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COLISTIN UTILISATION AND CLINICAL OUTCOMES AT A PUBLIC HOSPITAL IN BLOEMFONTEIN, SOUTH AFRICA

BY

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DECLARATION BY CANDIDATE

I, Gaalebale Prudence Matshediso, hereby declare that this mini-dissertation submitted for the degree Master of Public Health, at the University of Fort Hare, is my own effort and has not been submitted to another tertiary institution. I also declare that all sources used in the mini dissertation have been acknowledged in the list of references.

G.P. Matshediso
20 July 2022

DEDICATION

This mini-dissertation is dedicated to myself, for the sacrifices I made in putting myself last over a period of years.

CERTIFICATION

Signature of the Supervisor: …  …… Date: 22/07/2022

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ABSTRACT

Background

Colistin is an antibiotic used as the last resort in the treatment of multi-drug resistant Gram-negative bacteria. Its use started in the 1950s but was decreased in the 1980s owing to its nephrotoxic side effects. The re-emergence of Colistin utilisation in 2012 in South Africa followed the emergence of multi-drug resistant Gram-negative bacteria. There is a dearth of information on the rationale use of Colistin in South Africa.

Aim

To describe the use of Colistin and its clinical outcomes at a tertiary hospital in Bloemfontein, South Africa.

Methodology

A retrospective cross-sectional study was conducted at a tertiary hospital in Bloemfontein between 2015 and 2019. Relevant data was extracted from the medical records of patients treated with Colistin. Stratified random sampling was used in selecting 50% of the eligible medical records of patients treated with Colistin per stratum. Data was analysed using simple descriptive and inferential statistics.

Results

Of the total sample (N=69), the majority were neonates (43.5%), while children constituted the lowest number of patients (18.8%). The highest contributor to the top diagnosis, septicaemia, were neonates (44.2%). Adherence to policy and Colistin treatment guidelines was suboptimal, more so in neonates (45.3%) than in adults (73.7%) and children (72.3%). Colistin was used as a last resort in 68.1% of the participants. Cure was achieved in 26.9%, 46.2% and 80% of adults, children and neonates, respectively. The highest rate of nephrotoxicity was seen in adults (57.7%). In the multivariate logistic regression model analysis, both adults [adjusted odds ratio (AOR)=25.54, 95% confidence interval (CI) 2.73-238.65] and children (AOR=8.56, 95%CI 1.06 – 69.10) had a higher risk of death than neonates. However, there was no significant difference in the odds for mortality by gender, co-morbidities, illness duration prior to admission and adherence to treatment.

Conclusions

This study found a suboptimal level of compliance with policy and recommended guidelines on the use of Colistin in a South African public sector tertiary hospital. In addition, there were variations in the level of compliance by age categories, with lower levels of compliance in neonates than in children and adults. The odds for mortality by gender, co-morbidities, illness duration prior to admission and adherence to treatment guidelines and policies were found to be insignificant, and age was the only predictor of mortality found in the study. The findings of the study highlight the need for improved clinical governance on antibiotic stewardship and monitoring of use of Colistin across all categories of patients in the hospital. Future studies should examine the contributing factors for suboptimal compliance, with evidence-based recommendations on the use of Colistin in the study setting as well as factors contributing to high mortality in adults.

Keywords: Antimicrobial Resistance; Antimicrobial Stewardship; Clinical Outcomes; Colistin; Multi-drug Resistance

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LIST OF ACRONYMS

AMR:	Antimicrobial Resistance
AMS:	Antimicrobial Stewardship
AMSC:	Antimicrobial Stewardship Committee
BRICS:	Brazil, Russia, India, China, South Africa
CEO:	Chief Executive Officer
CMS:	Colistemethate Sodium
CRGNB:	Colistin Resistant Gram-negative Bacteria
DHET:	Department of Higher Education and Training
FSDOH:	Free State Department of Health
GAP-AMR:	Global Action Plan on Antimicrobial Resistance
GLASS:	Global Antimicrobial Surveillance System
HIV:	Human-immunodeficiency Virus
HOD:	Head of the Department
HREC:	Health Research Ethics Committee
ICU:	Intensive Care Unit
ICT:	Information Communications and Technology
IU:	International Units
IPC:	Infection Prevention and Control
MCC:	Medicine Control Council
MCS:	Microscopy Culture and Sensitivity
MDR:	Multi-Drug Resistance
MU:	Million Units
NICD:	National Institute of Communicable Diseases
NSAID:	Non-steroidal Anti-inflammatory Drugs

PICU:	Paediatrics Intensive Care Unit
UFH:	University of Fort Hare
SAHPRA:	South African Health Products Regulatory Authority
SPSS:	Statistical Package for Social Sciences
TPB:	Theory of Planned Behaviour
TRA:	Theory of Reasoned Action
WHO:	World Health Organisation

CHAPTER 1: INTRODUCTION

1.1. Background

Colistin is an antibiotic used for the treatment of infections with Gram-negative bacteria that are resistant to multiple antibiotics (Labuschagne et al., 2016). It is a Section-21 drug, and its use is regulated and monitored by the South African Health Products Regulatory Authority (SAHPRA) (Republic of South Africa, 2017). It is mainly used in an intensive care unit (ICU) setting (Zusman et al., 2017). It is approved for use only in tertiary hospitals in South Africa (Mendelson et al., 2018).

It was first used in the 1950s, but because of its nephrotoxicity, its use in humans decreased in the 1980s. It has since been used mainly to treat Gram-negative bacteria in gastrointestinal tract colonisation in poultry and pigs (Mendelson et al., 2018). The re-emergence of Colistin use in humans – which occurred around 2012 – was due to the fact that Gram-negative bacteria had developed resistance to multiple drugs, in the form of Multi-Drug Resistant (MDR) Gram-negative bacteria (Mendelson et al., 2018). It is currently used as the last resort to treat Gram-negative bacteria resistant to first, second, and third-line antibiotics (Centre for Disease Dynamics, Economics and Policy, 2015).

Resistance to Colistin has emerged globally and has been reported in South Africa (Messina et al., 2017). Cases of resistance to Colistin at the facility where the study was conducted came to the attention of the researcher between 2015 and 2017. South African studies conducted on Colistin use and its clinical outcomes have been conducted in private sector hospitals; however, there are currently no published studies on Colistin use and its clinical outcomes in public sector hospitals for both children and adults in South Africa.

The irrational use of antimicrobials such as Colistin could potentially render them ineffective, threaten modern medicine, and cause a global health crisis (Brink et al., 2016). The rational use of antimicrobials by clinicians is influenced resistance patterns and the availability of relevant data on antimicrobial resistance (WHO, 2017). Surveillance and research on antimicrobial resistance are vital for establishing familiarity with the drug and providing a comprehensive evidence base. Mendelson and Matsoso (2015) and WHO (2015) recommend tracing total global antimicrobial

use as well as the organisms against which they are used (WHO, 2019). In alignment with the Global Action Plan on Antimicrobial Resistance (GAP-AMR), the South African Antimicrobial Resistance National Strategy Framework prioritises the reinforcement of antimicrobial resistance (AMR) surveillance and monitoring of antimicrobial utilisation. It stresses the rational use of antibiotics, and the significance of operational and behavioural studies to conserve the efficacy of antimicrobials currently used (South African National Department of Health (2018b). These considerations necessitate the current study.

1.2. Research problem

The WHO's GAP for AMR objectives include the strengthening of knowledge and the evidence base through surveillance and research, as well as the optimisation of the use of antimicrobials in humans and animals (WHO, 2015). The WHO further identified a lack of data regarding degrees of resistance, especially in low- and middle-income countries (WHO, 2015).

An analysis of AMR in the WHO African region showed that no African countries have representative national surveillance systems (Essack, Desta, Abotsi & Agoba, 2017). These findings were confirmed by a study conducted by Tadesse et al. (2017) on AMR in the African region, where data unavailability was discovered in over 40% of the countries. Data that existed was found to be of poor quality.

The Global Antimicrobial Resistance Surveillance System (GLASS) report also indicates that data submitted by South Africa regarding the origin and susceptibility of microorganisms was insufficient (WHO, 2018). These findings are similar to the findings made in a situational analysis of antimicrobial governance, regulation and utilisation in South Africa, which indicated that surveillance data for antimicrobial usage is not routinely available (Schellack et al., 2017).

There is no information regarding the use of Colistin and compliance with the recommended dosing guidelines locally (Messina et al., 2017). There is minimal data on the outcomes of treatment with Colistin in paediatric patients (Çağan, Kıray Baş & Asker, 2017).

Contrary to the objectives of the WHO-GAP on AMR, studies conducted by the WHO and other researchers show that there is minimal data available on AMR patterns, the

use of antimicrobials, and clinical outcomes. There is currently no published study on Colistin utilisation and clinical outcomes in public hospitals for both children and adults in South Africa. There is also no published study on the effects of treatment on patients infected by bacteria sensitive to only Colistin, and no information on compliance with treatment guidelines in the public hospital where the study was conducted. The emergence of resistance to Colistin – an antibiotic used as a last resort to treat Gram-negative bacteria resistant to multiple antimicrobials – makes the knowledge of antimicrobial utilisation and the clinical outcomes imperative (Schellack et al., 2017).

1.3. Central theoretical/conceptual framework

The Theory of Reasoned Action (TRA) was proposed by Fishbein and Ajzen in 1980. It is grounded on the concept of intention, which is the degree to which an individual aims to take a particular action (Yzer, 2017). The theory proposes that an individual's action is a result of their intention to engage in that action; that is, individuals tend to take action if they plan or aim to do so (Fishbein, 2019). The intention to take a particular action is influenced by attitudes, subjective norms and volitional control. In 1991, a construct of behavioural control was added by Ajzen to the theory, which gave rise to the Theory of Planned Behaviour (TPB).

Attitudes develop from beliefs and values assumed to exist in the outcome of taking the action (Nguyen et al., 2018.) The study will, therefore, analyse doctors' compliance with protocols and procedures (their overall behaviour) and the management of patients infected with resistant Gram-negative bacteria (their specific actions) to achieve the desired outcome, based on the assumptions made by these theories.

The intention to carry out a certain action may also be fuelled by perceived social pressure (subjective norms) (Nguyen et al., 2018). In the case of this study, this would include perceived pressure from other doctors, healthcare workers or the patient's family. The study will also reveal any actions that doctors take that are contrary to the set protocols and procedures.

According to the two theories, for any action to be carried out, the intention has to be supported by volitional control (Yzer, 2017), i.e. the willingness to take the action. If there are conditions that must be met before a certain drug is prescribed, and a doctor

wants to use that drug, the doctor must be willing to comply with the protocols and procedures for that drug.

Behavioural control is a construct that gave rise to the Theory of Planned Behaviour. This is the perception that an individual has regarding their control over their performance of a task, and the various beliefs they may hold that could hinder or promote their performance of it (Yzer, 2017).

The two theories are used to inform this study. The study analyses the behaviour and actions of doctors, nurses, pharmacists and hospital management's compliance with regulations and guidelines (their behaviour), as well as the management of patients infected with resistant Gram-negative bacteria (their actions) to achieve the desired outcome, using the assumptions of these two theories.

1.4. Research questions

1. How is Colistin utilised at a Bloemfontein public hospital?
2. What are the clinical outcomes of treatment with Colistin at a Bloemfontein public hospital?
3. How does Colistin utilisation and its clinical outcomes in neonates differ from those of children and adults?

1.5. Hypothesis

1. There is adherence to policy and regulations of Colistin utilisation at a Bloemfontein public hospital.

2. Colistin is utilised appropriately, and neonates have better clinical outcomes than children and adults.

1.6. Objectives

1. To assess the utilisation of Colistin at a Bloemfontein public hospital.
2. To describe the clinical outcomes of Colistin utilisation at a Bloemfontein public hospital.
3. To compare Colistin utilisation and its clinical outcomes in neonates to those of children and adults in the study setting.

1.7. Significance of the study

South Africa is a member state of the WHO and is therefore obliged to meet its objectives. This study will assist the country in meeting the objectives of the Global Action Plan for antimicrobial resistance (AMR), which are to strengthen knowledge and the evidence base through surveillance and research, and to optimise the correct use of antimicrobials. Previous studies conducted globally, in Africa and locally reveal a lack of data regarding AMR and its utilisation (WHO, 2015; Essack et al., 2017; Tadesse et al., 2017; WHO, 2018; Schellack et. al., 2017; Messina et al., 2017). The study provides data for future research and baseline data for the institution to use for further monitoring.

Studies similar to the current study have been conducted in private health facilities in South Africa. This study will provide a public health facility perspective of Colistin use and its clinical outcomes. Depending on the outcomes, it may influence policy change, make contributions to the current guidelines, and stimulate antimicrobial stewardship in healthcare workers locally and globally to preserve this important drug.

1.8. Delimitations of the study

The study will cover all patients – adults, children and neonates – treated with Colistin at a public hospital in Bloemfontein, between 2015 and 2019, and admitted in the Multidisciplinary Intensive Care Unit, Paediatrics Intensive Care Unit, Neonatal Intensive Care Unit and Neonatal High Care Unit.

1.9. Limitations of the study

The study was limited by the unavailability of some clinical notes, both the physical file and the electronic version. Some available clinical records were incomplete and lacking in essential information for the study. To avoid data collection and data analysis bias missing clinical records were replaced by other randomly selected clinical records.

1.10 Operational definitions of key terms and concepts

Antimicrobials: Agents or medicines that can eradicate or prevent the multiplication of microorganisms, include antibiotics, antivirals, antifungals, antihelminthics and antiprotozoals (South African National Department of Health, 2018c).

Antimicrobial stewardship (AMS): This comprises strategies and a set of coordinated activities aimed at promoting the utilisation of antimicrobials in a manner that safeguards continued access to effective treatment for those who need it (Dyar, Huttner, Schouten & Pulcini, 2017).

1.11 Study outline

Chapter One: This chapter provides the background of the study, the theoretical framework upon which the study is based, research questions, objectives, hypothesis, contribution of the study and study limitations.

Chapter Two: This chapter reviews the relevant literature.

Chapter Three: This chapter gives an overview of the design and methodology used in the study. It covers the study design, population, sampling method, research instrument used, data collection, data analysis, pilot study done, validity and reliability tests, as well as ethical considerations.

Chapter Four: The study results are presented in this chapter.

Chapter Five: This chapter discusses and interprets the results and makes recommendations based on the study findings. Finally, it draws conclusions.

CHAPTER 2:LITERATURE REVIEW

2.1 Search methods

The literature review was conducted by searching for peer-reviewed articles from various databases such as PubMed, Elsevier and BioMed Central, as well as various websites such as the WHO, the Department of Health and SAHPRA. Keywords used to search included: Colistin, colistin resistance, colistin utilisation, antimicrobial resistance, and antimicrobial stewardship. Full-text journal articles were retrieved after reviewing abstracts. Legislation, regulations and policies were also obtained from relevant websites. A total of 84 papers were reviewed. These included Acts, regulations, policies and peer-reviewed articles. Only 43 papers were used in the final review; the rest were culled owing to duplication of information or lack of relevance to the study.

2.2 Introduction

The literature was reviewed to highlight what is known about Colistin utilisation and the clinical outcomes thereof, and to identify any differences in its use and clinical outcomes between children and adults, in order to address the research objectives. The literature was also reviewed to identify gaps in knowledge regarding Colistin use and its clinical outcomes, and to determine the significance of the study, as outlined in the previous chapter.

This section covers antimicrobial stewardship (AMS), which is essential in the promotion of the rational use of antimicrobials by health professionals. It also gives insight into the state of antimicrobial use and resistance globally, in Africa and in South Africa. Colistin is discussed under the following headings: Policy and legislation regarding Colistin use in South Africa, Colistin utilisation, Colistin pharmacodynamics and pharmacokinetics, resistance to Colistin, clinical outcomes of treatment with Colistin based on research, the current South African treatment guidelines for Colistin utilisation in both children and adults, Colistin adverse effects, Colistin pathophysiology and risk factors for developing resistance to Colistin.

2.3 Antimicrobial stewardship

Antimicrobial stewardship comprises strategies and a set of coordinated activities aimed at promoting the utilisation of antimicrobials in a manner that safeguards continued access to effective treatment for those who need it (Dyar et al., 2017).

Antimicrobial stewardship has four components: structures, facility-level interventions, patient-level interventions and monitoring and evaluation of interventions (South African National Department of Health, 2018c).

'Structures' refers to the establishment of an institutional Antimicrobial Stewardship Committee (AMSC), which, among its many agenda points, discusses healthcare associated infections surveillance, resistance patterns, AMS programme compliance, training needs and communication with prescribers (South African National Department of Health, 2018c).

Facility-level interventions may include: enforcing the use of guidelines for prescribing, obtaining authorisation before prescribing when required by the regulations, and conducting audits (South African National Department of Health, 2018c).

Patient-level interventions require the establishment of an Antimicrobial Stewardship Team, which will conduct rounds to assess the indication for antimicrobial prescription, the appropriateness of the antimicrobial, appropriateness of administration, and whether or not there is a continued need (South African National Department of Health, 2018c).

Monitoring and evaluation of interventions begins with obtaining the baseline compliance with AMS principles, and the development and implementation of quality improvement plans, based on gaps identified (South African National Department of Health, 2018c). The current study focuses on facility- and patient-level interventions in the study setting.

While the main objective of AMS is to sustain the efficacy of antimicrobials for future use, with the focus on micro-organisms, antimicrobials, policy, governance, audits and the actions of clinicians, there appears to be little emphasis on the immediate needs of patients (Charani & Holmes, 2019). Since it is well known that the clinician's actions are motivated by the curative needs of an individual patient, there is, therefore, a need

to strike a balance between AMS's future goals and the immediate needs of a given patient (Charani & Holmes, 2019).

2.4 Global and local antimicrobial utilisation and resistance patterns

The One health concept is a collaborative effort between sectors such as environmental, animal and human health to optimize environmental, animal and human health (Collignon, P.J. and McEwen, S.A., 2019). It is pivotal in combatting AMR within and between the environment, animals and humans (Collignon, P.J. and McEwen, S.A., 2019) since antimicrobials are used in livestock, agriculture, in the environment and in humans (Shankar, Piryani & Piryani, 2017). The use of antimicrobials in livestock, agriculture, and the environment is higher than in humans, with the world having seen a massive increase in their use in livestock, predominantly in third-world countries (Shankar, Piryani & Piryani, 2017). This is not the case in South Africa, where surveillance for antimicrobial resistance and consumption of antibiotics conducted by the National Department of Health discovered that 74% of antibiotics are consumed by humans (South African National Department of Health (2018a, unpublished).

Van Boekel et al., as cited in a 2015 publication by the Center for Disease Dynamics, Economics and Policy, discovered that between 2000 and 2014, the world's antimicrobial use increased by more than 30%, BRICS countries being the major contributors to this increase. This increase was attributed to improved access to antibiotics through primary health care revitalisation and the strengthening of pharmaceutical systems in these countries (South African National Department of Health, 2018a, unpublished).

South Africa had a high per capita consumption of antimicrobials compared to most countries, which was attributed to the high consumption of co-trimoxazole administered as a prophylaxis for some opportunistic infections in HIV-positive patients (Center for Disease Dynamics, Economics and Policy, 2015). This finding is supported by the 2012-2017 surveillance conducted by the South African National Department of Health, which revealed that the procurement of Co-trimoxazole constituted half of the antibiotics procured in the public sector (South African National

Department of Health, 2018a, unpublished). This is despite a decline in the use of co-trimoxazole over the years.

Resistance to antimicrobials has escalated globally to a point where a world without antibiotics is foreseen, since antimicrobials lose their efficiency when used for prolonged periods (Shankar, Piryani & Piryani, 2017). This global challenge of resistance poses a threat to public health and the world's economy, as it is likely to prolong the duration of disease in affected patients, increase mortality, and the costs associated with alternate antimicrobials (Essack et al., 2017).

The WHO's 2014 Antimicrobial Resistance Global Report on Surveillance of Antimicrobial Resistance (AMR) revealed that resistance by commonly cultured bacteria in hospitals, in the community and in food ranges between 25% and 50% in all WHO regions, while resistance in the African region ranges between 0% and 100% for different species of bacteria (Essack et al., 2017). Similar findings were made in an African study conducted by Leopold et al. (2014), using data from 1990-2013, where resistance patterns for commonly used antibiotics also ranged between 0% and 100% (Essack et al., 2017). Another study on AMR in Africa based on reports published between 2013 and 2016 also confirmed a high prevalence of resistance against commonly used antibiotics and lower resistance to less frequently prescribed antibiotics such as carbapenems (Tadesse et al., 2017).

The African studies mentioned above were conducted using data mainly from the East African region, and very little data from the central and South African regions owing to the insufficiency of data from these regions (Essack et al., 2017; Tadesse et al., 2017). The South African National Department of Health conducted surveillance for resistance and consumption of antibiotics in South Africa, covering both the public and private health sectors, using data from 2012-2017 from all provinces (South African National Department of Health, 2018a, unpublished). In this study, the top four bacteria cultured in 2017 were Klebsiella pneumonia (25%), Staphylococcus aureus (25%), Escherichia coli (19%), and Acinetobacter baumannii (15%) (South African National Department of Health, 2018a, unpublished).

The antimicrobial utilisation and resistance patterns discussed above apply to Colistin, among others. Colostin is the focus of the current study.

2.5 Colistin

Colistin falls under a group of antibiotics called polymixins. It is bactericidal and is used to treat sensitive carbapenem-resistant Gram-negative bacteria (CRGNB), and its side effects include nephrotoxicity and neurotoxicity (Messina et al., 2017). It is available in two forms: Colistimethate Sodium (CMS) and Colistin Sulphate (Gurjar, 2015). Colistin Sulphate is active against micro-organisms and is available for use orally, topically and via inhalation, while CMS must first be converted in vivo or in vitro to its active form -Colistin- and it is used parenterally (Gurjar, 2015).

2.5.1 Colistin pharmacokinetics and pharmacodynamics

Approximately 20% of the administered CMS is converted to the active form of the drug, Colistin, and the remaining is excreted by the kidneys (Labuschagne et al., 2016). In patients with impaired kidney function, there will be a reduction in the excretion of the non-active form of Colistin and therefore a higher percentage that is converted to the active form (Labuschagne et al., 2016). Colistin's bactericidal effect is both concentration and duration dependent (Hengzhuang et al., 2011).

After parenteral administration, Colistin shows a low plasma protein binding - which has been reported to be approximately 50% - and it reaches the steady-state concentration after 48 hours of administration (Gurjar, 2015). Although Colistin can be extensively circulated through the body tissues, it does not cross the blood-brain barrier, the pleural lining, synovial joint membranes or the pericardial lining (Labuschagne et al., 2016). It is also poorly distributed through lung parenchyma (Michalopoulos & Falagas, 2011). Therefore, the site of infection also determines the antimicrobial therapeutic effect of Colistin (Gurjar, 2015).

The half-life of Colistin in children is between two and three hours (Labuschagne et al., 2016) and two to four hours in adults (Gurjar, 2015). However, a study conducted by Michalopoulos and Falagas (2011) showed that Colistin has a significantly longer half-life in critically ill adults, in whom its half life is estimated to be approximately 14 hours. Data on the pharmacodynamics and pharmacokinetics is inadequate in the available literature (Labuschagne et al., 2016). The available literature makes no major differentiation in the pharmacodynamics and pharmacokinetics of Colistin in children and adults.

2.5.2 Colistin's adverse effects

The two known adverse effects of Colistin are nephrotoxicity and neurotoxicity (Labuschagne et al., 2016). The nephrotoxic adverse effects of Colistin are usually seen in patients with impaired kidney function, hypo-albuminemia, in patients on non-steroidal anti-inflammatory drugs (NSAID) and in the elderly (Labuschagne et al., 2016). The concurrent use of Colistin and nephrotoxic antibiotics such as vancomycin may lead to nephrotoxicity (Yahav, Farbman & Leibovici, 2012). The nephrotoxic adverse effects of Colistin are also associated with the dosage, are reversible and can be prevented by ensuring that the patient is well hydrated, by adjusting the dosage when indicated, by monitoring the kidney function and by avoiding concurrent use of nephrotoxic drugs (Labuschagne et al., 2016). Although old studies showed a nephrotoxic adverse effect of around 50%, recent studies show nephrotoxicity of between 10 and 30% (Labuschagne et al., 2016).

Neurotoxicity is a rare adverse effect of Colistin. Its predisposing factors are hypoxia, renal insufficiency and concurrent treatment with muscle relaxants, narcotics and sedatives (Labuschagne et al., 2016). The clinical signs of neurotoxicity are muscle weakness, dizziness, visual impairment, confusion, hallucinations, unsteady gait and convulsions (Labuschagne et al., 2016). Other manifestations of neurotoxicity include paraesthesia, partial deafness, vertigo, and neuromuscular blockade, with paraesthesia found to be the most common neuromuscular adverse effect (Yahav et al., 2012). As with nephrotoxicity, neurotoxicity is dose dependent and reversible upon discontinuation of the drug (Çağan et al., 2017).

2.5.3 Recommended Colistin dosing for South Africa

While the toxic effects of Colistin need to be minimised, its dosage must be optimised and resistance must be prevented (Labuschagne et al., 2016). In critically ill patients, a loading dose of 9 to 12MU, with a maintenance dose of 4,5MU twelve hourly, is reported to reach higher plasma levels faster than a regimen that uses a maintenance dose of 3MU eight hourly (Gurjar, 2015).

Inhaled Colistin is commonly used for patients with bronchiectasis and cystic fibrosis and to prevent broncho-constriction. In such cases, it is recommended that patients be nebulised with a beta-agonist before Colistin is administered (Labuschagne et al., 2016).Table 2.1 shows recommended Colsitin dosing amounts in South Africa.

Table 2.1: Recommended Colistin dosing

Non-Critical Adults (Intravenous Administration)		
Loading dose	12MU	
Maintenance dose	3MU 8 hourly OR 4.5MU 12 hourly	
Critical Adults (Intravenous Administration)		
Normal renal function	Loading dose	9MU
	Maintenance dose	4.5MU 12 hourly OR 2-3MU 8 hourly
Impaired renal function	Loading dose	12MU
• **Creatinine clearance (40-60ml/min)**	Maintenance dose	2MU 12 hourly
• **Creatinine Clearance (10-40ml/min)**	Maintenance dose	2MU 24 hourly
• **Creatinine Clearance (<10ml/min)**	Maintenance dose	1.5MU every 36 hours
Renal replacement therapy	Loading dose	12MU
• **Haemodialysis**	Maintenance dose	2MU 12 hourly and after dialysis
• **Continuous veno-venous haemodialysis**	Maintenance dose	Dosing as for normal renal function
Paediatric Dosages (Intravenous Administration)		
Neonates	50 000-75 000IU/kg/day in 3 divided doses	
Infants and Children	75 000-150 000IU/kg/day in 3 divided doses	
Inhalational Colistin		
• **< 40kg**	500 000IU every 12 hours	
• **> 40kg**	1000 000IU (1MU) every 12 hours	
• **Recurrent Pulmonary Infections**	2000 000IU (2MU) every 8 hours	

MU-Million Units; IU-International Units (Labuschagne et al., 2016)

2.6 Colistin utilisation

2.6.1 Global and local Colistin utilisation

The world has seen an increase in the use of two groups of antibiotics, usually used as a last resort when treatment with other antibiotics has failed. The two groups are the carbapenems e.g. meropenem, imipenem and polymixins, e.g. Colistin (Shankar,

Piryani & Piryani, 2017). The compound annual growth rate of Colistin consumption in South Africa from 2012 to 2016 was 5% (Mendelson et al., 2018).

A study conducted in four South African private hospitals showed that 76.6% of patients on Colistin were in ICU, 73.4% were on definitive treatment, and 26.6% were on empirical therapy (Messina, Van Vuuran & Brink, 2017). In this study, 35.9% were treated for Klebsiella pneumoniae, 26% for Pseudomonas aeruginosa, and 15.6% for Acinetobacter baumannii (Messina, Van Vuuran & Brink, 2017). The use of Colistin in South Africa is regulated by SAHPRA.

2.6.2 Policy and legislation guiding Colistin use in South Africa

The Medicines and Related Substances Act No. 101 of 1965, as amended, classifies Colistin as a Schedule 4 drug, which means it can only be prescribed by a doctor and only issued from a pharmacy (Republic of South Africa, 2017). Since it is not registered in the country according to Section 21 of the Act, its use can only be approved by the South African Health Products Regulations Authority (SAHPRA) (Republic of South Africa, 2017). Colistin is only approved to be used in tertiary hospitals; it may be prescribed only if it is the only antibiotic to which the cultured bacteria is sensitive, and the prescribing doctor must: provide his/her details, the details of the patient, the patient's diagnosis, comorbidities, other drugs the patient is on, microscopy, culture, and sensitivity results, obtain consent from the patient and, finally, compile a progress report on the outcome of treatment (Mendelson et al., 2018). A study conducted by Messina et al. (2018) in South Africa showed 99% compliance with obtaining culture and sensitivity before initiating treatment.

2.6.3 Utilisation of Colistin in a clinical setting

The re-introduction of polymixins (Colistin and tigecycline) in humans followed the emergence of MDR-GNB especially resistant to carbapenems (Garbati, Sakkijha & Abushaheen, 2016). This resulted in the development of resistance against polymixins (Garbati et al., 2016). There is limited clinical evidence to guide treatment with Colistin, and current guidance is based on observational research conducted retrospectively (Garbati et al., 2016).

Colistin may be used either as monotherapy or in combination with other antimicrobials, with the use of combination therapy commonly practiced by clinicians owing to high mortality rates associated with monotherapy (Garbati et al., 2016).

Colistin monotherapy is of concern because of bacterial regrowth demonstrated in numerous *in vitro* studies (Yahav et al., 2012). The selection for the regrowth of Colistin-resistant subpopulations of micro-organisms post-Colistin monotherapy has been attributed to hetero-resistance exhibited by Gram-negative bacterial subpopulations (Yahav et al., 2012).

The use of Colistin in combination with other groups of antimicrobials such as carbapenems, in some in vitro studies, showed synergy, a decrease in regrowth as well as a decline and delay in the development of Colistin-resistant subpopulations (Yahav et al., 2012). The two suggested synergy mechanisms are subpopulation and mechanistic synergy. Subpopulation synergy occurs when antimicrobials kill a subpopulation of microorganisms not killed by the other antimicrobial, and mechanistic synergy occurs when the bactericidal rate is increased owing to the use of different pathways by antimicrobials targeting the same microorganism (Yahav et al., 2012).

Although *in vitro* studies seem to provide a strong theoretical basis for the use of Colistin combination therapy, clinical studies have yet to prove its advantages (Yahav et al., 2012). A retrospective study carried out by Falagas et al. (2010), cited in Yahav et al. (2012), showed in an adjusted analysis, an 83.3% cure rate in patients on Colistin monotherapy, whereas combination therapy showed no advantage for the survival of patients infected with micro-organisms only sensitive to Colistin.

Some researchers have seen a synergistic effect of using Colistin in combination with carbapenems in the treatment of Acinetobacter baumannii, and thus recommend combination therapy to maximise its bactericidal effect and to reduce the chances of resistance (Labuschagne et al., 2016). Some researchers who found no synergistic effect of combination therapy against resistant Klebsiella pneumoniae do not recommend polymixins combination therapy, as it may cause the spread of carbapenem-resistant Gram-negative bacteria (CRGNB) (Zusman et al., 2017).

Colistin has been used for different reasons and in different ways by clinicians. In a study conducted by Messina et al. (2018), Colistin was used as definitive therapy in 60.8% of cases, as empirical treatment in 31.1% of cases and as salvage therapy in 7.5% of cases. In all but three patients, Colistin was used in combination with other antibiotics (Messina et al., 2018).

This study analysed how Colistin was utilised in the study setting in the chosen period.

2.7 Clinical outcomes of Colistin utilisation

Patients on Colistin can be cured, die or develop adverse effects, and/or resistance. This section covers the clinical outcomes of Colistin use as revealed by various studies. Most studies regarding treatment with Colistin and the clinical outcomes thereof focus on the treatment of multidrug-resistant Klebsiella pneumoniae (Lee et al., 2016).

Findings of a retrospective study on the efficacy of Colistin in newborns showed high tolerance and efficacy of treatment with Colistin, and acceptable adverse effects (Çağan, Kıray Baş & Asker, 2017). Çağan et al's (2017) study showed a 78.5% cure rate and 21.5% mortality rate. Although 13.8% of patients in the study were treated with a nephrotoxic drug such as ibuprofen, only 4.6% developed nephrotoxic side effects, which improved after discontinuation of Colistin (Çağan, Kıray Baş & Asker, 2017). Neurotoxicity was observed in 6.2% of patients and no Colistin resistance occurred in the study (Çağan, Kıray Baş & Asker, 2017). Although the sensitivity of microorganisms to another antibiotic over and above Colistin may have an impact on the clinical outcome, this study showed no discrepancy between the clinical outcomes of patients who were sensitive to Colistin only and those of patients who were sensitive to both Colistin and another antibiotic (Çağan, Kıray Baş & Asker, 2017). The results of this study suggest that Colistin was effective and tolerated well by the new-borns however, minimal adverse effects were noted: nephrotoxicity as evidenced by high creatinine levels and neurotoxic effects seen included seizures and apnoea (Çağan, Kıray Baş, and Asker, 2017).

Falagas et al. (2010) conducted a large cohort retrospective study on Colistin efficacy, which involved 258 critically ill adult patients with MDR-GNB infections. The study assessed cure from infection, hospital survival and nephrotoxicity (Falagas et al., 2010). Pathogens identified included: Acinetobacter baumannii, Pseudomonas aeregunosa, Klebsiella pneumoniae, Stenotrophomonas maltophilia and Enterobacter cloacae (Falagas et al., 2010). Cure was seen in 79.1% of patients, nephrotoxicity in 10% of patients, and hospital survival in 65.1% of patients. According to Falagas et al. (2010), Colistin is a valuable antimicrobial with acceptable nephrotoxic adverse effects with an efficacy that is not associated with the microbe identified.

The mortality rates of treatment with Colistin are dependent on underlying medical conditions and whether it was used alone (49%) or in combination (25%) with other antibiotics (Labuschagne et al., 2016).

Although old studies have shown nephrotoxic adverse effects of Colistin to be approximately 50%, recent studies have shown Colistin nephrotoxic effects to range between 10 and 30% (Visser Kift, Maartens & Bamford, 2014). In a study conducted by Yahav et al. (2012), it was found that most cases of nephrotoxicity happen in the first week of initiating treatment and 88% of nephrotoxicity was found to be reversible upon discontinuation of the drug.

The results of a retrospective study on the utilisation of Colistin in adult patients, conducted in four South African private hospitals, showed 99% compliance with culture and sensitivity testing before initiating treatment, and 93.5% compliance in prescribing the loading dose. However, the loading and maintenance doses were used inappropriately. Colistin combination therapy was given in 98.5% of cases. There was no dose adjustment aligned with the renal function tests in 48.2% of cases and no de-escalation of treatment to a broad-spectrum antibiotic in line with the culture and sensitivity results in 69.9% of cases (Messina et al., 2018).

The clinical outcome in this study showed 70.4% cure, 29.6% mortality, and insignificant nephrotoxicity as evidenced by a mean glomerular filtration rate of 79ml/min before and after treatment. The study also found a significant correlation between the outcome and the maintenance dose; the higher the maintenance dose, the higher the survival rate (Messina et al. 2018).

The parameters discussed in this section will be highlighted in the proposed study.

2.8 Resistance to Colistin

Resistance to Colistin was first seen in the United States in the late 1990s (Van Duin & Doi, 2015) and in the Czech Republic in 1999 (Visser Kift, Maartens & Bamford, 2014), and quickly spread globally. A study conducted in an Italian hospital revealed a rapid increase in *K. pneumoniae* Colistin resistance as shown in the following figures: 2011 (12% resistance rate), 2012 (65% resistance rate), 2013 (57% resistance rate). This was attributed to an increase in the use of Colistin in those years (Van Duin & Doi, 2015). Jain et al. (2014), cited in Van Duin and Doi (2015), observed a 10%

Colistin resistance in the United Kingdom. Mansour et al. (2017) reported a resistance rate of 24% in a study conducted in a Tunisian hospital in 2015-16.

In South Africa, Colistin resistance was first seen in animals. *Escherichia coli* resistance to Colistin was first seen in animals in South Africa between 1997 and 1999 (17% resistance rate) (Mendelson et al., 2018). A gradual increase in the total prevalence of resistance was seen in animals from 2012 to 2015, with 2012 having a 3% resistance rate, 2014 a 13% resistance rate and 2015 a 95% resistance rate (Mendelson et al., 2018). In humans, 13.6% A. baumannii resistance was seen in Groote Schuur Hospital in 2011 (Visser Kift, Maartens & Bamford, 2014).

A national surveillance of blood culture isolates, conducted by the National Institute of Communicable Diseases (NICD) across provinces in South African health facilities between 2014 and 2015, found that the prevalence of Colistin resistance by various microorganisms in humans ranged between 0% and 10% (Mendelson et al., 2018).

2.8.1 Mechanisms of Colistin resistance

A mechanism of Colistin resistance seen in carbapenem-resistant Klebsiella pneumoniae was the deletion or inactivation of a gene sequence in the mgrB gene, followed by the expansion of the resistant clones of bacteria (Giani et al., 2015). This mechanism of resistance was believed to be the only mechanism of bacterial resistance to Colistin; however, in 2016, plasmid-mediated genes, mobilised Colistin resistance-1 (mcr-1) and mobilised Colistin resistance-2 (mcr-2), were discovered (Mendelson et al., 2018). These genes' Colistin resistance is transmissible between bacteria of the same or different species through horizontal gene transfer (Mendelson et al., 2018).

The mobilised Colistin resistance-1 (mcr-1) gene was discovered in food-producing animals and abattoirs, and on meat in retail outlets in South Africa. Cases of community-acquired Colistin-resistant Escherichia coli were also seen and managed by general practitioners (Mendelson et al., 2018).

2.8.2 Risk factors and pathophysiology of Colistin resistance

There is evidence that consumption of meat colonised with Colistin-resistant micro-organisms and contact with the environment colonised with Colistin-resistant micro-organisms can transmit Colistin resistance (Mendelson et al., 2018). The colonisation of medical equipment with resistant strains and poor infection prevention and control

practices in hospitals contribute to the spread of resistance (Chen, Chang & Chen, 2015).

The misuse or overuse of Colistin may also result in the development of resistance (Labuschagne et al., 2016). The bactericidal effect of Colistin is both concentration and duration dependent, and the development of resistance against Colistin has also been ascribed to suboptimal dosages and the use of regimens with prolonged intervals between dosages (Michalopoulos & Falagas, 2011).

2.8.3 Intervention measures for Colistin resistance in South Africa

Following the identification of Colistin resistance in both animals and humans in South Africa and in alignment with the South African One Health National Strategy Framework for Antimicrobial Resistance, the South African Medicines and Control Council (MCC) formed the Colistin Working Group in 2016, whose mandate was to evaluate the extent of Colistin utilisation and resistance and to revisit Colistin utilisation legislation in South Africa (Mendelson et al., 2018).

In light of the findings by a European Medicines Agency publication which detailed the transmissibility of Colistin resistance by food consumption or contact with the environment, the Colistin Working group decided in 2016 to stop Colistin use in animals unless a veterinarian can provide sensitivity results (Mendelson et al., 2018).

The management of the Colistin Working Group was transferred from the MCC to a newly established Ministerial Advisory Committee on Antimicrobial Resistance in 2016 (Mendelson et al., 2018). Following the amendment of the Medicines and Related Substances Act 101, 1965) in May 2017 and the abolishment of MCC in January 2018, the South African Health Products Regulation Authority (SAHPRA) was phased in (Molokwane, 2018). SAHPRA has a Technical Working Group on Colistin and AMR (Mendelson et al., 2018). According to the Medicines and Related Substances Act No.101 of 1965 as amended, SAHPRA's mandate is to monitor, evaluate, regulate, investigate, inspect, register and control medicines, medical devices and research in the interest of the public.

2.9 Gaps in the literature

Antimicrobial stewardship is at the centre of the rational use of antimicrobials and requires the involvement of clinicians and management at the health facility level, as well as government at provincial and national levels. Although antimicrobial utilisation

in agriculture and livestock is higher than in humans globally, in South Africa approximately two-thirds of antimicrobials are used in humans. The use of antimicrobials has increased globally in the past decade, especially in the BRICS countries, and South Africa has a higher consumption than most countries worldwide. An increase in antimicrobial use, in general, has contributed to an increase in antimicrobial resistance globally, which is a threat to public health and the global economy. The prevalence of resistance is higher in commonly used antimicrobials than in antimicrobials that are used less frequently.

Colistin can be used as monotherapy or in combination with other antimicrobials. There are different schools of thought regarding monotherapy and combination therapy. Researchers who find a synergistic effect of combination therapy recommend it, but those who do not find such an effect do not recommend it and are of the view that combination therapy can result in the development of more resistant strains of micro-organisms. Despite different dosage recommendations made by different manufacturers, South Africa published recommended Colistin dosing guidelines for both children and adults in 2016.

Although there are no studies that specifically focus on comparing the use and clinical outcomes of Colistin between children and adults in the available literature, the studies that were conducted in either children or adults show a cure rate of over 70%. Of the two known adverse effects of Colistin, nephrotoxicity is the more common, and both are reversible upon discontinuation of the drug. Older studies show a higher incidence of nephrotoxicity than recent studies, which has been attributed to new formulations of Colistin. As with other antimicrobials, the emergence of Colistin resistance has been attributed to an increase in its use.

The current study examines Colistin utilization, its clinical outcomes, and the comparison between utilization and clinical outcomes between children and adults at the chosen study setting.

2.10 Summary of Chapter 2

This chapter has reviewed the literature on Colistin utilisation and its clinical outcomes globally, in Africa and in South Africa. The emphasis was on Colistin pharmacodynamics and pharmacokinetics, the recommended dosing in South Africa, adverse effects, resistance, and policy and legislation regarding its use in South Africa.

The basics of antimicrobial stewardship, the use of antimicrobials in general, and resistance patterns were also discussed. Chapter three decribes the methodology used in this study.

CHAPTER 3: METHODOLOGY

3.1 Introduction

This chapter presents an overview of the design and methodologies used in the study. It covers the study design, population, sampling method, research instrument, data collection, data analysis, pilot study,validity and reliability tests, and ethical considerations.

3.2 Study design

A retrospective study design is a study in which an investigation focuses on what happened in the past, while a descriptive study design attempts to describe a situation, a challenge, a programme or service (Kumar, 2019).

A retrospective cross-sectional study design was used to analyse how Colistin was utilised in both adults and children between 2015 and 2019 at the study setting. This design was also used to describe and compare the clinical outcomes of treatment with Colistin in neonates to outcomes of treatment in both adults and children.

Quantitative research is a research method in which data collection techniques and data analysis generate or make use of numbers (Saunders et al., 2012). This study was conducted using quantitative methods. Since it is well organised, precise and predetermined to guarantee validity and reliability, its design tends to give enough detail, allowing it to be replicated for authentication (Kumar, 2019). The findings of quantitative research may be generalised to the whole population (Kumar, 2019). The study was, therefore, conducted using a retrospective, quantitative and descriptive methodology.

3.3 Population

The population used in the study was made up of clinical records of all patients treated with Colistin between 2015 and 2019 at the chosen study setting.

3.4 Sample

This study adopted a stratified random sampling technique. The exact total number of patients treated with Colistin at the chosen study setting per year was unknown, therefore a sample frame – a list of all patients treated with Colistin in the specified period – was drawn from the information gathered from the hospital pharmacy.

The sample frame was divided into strata made up of clinical records of adults, children and neonates. Sampling was conducted per stratum, as it was impractical to gather data from all clinical records, given the time allocated to conduct the study (Saunders et al., 2012). Sampling also allowed the collection of accurate data (Kumar, 2019).

The estimated number of patients treated with Colistin during the period under review was 150. In total, 50% of the clinical records per stratum per year were used, since a larger sample tends to produce more accurate results (Kumar, 2019). The estimated sample size for the chosen period was therefore 75 files.

Random sampling was used per stratum which afforded each clinical record an equal and independent probability of being selected (Kumar, 2019). The study, therefore, made use of the stratified random sampling method (Kumar, 2019). To ensure random selection of each patient, an annual stratified sample frame of patients treated with Colistin was submitted to the records department by the researcher, but a specific number of files – the predetermined sample size per stratum per year – was requested. Therefore files were randomly selected by the administrative official in the records department, depending on availability.

3.5 Research instruments

The study was conducted by making use of primary data, which is described by Kumar (2019) as data collected from a primary source. Primary data was collected from both the electronic version of clinical records and the physical files of patients treated with Colistin.

Numerical data was gathered by making use of a questionnaire and analysing the results (Kumar, 2019). A questionnaire makes collection and comparison of standard data feasible, and is an efficient manner of collecting data from a large sample (Saunders et al., 2012).

A data-sheet was designed to answer research questions and to test the hypothesis (Saunders et al., 2012). It was based on compliance with Section 21 of the Medicines and Related Substance Act 101 of 1965, the SAHPRA requirements, and the recommended treatment guidelines for South Africa.

Some concepts were first converted to indicators and then to variables before data was collected; for example, the indicator of nephrotoxicity was the elevation of urea and creatinine above the normal range for the local laboratory used (Kumar, 2019). Three types of variables were used in the study: independent variables (variables that are responsible for effecting change, such as the Colistin loading dose prescribed and administered); dependent variables (variables that are an effect of an independent variable, such as a cure); and extraneous variables (other variables that could have an impact on the relationship between the dependent and independent variables, such as a nephrotoxic drug used together with Colistin) (Kumar, 2019).

The datasheet had sections on patient demographics, compliance with policy and legislation, compliance with treatment guidelines, and a section on clinical outcomes.

3.6 Pilot study

The research instrument was pretested using files from each stratum to identify any challenges with the questions, following which adjustments were made to ensure content and construct validity of the instrument. The pre-designed datasheet was piloted using ten clinical records from the study setting. Preliminary findings were analysed and cross-checked with the study objectives, then feedback was obtained from the supervisor to verify whether the variables had captured the relevant data to answer the research questions. Fieldwork was conducted after making final adjustments to the datasheet.

3.7 Validity and reliability

3.7.1 Validity

The concept of validity is described as the capability of a research instrument to measure what it intends to measure (Kumar, 2019). Face and content validity was used to test the validity of the research instrument. Content validity was achieved by structuring questions in the research instrument in a manner that ensured that research questions were answered (Kumar, 2019). Face validity was tested by means

of a pilot study and expert advice from the research supervisor to ensure that the research questions had a logical link with the objectives of the study (Kumar, 2019).

3.7.2 Reliability

Reliability refers to the extent to which a research instrument consistently produces the same or similar measurements under the same or similar circumstances (Kumar, 2019). To establish reliability in the current study, the internal consistency procedure was used, whereby similar results should be obtained despite the number of questions used per section of the research instrument (Kumar, 2019). The reliability of the research instrument was determined by making use of the Cronbach α test (Heale & Twycross, 2015).

3.8 Data collection procedures

Lists of all patients treated were drawn from the pharmacy manager and managers of all wards prescribing Colistin. After permission was obtained from the Head of the Free State Department of Health (FSDOH) and the Chief Executive Officer (CEO) of the chosen health facility, the clinical records were requested from the records department and all wards concerned. The clinical records were then collected by the researcher for review. Activation of all purged relevant electronic records was also requested from the Information Communication and Technology Department. Primary data was then gathered from the randomly selected clinical records by the researcher, using the research instrument.

3.9 Ethical considerations

Study approval was obtained from the Faculty of Health Sciences Research and Ethics Committee, University of Fort Hare (Reference number: 2020=12=08=MatshedisoG). Permission was obtained from the head of the Free State Department of Health (FSDOH) and the Bloemfontein Public Hospital Chief executive officer. Given that this was a retrospective study, no written consent forms were signed by the individual participants as the formal ethics clearance and FSDOH permission were sufficient.

No patient identifiers were obtained, to ensure the privacy and confidentiality of medical information. All medical data obtained during the study was protected; soft

copies were assigned passwords on a secured laptop while hard copies were kept safely under lock and keys. No unauthorised persons were granted access to the data or study materials.

3.10 Data analysis

Data was analysed with the use of IBM Statistical Package for Social Sciences (SPSS) Version 24.0 for Windows (Armonk, Chicago, Ill, USA). Simple descriptive statistics were employed to analyse the use of Colistin in the study setting. Data was expressed as mean values (standard deviation) for continuous variables, counts/frequencies (n) and proportions for categorical variables. Percentages of use of Colistin were compared for years and among adults, children and neonates using the chi-square test. Independent associations of the factors influencing mortality were examined by using logistic regression model analysis. A p-value of less than 0.05 was considered statistically significant.

3.11 Summary of Chapter 3

This chapter has given an overview of the design and methodologies used in the study. It covered the study design, population, sampling method, research instrument used, data collection methods, data analysis, the pilot study done, validity and reliability tests and ethical considerations.

CHAPTER 4: RESULTS

4.1. Introduction

This chapter provides a detailed summary of the findings of the study. Descriptive data is presented in the form of tables and figures. A concise narrative of the results is presented in a logical flow and arranged sequentially according to the study objectives.

4.2 The study sample

Table 4.1 shows the overall data disaggregated by year of admission (2015 to 2019) and category of patients (neonates, children and adults). The study sample consisted of 50% of the patients who had been treated with Colistin per stratum per year from 2015 to 2019. Of the total sample (N=69), the majority were neonates (43.5%) while children constituted the catgory with the lowest number of patients (18.8%). Each year, there were least 11 patients (2015), with a maximum of 17 (2018).

Table 4.1 Stratified annual sample of patients

	2015	2016	2017	2018	2019	Totals
Adults	8	5	5	5	3	26 (37.7%
Children	1	3	3	4	2	13 (18.8 %)
Neonates	2	5	5	8	10	30 (43.5%)
Totals	11	13	13	17	15	69

4.3 Patient characteristics

The majority of the participants were males (58%), among whom most were adults (45%). The mean age of participants on admission was 41 years in adults, 3 years in children, and 1.1 days in neonates.

The duration of illness for the majority (63.8%) of the participants prior to admission was not longer than a day, largely in neonates (24 of 30 neonates were admitted on the day of delivery). Adults made up 87.5% of the participants that had prolonged duration (6-240 days) of illness prior to admission.

A high proportion of patients were treated in the Intensive Care Unit (95.5%). The remaining 4.5% were treated in the adult general wards.

Colistin was predominantly used to treat septicaemia (75.4%) in the study setting. Although septicaemia was the leading diagnosis in all three categories, neonates made up the largest proportion of the three (44.2%). The second-most prevalent diagnosis of the total sample was respiratory distress syndrome of the new-born, which accounted for 10.1% of the participants sampled, followed by pneumonia at 7.3%. Patients also had other diagnoses, such as burns, poly-trauma and meningitis. These accounted for less than 7.5% of the sample.

A significant proportion of the participants did not have comorbidities (44.9%). Prematurity accounted for 31.9% of the remaining proportion of participants who had comorbidities. The rest had a combination of multiple conditions such as tuberculosis, epilepsy and schizophrenia (Table 4.2).

Table 4.2: Patient characteristics

Variables	Totals	Adults	Children	Neonates
Sample size	69	26(37.7%)	13(18.8%)	30(43.5%)
Mean age		41 years	3 years	1.1 days
Gender				
Female Male	29(42 %) 40(58%)	8(27.6%) 18(45%)	8(27.6%) 5(12.5%)	13(44.8%) 17(42.5%)
Duration of illness prior to admission (days)				
0	44(63.8%)	12(27.3%)	8(18.2%)	24(47.6%)
1-4	17(25.4%)	7(41.2%)	4(23.5%)	6(35.3%)
6-240	8(11.9%)	7(87.5%)	1(12.5%	0(0)
Admission ward				
ICU	26	26	0	0
PICU	12	0	12	0
NICU	31	0	1	30
Medical Ward	1	1	0	0
Surgery Ward	1	1	0	0
Trauma Ward	1	1	0	0
Definitive diagnosis				
Septicaemia	52(75.4%)	17(32.7%)	12(23.1%)	23(44.2%)
Respiratory Distress Syndrome of the New-born	7(10.1%)	0	0	7(100%)
Pneumonia	5(7.3%)	5(100%)	0	0
Poly-trauma	3(4.4%)	3(100%)	0	0
Meningitis	1(1.5%)	1(100%)	0	0
Burns	1(1.5%)	0	1(100%)	0
Comorbidities				
None	31(44.9%)	19(61.3%)	9(13.1%)	3(4.4%)
Prematurity	22(31.9%)	0	0	22(100%)
Diabetes and Hypertension	2(2.9%)	2(100%)	0	0
Diabetes	0	0	0	0
Hypertension	1(1.5%)	1(100%)	0	0
Renal Failure	2(2.9%)	2(100%)	0	0
*Others	11(15.9%)	2(18.2%)	4(36.4%)	5(45.5%)

*Tuberculosis, epilepsy, HIV, schizophrenia, anaemia, neonatal jaundice, malnutrition etc.; ICU = Intensive Care Unit; PICU = Paediatrics Intensive Care Unit; NICU = Neonatal Intensive Care Unit; HIV = Human Immuno-deficiency Virus.

4.4 Colistin utilisation

4.4.1 Empirical treatment prior to culture and sensitivity results

Prior to receiving culture and sensitivity results, the antimicrobials of choice for neonates were Ampicillin (59.1%) and Gentamycin (93.8%). However, the empirical treatment for children were Meropenem (28.6%) and Piperacillin-Tazocin (23.5%) while in adults, it was Amikacin (33.3%) and Imipenem (77.8%).After the culture and sensitivity results had been reviewed, the overall treatment de-escalation was

significantly high (82.1%), but was higher in neonates (88.5%) in comparison to adults and children (Table 4.3).

Table 4.3: Empirical treatment prior to culture and sensitivity results

Variables	Totals	Adults	Children	Neonates
Ampicillin, Amoxicillin, Amoxy-Clavulanic Acid	22(33.3%)	7(31.8%)	2(9.1%)	13(59.1%)
Meropenem	21(31.8%)	4(19.1%)	6(28.6%)	11(52.4%)
Amikacin	18(27.3%)	6(33.3%)	2(11.1%)	10(55.6%)
Imipenem	18(27.3%)	14(77.8%)	2(11.1%)	2(11.1%)
Piperacillin-Tazocin	17(25.8%)	1(5.9%)	4(23.5%)	12(70.6%)
Gentamycin	16(24.2%)	0	1(6.3%)	15(93.8%)
Empirical treatment de-escalation following culture and sensitivity results	82.1%	76.2%	77.8%	88.5%

4.4.2 Culture and sensitivity profile

Culture and sensitivity results were obtained in 53 (76.9%) of the total number of participants. There was 68.1% compliance in the use of Colistin as a last resort. Colistin was used to treat patients infected by micro-organisms also sensitive to other antimicrobials (4.4%), over and above Colistin. It was also used in participants who had no Colistin sensitivity results (23.2%), and those who were resistant to Colistin (4.4%). Neonates accounted for 62.5% of the participants treated without Colistin sensitivity results (Table 4.4).

4.4.3 Indication for treatment

Of the total number of participants (N=69), 49 patients (71%) received definitive treatment for the organisms cultured, while 14 (20.3%) were treated empirically and 6 (8.7%) received salvage therapy.

4.4.4 Monotherapy versus combination therapy

Upon receiving culture and sensitivity results indicating sensitivity to Colistin only, prescribing doctors ceased empirical treatment for some patients but continued for others to complete the course of the antibiotics used. For some patients,

discontinuation of empirical treatment was followed by the use of an antimicrobial from a group of carbapenems in combination with Colistin, although the microorganism cultured was resistant to carbapenems. In the chosen study setting, the clinicians showed a preference for monotherapy (56.5%) over combination therapy (43.5%) (Table 4.4).

4.4.5 Other drugs used in patient management

In the management of patients, other drugs were administered for various reasons. These may have been other antimicrobials to treat concurrent infections, or other drugs to treat comorbidities or electrolyte imbalances. A significant percentage of participants (93.4%) were treated for other infections, and more were given nephrotoxic agents (68.2%) than neurotoxic agents (56%). See Table 4.4 below.

4.4.6 Adherence to doctors' prescription

Dosage prescribed, frequency of administration, timing and duration of treatment were used to assess adherence to the doctors' prescriptions. Adherence to dosage was the highest (89.1%) among the four indicators, while the lowest adherence was found with duration of treatment (34.9%) (Table 4.4).

Table 4.4: Colistin utilisation at the study setting

Variables	Totals	Adults	Children	Neonates
Culture and sensitivity profile				
Sensitivity to Colistin only	47(68.1%)	18(38.3%)	11(23.4%)	18(38.3%)
Sensitivity to other antimicrobials	3(4.4%)	3(100%)	0	0
No Colistin sensitivity results	16(23.2%)	4(25%)	2(12.5%)	10(62.5%)
Total resistance	3(4.4%)	1(33.3%)	0	2(66.7%)
Indication for treatment				
Definitive treatment	49(71%)	20(40.8%)	11(22.5%)	18(36.7%)
Empirical therapy	14(20.3%)	5(35.7%)	1(7.1%)	8(57.1%)
Salvage therapy	6 (8.7%)	1(16.7%)	1(16.7%)	4(66.7%)
Monotherapy vs. combination therapy				
Monotherapy	39 (56.5%)	10(25.6%)	11(28.2%)	18(46.4%)
Combination therapy	30 (43.5%)	16(53.3%)	2(6.7%)	12(4%)
Other drugs used in patient management				
Antimicrobials	62(93.9%)	23(37.1%)	13(21%)	26(41.9%)
Nephrotoxic agents	45(68.2%)	16(35.6%)	10(22.2%)	19(42.2%)
Neurotoxic agents	37(56.1%)	13(35.1%)	6(16.2%)	18(48.7%)
Adherence to doctors' prescriptions				
Dosage	59(89.4%)	23(39%)	9(15.3%)	27(45.8%)
Frequency	43(65.2%)	18(41.9%)	4(9.3%)	21(48.8%)
Timeously	44(66.7%)	17(38.6%)	5(11.4%)	22(50%)
Duration	23(34.9%)	6(26.1%)	2(8.7%)	15(65.2%)

4.5 Compliance with policy and guidelines

4.5.1 Processes followed

There was full compliance with microscopy, culture and sensitivity testing prior to prescribing Colistin, although not all results were obtained prior to commencement of treatment. Patient consent was obtained in only 63.8% of participants; however, a large proportion of patients (88.4%) had baseline renal function tested prior to the administration of the drug. There was poor adherence to the processes by the facility

pharmacy regarding SAHPRA applications to utilise Colistin (43.5%), although in most cases (62.3%) hospital management had granted permission to apply.

4.5.2 Prescription compliance by doctors

The majority of the doctors (84.06%) adhered to the legality of prescription with their names, qualifications and signatures written on the scripts. All the prescriptions for children were legal (100%) in comparison to neonates (83.33%) and adults (76.92%).

4.5.3 The manner in which treatment was administered

Three adults' ward prescriptions were missing from the clinical records. Therefore, the total used for adults regarding the administration of the drug was 66. Contrary to the published guidelines, the loading dose was prescribed and administered in only 16 cases (24.2%). Colistin was administered intravenously in all patients, and three adults (4.6%) received additional inhalational doses. Regarding the frequency of administration, 33.3% of patients received a twice-daily dose and 44 (66.67%) received the dose three times a day. A greater proportion of three daily doses was administered in children and neonates; 100% and 93.3% respectively. The twice daily dose was given mainly to adults – 20 in total (86.96%). All patients were monitored for signs of neurotoxicity and nephrotoxicity while on treatment (Table 4.5).

Table 4.5 Compliance with policy and guidelines

Variable	Totals	Adults	Children	Neonates
Process followed				
Patient consent obtained	44(63.8%)	20(45.5%)	12(27.3%)	12(27.3%)
Baseline renal function done	61(88.4%)	24(39.3%)	13(21.3%)	24(39.3%)
Hospital management approval granted	43(62.3%)	19(44.2%)	10(23.3%)	16(37.2%)
SAHPRA application done	30(43.5%)	16(53.3%)	6(20%)	8(26.7%)
SAHPRA approval granted	30(43.5%)	16(53.3%)	6(20%)	8(26.7%)
Doctors' prescription compliance (Form H101)				
Name	58(84.1%)	20(34.5%)	13(22.4%)	25(43.1%)
Qualifications	58(84.1%)	20(34.5%)	13(22.4%)	25(43.1%)
Signature	58(84.1%)	20(34.5%)	13(22.4%)	25(43.1%)
Recommendation by specialist	55(79.7%)	20(36.4%)	13(26.6%)	23(41.8%)
The manner in which treatment was administered				
Loading dose given	16(24.2%)	15(93.8%)	0	1(6.3%)
Maintenance dose given	66(100%)	23(100%)	13(100%)	30(100%)
Administration route				
Intravenous	66(100%)	23(100%)	13(100%)	30(100%)
Inhalational	3(4.6%)	3(100%)	0	0
Frequency of administration				
Two times a day	22(33.3%)	20(87%)	0	2(6.7%)
Three times a day	44(66.7%)	3(13.1%)	13(100%)	28(93.3%)

SAHPRA = South African Health Products Regulatory Authority

4.6 Clinical outcomes

Of the total participants (N=69), clinical cure was achieved in 53.6% of the participants, predominantly among neonates (64.9%), while mortality occurred in 32 patients (46.4%). The highest proportion of deaths occurred in adult patients (59.4%). Adverse drug reactions occurred in 30 patients (43.48%). This was most notable among adults (50%). Nephrotoxicity was seen in all patients who developed adverse reactions, and four patients (5.8%) developed neurotoxic side effects. While more cases of

nephrotoxicity were reported in adults (50%) than in other categories, more neurotoxicity occurred in neonates (Table 4.6).

Table 4.6: Clinical outcomes

Variables	Totals	Adults	Children	Neonates
Adverse drug reactions	30(43.5%)	15(50%)	6(20%)	9(30%)
Elevated creatinine	30(43.5%)	15(50%)	6(20%)	9(30%)
Neurotoxicity signs	4(5.8%)	1(25%)	1(25%)	2(50%)
Cure	37(53.6%)	7(18.9%)	6(16.2%)	24(64.9%)
Mortality	32(46.38%)	19(59.4%)	7(21.9%)	6(18.6%)

4.7 Comparison of Colistin use and clinical outcomes in adults, children and neonates

4.7.1 Comparison of colistin utilisation

4.7.1.1 Admission ward

There was 100% compliance with the treatment of children and neonates in the intensive care unit and 95.7% compliance in adults. In total, 4.35% of adults were treated in the normal wards.

4.7.1.2 Culture and sensitivity profile

The lowest compliance for using Colistin as a last resort for multidrug-resistant Gram-positive bacteria with exclusive Colistin sensitivity was in neonates (60%), and the highest was in children (84.6%). The use of Colistin where there was sensitivity to other antimicrobials was seen only in adults (11.5%). Neonates accounted for the largest proportion (33.3%) of patients treated without Colistin sensitivity results. Total resistance was minimal (4.35%); adults (3.8%) and neonates (6.7%).

4.7.1.3 Indication for treatment

Compliance with treating only those patients where the cultured micro-organism showed multi-drug resistance and exclusive Colistin sensitivity was the highest in children (84.6%), followed by adults (76.92%), and neonates (60%). Neonates received higher percentages of empirical (26.7%) and salvage (13.3%) treatment than adults and children.

4.7.1.4 Monotherapy versus combination therapy

Children and neonates were mainly treated using monotherapy – 84.6% and 60% respectively, while adults were mainly treated using combination therapy (61.5%).

4.7.1.5 Other drugs used in patient management

In addition to Colistin, all adults and children were treated with other antimicrobials, while only 86.7% of neonates received other antimicrobials. Of the three strata, children received the highest percentage of nephrotoxic agents (76.9%), while neonates received the highest proportion of neurotoxic agents (60%).

4.7.1.6 Adherence to doctors' prescriptions

The lowest percentage of adherence to the dosage prescribed, the frequency of administration, timing, and the duration of treatment was seen in children - (69.2%), (30.8%), (38.5%) and (15.4%) respectively, and adherence regarding the same variables was the highest in adults. Neonates had the highest proportion of participants that were treated for the full duration prescribed (50%) (Table 4.7).

Table 4.7: Comparison of Colistin utilisation in adults, children and neonates

Variables	Totals	Adults	Children	Neonates
Culture and sensitivity profile				
Sensitivity to Colistin only	47(68.1%)	18(69.3%)	11(84.6%)	18(60%)
Sensitivity to other antimicrobials	3(4.4%)	3(11.5%)	0	0
No Colistin sensitivity results	16(23.2%)	4(15.4%)	2(15.4%)	10(33.3%)
Total resistance	3(4.4%)	1(3.8%)	0	2(6.7%)
Indication for treatment				
Definitive treatment	49(71%)	20(76.9%)	11(84.6%)	18(60%)
Empirical therapy	14(20.3%)	5(19.2%)	1(7.7%)	8(26.7%)
Salvage therapy	6 (8.7%)	1(5.9%)	1(7.7%)	4(13.3%)
Monotherapy vs. combination therapy				
Monotherapy	39 (56.5%)	10(38.5%)	11(84.6%)	18(60%)
Combination therapy	30 (43.5%)	16(61.5%)	2(15.4%)	12(40%)
Other drugs used in patient management				
Antimicrobials	62(93.9%)	23(100%)	13(100%)	26(86.7%)
Nephrotoxic agents	45(68.2%)	16(69.6%)	10(76.9%)	19(63.3%)
Neurotoxic agents	37(56.1%)	13(56.5%)	6(46.2%)	18(60%)
Adherence to doctors' prescription				
Dosage	59(89.4%)	23(100%)	9(69.2%)	27(90%)
Frequency	43(65.2%)	18(78.3%)	4(30.8%)	21(70%)
Timeously	44(66.7%)	17(73.9%)	5(38.5%)	22(73.3%)
Duration	23(34.9%)	6(26.1%)	2(15.4%)	15(50%)

4.7.2 Comparison of compliance with policy and guidelines

4.7.2.1 Microscopy, culture and sensitivity testing

There was full compliance with microscopy culture and sensitivity testing in all three strata.

4.7.2.2 Processes followed

The lowest percentage of consents obtained prior to prescribing and administering Colistin was in neonates (40%) and the highest was in children (92.3%). Compliance with baseline renal function tests was relatively high in the three groups – 100%, 92.31% and 80% for children, adults and neonates respectively. Although facility management approved 62.3% of requests to apply for SAHPRA approval to use Colistin, only 43.5% of applications were generated by the hospital pharmacy, the highest of which was children (76.9%). Of all patients treated with Colistin, only 43.5% were approved by SAHPRA and the highest were in adults (61%).

4.7.2.3 Prescription compliance by doctors

Compliance by doctors regarding prescriptions was relatively high in the three groups investigated; 100%, 83.3% and 76.9% for children, neonates and adults respectively.

4.7.2.4 The manner in which treatment was administered

Contrary to the recommended Colistin dosing guidelines for South Africa, only 65.2% of adults received a loading dose. A loading dose is not recommended for neonates, but 3.3% of neonates were given a loading dose. Adherence to the frequency of administration was high in all three strata; 100%, 93.3% and 87% for children, neonates and adults respectively. All patients were monitored for signs of neuro- and nephrotoxicity (Table 4.8).

Table 4.8: Comparison of compliance with policy and guidelines

Variables	Totals	Adults	Children	Neonates
Processes followed				
Patient consent obtained	44(63.8%)	20(79.9%)	12(92.3%)	12(40%)
Baseline renal function done	61(88.4%)	24(92.3%)	13(100%)	24(80%)
Hospital management approval granted	43(62.3%)	19(73.1%)	10(76.9%)	16(53.3%)
SAHPRA application done	30(43.5%)	16(61.5%)	6(46.2%)	8(26.7%)
SAHPRA approval granted	30(43.5%)	16(61.5%)	6(46.2%)	8(26.7%)
Doctors' prescription compliance (Form H101)				
Name	58(84.1%)	20(76.9%)	13(100%)	25(83.3%)
Qualifications	58(84.1%)	20(76.9%)	13(100%)	25(83.3%)
Signature	58(84.1%)	20(76.9%)	13(100%)	25(83.3%)
Recommendation by specialist	55(79.7%)	20(76.9%)	13(100%)	23(76.7%)
The manner in which treatment was administered				
Loading dose given	16(24.2%)	15(65.2%)	0	1(3.3%)
Maintenance dose given	66(100%)	23(100%)	13(100%)	30(100%)
Administration route				
Intravenous	66(100%)	23(100%)	13(100%)	30(100%)
Inhalational	3(4.6%)	3(13.1%)	0	0
Frequency of administration				
Two times a day	22(33.3%)	20(87%)	0	2(6.7%)
Three times a day	44(66.7%)	3(13%)	13(100%)	28(93.3%)
Patient monitoring				
Follow up renal functions	69(100%)	26(100%)	13(100%)	30(100%)
Neurotoxicity monitoring	69(100%)	26(100%)	13(100%)	30(100%)

SAHPRA = South African Health Products Regulatory Authority

4.7.3 Comparison of the clinical outcomes

Of the 30 patients who experienced adverse drug reactions, adults account for the majority (57.7%), while children accounted for 46.2% and neonates for 30%. All the patients who reported adverse drug reactions had nephrotoxicity with similar trends by

age category. The data also shows that the incidence of nephrotoxicity (43.5%) was significantly higher than of neurotoxicity (5.8%).

Cure was achieved in 53.6% of the patients treated with Colistin. Of the three strata, neonates had the largest proportion of participants cured (80%). The largest proportion of participants who died were adults (73.1%) (Table 4.9).

Table 4.9: Comparison of clinical outcomes

Variables	Totals	Adults	Children	Neonates
Adverse drug reactions	30(43.5%)	15(57.7%)	6(46.2%)	9(30%)
Nephrotoxicity signs	30(43.5%)	15(57.7%)	6(46.2%)	9(30%)
Neurotoxicity signs	4(5.8%)	1(3.5%)	1(7.7%)	2(6.7%)
Cure	37(53.6%)	7(26.9%)	6(46.2%)	24(80%)
Mortality	32(46.4%)	19(73.1%)	7(53.9%)	6(20%)
Average length of stay (Days)		36 days	50days	47days

4.8 Predictors of mortality

A regression model analysis was used to predict mortality in the cohort. Variables used in the model were level of maturity, co-morbidities, illness duration prior to admission, and adherence to prescriptions. In comparison to neonates, both adults and children had higher odds of death. Adults were 26 times more likely to die during treatment with Colistin, while children were nine times more likely to die in the adjusted model. A similar trend was observed in the unadjusted model for magnitude and direction.

However, there was no significant difference in the odds for mortality by gender, co-morbidities, illness duration prior to admission and adherence to treatment (Table 4.10).

Table 4.10: Regression model showing predictors of mortality

Variables	Unadjusted model	Adjusted model
Maturity		
Neonates (ref)	1	1
Children	4.67 [1.14,19.12]*	8.56 [1.06,69.10]*
Adults	10.86 [3.12,37.72]***	25.54[2.73,238.65]**
Gender		
Female (ref)		
Male	1.42[0.54,3.72]	1.06[0.29,3.82]
Comorbidities		
No (ref)		
Yes	0.54[0.21,1.40]	3.21[0.49,21.16]
Illness duration before admission		
1-4	2.50[0.81,8.15]	1.27[0.28,5.77]
6-240	5.25[0.95,29.15]	0.98[0.11,8.58]
Adherence		
Poor (ref)		
Average	0.85 [0.28,2.59]	1.21[0.27,5.46]
Perfect	0.28[0.08,1.02]	0.45[0.09,2.24]

Exponentiated coefficients; 95% confidence intervals in brackets
* p < 0.05, ** p < 0.01, *** p < 0.001; ref = reference

CHAPTER 5: DISCUSSION AND INTERPRETATION OF RESULTS

5.1 Introduction

The emergence of reports on Colistin resistance has made compliance with legislation, regulations and treatment guidelines imperative in order to prevent its spread at the population level. It is also critical to preserve Colistin for future use, since it is the last resort in the treatment of MDR-GNB. Since its re-introduction as a result of carbapenem resistance, there has been a perception at the study site that paediatric patients have better clinical outcomes than adult patients treated with Colistin, but this has never been studied.

This study, therefore, assessed Colistin stewardship at the study site to evaluate the facility's contribution to preserving this important antibiotic. In addition, this study assessed the compliance of the hospital with legislation and guidelines governing the use of Colistin at the management level, the pharmacy level and patient treatment level. The study also compared utilisation of Colistin and clinical outcomes in adults and paediatric patients. There are fewer studies on Colistin in children and neonates than in adults globally and locally. There has also been a paucity of primary research on Colistin in the past ten years. Most of the available literature comprises reviews of published studies that were conducted over a decade ago. Worse, very few studies focused on compliance with legislation and guidelines on the use of Colistin. The current study focused on these critical gaps on the use of Colistin in a South African tertiary hospital. The results are discussed in this chapter.

5.2 Overall Colistin use at the study site

5.2.1 Study participants

There was a gradual annual increase in the number of neonates treated with Colistin in the study period. This may be due to colonization of the NICU with resistant micro-organisms, poor infection control practices or an increase in local experience in the treatment of healthcare associated infections as well as commonly isolated micro-organisms.

5.2.2 Compliance with obtaining culture and sensitivity results

It is a mandatory requirement that culture and sensitivity tests are conducted and the results submitted to SAHPRA for approval to use Colistin in any facility, however the current study showe that neonates were more likely than adults to be treated with Colistin without culture and sensitivity results. Urgency to initiate Colistin in neonates may have been influenced by the local experience of the clinicians. While the overall compliance with Colistin recommendations in this study (76.8%) is commendable, there is still room for improvement. The findings in this study differ greatly with regard to level of compliance reported on the use of Colistin in Gauteng, where culture and sensitivity results were obtained in 48.1% of adults and 93.8% of children (Majavie et al., 2021). Interestingly, the level of compliance with Colistin guidelines in the private sector hospitals in Gauteng, South Africa was 99% (Messina et al., 2018). A study by Giacobbe et al. (2020) in Italy showed that a high level of compliance (92%) can be achieved in public sector hospitals with better clinical governance. Further studies are needed to examine the contributing factors for the sub-optimal compliance in the public sector hospitals in South Africa.

Compliance with culture and sensitivity in paediatric patients – children and neonates combined – in the current study (75%) is comparable to the findings of Bal et al. (2018) in their Turkish hospital PICU study, where 78.8% compliance was found for paediatric patients. The findings from the current study regarding neonates showed a compliance level of 66.7%, with confirmed results for microscopy, culture and sensitivity, which was lower than the findings of another Turkish tertiary hospital study on neonates, where sensitivity tests were done on all participants prior to the initiation of treatment (Çağan et al., 2017). Only patients who had MDR-GNB infections and were not responsive to broad-spectrum antimicrobials were included in the Turkish tertiary hospital neonatal ICU study, although Colistin sensitivity was not specified (Çağan et al., 2017).

Compliance with confirmation of Colistin sensitivity prior to treatment varies from study to study. A comprehensive list of patients treated with Colistin in the current study was obtained from the hospital pharmacy. Therefore, the treatment of patients without confirmed sensitivity to Colistin revealed in this study implies non-compliance with SAHPRA regulations at the hospital pharmacy level. The conditions under which this happened were, however, not the focus of the current study. Non-compliance with

sensitivity testing is also indicative of some degree of irrational use of Colistin at the facility, and poses a risk of increasing resistance to this antibiotic.

5.2.3 Indications for treatment: Empirical, definitive or salvage therapy

Since Colistin is a Section 21 drug and a last-resort antibiotic, there should be proven sensitivity before it is used; therefore, technically, there should be no empirical use of Colistin. The overall use of Colistin as definitive therapy in this study was satisfactory (71%). The empirical use of Colistin was observed in 20.3% of the participants; of the three cohorts, empirical therapy was highest in neonates.

In a local study among adults by Messina et al., (2018), conducted in four Gauteng private hospitals, 60.8% of the participants received definitive therapy and 31.1% were treated empirically. Thus there was a slightly higher rate of empirical use of Colistin in that study than in the current study. An Italian study by Giacobbe et al. (2020) showed that 24% of adult participants were treated empirically, which is comparable to the findings of the current study. The empirical use of Colistin in children and neonates in that study was 7.7% and 26.7% respectively. The result of 24% empirical use is comparable to 26.3% empirical use found in a Turkish hospital PICU study by Karbuz et al. (2014). Another Turkish hospital PICU study by Bal et al. (2018) revealed a 21.2% empiric use of Colistin. The findings of the two Turkish hospitals' studies are comparable to the finding of 20.3% empirical use in the current study.

A cross-sectional survey covering 95 countries revealed that the empirical use of Colistin was preferred in high-income countries (80%) than in middle- and low-income countries (50%). The high usage in high-income countries was mainly based on the clinical severity of patients, and empirical use in middle- and low-income countries was associated with availability (Carrara et al., 2022). Any empirical use of Colistin locally is indicative of non-compliance with legislation and guidelines. The findings in this study and a host of other studies show a degree of irrational use of Colistin, i.e., the degree to which it is used empirically, which is unlikely to preserve this drug for future use and could open doors for Colistin resistance. Furthermore, the findings of a secondary analysis of adult studies conducted in Israel, Italy and Greece over five years on empirical treatment with Colistin revealed that *'… empirical antibiotic treatment was not associated with survival, rather there was a weak association with*

mortality' (Zak-Doron et al., 2018). The empirical use of Colistin should be discouraged locally and globally in order to preserve its future use.

5.2.4 Adherence to treatment guidelines

According to the recommended dosing guidelines for South Africa, critically ill adult patients must be given a loading dose of Colistin, however, a loading dose is not recommended for paediatric patients (Labuschagne et al., 2016). Adherence to prescribing and administering the loading dose in adults in this study was only 65%. This result is another demonstration of poor compliance with treatment guidelines in comparison to other studies. According to Plachouras et al. (2009), cited in Spapen et al. (2011), it can take up to three days for Colistin to reach the maximum mean steady-state concentration (Cmax); therefore, to achieve Cmax faster, a 9-12MU loading dose with a 4.5MU maintenance dose is recommended. Dalfino et al., in their 2012 study, cited in Messina et al. (2018), emphasise that the loading dose is significant for the rapid attainment of the desired therapeutic plasma concentration levels of Colistin.

Despite the published dosing guidelines for South Africa by Labuschagne et al. (2016), the level of compliance with prescribing the loading dose in adults in the current study was lower than that of other local and international studies. Majavie et al. (2021) reported a higher level of compliance of 81.5% for loading dose administered to adult patients in Gauteng Province in South Africa. Another study involving four Gauteng private hospitals revealed 93.5% adherence to the prescription of the loading dose in adults (Messina et al., 2018). In the Italian study by Giacobbe et al. (2020), in adults admitted to 20 hospitals, the loading dose was administered to 79% of the participants. Similarly, a higher level of compliance (71.8%) was reported in a Greek study, which focused on sparing carbapenems in one group and using it in another group in combination with Colistin (Makina et al., 2019). Compliance in administering the loading dose in these studies far exceeds the compliance in the current study. This therefore raises questions on the availability and awareness of the dosing guidelines by the attending doctors.

A cross-sectional survey covering 95 countries revealed that the loading dose was more commonly administered by frequent prescribers than by prescribers who used Colistin less frequently (Carrara et al., 2022). It is therefore plausible that the high turnover of doctors in the adult multi-disciplinary intensive care unit may lead to

insufficient experience with the use of Colistin at the study setting. Administration of the loading dose is not only essential in achieving therapeutic concentrations, but can also contribute to a reduction in the development of resistance (Visser Kift et al., 2014). Therefore, poor adherence to the administration of the loading dose in adults in the current study could potentially lead to the emergence of resistance to Colistin. In addition, it is unclear in this study if the suboptimal adherence to the dosing guidelines may be linked to the high mortality among adults in the study.

5.2.5 Monotherapy versus combination therapy

Although there is a strong theoretical foundation derived from *in vitro* studies to utilise Colistin in combination with other agents (Yahav et al., 2012), the recommendation to use Colistin as monotherapy or combination therapy is based on research findings (Zusman et al., 2017). The overall use of Colistin in combination with other agents in this study was 43.5%; 61.5% for adults, 15.4% for children and 40% for neonates. The use of Colistin in combination with other antibiotics in adults in the current study was found to be much lower than in many local and international studies. Many studies have also demonstrated a better cure rate when Colistin is used in combination with other antibiotics than as monotherapy. In a local study conducted in a Gauteng tertiary hospital, the most commonly co-administered antibiotic was cotrimoxazole, which was used in 63% of the adult patients (Majavie et al., 2021). A multicentre South African study conducted in Gauteng private hospitals by Messina et al. (2018) revealed a 98.5% use of Colistin in combination with other antibiotics, and yielded a 70.4% cure rate.

A Saudi Arabian case-controlled study by Garbati et al. (2016), which involved adult patients infected with carbapenem-resistant Enterobacteriaceae, showed that of the 55% of participants treated with Colistin, 68.8% received monotherapy and 31.2% received combination therapy, and the cure rate was 50%. A Greek tertiary hospital study by Makina et al., (2019), which was done in patients that were infected by carbapenem-resistant microorganisms, explored the sparing of carbapenems in one group of participants. In this group of participants, there was 95.2% use of Colistin in combination with other agents either than carbapenems which yielded a 73.8% cure rate.

Regarding children, this study showed 15.4% use of Colistin in combination with other antimicrobials and a cure rate of 46.2%. The most commonly co-administered antimicrobial, cotrimoxazole, was used in 93.8% of paediatric participants in a local Gauteng tertiary hospital study by Majavie et al. (2021). The Turkish study by Bal et al. (2018), which evaluated the safety and effectiveness of Colistin in the PICUs of two selected hospitals, revealed an 84.6% use of Colistin in combination with other antibiotics and a cure rate of 76%. Similarly, the Turkish PICU study by Karbuz et al. (2014) with 86.8% combination therapy use revealed a 65.5% cure rate.

As in the adult population, the use of Colistin in combination with other antimicrobials in children was much lower in the current study than in other local and international studies. Combination therapy was used in all neonates treated with Colistin in the study by Çağan et al. (2017), while in the current study, only 40% of neonates received combination therapy. However, the cure rates in both studies are comparable; 78.5% and 80% respectively. The higher rate of utilisation of combination therapy in previous studies yielded a higher cure rate, especially in adults and children.

Although it may seem that combination therapy should be recommended based on the findings of previous studies, none of these studies were based on randomised control trials. Carrara et al. (2022) demonstrated that the use of two-drug combination therapy was preferred over monotherapy and three-drug combination therapy mainly to improve clinical outcomes and to reduce the risk of resistance.

> *"The majority of prescribers seemed to recognize that the use of combination therapy for treating Carbapenem Resistant-Gram Negative Bacterial infections comes from 'expert' recommendations and that the supporting evidence is very poor and of low quality, being composed almost exclusively of observational and in vitro studies."* (Carrara et al., 2022).

5.2.6 Clinical outcomes of Colistin utilisation

The treatment outcomes evaluated in the current study were adverse reactions, cure and mortality.

5.2.6.1 Adverse drug reactions

The two known adverse reactions to Colistin are nephrotoxicity and neurotoxicity. Older studies showed higher rates of nephrotoxic adverse effects, at around 50%, while recent studies show nephrotoxicity rates ranging from 10% to 30%

(Labuschagne et al., 2016). The overall nephrotoxicity in the current study was 43.5%, with a higher rate among adults (57.7%). In a more recent South African multi-site adult study by Messina et al. (2018), the nephrotoxicity rate was negligible. Regarding children and neonates, the current study showed nephrotoxicity of 46.2% and 30% in children and neonates respectively, which is higher than in previous studies conducted on paediatric patients. The study by Karbuz et al. (2014) on children showed only 3.4% of nephrotoxicity. Similarly, the study done in a Turkish paediatric ICU revealed nephrotoxicity of 10.5% (Bal et al., 2018). Nephrotoxicity was seen in 4.6% of neonates in a Turkish study done by Çağan et al. (2017).

Nephrotoxicity has been associated with concurrent use of Colistin and other nephrotoxic agents. The concurrent use of nephrotoxic agents such as aminoglycosides, e.g. gentamycin and amikacin, and a glycopeptide (vancomycin) across all three cohorts in this study was 68.2%. The proportional distribution in the use of nephrotoxic agents was 69.6%, 76.9% and 63.3% for adults, children and neonates respectively. This may have contributed to the higher degree of nephrotoxicity seen in the current study than in other studies.

In the current study, neurotoxicity was seen in 5.8% of the participants; 3.5%, 7.7% and 6.7% for adults, children and neonates respectively. No signs of neurotoxicity were evident in the Turkish study on children by Karbuz et al. (2014). Unlike in many studies, neurotoxicity was higher (9.2%) than nephrotoxicity in the study by Çağan et al. (2017) on neonates admitted to two tertiary hospitals in Turkey. However, another Turkish study on paediatric ICU patients showed no incidents of neurotoxicity (Bal et al., 2018). As in many studies in the literature, the rate of neurotoxicity in the current study was lower than that of nephrotoxicity.

5.2.6.2 Cure and mortality rates

The overall cure rate for the current study was 53.6%, with a distribution of 26.9%, 46.2% and 80% for adults, children and neonates respectively. The cure rate in most other studies on Colistin – not all – is well above 70%, with mortality around 30%. This was confirmed by a review of studies on adult participants conducted over fifteen years by Spapen et al. (2011), which revealed that the global cure rate resulting from treatment with Colistin was approximately 70%. In a large cohort study conducted by Falagas et al. (2010) on adults, a cure rate of 79.1% was achieved. A similar trend of

higher cure rates of 70.4% and 73.8% were reported in Gauteng, South Africa by Messina et al. (2018) and in Greece by Makina et al. (2019), respectively.

Some recent studies have, however, revealed a mortality rate higher than 30% among adults treated with Colistin. This was shown in a South African study by Majavie et al. (2021) in which the total mortality rate was 41.9%. A similar trend of high mortality rates have been reported internationally; 50% by Garbati et al. (2016) in Saudi Arabia, and 40.6% by Benatter et al. (2016) in Israel. The findings of these three studies are comparable to the current study's findings, which reveal an overall mortality rate of 46.4%. This implies that the mortality rate of Colistin utilisation in adults may be slightly increasing over the years, which could be disastrous to clinical medicine if alternative treatment is not found.

Concerning paediatric participants, the current study showed a 46.2% cure rate in children, which is lower than that of other studies conducted on paediatric patients. The cure rate reported in Turkey by Karbuz et al. (2014) was 73.7% and by Bal et al. (2018) was 76%, both higher than in the present study. Of note is that the cure rate among neonates (80%) in the current study is comparable to reports emerging internationally. The cure rate in a Turkish study among neonates by Çağan et al. (2017) was 78.5%. Çağan et al. (2017) further asserted that 'Colistin was found to be effective and safe for treatment of MDR-GNB infections in pre-terms and infants with very low birth weight.'

5.2.6.3 Predictor of mortality

Despite better compliance with policy and procedures and better adherence to treatment guidelines in adults than in paediatric patients, the adult patients had the poorest clinical outcomes than others in the current study. It should be noted that adult patients had higher rates of adverse effects and mortality rates than those of neonates and children. Although maturity was found to be a significant predictor of mortality in this study, the link is unclear. Further studies are needed to examine the contributing factors for mortality in the adult population treated with Colistin in the region. Çağan et al. (2017), in their study on neonates, also concluded that "*Colistin was effective and safe for treatment of MDR-GNB infections in pre-terms and infants with very low birth weight"*. An Israel adult study by Benatter et al., (2016) also found in their large cohort

(529) on the effectiveness of high doses of Colistin that advanced age was independently associated with mortality.

5.3 Limitations of the study

While this study is the first of its kind in Free State Province and highlights important findings in the use of Colistin in a tertiary hospital, its limitations cannot be ignored. This is a single centre study with small samples of adults, children and neonates. Therefore the findings largely reflect the practice of antimicrobial use in the study setting rather than the broader use of Colistin and compliance with regulations in all public sector hospitals in the region or country. Notwithstanding the identified limitations, this study has opened doors for other studies on antimicrobial stewardship in the hospital, Free State Province and South Africa.

5.4 Conclusion

This study found a suboptimal level of compliance with policy and guideline recommendations on the use of Colistin in a South African public sector tertiary hospital. This compliance gap reflects on the practice of the attending clinicians, pharmacists, and clinical governance in relation to antibiotic stewardship at the hospital setting. In addition, there were significant variations in the level of compliance by age categories, with a lower level of compliance in neonates than in children and adults. Similarly, a suboptimal level of compliance with the dosing recommendations of loading dose for adults was observed in the study setting. However, the odds for mortality by gender, co-morbidities, illness duration prior to admission and adherence to treatment were found to be insignificant, and age was the only predictor of mortality found in the study. Among other findings, a higher rate of nephrotoxicity was observed, largely owing to the concomitant use of other nephrotoxic drugs in combination with Colistin. Indeed, the findings of the current study highlight the need for improved clinical governance on antibiotic stewardship and monitoring of the use of Colistin across all categories of patients in the hospital. Future studies should examine the contributing factors for suboptimal compliance with evidence-based recommendations on the use of Colistin and other antimicrobials, in this hospital and other public sector hospitals in the country.

5.5 Recommendations

Policymakers

Given the high cure rate in neonates - despite poor compliance to treatment guidelines and policies - and to mitigate the risk associated with the prolonged procedure that has to be followed prior to the delivery and administration of the drug to the relevant patient in the intensive care unit, it is highly recommended that the guidelines relating to the availability of the drug in the facility be reviewed. This may reduce the degree of empirical use of Colistin in neonates and will promote early treatment intervention.

Facility clinical governace structures

In light of inadequate adherence to policy and treatment guidelines regarding Colistin utilisation in this study, the degree of empirical use of Colistin and the fact that the pharmacy is dispensing the antibiotic without SAHPRA approval, there is a great need for antimicrobial stewardship at the facility to preserve this drug. There is a need for an Antimicrobial Stewardship Committee that will establish an antimicrobial stewardship programme to promote compliance with policy and guidelines, carry out antimicrobial resistance surveillance, monitor performance and identify training needs in the facility.

Given the high degree of septicaemia secondary to multi-drug resistant-gram negative bacteria, especially in the NICU, as demonstrated in this study, further investigation on the cause of the high infection rate in the NICU is recommended.

The high mortality rate observed in the adult population in this study in comparison to other studies, warrants further investigation.

The results of this study provide a reflection of the baseline performance of the facility regarding Colistin utilisation and the clinical outcomes thereof. A post-intervention reporting tool should be designed whereby clinicians proactively report on the utilisation and treatment outcome of patients. This would promote effective clinical governance on the use of Colistin in the hospital.

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Annexures

A: Research instrument

A) PATIENT DEMOGRAPHICS			
Age	Gender	Ward	Hospital ID
B) DIAGNOSIS			
C) COMORBIDITIES			
D) OTHER DRUGS ADMINISTERED			
antimicrobials	Nephrotoxic agents	Neurotoxic agents	
E) CULTURE AND SENSITIVITY PROFILE			
Sensitivity to Colistin only	Sensitivity to other antimicrobials		
F) INDICATION FOR TREATMENT			
Definitive treatment	Salvage therapy	Empirical treatment	
G) PRESCRIBING DOCTORS DETAILS			
Name (Y/N)	Qualifications(Y/N)	Signature (Y/N)	Recommendation by a specialist (Y/N)
H) PROCESS FOLLOWED			
Patient Consent obtained (Y/N)	Baseline renal functions test done (Y/N)	SAHPRA application (Y/N)	Hospital management approval granted(Y/N)
I) PATIENT MANAGEMENT			
Loading dose administered (Y/N)	Maintenance Dose administered	Administration route (Inhalational or IV)	Frequency of administration
Follow-up renal function tests (Y/N)	Monitoring of signs of neurotoxicity (Y/N)	Appropriate Treatment de-escalation (Y/N)	SAHPRA approval granted (Y/N)
J) ADVERSE DRUG REACTION			
Elevated creatinine	Neurotoxicity signs		
J) ADJUSTMENT OF MAINTENANCE DOSE IN RESPONSE TO ADVERSE EFFECTS (Y/N)			
K) DE-ESCALATION FOLLOWING CULTURE AND SENSITIVITY RESULTS WHILE ON TREATMENT (Y/N)			
L) ANTIMICROBIALS WERE ADMINISTERED AS PRESCRIBED			
Dosage (Y/N)	Frequency (Y/N)	On-time (Y/N)	Duration (Y/N)
M) DURATION OF TREATMENT			
NO. Days			
N) TREATMENT OUTCOME			
Adverse reactions	Cure/response to treatment	Mortality	

Annexure B: Ethical Clearance by the UFH HREC

University of Fort Hare
Together in Excellence

HEALTH RESEARCH ETHICS COMMITTEE

P.O Box 1054
East London 5200
Tel: +27 (0) 43 704 7368
E-mail: dgoon@ufh.ac.za

ETHICAL CLEARANCE CERTIFICATE
REC-100118-054

Certificate Reference Number:	**Ref # 2020=12=08=MatshedisoG**
Project title:	**Colistin utilization and clinical outcomes at a public hospital in Bloemfontein, South Africa**
Nature of Project	Masters of Public Health
Principal Researcher:	Matshediso G
Student Number:	201928105
Supervisor:	Dr OV Adeniyi

On behalf of the University of Fort Hare Health Research Ethics Committee (HREC), I hereby give ethical approval in respect of the undertakings contained in the above-mentioned project and research instruments(s). Should any other instruments be used, these require separate authorization. The Researcher may therefore commence with the research as from the date of this certificate, using the reference number indicated above.

Please note that the HREC must be informed immediately of

- Any material change in the conditions or undertakings mentioned in the document
- Any material breaches of ethical undertakings or events that impact upon the ethical conduct of the research

The Principal Researcher must report to the HREC in the prescribed format, where applicable, annually, and at the end of the project, in respect of ethical compliance.

University of Fort Hare
HEALTH RESEARCH ETHICS COMMITTEE

P.O Box 1054
East London 5200
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E-mail: dgoon@ufh.ac.za

The HREC retains the right to

- Withdraw or amend this Ethical Clearance Certificate if
  - Any unethical principles or practices are revealed or suspected
  - relevant information has been withheld or misrepresented
  - regulatory changes of whatsoever nature so require
  - the conditions contained in the Certificate have not been adhered to

- Request access to any information or data at any time during the course or after completion of the project.
- In addition to the need to comply with the highest level of ethical conduct principal investigators must report back annually as an evaluation and monitoring mechanism on the progress being made by the research. Such a report must be sent to HREC monitoring@ufh.ac.za.

The Ethics Committee wishes you well in your research endeavours.

Yours sincerely

Professor DT Goon
Chairperson: HREC
15 December 2020

Annexure C: Permission by the Head of the Free State Department of Health

health
Department of Health
FREE STATE PROVINCE

10 March 2021

Dr G Matshediso
Dept. of Public Health
UFH

Dear Dr G Matshediso
Subject: Colistin utilization and clinical outcomes at a public hospital in Bloemfontein, South Africa.

- Please ensure that you read the whole document. Permission is hereby granted for the above – mentioned research on the following conditions:
- Participation in the study must be voluntary
- A written consent by each participant must be obtained.
- Serious Adverse events to be reported to the Free State department of health and/ or termination of the study
- Ascertain that your data collection exercise neither interferes with the day to day running of **Pelonomi Hospital** nor the performance of duties by the respondents or health care workers.
- Confidentiality of information will be ensured and please do not obtain information regarding the identity of the participants.
- **Research results and a complete report should be made available to the Free State Department of Health on completion of the study (a hard copy plus a soft copy).**
- Progress report must be presented not later than one year after approval of the project to the Ethics Committee of the University of Fort Hare and to Free State Department of Health.
- Any amendments, extension or other modifications to the protocol or investigators must be submitted to the Ethics Committee of the University of Fort Hare and to Free State Department of Health.
- **Conditions stated in your Ethical Approval letter should be adhered to and a final copy of the Ethics Clearance Certificate should be submitted to [redacted] before you commence with the study**
- No financial liability will be placed on the Free State Department of Health
- **Please discuss your study with Institution Manager on commencement for logistical arrangements see 2nd page for contact details.**
- Department of Health to be fully indemnified from any harm that participants and staff experiences in the study
- **As part of feedback you will be required to present your study findings/results at the Free State Provincial health research day**

I trust you find the above in order.

Kind Regards

Dr D Motau
HEAD: HEALTH
Date: 12/03/2021

Head : Health
PO Box 227, Bloemfotein, 9300
4th Floor, Executive Suite, Bophelo House, cnr Maitland and, Harvey Road, Bloemfotein
Tel: (051) 408 1646 Fax: (051) 408 1558 e-mail: [redacted]chikobvup@fshealth.gov.za
www.fs.gov.za

Annexure D: Permission letter from the study site

pelonomi hospital
Department of Health
Pelonomi Tertiary Hospital
FREE STATE PROVINCE

DATE:	25 March 2021		ENQUIRIES
TO:	Dr GP Matshediso Chief Medical Officer MatsehdiGP@fshealth.gov.za Bloemfontein 9301	FROM:	Dr U Sirsawy Acting: Head of Clinical Services usamasirsawy@yahoo.com 051 405 1936 Bloemfontein 9301

SUBJECT: Colistin utilization and clinical outcomes at a public hospital in Bloemfontein, South Africa.

Pelonomi Tertiary Hospital **grants you permission** to conduct researches/studies and the following criteria must be met.

- [x] That you obtain ethical clearance from the human research ethics committee of the relevant university and approval by the Head of Health of the Free State.
- [x] That the Hospital incurs no cost in the course of your research.
- [x] That access to the staff and patients at the Pelonomi Hospital will not interrupt the daily provision of services.
- [x] That prior to conducting the research you will liaise with the supervisors of the relevant sections and introduce yourself with permission letter and to make arrangements with them in a manner that is convenient to the sections.

Yours Sincerely

PELONOMI TERTIARY HOSPITAL
25 -03- 2021
PRIVATE BAG X20581
BLOEMFONTEIN 9300

Dr U Sirsawy
Acting: Head of Clinical Services
Pelonomi Tertiary Hospital