antimicrobial agents used

Drug 1 .....

Dose.....

Frequency.....

Date started (date/month/year).....

Date stopped (date/month/year).....

Duration.....

Route of administration.....

Hang time.....

Drug 2

.....

Dose.....

Frequency.....

Date started (date/month/year).....

Date stopped (date/month/year).....

Duration.....

Route of administration.....

Hang time.....

Drug 3 .....

Dose.....

Frequency.....

Date started
(date/month/year).....

Date stopped
(date/month/year).....

Duration.....

Route of
administration.....

Hang time.....

Drug 5 .....

Dose.....

Frequency.....

Date started
(date/month/year).....

Date stopped
(date/month/year).....

Duration.....

Route of
administration.....

Hang time.....

Drug 4 .....

Dose.....

Frequency.....

Date started
(date/month/year).....

Date stopped
(date/month/year).....

Duration.....

Route of
administration.....

Hang time.....

Drug 6 .....

Dose.....

Frequency.....

Date started
(date/month/year).....

Date stopped
(date/month/year).....

Duration.....

Route of
administration.....

Hang time.....

Section F: Laboratory measurements

	≤24 of initiating treatment	≤36hrs But ›24hrs	≤48hrs But ›24hrs	≤5days But ›48hrs	≤7days But ›5days	≤10days But ›7days	›10days
C-Reactive Protein (mg/L)							
Serum Creatinine (mg/dL)							
Leukocyte levels /L (WBC)							
Fever (^{0}C)							
Other (diagnostics e.g Radiology)							

Appendix B: BMREC-UWC Approval Certificate

UNIVERSITY of the WESTERN CAPE

OFFICE OF THE DIRECTOR: RESEARCH
RESEARCH AND INNOVATION DIVISION

Private Bag X17, Bellville 7535
South Africa
T: +27 21 959 4111/2948
F: +27 21 959 3170
E: research-ethics@uwc.ac.za
www.uwc.ac.za

19 November 2018

Prof M Viljoen
School of Pharmacy
Faculty of Natural Science

Ethics Reference Number: BM18/9/7

Project Title: Rational use of empiric carbapenem-sparing regimens versus carbapenum antibiotics in non-intensive care adult patients in district hospitals of Cape Town.

Approval Period: 09 November 2018 – 09 November 2019

I hereby certify that the Biomedical Science Research Ethics Committee of the University of the Western Cape approved the scientific methodology and ethics of the above mentioned research project.

Any amendments, extension or other modifications to the protocol must be submitted to the Ethics Committee for approval.

Please remember to submit a progress report in good time for annual renewal.

The Committee must be informed of any serious adverse event and/or termination of the study.

Ms Patricia Josias
Research Ethics Committee Officer
University of the Western Cape

BMREC REGISTRATION NUMBER -130416-050

UNIVERSITY of the WESTERN CAPE

OFFICE OF THE DIRECTOR: RESEARCH
RESEARCH AND INNOVATION DIVISION

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T: +27 21 959 4111/2948
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E: research-ethics@uwc.ac.za
www.uwc.ac.za

02 September 2019

Prof M Viljoen
School of Pharmacy
Faculty of Natural Sciences

Ethics Reference Number: BM18/9/7

Project Title: Rational use of empiric carbapenem-sparing regimens versus carbapenem antibiotics in non-intensive care adult patients in district hospitals of Cape Town Metropole.

Approval Period: 14 June 2019 – 14 June 2020

I hereby certify that the Biomedical Science Research Ethics Committee of the University of the Western Cape approved the scientific methodology and ethics of the above mentioned research project.

Any amendments, extension or other modifications to the protocol must be submitted to the Ethics Committee for approval.

Please remember to submit a progress report in good time for annual renewal.

The Committee must be informed of any serious adverse event and/or termination of the study.

Ms Patricia Josias
Research Ethics Committee Officer
University of the Western Cape

BMREC REGISTRATION NUMBER -130416-050

Appendix C: Department of Health, Western Cape Government Approval Letter.

Western Cape Government
Health

HEALTH IMPACT ASSESSMENT
HEALTH RESEARCH SUB-DIRECTORATE
Health.Research@westerncape.gov.za
tel: +27 21 483 0866: fax: +27 21 483 9895
5th Floor, Norton Rose House,, 8 Riebeek Street, Cape Town, 8001
www.capegateway.gov.za)

REFERENCE: WC_201901_011
ENQUIRIES: Dr Sabela Petros

University of Western Cape

Robert Sobukwe Road

Bellville

Cape Town

7535

For attention: Prof Michelle Viljoen, Mr Isaac Mugoya, Dr Renier Coetzee, Dr Jantjie Taljaard, Dr George Muntingh

Re: **Rational use of empiric carbapenem-sparing regimens versus carbapenem antibiotics in non-intensive care adult patients in district hospitals of Cape Town Metropole**

Thank you for submitting your proposal to undertake the above-mentioned study. We are pleased to inform you that the department has granted you approval for your research.

Please contact following people to assist you with any further enquiries in accessing the following sites:

Khayelitsha Hospital	**Dr Moses Witbooi**	**021 360 4386**

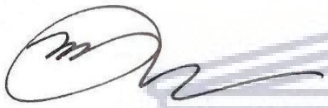
Kindly ensure that the following are adhered to:

1. Arrangements can be made with managers, providing that normal activities at requested facilities are not interrupted.
2. By being granted access to provincial health facilities, you are expressing consent to provide the department with an electronic copy of the final feedback (**annexure 9**) within six months of completion of your project. This can be submitted to the provincial Research Co-ordinator (Health.Research@westerncape.gov.za).

3. In the event where the research project goes beyond the *estimated completion* date which was submitted, researchers are expected to complete and submit a progress report (**Annexure 8**) to the provincial Research Co-ordinator (Health.Research@westerncape.gov.za).

4. The reference number above should be quoted in all future correspondence.

Yours sincerely



DR M MOODLEY

DIRECTOR: HEALTH IMPACT ASSESSMENT

DATE: 14 -03 - 2019

Appendix D: NHLS Approval Letter

NATIONAL HEALTH LABORATORY SERVICE

Academic Affairs and Research
Modderfontein Road, Sandringham, 2031
Tel: +27 (0)11 386 6142
Fax: +27 (0)11 386 6296
Email: babatyi.kgokong@nhls.ac.za
Web: www.nhls.ac.za

21 June 2019

Applicant: Prof Michelle Viljoen
Institution: University of the Western Cape
Faculty: Health Sciences
Department: School of Pharmacy
Email: mviljoen@uwc.c.za
Cell: 074 101 3728

Re: Approval to access National Health Laboratory Service (NHLS) Data

Your application to undertake a research project "**Rational use of empiric carbapenem-sparing regimens versus carbapenem antibiotics in nonintensive care adult patients in district hospitals of Cape Town Metropole**" using data from the NHLS database has been reviewed. This letter serves to advise that the application has been approved and the required data will be made available to you ***as per patient list submitted*** to conduct the proposed study as outlined in the submitted application. No additional patient identifiers will be provided.

Please note that approval is granted on your compliance with the NHLS conditions of service and that the study can only be undertaken provided that the following conditions have been met.

- Processes are discussed with the relevant NHLS departments (i.e. Information Management Unit and Operations Office) and are agreed upon.
- Confidentiality is maintained at participant and institutional level and there is no disclosure of personal information or confidential information as described by the NHLS policy.
- NHLS Data cannot be used to track patients as no pre-approval/consent is obtained from Patients.
- CDW form is to be completed for the request with clear indications of the data required.
- All data requested should be in accordance with the research protocol submitted and approved by the relevant Ethics Committee.
- Request for the inclusion of the NHLS as a source of data in the original protocol to be approved by Ethics as NHLS does not have a Human Research Ethics Committee.
- A final report of the research study and any published paper resulting from this study are submitted and addressed to the NHLS Academic Affairs and Research office and the NHLS has been acknowledged appropriately.

Please note that this letter constitutes approval by the NHLS Academic Affairs and Research Office. Any data related queries may be directed to NHLS Corporate Data Warehouse, contact number: 011 386 6074 email: zarina.sabat@nhls.ac.za

Dr Babatyi Malope-Kgokong
National Manager: Academic Affairs and Research