INVESTIGATING THE EXTENT AND TREATMENT OF INFECTIONS CAUSED BY ESKAPE PATHOGENS IN AN INTENSIVE CARE UNIT

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A Dissertation submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in fulfilment of the requirements for the degree of Master of Pharmacy

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DECLARATION

I, Bianka Kelly (Naude), declare that this dissertation is my own, unaided work. It is being submitted for the Degree of Master of Pharmacy at the University of Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.

Signature	Date
	20/05/2025

DEDICATION

I dedicate this research to my supportive husband and family, without all of you this would have never been possible.

ABSTRACT

Background: The ESKAPE acronym represents six multi-drug-resistant bacterial pathogens that account for a large proportion of healthcare-associated infections. Antimicrobial resistance surveillance provides information about the extent and prevalence of antimicrobial resistance. This information can be used to provide guidance on appropriate antimicrobial treatment. Rectal swab screening is another intervention that may assist in choosing empiric antimicrobial treatment.

Aim: The aim of this study was to investigate the extent and treatment of infections caused by ESKAPE pathogens in an intensive care unit (ICU) at a public hospital in Johannesburg, and to determine whether rectal swab screening for bacterial colonization leads to earlier initiation of appropriate antimicrobial therapy.

Methods: A cross-sectional, retrospective, records review was conducted at the ICU at Charlotte Maxeke Johannesburg Academic Hospital. The study involved records review of all patients admitted to the ICU from September 2021 to September 2022. This retrospective study used National Health Laboratory Service data.

Results: Of the 690 patients admitted to the ICU during the study period, one or more of the ESKAPE pathogens were isolated from 132 patients. The most common sample type collected from patients was blood cultures (33.9%, n = 259) with the most frequent ESKAPE pathogen being *Klebsiella pneumoniae* (n=38) followed by *Acinetobacter baumannii* (n=29) and *Escherichia coli* (n=12). Only 48.5% of patients received appropriate empiric antimicrobial therapy. Rectal swab screening was performed in 91 (69%) of the patients.

Conclusion: The most common specimen type was blood cultures (44.9%), and the most frequently isolated ESKAPE pathogen from blood cultures was *K. pneumoniae* followed by *A. baumannii* and *E. coli*. These findings are similar to findings from studies in other lower-middle income countries. There was a lack of other studies on the ESKAPE pathogens found in the other specimen types, indicating a need for future studies on the prevalence and resistance of ESKAPE pathogens across the various specimen types. Commonly prescribed antimicrobial treatments included piperacillin-tazobactam, amoxicillin-clavulanic acid and carbapenems.

The findings revealed a higher usage of carbapenems than in other studies, which could be accounted for by the high prevalence of ESBL-producing Enterobacterales. The rectal swab screening data was sparse, and a longer more inclusive study would be valuable to draw more meaningful conclusions on the impact of screening using rectal swabs.

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TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF ABBREVIATIONS

AMR	Antimicrobial resistance
CAP	Community-acquired pneumonia
CDC	Centers for Disease Control and Prevention
CPE	Carbapenemase-Producing Enterobacterales
CR	Carbapenem-resistant
CRE	Carbapenem-resistant Enterobacterales
CRKP	Carbapenem-resistant *Klebsiella pneumoniae*
DAAT	Delayed appropriate antimicrobial therapy
DNA	Deoxyribonucleic acid
ESBL	Extended-spectrum β-lactamase
ESKAPE	*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa*, and *Enterobacter* species
hVISA	Heteroresistant (heterogenous) vancomycin-intermediate *Staphylococcus aureus*
ICU	Intensive care unit
KPC	*Klebsiella pneumoniae* carbapenemase
MDR	Multidrug-resistant
MRSA	Methicillin-resistant *Staphylococcus aureus*
NHLS	National Health Laboratory Service
PCR	Polymerase chain reaction
PDR	Pan-drug-resistant
Piptaz	Piperacillin-tazobactam
SSI	Skin or soft tissue infection
Sub-MIC	Subminimal inhibitory concentrations
VISA	Vancomycin-intermediate *Staphylococcus aureus*
VRE	Vancomycin-resistant *Enterococcus faecium*
VRSA	Vancomycin-resistant *Staphylococcus aureus*
WHO	World Health Organisation
XDR	Extensively drug-resistant

DISSERTATION STRUCTURE

Chapter 1: serves as an introduction to the dissertation and provides a brief background on the ESKAPE pathogens, antimicrobial resistance, and the importance of antimicrobial resistance screening.

Chapter 2: provides a literature review of the infections and resistance patterns of the ESKAPE pathogens. It also describes antimicrobial resistance, DAAT and rectal swab screening.

Chapter 3: discusses the methodology of the study. It describes the study design, study site, study period, data collection, statistical analysis, and ethical considerations.

Chapter 4: presents the results of the data collected.

Chapter 5: discusses the study findings.

Chapter 6: highlights the key findings and conclusions.

CHAPTER 1
INTRODUCTION

1.1 Background

The ESKAPE acronym represents six bacterial nosocomial pathogens that show rapidly growing multi-drug-resistant (MDR) properties: *Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa*, and *Enterobacter* species (Pendleton et al., 2013, Najafi, 2016, Ramsamy et al., 2018, de Oliveira et al., 2020, Ma et al., 2020, Nasser et al., 2020, Mancuso et al., 2021, Pandey et al., 2021). Aptly named, the acronym also refers to the ability of these bacterial pathogens to "escape" being killed by antibiotics due to their resistance mechanisms (Ramsamy et al., 2018, Mulani et al., 2019, Ma et al., 2020).

Patients who present with infections caused by the ESKAPE pathogens have poorer clinical outcomes, higher mortality rates, longer duration of hospital stay, and a delay in implementing appropriate antimicrobial therapy (Ramsamy et al., 2018, Bonine et al., 2019, Benkő et al., 2020, Ma et al., 2020). Delayed appropriate antimicrobial therapy (DAAT) can be used as a predictor for poor clinical outcomes (Pogue et al., 2015, Bonine et al., 2019). Strategies aimed at reducing DAAT lead to better clinical outcomes in patients with infections caused by the ESKAPE pathogens (Pogue et al., 2015).

The ESKAPE pathogens account for the majority of healthcare-associated infections and display alarmingly high rates of antimicrobial resistance (Ismail et al., 2019, Mulani et al., 2019). A key factor in understanding the extent of antimicrobial resistance within the healthcare system, as purposed by the Antimicrobial Resistance National Strategy Framework of South Africa, is antimicrobial resistance surveillance (Ismail et al., 2019). These reports assist in choosing the most appropriate antimicrobial therapy. The South African Department of Health released a surveillance report in 2018 describing antimicrobial consumption and resistance during the period of 2012-2017 (South Africa Department of Health, 2018b). Data from the National Health Laboratory Service (NHLS) was used to determine the burden of bacteraemia due to infections with the ESKAPE pathogens in the public health sector (South Africa Department of Health, 2018b). In 2017, a total of 284 669 blood samples were submitted to the NHLS. Of the samples, 24% were positive for microorganisms with the ESKAPE

pathogens accounting for 33% of the positive blood samples, and 8% of the total number of submitted blood samples (South Africa Department of Health, 2018b). Collaboration with laboratories servicing the private sector revealed that the most common isolate obtained from blood samples in both sectors was *K. pneumoniae*, followed by *E. coli*, *P. aeruginosa* and *A. baumannii* (South Africa Department of Health, 2018b). Determining the occurrence and resistance trends of the ESKAPE pathogens may assist in making an informed decisions for effective antibiotic treatment for patients and facilitate in reducing DAAT (Pogue et al., 2015, Singh-Moodley et al., 2018, Bonine et al., 2019, Benkő et al., 2020).

Antimicrobial stewardship (AMS) is a coordinated systematic programme designed to ensure optimisation of antimicrobial use to limit the development of antimicrobial resistance, while also improving clinical outcomes (South Africa Department of Health, 2018a). Antimicrobial stewardship programmes help to improve patient safety and patient care through reduced treatment failures, increased infection cure rates, and appropriate prescribing for both prophylaxis and treatment of infections (Centers for Disease Control and Prevention, 2014).

Screening of patients on admission for bacterial colonization using rectal swabs, is an intervention that may be used to facilitate appropriate empiric antimicrobial treatment and limit the spread of antimicrobial resistant pathogens (Foschi et al., 2019). Early identification of antimicrobial resistant bacteria, such as the ESKAPE pathogens, allow for isolation of the patients to a separate ward or ICU, away from other patients, to prevent spread and facilitate earlier initiation of appropriate antimicrobial therapy (Otter et al., 2016). Polymerase chain reaction (PCR) based tests can be directly applied to rectal swabs, and these tests have a faster turnaround time than culture-based tests (Otter *et al.*, 2016, Foschi *et al.*, 2019).

The intensive care unit (ICU) at the study site implemented a screening system, whereby rectal swabs are taken upon admission of patients to the ICU, with the hope of improving clinical outcomes by assisting in making earlier informed decisions regarding appropriate antimicrobial therapy.

1.2 Motivation for the study

Previous surveillance reports demonstrate that infections caused by the ESKAPE pathogens are increasing within South Africa (Singh-Moodley et al., 2018, South Africa Department of Health, 2018b, Ismail et al., 2019, South Africa Department of Health, 2021). Determining the

occurrence and resistance trends of the ESKAPE pathogens can lead to reduced DAAT, improved clinical outcomes, and cost savings (Pogue et al., 2015, Singh-Moodley et al., 2018, Bonine et al., 2019). There is no current surveillance data for the resistance patterns of the ESKAPE pathogens in the Charlotte Maxeke Academic Hospital ICU. Investigating the nosocomial infections caused by the ESKAPE pathogens in the ICU may lead to better decision making regarding the empiric treatment given to patients presenting with infections in the ICU at Charlotte Maxeke Academic Hospital.

The ICU implemented a rectal swab screening system for patients admitted to the ICU. It has yet to be determined whether the pre-admission rectal swabs led to better management of patients who were colonised with ESKAPE pathogens. Thus, this study sought to establish whether pre-admission rectal swabs assisted in reducing DAAT. In doing so, recommendations could be established regarding the utility of a pre-admission rectal swab screening protocol in the ICU setting.

1.3 Aim

The study aimed to investigate the extent and treatment of infections caused by all ESKAPE pathogens in an intensive care unit (ICU) at Charlotte Maxeke Johannesburg Academic Hospital in South Africa for the study period September 2021 to September 2022, and to determine whether screening for bacterial colonization using rectal swabs leads to a decrease in DAAT.

1.4 Objectives

The following objectives were outlined to achieve the study aim:

1. To investigate the proportion of patients in the ICU at Charlotte Maxeke Academic Hospital with infections and the proportion of infections caused by the ESKAPE pathogens during the study period (September 2021 – 2022) as identified from all specimens cultured from patients over this period.
2. To investigate the resistance patterns of the ESKAPE pathogens isolated from specimens from patients in the ICU over the study period (September 2021 – 2022).
3. To describe the empiric and definitive treatment prescribed for infections caused by the ESKAPE pathogens and to establish whether the antimicrobial treatment was appropriate based on the resistance patterns of the ESKAPE pathogens.

4. To investigate the effectiveness of pre-admission rectal swabs in the management of patients with prior colonisation with the screened for ESKAPE pathogens by comparing length of stay for patients with and without a pre-admission rectal swab taken during the study period (September 2021-2022).

CHAPTER 2
LITERATURE REVIEW

2.1 Introduction

This chapter reviews the ESKAPE pathogens, and the infections caused by these pathogens. The chapter also describes antimicrobial resistance, the importance of antimicrobial resistance screening, DAAT and the use of rectal swabbing as a screening tool.

2.2 ESKAPE pathogens and their role in causing infection

The ESKAPE pathogens are a group of multi-drug-resistant bacteria responsible for causing life-threatening infections and are a global threat to human health (Benkő et al., 2020, de Oliveira et al., 2020). The ability of the ESKAPE pathogens to acquire and disseminate antimicrobial resistance genes has increased the rates of treatment failure and the burden of disease (Benkő et al., 2020, de Oliveira et al., 2020).

Enterococci are Gram-positive, facultative anaerobic cocci which form part of the normal enteric microbiota (Lebreton et al., 2014, Navidinia, 2016, Riedel et al., 2019). There are more than 50 enterococcal species with only a few causing diseases in humans, most notably *Enterococcus faecium* and *Enterococcus faecalis* (Najafi, 2016, Riedel et al., 2019, Mancuso et al., 2021). The pathogenesis of enterococci remains poorly understood. Several factors that influence the virulence have been identified; however, none have been established as the major cause of enterococcal infections (Riedel et al., 2019). *Enterococcus faecalis* is the more pathogenic species; however, *E. faecium* shows greater resistance to many antimicrobial agents (Navidinia, 2016, Mancuso et al., 2021).

Staphylococci are Gram-positive, aerobic cocci found within the normal human microbiota of the skin, respiratory tract, and gastrointestinal tract (Najafi, 2016, Arumugam et al., 2017, Riedel et al., 2019, Mancuso et al., 2021). *Staphylococcus aureus* is commonly encountered on the skin, especially the moist areas, such as the nostrils and axillae (Pendleton et al., 2013, Navidinia, 2016, Riedel et al., 2019). Due to its location, *S. aureus* is a prominent cause of skin and soft tissue infections and can result in acute or chronic infections due to the micro-organism's ability to form a biofilm (Pendleton et al., 2013, Najafi, 2016, Mancuso et al., 2021). *Staphylococcus aureus* can cause infections ranging from mild to life-threatening,

(Najafi, 2016, Mancuso et al., 2021), is highly contagious and can cause chronic infections (Pendleton et al., 2013, Mancuso et al., 2021). The pathogenicity of *S. aureus* is due to the combined effect of toxins and extracellular factors, together with the invasive nature of the given strain (Pendleton et al., 2013, Mancuso et al., 2021).

Klebsiella pneumoniae is a facultative anaerobe that forms part of a group of Gram-negative rod-shaped bacteria known collectively as Enterobacterales (Navidinia, 2016, Kumar and Park, 2018, Riedel et al., 2019, Mancuso et al., 2021). *Klebsiella pneumoniae* can be found in low numbers as part of the microbiota of the mouth, skin, and intestines (Pendleton et al., 2013, Najafi, 2016), and is known to cause community and healthcare-associated pneumonia, which can ultimately result in necrosis, inflammation, and haemorrhage of the lung tissue (Najafi, 2016, Riedel et al., 2019). Person-to-person contact is required for the spread of infection (Mancuso et al., 2021). *Klebsiella pneumoniae* is capable of invasive infections owing to its thick capsule and fimbrial adhesins, which acts as an antiphagocytic factor (Pendleton et al., 2013).

Another notable bacterium from the Enterobacterales family is *Escherichia coli* (Pendleton et al., 2013, Riedel et al., 2019) which, despite being part of the normal human intestinal flora, can have several pathogenic strains (Pendleton et al., 2013, Najafi, 2016, Riedel et al., 2019). *Escherichia coli* is commonly involved in urinary tract infections, diarrhoeal disease, sepsis, and meningitis (Najafi, 2016; Riedel et al., 2019). These pathogenic strains of *E. coli* make use of adhesion factors and toxins to enable colonization and lead to infection (Pendleton et al., 2013).

Acinetobacter species are aerobic, Gram-negative coccobacilli, commonly encountered in water and soil (Mortensen and Skaar, 2012, Najafi, 2016, Riedel et al., 2019, Mancuso et al., 2021). *Acinetobacter baumannii* is the most prevalent species isolated in clinical laboratories (Pendleton et al., 2013, Mancuso et al., 2021). It is an opportunistic bacterium, often causing nosocomial infections, including wound infections, respiratory and urinary tract infections, (Navidinia, 2016, Riedel et al., 2019). The pathogenicity of these strains relates to the ability of *Acinetobacter* spp. to form biofilms on human cells and surfaces (Pendleton et al., 2013).

Pseudomonas aeruginosa is an opportunistic Gram-negative, rod-shaped, aerobic-facultatively-anaerobic bacterium, commonly found in moist environments (Najafi, 2016,

Riedel et al., 2019, Mancuso et al., 2021). It does not form part of the normal human microbiota; however, it can colonize a variety of body sites (Navidinia, 2016, Riedel et al., 2019). Biofilm formation by this micro-organism contributes to the high virulence of *P. aeruginosa* (Najafi, 2016, Riedel et al., 2019).

Enterobacter species are also part of the Gram-negative Enterobacterales family, typically involved in infections of the urinary and respiratory tracts, and, in some instances, bloodstream infections (Najafi, 2016, Riedel et al., 2019, Mancuso et al., 2021). The two most prominent species causing infections in humans are *Enterobacter cloacae* and *Enterobacter aerogenes* (reclassified as *Klebsiella aerogenes*) (Najafi, 2016, Mancuso et al., 2021).

2.3 The ESKAPE pathogens in the ICU

Intensive care unit (ICU) acquired nosocomial infections have been increasing in recent years with an escalating prevalence of infections caused by ESKAPE pathogens and, more concerningly, MDR ESKAPE pathogens (Trifi et al., 2018, Bereanu et al., 2024, Maraki et al., 2025).

Studies or reviews conducted on the prevalence of ESKAPE pathogens are spread across different countries (European Centre for Disease Prevention and Control, 2019b, Saharman et al., 2021, Bereanu et al., 2024, Maraki et al., 2025). Notably, the studies found that lower-middle income countries have a higher proportion of infections caused by *A. baumannii, K. pneumoniae* and *P. aeruginosa*, than higher income countries (Saharman et al., 2021). There is a higher proportion of Gram-negative ESKAPE pathogens isolated in lower-middle income countries, whereas in the European setting there is a higher proportion of Gram-positive ESKAPE pathogens (Scholte et al., 2015, European Centre for Disease Prevention and Control, 2019a, Saharman et al., 2021).

A scoping review by Saharman *et al* (2021) on the prevalence of infections and antimicrobial resistance in ICUs in lower-middle income countries, aimed to look at ICU-acquired infections across a 13-year study period. The most common nosocomial pathogens in these ICUs were *A. baumannii* (24%), *P. aeruginosa* (16%) and *K. pneumoniae* (15%) (Saharman et al., 2021). Vancomycin-resistance was found in > 50% of the *Enterococcus* isolates in Vietnam and methicillin-resistance was identified in > 50% of the *S. aureus* isolates in most of the lower-middle income countries (Saharman et al., 2021).

In contrast to the findings of the study in lower-middle income countries, some reports were from higher income countries in Europe (Scholte et al., 2015, European Centre for Disease Prevention and Control, 2019a, Maraki et al., 2025). A retrospective analysis was conducted by Scholte *et al* (2015) on the bacterial isolates obtained in endotracheal aspirates in the ICUs of two Dutch Hospitals in 2007 and 2012. Of the 1147 identified isolates, *P. aeruginosa* was the most frequently identified, followed by *S. aureus*, *E. coli* and *Klebsiella* spp. (Scholte et al., 2015). A contrast can be seen between the lower-middle income countries, where *A. baumannii* is more commonly isolated than the isolates from the higher income countries.

A surveillance report compiled by the European CDC assessed the surveillance data for nosocomial infections in ICUs in Europe for 2017 (European Centre for Disease Prevention and Control, 2019a). The most common causative pathogens in ICU-acquired pneumonia were *P. aeruginosa*, followed by *S. aureus*, *Klebsiella* spp., and *E. coli* (European Centre for Disease Prevention and Control, 2019a). The most common causative pathogens in septicaemia ere coagulase-negative staphylococci, followed by *Enterococcus* spp., *Klebsiella* spp., and *S. aureus* (European Centre for Disease Prevention and Control, 2019a). The most common causative pathogens in ICU-acquired urinary tract infections were *E. coli*, followed by *Enterococcus* spp., *Klebsiella* spp., and *P. aeruginosa* (European Centre for Disease Prevention and Control, 2019a).

A study conducted at the ICU at a Greek University Hospital across a ten-year period, found that the most prevalent ESKAPE microorganisms were *A. baumannii*, *P. aeruginosa* and *K. pneumoniae* (Maraki et al., 2025). This study also found a high prevalence of carbapenem-resistant *A. baumannii* (96.7%) and *K. pneumoniae* (57.4%) (Maraki et al., 2025).

2.4 Empiric antimicrobial therapy

Infections in the ICU are associated with increased mortality and costs (Scholte et al., 2015, Trifi et al., 2018). The administration of early and appropriate antimicrobial therapy reduces mortality and may have an impact on reducing unnecessary side effects, ICU costs and the development of antimicrobial resistance (Calbo et al., 2013, Scholte et al., 2015). The selection of empirical antimicrobial therapy should be based on various factors, including the suspected pathogen, local resistance patterns, local protocols, and antimicrobial therapy costs (Scholte et al., 2015).

Most antimicrobial prescribing errors occur when selecting empiric antimicrobial treatment , largely due to difficulty in predicting the causative pathogen or knowledge of the unit's antimicrobial resistance patterns (Calbo et al., 2013). Several interventions can be implemented to improve empirical treatment, including facilitating access to local antimicrobial resistance patterns and the use of evidence-based guidelines (Calbo et al., 2013, Benkő et al., 2020).

Considering the widespread acknowledgement of the importance of efficient antimicrobial stewardship, along with the necessity of accessing essential antibiotics and appropriate prescribing, the WHO Expert Committee suggested grouping antimicrobial agents into three categories: Access, Watch, and Reserve groups (World Health Organization, 2022, World Health Organization, 2023). Antibiotics used as first- and second-line treatment are included in the Access group. Broader spectrum antibiotics with a higher risk of antimicrobial resistance developing against them are included in the Watch group. Lastly, the Reserve group includes the last-resort antibiotics reserved for MDR infections (World Health Organization, 2022, World Health Organization, 2023).

2.5 Antimicrobial resistance

Antimicrobial agents have made it possible to treat infections that were previously considered untreatable or fatal (Mancuso et al., 2021). The WHO classifies antimicrobial resistance as a natural phenomenon in which micro-organisms are no longer susceptible to the antimicrobial agents that were previously used to treat infections caused by these micro-organisms (World Health Organization, 2014, Mancuso et al., 2021). Though a natural process, resistance is fuelled primarily through overuse and misuse of antimicrobial agents (Duse, 2011, Wasserman et al., 2014, Mancuso et al., 2021, Zhou et al., 2022)

Antimicrobial resistance threatens the treatment of community-acquired and nosocomial infections worldwide (World Health Organization, 2014, Ramsamy et al., 2018, Mancuso et al., 2021). The increase in the rate of antimicrobial resistance is an indication that previously viable treatment options for bacterial infections are now less potent (World Health Organization, 2014). The use of Reserve antimicrobial treatment options are also increasing (World Health Organization, 2014, South Africa Department of Health, 2024).

Antimicrobial resistance is classified as either intrinsic or acquired (Mancuso et al., 2021, Saha and Sarkar, 2021). Intrinsic resistance is a result of inherent or natural, chromosomally-encoded

resistance patterns without exposure to the antibiotic classes. Acquired resistance occurs when a micro-organism develops resistance to an antimicrobial agent to which it was previously susceptible by means of mutation, gene transfer, or alteration of target binding site (Giedraitienė et al., 2011, Riedel et al., 2019, Afzal and Altaf, 2021, Mancuso et al., 2021, Saha and Sarkar, 2021).

Multi-drug-resistant (MDR), extensively-drug-resistant (XDR), and pan-drug-resistant (PDR) micro-organisms have been well defined by the Center for Disease Control (CDC) (Ma et al., 2020, Saha and Sarkar, 2021). Multidrug resistance is the acquisition of resistance to at least one antimicrobial agent in three or more antimicrobial classes (Ramsamy et al., 2018, Ma et al., 2020, Saha and Sarkar, 2021). Extensively drug resistance is the susceptibility of bacterial isolates to only one or two antimicrobial categories (Ma et al., 2020, Saha and Sarkar, 2021). Pan-drug resistance refers to nonsusceptibility to all antimicrobial agents in all the categories (Ma et al., 2020, Saha and Sarkar, 2021). These highly resistant micro-organisms are a serious threat to human health as there are fewer viable treatment options as the micro-organisms acquire more resistance (Ma et al., 2020, Zhou et al., 2022).

2.5.1 Factors contributing to antimicrobial resistance

Factors that influence antimicrobial resistance include the inappropriate use of broad-spectrum antibiotics, self-medication, and antimicrobial use within the agricultural, food and animal industry (Duse, 2011, Mancuso et al., 2021). Poor infection control procedures in healthcare environments and poor hygiene in the community are also implicated in AMR, (Duse, 2011, Mancuso et al., 2021). The main factor that contributes to antimicrobial resistance remains the inappropriate use of antimicrobial agents, facilitated by the unnecessary antimicrobial prescribing, use of antimicrobial agents with inadequate or excessive cover, delay in antimicrobial administration, and prescribing the incorrect dose or duration of antimicrobial treatment (Wasserman et al., 2014, Mancuso et al., 2021).

The fundamental principles of antibiotic prescribing and responsible antibiotic use involves using the right antibiotic, for the right indication, at the right time and with the right dose (Dryden et al., 2011, Wasserman et al., 2014, Majumder et al., 2020). If implemented correctly, these principles will ensure that appropriate antimicrobial treatments are being prescribed (Dryden et al., 2011, Majumder et al., 2020). Benefits of appropriate antibiotic use include improved clinical outcomes, fewer adverse effects, cost effectiveness, and reduced antimicrobial resistance emergence (Calbo et al., 2013).

2.5.2 Mechanisms of resistance

The rapid spread of antimicrobial resistance can also be attributed to the variety of resistance mechanisms used by bacteria (Mancuso et al., 2021). The mechanism of resistance used by bacteria to escape the bactericidal effects of antibiotics are related to the mechanism of action of the antibiotic (Mancuso et al., 2021). Table 2.1 summarizes the mechanisms of action of the main groups of antimicrobial agents and the corresponding resistance mechanisms used by bacteria.

Table 2.1: Mechanism of action and resistance mechanisms (Aghapour et al., 2019, Mancuso et al., 2021)

Antimicrobial Groups	Mechanism of Action	Resistance Mechanism
β-Lactams: Penicillins Cephalosporins Carbapenems	Inhibits cell wall synthesis	Production of enzymes (including β-lactamase, penicillinase, cephalosporinase and carbapenemase) Alteration of binding sites
β-lactam β-lactamase inhibitors: Amoxycillin/Clavulanic Acid Ampicillin/Sulbactam Piperacillin/Tazobactam	Block the activity of β-lactamase enzymes	Extended-spectrum β-lactamase (ESBL)
Aminoglycosides, Chloramphenicol Macrolides, Tetracyclines	Inhibit ribosome assembly by binding to the bacterial 30S or 50S (inhibit protein synthesis)	Enzymatic modification, target site modification and efflux pumps
Fluoroquinolone	Inhibit DNA replication	Target-site gene mutations, efflux pumps and modifying enzyme
Sulfonamides and trimethoprim	Inhibit folic acid metabolism	Horizontal spread of resistance genes, mediated by transposons and plasmids, expressing non-susceptible variants of the target enzymes.
Polymyxins	Disruption of outer cell membrane	Alteration of outer membrane, horizontal gene transfer

Many micro-organisms produce enzymes that can inactivate or irreversibly modify antibiotics (Santajit and Indrawattana, 2016, Saha and Sarkar, 2021). These enzymes include β-lactamases, carbapenemases, aminoglycoside-modifying enzymes, and acetyltransferases (Jacoby and Munoz-Price, 2005, Giedraitienė et al., 2011, Santajit and Indrawattana, 2016,

Mancuso et al., 2021). The β-lactamases are very prevalent across different micro-organisms, and they act by hydrolyzing the β-lactam ring, rendering β-lactam antibiotics inactive (Jacoby and Munoz-Price, 2005, Giedraitienė et al., 2011, Santajit and Indrawattana, 2016).

Several micro-organisms modify the target site of antimicrobial agents to avoid recognition and binding of the antimicrobial agent to the bacteria (Santajit and Indrawattana, 2016). Modification of target sites can include the mutation of genes that encode for binding proteins, such as the penicillin-binding proteins, or by altering the composition of the bacterial cell wall glycopeptides (Giedraitienė et al., 2011, Santajit and Indrawattana, 2016).

Bacteria can reduce the uptake and thus accumulation of antimicrobial agents by reducing the amount of antimicrobial agent that passes through the bacterial cell membrane (Santajit and Indrawattana, 2016). The uptake can be reduced by decreasing the protein channels found within the bacterial cell membrane and/or the use of efflux pumps to pump out the antimicrobial agent if it has passed through the cell membrane (Giedraitienė et al., 2011, Santajit and Indrawattana, 2016, Saha and Sarkar, 2021).

Some micro-organisms can form a biofilm and embed within a matrix of polymeric substances, including proteins, polysaccharides, and lipids (Sharma et al., 2013, Santajit and Indrawattana, 2016). The matrix of the biofilm can act as a shield providing conditions that reduce the activity of antimicrobial agents (Sharma et al., 2013, Santajit and Indrawattana, 2016). Common pathogens that can be found within biofilms include *S. aureus*, *P. aeruginosa*, *A. baumannii*, and *K. pneumoniae* (Santajit and Indrawattana, 2016).

2.5.3 Resistance in ESKAPE pathogens

2.5.3.1 Resistance in Enterococci

Enterococci are showing increasing levels of resistance mainly due to the overuse of broad-spectrum antimicrobial agents, intrinsic resistance and the ability of enterococci to acquire and spread determinants, for example transposons and plasmids, for antimicrobial resistance (Navidinia, 2016, Mancuso et al., 2021). Enterococci are known to be intrinsically resistant to cephalosporins, penicillinase-resistant penicillins, and monobactams in addition to intrinsic low-level resistance to aminoglycosides and fluoroquinolones (Navidinia, 2016, Riedel et al.,

2019, Mancuso et al., 2021). Table 2.2 summarizes the main resistance mechanisms employed by Enterococci against antibiotics.

Table 2.2: Resistance mechanisms of Enterococci to antibiotics (Karaman et al., 2020, Mancuso et al., 2021)

Antibiotic	**Resistance mechanisms**
Aminoglycosides	Production of aminoglycoside-modifying enzymes, decreased permeability
Fluoroquinolones	Gene mutation and efflux pumps
Vancomycin	Target site modification

Aminoglycoside resistance is mediated by the production of aminoglycoside-modifying enzymes (Karaman et al., 2020, Mancuso et al., 2021). Fluoroquinolone resistance is linked to mutations in genes that encode subunits of DNA gyrase and topoisomerase IV or with the presence of efflux pumps (Karaman et al., 2020, Mancuso et al., 2021). Although enterococci show low levels of resistance to aminoglycosides, this resistance can be overcome by the synergistic activity between cell-wall synthesis inhibitors and aminoglycosides (Riedel et al., 2019). Vancomycin is an important therapeutic alternative for treating enterococcal infections; however, vancomycin resistance has been recorded with the first vancomycin-resistant *E. faecium* (VRE) isolate found in the 1980's (Pendleton et al., 2013, Navidinia, 2016, Riedel et al., 2019, de Oliveira et al., 2020, Mancuso et al., 2021). Vancomycin acts by binding to the D-alanyl-D-alanine terminus of peptidoglycan, thus inhibiting cell wall synthesis (Karaman et al., 2020, Mancuso et al., 2021). Vancomycin-resistance in enterococci is mediated by *van* gene clusters causing the replacement of the terminus with D-alanine-D-lactate or D-alanine-D-serine. Thus, vancomycin binds with low affinity to this terminus leading to vancomycin resistance (Karaman et al., 2020, Mancuso et al., 2021).

2.5.3.2 Resistance in Staphylococcus aureus

Staphylococcus aureus may acquire resistance to a variety of antibiotics using gene transfer (Navidinia, 2016, de Oliveira et al., 2020, Mancuso et al., 2021). The main resistance mechanisms employed by *S. aureus* include mutation in target genes, efflux pumps, target alterations, and enzymatic modifications (Mancuso et al., 2021). Table 2.3 summarizes the main resistance mechanisms employed by *S. aureus* against antibiotics.

Table 2.3: Resistance mechanisms of *S. aureus* to antibiotics (Lee et al., 2018, Mancuso et al., 2021)

Antibiotic	**Resistance mechanisms**
β-lactam antibiotics	Target site modification
Vancomycin	Modification of bacterial cell wall

The most common resistant strain is methicillin-resistant *S. aureus* (MRSA) (Pendleton et al., 2013, Lee et al., 2018, de Oliveira et al., 2020). Methicillin resistance and resistance to other β-lactam antibiotics are acquired via horizontal gene transfer. The genes *mecA* and *mecC* are responsible for the synthesis of an alternative penicillin-binding protein, thereby reducing the binding affinity for β-lactam antibiotics (Lee et al., 2018, Mancuso et al., 2021). The treatment for MRSA worldwide is commonly glycopeptide antibiotics, namely vancomycin and teicoplanin. The selective use of glycopeptides in the treatment of MRSA, has inevitably led to the development of vancomycin-intermediate, heteroresistant (heterogenous) vancomycin-intermediate and vancomycin-resistant *S. aureus* strains (VISA, hVISA and VRSA, respectively) (Pendleton et al., 2013, Santajit and Indrawattana, 2016, Shariati et al., 2020, Mancuso et al., 2021). Vancomycin resistance developed as a result of changes in the cell wall composition and thickness of *S. aureus*, which traps vancomycin and prevents it from reaching its site of action (Pendleton et al., 2013). Resistant VISA strains are generally not susceptible to most antibiotics other than reserved agents. Heteroresistant VISA has a subpopulation that expresses a resistant gene, even though the specimen yields MICs within the target range (Chen et al., 2011). Multi-drug resistant VRSA strains demonstrate the same resistance mechanisms as MRSA and VRE, due to interspecies genetic transfer (Pendleton et al., 2013, Navidinia, 2016). Extended hospitalizations due to treatment failure from infection with VISA and hVISA strains is an emerging concern (Shariati et al., 2020). According to the World Health Organization, the antimicrobial resistance patterns of *S. aureus* pose a severe threat to human health. The multi-drug-resistant VISA, hVISA and VRSA are seen as high priority strains because, without effective antimicrobial treatment options and containment, they can create impossible to treat infections (Navidinia, 2016, Shariati et al., 2020, Mancuso et al., 2021).

2.5.3.3 Resistance in Klebsiella pneumoniae

Klebsiella pneumoniae is known to rapidly accumulate and disseminate multi-drug-resistant determinants, in addition to gene-encoding enzymes, for example extended spectrum β-lactamases (ESBLs), and carbapenemases (Navidinia, 2016, de Oliveira et al., 2020, Nasser et

al., 2020, Mancuso et al., 2021). The acquisition of these enzymes has conferred resistance to β-lactam antibiotics, including penicillins, cephalosporins, and carbapenems (Pendleton et al., 2013, Navidinia, 2016, Mancuso et al., 2021). Table 2.4 summarizes the main resistance mechanisms employed by *K. pneumoniae* against antibiotics.

Table 2.4: Resistance mechanisms of *K. pneumoniae* to antibiotics (Mancuso et al., 2021, Pendleton et al., 2013)

Antibiotic	**Resistance mechanisms**
β-lactam antibiotics	Production of extended spectrum β-lactamases (ESBLs)
Carbapenems	Production of carbapenemases

Carbapenems are usually reserved as a last resort antibiotic for the treatment of multidrug resistant Gram-negative bacteria. Thus, carbapenem-resistant *K. pneumoniae* (CRKP) poses a significant challenge that has resulted in high mortality rates (Pendleton et al., 2013, Najafi, 2016, Mancuso et al., 2021).

Escherichia coli can acquire resistance traits from *K. pneumoniae* via horizontal gene transfer (Pendleton et al., 2013). Carbapenem-resistant Enterobacterales pose a big challenge because of multiple combinations of carbapenemases and ESBLs (Pendleton et al., 2013, Nasser et al., 2020). The expression of ESBL alone is a predictor of high mortality and prolonged hospital stay. Thus, the development of carbapenemase-mediated resistance can have a dire clinical impact (Pendleton et al., 2013).

2.5.3.4 Resistance in Acinetobacter baumannii

Acinetobacter baumannii shows intrinsic resistance to antimicrobials due to the synergistic activity of active efflux pump systems, low expression of outer membrane porins, and the protection of the Gram-negative outer membrane (Lupo et al., 2018, Riedel et al., 2019, Mancuso et al., 2021). Furthermore, *A. baumannii* can develop resistance to antibiotics by mechanisms such as the production of β-lactamases, the expression of efflux pumps, the enzymatic modification of aminoglycosides, the production of modified porins that decreases outer membrane permeability, and the modification of antibiotic target sites (Lupo et al., 2018, Abdi et al., 2020, Mancuso et al., 2021). Table 2.5 summarizes the main resistance mechanisms employed by *A. baumannii* against antibiotics.

Table 2.5: Resistance mechanisms of *A. baumannii* to antibiotics (Mancuso et al., 2021, Navidinia, 2016)

Antibiotic	**Resistance mechanisms**
β-lactam antibiotics	Production of β-lactamases
Aminoglycosides	Production of aminoglycoside-modifying enzymes
Carbapenems	Production of carbapenemases and efflux pumps
Polymixins (colistin)	Mutation of genes involved in lipopolysaccharide synthesis

Multi-drug-resistant strains of *Acinetobacter* spp. are commonly isolated in the hospital setting (Pendleton et al., 2013, Navidinia, 2016, de Oliveira et al., 2020). Approximately 45% of all global *A. baumannii* isolates are classified as MDR (de Oliveira et al., 2020). Carbapenems including imipenem and meropenem were the most effective treatment option for infections caused by *A. baumannii*, until a few years ago when emerging carbapenem-resistant (CR) strains became prominent (Mancuso et al., 2021). Tetracycline (minocycline) and glycylcycline (tigecycline) resistance emerged, leaving treatment options for carbapenem-resistant *A. baumannii* to now include ampicillin-sulbactam and colistin (Pendleton et al., 2013, Zhou et al., 2019, Mancuso et al., 2021). Pan-drug resistant isolates are emerging, resulting in last-resort antibiotics, namely carbapenems and polymyxins no longer being effective (Navidinia, 2016, de Oliveira et al., 2020, Mancuso et al., 2021).

2.5.3.5 Resistance in Pseudomonas aeruginosa

Pseudomonas aeruginosa is intrinsically resistant to numerous antibiotics and additional resistance is acquired by horizontal gene transfer and mutations (Riedel et al., 2019, de Oliveira et al., 2020). The main mechanisms of resistance are efflux pumps, decreased permeability of the bacteria's outer membrane, and acquisition or mutation of genes encoding proteins that control the passive diffusion of antimicrobial agents across the outer membrane (Navidinia, 2016, Lupo et al., 2018, Mancuso et al., 2021). Table 2.6 summarizes the main resistance mechanisms employed by *P. aeruginosa* against antibiotics.

Table 2.6: Resistance mechanisms of *P. aeruginosa* to antibiotics (Lupo et al., 2018, Mancuso et al., 2021)

Antibiotic	**Resistance mechanisms**
β-lactam antibiotics	Production of β-lactamases (ESBLs)
Aminoglycosides	Production of aminoglycoside-modifying enzymes
Fluoroquinolones	Gene mutation
Carbapenems	Production of carbapenemases

Pseudomonas aeruginosa shows intrinsic resistance to most β-lactam antibiotics due to its ability to produce β-lactamases (Lupo et al., 2018, Mancuso et al., 2021). Aminoglycoside resistance is mediated by aminoglycoside-modifying enzymes that decreases the binding affinity of the aminoglycoside (Mancuso et al., 2021, Ontong et al., 2021). *Pseudomonas aeruginosa* is known to be resistant to fluoroquinolones due to target mutations on DNA gyrase and/or topoisomerase IV, enzymes that are needed for bacterial cell growth and division (Pendleton et al., 2013, Riedel et al., 2019). Multidrug resistance has become a large issue due to the acquisition of broad-spectrum ESBLs and *K. pneumoniae* carbapenemase (KPC), resulting in high levels of carbapenem resistance (Pendleton et al., 2013). The treatment of infections caused by MDR *P. aeruginosa* involves a combination of colistin together with other antimicrobial agents showing anti-pseudomonal activity, such as piperacillin, imipenem, aztreonam, and ceftazidime (Mancuso et al., 2021, Ontong et al., 2021).

2.5.3.6 Resistance in Enterobacter

Enterobacter strains possess *amp*C, a chromosomal β-lactamase, rendering these strains resistant to ampicillin and the 1st and 2nd generation cephalosporins (Najafi, 2016, Riedel et al., 2019). Table 2.7 summarizes the main resistance mechanisms employed by *Enterobacter* spp. against antibiotics.

Table 2.7: Resistance mechanisms of *Enterobacter* spp. to antibiotics (Karaman et al., 2020, Mancuso et al., 2021)

Antibiotic	**Resistance mechanisms**
β-lactam antibiotics	Production of β-lactamases (ESBLs)
Carbapenems	Production of carbapenemases

Multidrug resistant *Enterobacter* spp. is becoming more prevalent due to plasmid-encoded ESBLs and carbapenemases, leaving only tigecycline and colistin as active antimicrobial agents (Pendleton et al., 2013, Navidinia, 2016, Mancuso et al., 2021). Moreover, pan-drug resistant *Enterobacter* spp. have emerged, displaying resistance to even the last-resort antibiotic colistin (de Oliveira et al., 2020, Mancuso et al., 2021). Newer β-lactam/β lactamase inhibitor agents including ceftazidime-avibactam, meropenem-vaborbactam and imipenem-relebactam have increased the armamentarium against pan drug-resistant strains (Lasko and Nicolau, 2020). Availability and cost of these interventions is a barrier to optimal treatment of patients requiring these agents (Lasko and Nicolau, 2020). These newer agents were not readily available at CMJAH during the time of the study period.

2.6 The significance of resistant ESKAPE pathogens and DAAT

Infections caused by the ESKAPE pathogens account for the majority of nosocomial infections (Navidinia, 2016, Pandey et al., 2021). Of note is the increasing rates of resistance among the ESKAPE pathogens and the dire outcomes of patients when compared to infections caused by more susceptible pathogens (Pogue et al., 2015).

Empiric antimicrobial therapy is prescribed based on the knowledge of local pathogen and susceptibility profiles n. Directed antimicrobial therapy is then prescribed after the susceptibility results are available. However, the delay in the implementation of appropriate and effective antimicrobial treatment increases the morbidity and mortality risks associated with these infections (Lee et al., 2012a, Pogue et al., 2015, Andersson et al., 2019, Bonine et al., 2019, Lodise et al., 2019, Zasowski et al., 2020). Patients with infections caused by the ESKAPE pathogens are often subjected to prolonged delayed appropriate antimicrobial therapy (DAAT) which can be used as a strong predictor for poor clinical outcomes (Pogue et al., 2015, Bonine et al., 2019, Lodise et al., 2019, Zasowski et al., 2020). In some cases, DAAT has been shown to be a stronger predictor of clinical outcomes than the resistance itself (Pogue et al., 2015). A systematic review by Zasowski *et al.* (2020), also found that the mortality rates were significantly lower in patients that were not subjected to DAAT. Every hour delay in implementing appropriate antibiotic treatment has an incremental disadvantage to the patient's clinical outcomes (Pogue et al., 2015). Strategies aimed at reducing DAAT for treating infections lead to better clinical outcomes in patients with infections caused by the ESKAPE pathogens (Pogue et al., 2015).

2.7 Antimicrobial resistance surveillance

Antimicrobial stewardship programs are designed to utilize different strategies to optimise antibiotic usage, limit the development and spread of antimicrobial resistance, and improve patient outcomes (Centers for Disease Control and Prevention, 2014, South Africa Department of Health, 2018a, von Knorring et al., 2019). The most important factors of an antimicrobial stewardship programme are communication, education, and monitoring (Human, 2017). Hospital-based antibiotic stewardship programmes incorporate the core elements of leadership commitment, accountability, drug expertise, action, tracking (both antibiotic prescribing and resistance patterns), reporting, and education to promote optimal treatment of infections with reduced treatment -related adverse events (Centers for Disease Control and Prevention, 2014, Huang et al., 2022).

The World Health Organization (WHO) first released its global antimicrobial resistance surveillance report in 2014 (World Health Organization, 2014, Singh-Moodley et al., 2018). This surveillance report stated that antimicrobial resistance is steadily increasing and highlighted the importance and the need for standardised surveillance systems (Singh-Moodley et al., 2018). The Centre for Disease Control and Prevention (CDC) defines surveillance as "*ongoing systematic collection, analysis and interpretation of health data essential to planning, implementation and evaluation of public health practice, closely integrated with the timely dissemination of these data to those who need to know*" (Centers for Disease Control and Prevention, 2012). Antimicrobial resistance surveillance reports provide information on facility-specific susceptibility patterns for the cultured micro-organisms (Yoon et al., 2021). This information can then be used to develop guidelines on the most appropriate empirical antimicrobial treatment options (Yoon et al., 2021).

2.7.1 Antimicrobial resistance surveillance in South Africa

South Africa has a high burden of infectious diseases largely due to bacterial pathogens (Singh-Moodley et al., 2018). Various reports have noted an increase in ESBL production, the emergence of CRKP, MDR *A. baumannii* and *P. aeruginosa*, and increase in MDR *E. coli* (Perovic et al., 2008, Perovic et al., 2014, Perovic et al., 2015, Perovic et al., 2016). Establishing a standardised antimicrobial resistance surveillance system provides important information on the common causative pathogens and their susceptibility patterns (Singh-Moodley et al., 2018). This information can be used to establish a consistent and systematic approach to determining

the most appropriate antimicrobial agent for the treatment of these infections (Singh-Moodley et al., 2018).

The South African Antimicrobial Resistance National Strategy Framework (AMR framework) outlines key objectives to prevent and slow down the spread and development of antimicrobial resistance and improve patient outcomes (South Africa Department of Health, 2018a). The strategic objectives are diagnostic stewardship, enhanced surveillance, prevention, and antimicrobial stewardship (South Africa Department of Health, 2018a). The AMR framework lists antimicrobial resistance surveillance reports as an objective for the early detection of antimicrobial resistance (Ismail et al., 2019). The South African Department of Health released surveillance reports in 2018, 2021 and 2024 representing information on antimicrobial consumption and resistance during the period 2012-2017, 2016-2020 and 2018-2022 (South Africa Department of Health, 2018b, South Africa Department of Health, 2021, South Africa Department of Health, 2024). Table 2.8 summarises the AMR surveillance reports published in 2018, 2021 and 2024.

Table 2.8: Antimicrobial resistance surveillance data from both public and private health sectors in South Africa for 2016, 2020 and 2022 (South Africa Department of Health, 2018b, South Africa Department of Health, 2021, South Africa Department of Health, 2024).

Bacterial pathogen	**Antibiotic**	**% Resistant (isolates)**		
		2016	**2020**	**2022**
Enterococcus faecalis	Ampicillin	12	8	7
	Vancomycin	1	1	1
Enterococcus faecium	Ampicillin	>90	95	>95
	Vancomycin	5	1	2
Staphylococcus aureus	Oxacillin	23	18	16
Klebsiella pneumoniae	Cephalosporins (3rd generation)	65	70	70
	Carbapenems	8	25	36
Escherichia coli	Cephalosporins (3rd generation)	23	26	28
	Fluoroquinolones	28	32	33

Bacterial pathogen	Antibiotic	% Resistant (isolates)		
		2016	2020	2022
Acinetobacter baumannii	Carbapenems	73	80	80
	Tigeycycline	8	21	4
Pseudomonas aeruginosa	Carbapenems	28	28	23
	Piperacillin-tazobactam	31	18	15

Enterococcus faecalis remains susceptible to ampicillin, with resistance only found in 7% of the isolates in 2022. Therefore, ampicillin remains the drug of choice to treat *E. faecalis* infections (South Africa Department of Health, 2018b, South Africa Department of Health, 2021, South Africa Department of Health, 2024). Vancomycin resistance is emerging in both *E. faecium*, and to a lesser extent *E. faecalis* (South Africa Department of Health, 2018b). With limited treatment options, this poses a concern for prescribers (South Africa Department of Health, 2018b, South Africa Department of Health, 2021, South Africa Department of Health, 2024).

Methicillin-resistance was found in 23% of the resistant *S. aureus* isolates in 2016, and a decline in resistance was noted to 16% in 2022 (South Africa Department of Health, 2024). The first line treatment for MRSA remains vancomycin (South Africa Department of Health, 2018b).

The prevalence of ESBL-producing *K. pneumoniae*, which often necessitates the use of carbapenems as treatment, remained between 63-70% during the reporting period (South Africa Department of Health, 2018b, South Africa Department of Health, 2024). Regarding carbapenem resistance, there has been a significant increase from 8% in 2016 to 25% in 2020 to 36% in 2022 (South Africa Department of Health, 2018b, South Africa Department of Health, 2021, South Africa Department of Health, 2024). *Escherichia coli* presents with increasing quinolone resistance as well as resistance to third generation cephalosporins (South Africa Department of Health, 2018b).

Resistance to carbapenems is reported in 28% of *P. aeruginosa* and 81% of *A. baumannii* isolates (South Africa Department of Health, 2018b, South Africa Department of Health,

2021). There has been a decline in the resistance of *P. aeruginosa* to piperacillin-tazobactam and carbapenems (South Africa Department of Health, 2024). Carbapenem resistance in *A. baumannii* has been increasing. Resistance to tigecycline has declined (South Africa Department of Health, 2024). Multidrug-resistant *A. baumannii* has limited treatment options, consisting of either colistin, tigecycline, or a combination of both (South Africa Department of Health, 2018b). Colistin is regarded as a last resort antibiotic to treat severe infections caused by carbapenem-resistant ESKAPE pathogens; however, colistin resistance has also been reported (South Africa Department of Health, 2018b, Ma et al., 2020, Mancuso et al., 2021).

2.8 Rectal swabs as screening tools

The delay in starting a patient on appropriate antimicrobial treatment is usually due to delayed culture-based susceptibility testing results (Zasowski et al., 2020). Faster screening methods, such as rectal swab screening are an option. However, these are not widely implemented (Zasowski et al., 2020).

Carbapenemase-producing Enterobacterales (CPE) are rapidly spreading and pose a serious global health risk (Thomas and Duse, 2018, Duze et al., 2023). Furthermore, carbapenemases in Enterobacterales live on mobile genetic elements, facilitating their transfer from person to person (Duze et al., 2023). The most common carbapenemases in South Africa are NDM and OXA-48 (Thomas and Duse, 2018). Routine susceptibility testing may overlook OXA-48 and its variants, as these show only low-level carbapenem resistance. Therefore, it is essential for infection prevention and control efforts to identify carbapenemases quickly and accurately through screening of high-risk individuals (Duze et al., 2023).

Rectal swab screening for resistant micro-organisms can be used to limit the spread of antimicrobial resistant bacteria (Foschi et al., 2019). Guidance documents from the CDC suggest that using active surveillance methods, such as rectal swab screening, for the early detection of patients colonized with carbapenemase-producing micro-organisms help prevent the spread and the transmission of these MDR micro-organisms (Centers for Disease Control and Prevention, 2009, Foschi et al., 2019). Active surveillance screening may allow for the early identification of antimicrobial resistant bacteria, such as the ESKAPE pathogens, as well as the institution of appropriate infection prevention and control measures (Otter et al., 2016). Active surveillance screening relies on using methods with a fast turnaround time, with PCR being more rapid than traditional culture-based tests (Otter et al., 2016, Foschi et al., 2019).

Despite being a useful screening tool, there are several limitations to active rectal swab screening. Firstly, rectal swabs can only be used for the detection of enteric bacteria such as enterococci and Enterobacterales (Glisovic et al., 2017, Foschi et al., 2019). Secondly, the sensitivity of the test is influenced by the sampling technique and sample quality (Glisovic et al., 2017). Thirdly, molecular based testing of rectal swabs can be subject to high laboratory costs and low levels of automation (Ambretti et al., 2019). Another limitation in the hospital setting is that high-risk patients awaiting screening results will require isolation which may confound space constraints (Ambretti et al., 2019).

In conclusion, the ESKAPE pathogens are a global threat to human health. Antimicrobial resistance surveillance provides information on the common causative pathogens and their resistance patterns. This information can be used to determine the most appropriate antimicrobial treatment. Faster screening tools, such as PCR-based rectal swab screening, can be used to limit the spread of antimicrobial resistant pathogens and allow for earlier initiation of appropriate antimicrobial treatment.

CHAPTER 3
METHODOLOGY

3.1 Introduction

This chapter discusses the study design, study site, study period, data collection, statistical analysis, and ethical considerations.

3.2 Study methodology and design

A retrospective, observational, cross-sectional, review of patient records was conducted at the main ICU at CMJAH for the period September 2021 to September 2022.

3.3 Study site and study period

The study was conducted at the multidisciplinary main ICU at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) in Johannesburg, South Africa. for the period September 2021 to September 2022. The unit, a 12-bed ICU, admits patients who, amongst others, have undergone complex surgical procedures, present with a medical emergency, or have severe sepsis (Johnston et al., 2018). The hospital services the population found across three districts, namely Johannesburg Metro, Ekurhuleni, and West Rand, through referrals from various cluster hospitals (Gauteng Provincial Government, 2022). The University of Witwatersrand's Faculty of Health Sciences uses CMJAH as its primary teaching facility.

3.4 Study population

The study population included all patients admitted to the ICU during the study period from which the study sample of all patients over 18 years of age with a suspected infection was drawn. Patients under the age of 18 years and patients who did not have an infection during the study period were excluded.

3.5 Study specimens

Only the first isolate per microbial species per patient was included. Where a microbial species was isolated in a variety of specimen types, preference was given to the blood cultures. In instances where two rectal screening swabs were recorded, only the rectal swab taken and registered on admission to the ICU was included. Rectal swab screening involve screening for carbapenem-resistant Enterobacterales.

3.6 Data collection

A purpose-designed data collection tool (Appendix A) was used to extract data from patient records. This tool was adapted from other studies investigating antimicrobial-resistant ESKAPE pathogens and resulting infections (Ismail et al., 2019, Benkő et al., 2020, Pandey et al., 2021). The reliability of the study requires that the data collection tool be consistent and dependable. In this study, a standardised data collection tool was used, which ensured that the same data was collected for each patient reviewed. The following data was extracted: patient demographic information, point of referral to the ICU, rectal swab results, suspected source of infection, empiric antimicrobial treatment, culture and susceptibility test results, definitive antibiotic treatment and the time between admission and administration of appropriate antimicrobial therapy.

Patient file numbers were retrieved from the ICU's paper-based admission records. The patient file numbers were then used to retrieve the necessary information from the digital patient files from the CMJAH database. All IDs, laboratory reports and files were checked for patient details to ensure that the data was correctly assigned to the patient. Data for rectal swab results, suspected source of infection, sample type, and microbiological culture and susceptibility were electronically retrieved from the National Health Laboratory Service database.

3.7 Statistical analysis

Collected data was captured and analysed in Microsoft Excel® (version 2409) using descriptive statistics and presented using tables and charts. The categorical data, including patient gender, type of specimen, microbial isolates and susceptibility testing, were summarised using tables of frequencies, proportions or percentages, and presented using charts. The continuous data, including patient age, length of hospital stay and time before initiation of appropriate antimicrobial therapy, were analysed using means or medians.

3.8 Ethical considerations

Ethical approval for this study (M220872) was granted by the Human Research Ethics Committee (Medical) of the University of the Witwatersrand (Appendix B) before the commencement of data collection. Permission to conduct the study at Charlotte Maxeke Johannesburg Academic Hospital was obtained from the Chief Executive Officer (Appendix

C) and the head of ICU (Appendix D). The protocol to conduct the study was approved by the University of the Witwatersrand Protocol Assessors Committee (M220872) (Appendix E).

This study did not involve any patient interaction or intervention. The data collected was not linked to the patient's identity and patient confidentiality was maintained by assigning a non-identifiable sequential number to each patient record. All data was stored on a password-protected Microsoft Excel® spreadsheet and will be kept for a period of 6 years from completion of the study. All paper records were destroyed by shredding after transfer to the spreadsheet and completion of data analysis.

CHAPTER 4

RESULTS

4.1 Patient demographics and specimen types

A total of 690 patients were admitted to the adult multi-disciplinary ICU at CMJAH during the study period. Of these patients, 36.60% (273 patients) received antimicrobial treatment, and are the cohort of patients used in the subsequent analysis. Of these 273 patients, one or more ESKAPE pathogens was isolated from 132 patients (48.35%, *n* = 273). There were 80 male patients (60.6%) and 52 female patients (39.4%) from whom 263 specimens were drawn. The average patient age, for patients colonized by an ESKAPE pathogen, was 43.2 years. The average length of stay in the ICU was 19.5 days (21 days for male patients versus for 17.5 days for female patients). Figure 4.1 depicts the specimen types which were obtained from the patients in the study sample.

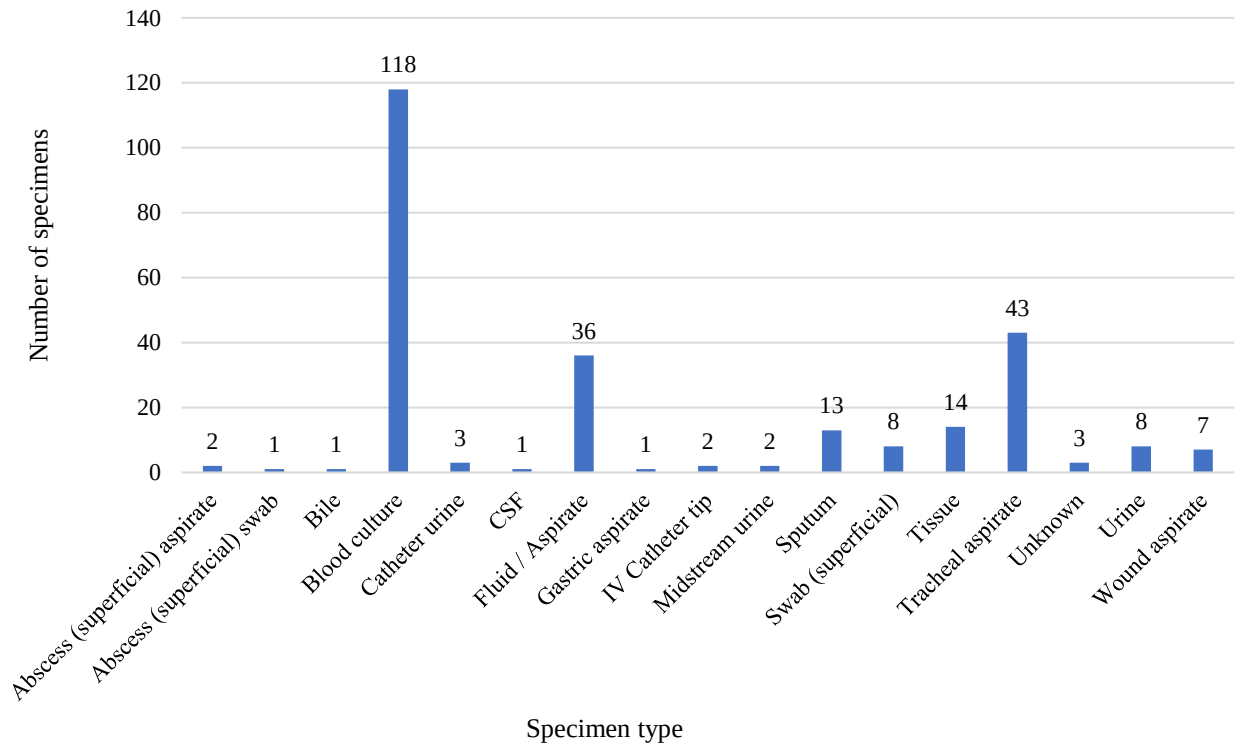

Figure 4.1: Specimens drawn (n=263) from 132 patients, with an ESKAPE pathogen isolated.

Specimens from patients were collected from various sites in the study sample. The most common specimen type was blood cultures (44.9%), followed by tracheal aspirates (16.3%)

and fluid aspirates (13.6%). These specimens were categorised into four groups, namely, blood cultures, respiratory specimens, fluids or aspirates, and other specimen types. Respiratory specimens included tracheal aspirates, sputum, and gastric aspirates. Fluids or aspirates included fluid/aspirate, bile, wound aspirate, and abscess aspirate. Other specimen types included tissue specimens, swabs, urine specimens, and specimens labelled as unknown. Figure 4.2 to 4.5 depicts the percentage of ESKAPE pathogens that were isolated from the different specimen types. The most frequently isolated ESKAPE pathogen from blood cultures was *K. pneumoniae* (38 isolates), followed by *A. baumannii* (29 isolates) and *E. coli* (12 isolates).

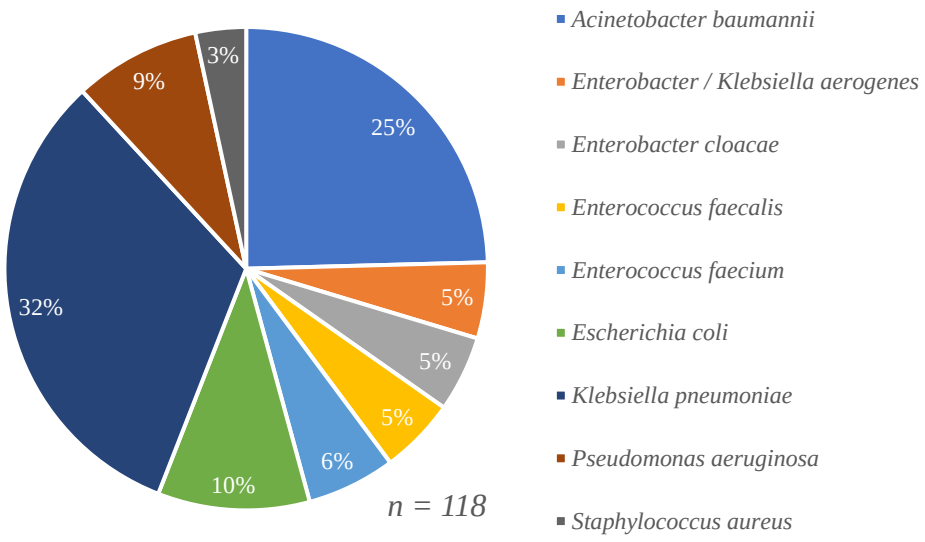

Figure 4.2: The percentage of ESKAPE pathogens that were isolated from blood cultures obtained from patients in the study sample (*n* = 118)

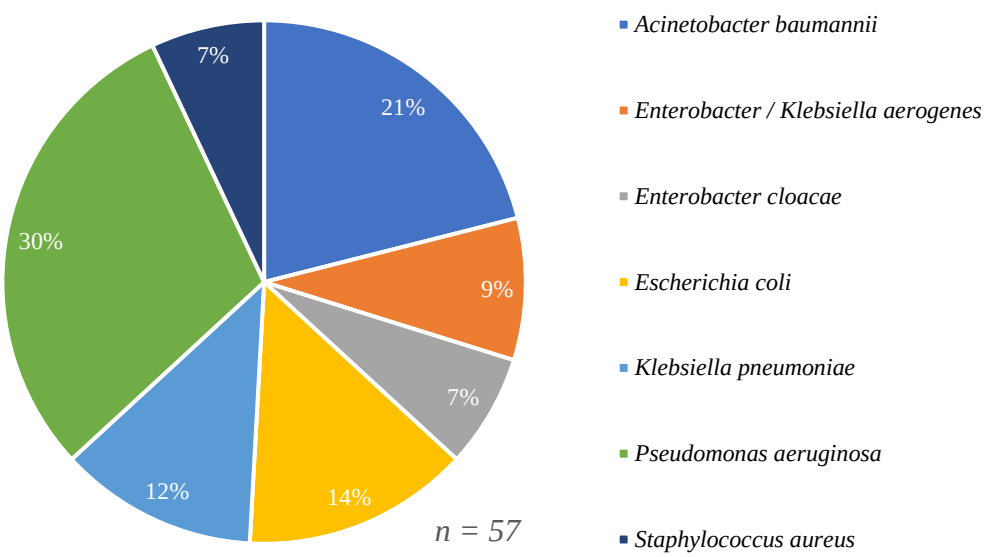

Figure 4.3: The percentage of ESKAPE pathogens that were isolated from respiratory specimens obtained from patients in the study sample (*n* = 57)

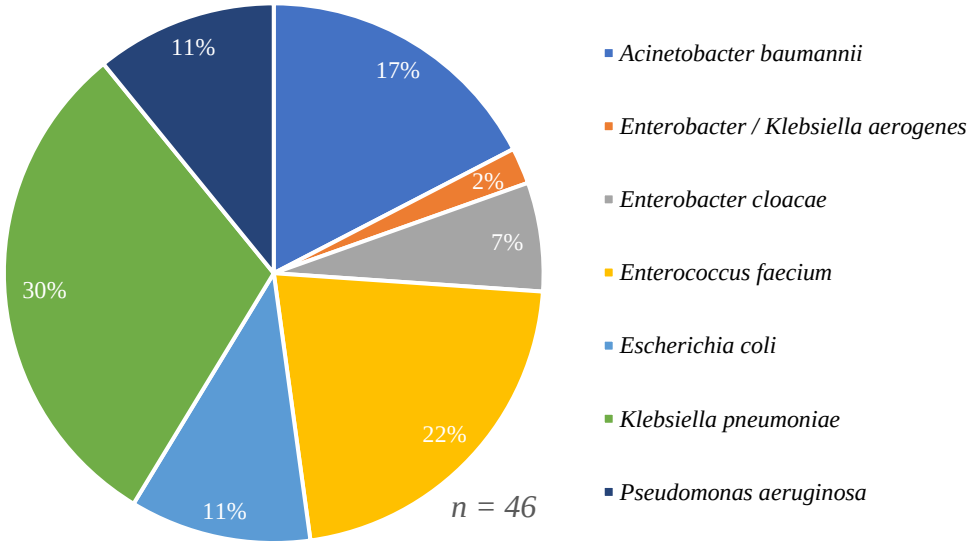

Figure 4.4: The percentage of ESKAPE pathogens that were isolated from fluids or aspirates obtained from patients in the study sample (*n* = 46)

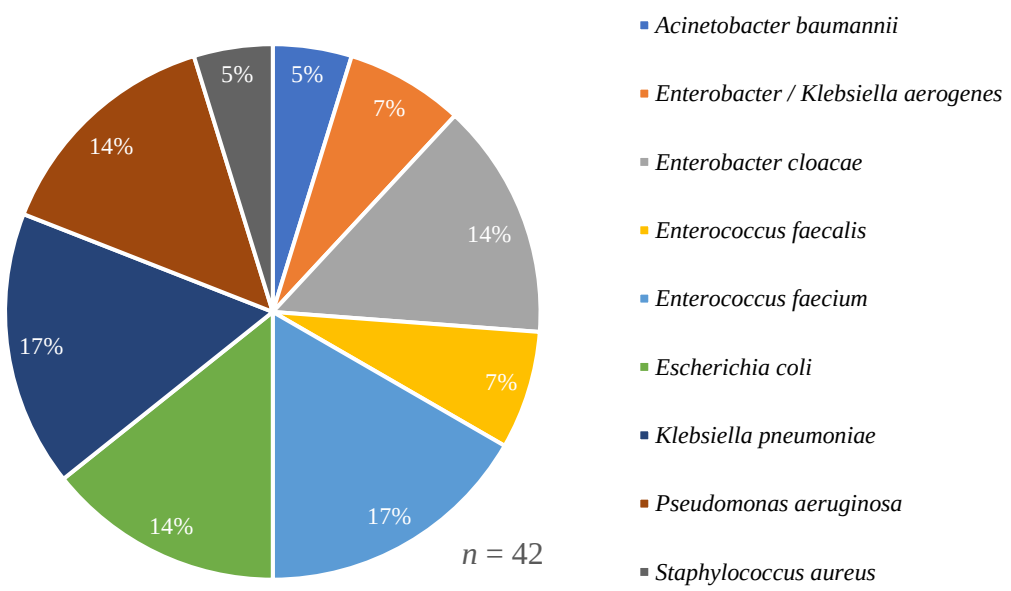

Figure 4.5: The percentage of ESKAPE pathogens that were isolated from other specimens obtained from patients in the study sample (*n* = 42)

The most frequently isolated ESKAPE pathogen from respiratory specimens was *P. aeruginosa* (17 isolates), followed by *A. baumannii* (12 isolates) and *E. coli* (8 isolates). The most frequently isolated ESKAPE pathogen from fluids or aspirates was *K. pneumoniae* (14 isolates), followed by *E. faecium* (10 isolates) and *A. baumannii* (8 isolates). The most frequently isolated ESKAPE pathogen from other specimen types was *K. pneumoniae* and *E. faecium* (7 isolates), followed by *E. cloacae*, *E. coli*, and *P. aeruginosa* (6 isolates).

4.2 Susceptibility patterns of the ESKAPE pathogens

Tables 4.1 – 4.8 summarizes the susceptibility patterns of the ESKAPE pathogens from the various sample types.

Table 4.1: Percentage Susceptibility (%) of the Gram negative ESKAPE pathogens isolated from the blood cultures

	AMK*	**AMC**	**AMP**	**CPM**	**CTX**	**FOX**	**CAZ**	**CXM (O)**	**CXM (P)**	**CIP**	**COL**	**ERT**	**GEN**	**IPM**	**MER**	**NFT**	**TAZ**	**TG**	**TOB**	**SXT**
A. baumannii (*n* = 29)	3.4	-	-	17.2	-	-	10.3	-	-	13.8	72.4	-	20.7	17.2	17.2	-	10.3	58.6	-	10.3
K. aerogenes (*n* = 6)	66.7	0	-	50	50	0	50	33.3	33.3	66.7	100	66.7	50	66.7	66.7	0	33.3	66.7	0	66.7
E. cloacae (*n* = 6)	100	0	-	83.3	66.7	0	83.3	50	50	83.3	83.3	100	83.3	100	100	0	66.7	50	0	66.7
E. coli (*n* = 12)	91.7	58.3	25	75	75	83.3	75	75	75	58.3	100	100	83.3	91.7	100	66.7	66.7	75.0	0	16.7
K. pneumoniae (*n* = 38)	52.6	15.8	0	18.4	18.4	26.3	18.4	13.2	15.8	26.3	94.7	28.9	23.7	28.9	39.5	7.9	18.4	44.7	2.6	18.4
P. aeruginosa (*n* = 10)	60	-	-	60	-	-	60	-	-	70	80	-	-	40	30	-	40	-	-	-

*Antibiotic key: AMK - amikacin , AMP – ampicillin/amoxicillin, AMC, amoxicillin + clavulanic acid, AZM – azithromycin/erythromycin, CAZ – ceftazidime, CPM – cefepime, CTX – Ceftriaxone/ cefotaxime, CXM – cefuroxime (O – oral; P – parenteral), CIP – ciprofloxacin, CM – clindamycin, CLX – cloxacillin, COL – colistin, FOX – cefoxitin, ERT – ertapenem, FA – fusidic acid, GEN – gentamicin, GEH – high level gentamicin resistance, IPM – imipenem, LVX – levofloxacin, LZD – linezolid, MER – meropenem, NFT – nitrofurantoin, PEN – penicillin / ampicillin, RIF – rifampicin, STR – high level streptomycin resistance, TAZ – piperacillin + tazobactam, TG – Tigecycline, TOB – tobramycin, SXT – trimethoprim + sulfamethoxazole, VAN - vancomycin

Table 4.2: Percentage Susceptibility (%) of the Gram positive ESKAPE pathogens isolated from the blood cultures

	AMP	CIP	CM	CLX	AZM	FA	GEN	GEH	LZD	PEN	RIF	STR	TG	STX	VAN
E. faecalis (*n* = 6)	100	50	-	-	0	-	-	50	100	50	-	50	66.7	-	100
E. faecium (*n* = 7)	0	0	-	-	0	-	-	42.9	100	0	-	14.3	71.4	-	42.9
S. aureus (*n* = 4)	-	75	75	75	75	100	75	-	100	25	100	-	75	0	100

Table 4.3: Percentage Susceptibility (%) of the Gram negative ESKAPE pathogens isolated from the respiratory specimens

	AMK	AMC	AMP	CPM	CTX	FOX	CAZ	CXM (O)	CXM (P)	CIP	COL	ERT	GEN	IPM	MER	NFT	TAZ	TG	TOB	SXT
A. baumannii (*n* = 12)	0	-	-	8.3	-	-	8.3	-	-	8.3	75	-	8.3	8.3	8.3	-	8.3	50	-	8.3
K. aerogenes (*n* = 5)	80	0	-	80	80	0	80	80	80	80	100	80	80	40	80	20	80	80	0	80
E. cloacae (*n* = 4)	100	0	-	100	75	0	100	25	50	100	100	100	100	75	100	50	100	100	0	75
E. coli (*n* = 8)	87.5	37.5	12.5	87.5	87.5	87.5	75	87.5	87.5	75	87.5	87.5	87.5	87.5	87.5	62.5	75	75	0	25
K. pneumoniae (*n* = 7)	57	14	0	29	14	14	14	14	14	14	100	14	29	43	29	43	14	86	0	14
P. aeruginosa (*n* = 17)	47.1	-	-	64.7	-	-	58.8	-	-	58.8	94.1	-	-	47.1	58.8	-	47.1	-	-	-

Table 4.4: Percentage Susceptibility (%) of the Gram positive ESKAPE pathogens isolated from the respiratory specimens

	CIP	**CM**	**CLX**	**AZM**	**FA**	**GEN**	**LZD**	**PEN**	**RIF**	**TG**	**SXT**	**VAN**
S. aureus (*n* = 4)	100	75	100	75	100	100	100	0	100	100	50	100

Table 4.5: Percentage Susceptibility (%) of the Gram negative ESKAPE pathogens isolated from fluids or aspirates

	AMK	**AMC**	**AMP**	**CPM**	**CTX**	**FOX**	**CAZ**	**CXM (O)**	**CXM (P)**	**CIP**	**COL**	**ERT**	**GEN**	**IPM**	**MER**	**NFT**	**TAZ**	**TG**	**SXT**
A. baumannii (*n* = 8)	0	-	-	12.5	-	-	12.5	-	-	12.5	75	-	12.5	12.5	12.5	-	12.5	50	25
K. aerogenes (*n* = 1)	100	0	-	100	100	0	100	100	100	100	100	100	100	0	100	0	100	100	100
E. cloacae (*n* = 3)	100	0	-	66.7	66.7	0	66.7	0	0	66.7	100	66.7	66.7	66.7	66.7	0	66.7	66.7	66.7
E. coli (*n* = 5)	80	60	40	80	60	80	80	60	40	80	100	100	80	100	100	80	100	100	60
K. pneumoniae (*n* = 14)	35.7	14.3	0	21.4	14.3	14.3	14.3	14.3	14.3	14.3	78.6	21.4	57.1	35.7	35.7	7.1	14.3	50	21.4
P. aeruginosa (*n* = 5)	80	-	-	100	-	-	100	-	-	100	60	-	-	100	100	-	80	-	-

Table 4.6: Percentage Susceptibility (%) of the Gram positive ESKAPE pathogens isolated from fluids or aspirates

	AMP	**CIP**	**AZM**	**GEH**	**LZD**	**PEN**	**STR**	**TG**	**VAN**
E. faecium (*n* = 10)	0	0	0	40	100	0	40	90	90

Table 4.7: Percentage Susceptibility (%) of the Gram negative ESKAPE pathogens isolated from other specimen types

	AMK	AMC	AMP	CPM	CTX	FOX	CAZ	CXM (O)	CXM (P)	CIP	COL	ERT	GEN	IPM	LVX	MER	NFT	TAZ	TG	TOB	SXT
A. baumannii (*n* = 2)	0	-	-	0	-	-	0	-	-	0	50	-	0	0	0	0	-	0	100	-	0
K. aerogenes (*n* = 3)	66.7	0	-	66.7	33.3	0	33.3	33.3	33.3	66.7	100	66.7	66.7	66.7	0	66.7	0	66.7	66.7	0	66.7
E. cloacae (*n* = 6)	83.3	0	-	50	16.7	0	33.3	0	0	33.3	100	66.7	50	66.7	0	100	50	33.3	50	0	50
E. coli (*n* = 6)	100	50	0	50	16.7	100	33.3	33.3	16.7	33.3	66.7	100	66.7	100	16.7	100	66.7	100	66.7	16.7	16.7
K. pneumoniae (*n* = 7)	57.1	14.3	0	28.6	14.3	14.3	14.3	14.3	14.3	14.3	85.7	14.3	14.3	14.3	0	14.3	0	14.3	57.1	0	0
P. aeruginosa (*n* = 6)	83.3	-	-	100	-	-	100	-	-	66.7	100	-	-	83.3	0	66.7	-	83.3	-	-	-

Table 4.8: Percentage Susceptibility (%) of the Gram positive ESKAPE pathogens isolated from other specimen types

	AMP	CIP	CM	CLX	AZM	FA	GEN	GEH	LZD	PEN	RIF	STR	TG	SXT	VAN
E. faecalis (*n* = 3)	100	33.3	-	-	0	-	-	66.7	100	33.3	-	66.7	66.7	-	100
E. faecium (*n* = 7)	0	0	-	-	0	-	-	14.3	100	0	-	28.6	100	-	71.4
S. aureus (*n* = 2)	-	50	50	50	50	100	50	-	50	50	100	-	100	50	100

Only 17.2% of the *A. baumannii* isolated from blood cultures were susceptible to imipenem or meropenem and 10% to ceftazidime, and 72.4% of isolates showed susceptibility to colistin. While 100% of the *K. aerogenes* isolates from blood cultures were susceptible to colistin, only 66.7% of the isolates were susceptible to imipenem or meropenem and 50% were susceptible to ceftazidime. Every isolate of *E. cloacae* from blood cultures were susceptible to the carbapenems; however, only 83.3% were susceptible to ceftazidime. All the *E. coli* isolates from blood cultures were susceptible to ertapenem or meropenem, with only 91.7% of the isolates being susceptible to amikacin and 75% susceptible to ceftazidime. Of the *K. pneumoniae* isolates obtained from blood cultures, only 28.9% were susceptible to imipenem or ertapenem, 52.6% to amikacin, and 94.7% to colistin. Only 60% of the *P. aeruginosa* isolates from blood cultures were susceptible to amikacin or ceftazidime, 40% were susceptible to imipenem, and only 80% were susceptible to colistin. These results suggest a pattern of built up of resistance in *A. baumannii*, *K. pneumoniae* and *P. aeruginosa*, whilst *K. aerogenes*, *E. cloacae* and *E. coli* remain susceptible to multiple antimicrobial agents.

All the *E. faecalis* isolates from blood cultures were susceptible to ampicillin, linezolid and vancomycin. None of the *E. faecium* isolates from blood cultures were susceptible to ampicillin; however, only 42.9% were susceptible to vancomycin, while all the isolates were susceptible to linezolid. Every isolate of *S. aureus* from blood cultures were susceptible to vancomycin and linezolid; however, only 75% were susceptible to cloxacillin. The results suggest that resistance is present in *E. faecium*, whilst *E. faecalis* and *S. aureus* remain susceptible.

Only 8.3% of the *A. baumannii* isolated from respiratory specimens showed susceptibility to imipenem, meropenem or ceftazidime; however, 75% of isolates showed susceptibility to colistin. While all of the *K. aerogenes* isolates from respiratory specimens were susceptible to colistin, only 80% of the isolates were susceptible to imipenem, meropenem or ceftazidime. Every isolate of *E. cloacae* from respiratory specimens were susceptible to ceftazidime, amikacin, meropenem, ertapenem and colistin. Only 87.5% of the *E. coli* isolates from respiratory specimens were susceptible to the carbapenems, amikacin, and colistin, whilst 75% of the isolates were susceptible to ceftazidime. Of the *K. pneumoniae* isolates obtained from respiratory specimens, only 14% were susceptible to ceftazidime, 29% to meropenem, 43% to imipenem, 57% to amikacin, and 100% to colistin. Only 58.8% of the *P. aeruginosa* isolates

from respiratory specimens were susceptible to ceftazidime, 47.1% were susceptible to amikacin or imipenem, and 94.1% were susceptible to colistin.

All *S. aureus* isolates from respiratory specimens were susceptible to cloxacillin, linezolid and vancomycin.

Only 12.5% of the *A. baumannii* isolated from fluids or aspirates demonstrated susceptibility to imipenem, meropenem or ceftazidime; however, 75% of isolates demonstrated susceptibility to colistin. Every *K. aerogenes* isolated from fluids or aspirates were susceptible to colistin, imipenem, meropenem or ceftazidime. Every isolate of *E. cloacae* from fluids or aspirates were susceptible to amikacin and colistin; however, only 66.7% of the isolates were susceptible to ceftazidime and the carbapenems. Only 80% of the *E. coli* isolates from fluids or aspirates were susceptible to the amikacin or ceftazidime, whilst 100% of the isolates were susceptible to colistin and carbapenems. Of the *K. pneumoniae* isolates obtained from fluids or aspirates, only 14.3% were susceptible to ceftazidime, 35.7% to meropenem, imipenem and amikacin, and 78.6% to colistin. All the *P. aeruginosa* isolates from fluids or aspirates were susceptible to ceftazidime and carbapenems, 80% to amikacin and only 60% to colistin.

Every isolate of *E. faecium* from fluids or aspirates showed susceptibility to linezolid; however, only 90% of isolates showed susceptibility to vancomycin. According to the results, *A. baumannii* and *K. pneumoniae* appear to be developing resistance, but *K. aerogenes*, *E. cloacae*, *E. coli*, *P. aeruginosa*, and *E. faecium* continue to be sensitive to a variety of antimicrobial agents.

None of the *A. baumannii* isolates from other specimen types were susceptible to amikacin, ceftazidime or carbapenems, and only 50% were susceptible to colistin. Of the *K. aerogenes* isolates from other specimen types, 33.3% showed susceptibility to ceftazidime, 66.7% to amikacin and carbapenems, and 100% to colistin. Every isolate of *E. cloacae* from other specimen types were susceptible to meropenem and colistin; however, only 83.3% of the isolates were susceptible to amikacin, 66.7% to imipenem and 33.3% to ceftazidime. Only 33.3% of the *E. coli* isolates from other specimen types were susceptible to ceftazidime, 66.7% to colistin, whilst 100% of the isolates were susceptible to amikacin and the carbapenems. Of the *K. pneumoniae* isolates obtained from other specimen types, only 14.3% were susceptible to ceftazidime and carbapenems, 57.1% to amikacin, and 85.7% to colistin. All the *P.*

aeruginosa isolates from other specimen types were susceptible to ceftazidime and colistin, 83.3% to amikacin and imipenem, and only 66.7% to meropenem. According to the results, *A. baumannii*, *E. cloacae,* and *K. pneumoniae* appear to be developing resistance, but *K. aerogenes*, *E. coli* and *P. aeruginosa*, continue to be susceptible to a variety of antimicrobial agents.

All the *E. faecalis* isolates from other specimen types were susceptible to ampicillin, linezolid and vancomycin. None of the *E. faecium* isolates from other specimen types were susceptible to ampicillin or penicillin; however, 71.4% were susceptible to vancomycin and all the isolates were susceptible to linezolid. Every isolate of *S. aureus* from other specimen types were susceptible to vancomycin; however, only 50% were susceptible to linezolid and cloxacillin. The results suggest that *E. faecalis* remain susceptible to antimicrobial agents, whilst *E. faecium* and *S. aureus* are displaying resistance to some of the antimicrobial agents.

4.3 Antimicrobial treatment

Table 4.9 and 4.10 summarize the empiric and definitive antimicrobial treatment prescribed for patients from whom ESKAPE pathogens were isolated while admitted in the ICU. Upon analysis of the results, it was evident that clinical input was required to draw the necessary conclusions. The ICU team provided clinical insights into the decision-making process, explained under the comment's column in table 4.9.

Table 4.9: The antimicrobial treatment in ICU for patients with ESKAPE pathogens isolated (*n* = 132)

Patient number	Empiric treatment ★	Appropriate Yes (Y) or No (N)	Specimen type(s)	Isolated ESKAPE pathogen(s)	Subsequent or definitive treatment ■	Appropriate Yes (Y) or No (N) or Inconclusive (I) or Clinical data not available (CDNA)	Comment
3	Amoxicillin + clavulanic acid (Augmentin)	N	Fluid / Aspirate	*E. faecium* *E. coli* (resistant to amoxicillin-clavulanic)	-	CDNA	Antibiotics to treat primary problem. Isolated pathogens deemed not to be invasive.
4	Imipenem + Amikacin	N	Fluid / Aspirate	*E. faecium*	Piperacillin - Tazobactam	CDNA	De-escalation. Isolated pathogen deemed not to be invasive.
5	Cefazolin + Clindamycin	N	Blood cultures	*A baumannii* (CR & ESBL) *K.pneumoniae* (CRE & ESBL) *P. aeruginosa*	1) Piperacillin - Tazobactam 2) Cefepime 3) Ertapenem 4) Colistin + Meropenem	Y	Empiric – possible skin or soft tissue infection (SSI). Directed therapy.

Patient number	Empiric treatment ★	Appropriate Yes (Y) or No (N)	Specimen type(s)	Isolated ESKAPE pathogen(s)	Subsequent or definitive treatment ■	Appropriate Yes (Y) or No (N) or Inconclusive (I) or Clinical data not available (CDNA)	Comment
6	Piperacillin – Tazobactam (Piptaz)	Y	1) Tracheal aspirate 2) Blood culture	1) *A. baumannii* 2) *E. cloacea*	1) Imipenem 2) Ertapenem	Y	Empiric – patient from within hospital. De-escalation to lesser spectrum carbapenem to cover *E. cloacae*. *A. baumannii* deemed to be a colonizer.
9	Ertapenem + Amikacin	Y	Blood cultures	*A. baumannii* (CR) *K. pneumoniae* (CRE)	1) Colistin + Imipenem 2) Tigecycline + Azithromycin 3) Ertapenem + Ciprofloxacin	Y	Empiric – patient from within hospital. Azithromycin – quorum sensing. Directed therapy.

Patient number	Empiric treatment ★	Appropriate Yes (Y) or No (N)	Specimen type(s)	Isolated ESKAPE pathogen(s)	Subsequent or definitive treatment ■	Appropriate Yes (Y) or No (N) or Inconclusive (I) or Clinical data not available (CDNA)	Comment
10	Augmentin + Azithromycin	Y	1) Tracheal aspirate 2) Midstream Urine	1) *K. aerogenes* 2) *K. pneumoniae* (CRE) (both resistant to amoxillin-clavulanic)	-	-	Empiric – severe community acquired pneumonia (CAP). CRE likely acquired in hospital – change catheter for CRE.
11	Augmentin + Azithromycin	N	1) Blood culture 2) Tracheal aspirate	1) *A. baumannii* (ESBL & CR) 2) *E. coli*	1) Piperacillin – Tazobactam 2) Colistin + Imipenem	Y	Empiric – severe CAP. Developed nosocomial infection. Escalation & directed therapy.
12	Ertapenem + Amikacin	N	Sputum	*A. baumannii* (CR & ESBL)	-	CDNA	Empiric – patient from within hospital.

Patient number	Empiric treatment ★	Appropriate Yes (Y) or No (N)	Specimen type(s)	Isolated ESKAPE pathogen(s)	Subsequent or definitive treatment ■	Appropriate Yes (Y) or No (N) or Inconclusive (I) or Clinical data not available (CDNA)	Comment
14	Augmentin + Azithromycin	N	Blood culture	*A. baumannii* (CR & ESBL)	Ceftriaxone + Moxifloxacin	CDNA	Empiric – severe CAP/meningitis Moxifloxacin - clinical concern for TB. Ceftriaxone - possible severe CAP/meningitis.
17	Piperacillin - Tazobactam + Amikacin	N	Fluid / Aspirate	1) *A. baumannii* (CR & ESBL) 2) *K. pneumoniae* 3) *E. faecium*	Imipenem + Amikacin	Y	Changed the Piptaz to broaden the cover.
20	Piperacillin - Tazobactam + Amikacin	Y	Tracheal aspirate	*S. aureus*	-	-	Empiric – patient from within hospital
23	Piperacillin - Tazobactam + Erythromycin	Y	Swab (superficial)	*P. aeruginosa*	-	-	Erythromycin – for prokinetic effect.
24	Piperacillin - Tazobactam + Amikacin	Y	Blood culture	*E. coli* (amoxicillin resistant)	-	-	Empiric – patient from within hospital.
26	Ertapenem + Amikacin	Y	Sputum	*E. cloacae*	-	-	Empiric – patient from within hospital.

Patient number	Empiric treatment ★	Appropriate Yes (Y) or No (N)	Specimen type(s)	Isolated ESKAPE pathogen(s)	Subsequent or definitive treatment ■	Appropriate Yes (Y) or No (N) or Inconclusive (I) or Clinical data not available (CDNA)	Comment
32	Piperacillin - Tazobactam + Azithromycin	Y	Blood culture	*K. pneumoniae*	Augmentin + Vancomycin	Y	Empiric – patient from within hospital. Susceptible *K. pneumoniae*, thus de-escalation. Vancomycin was not directed towards *K. pneumoniae*, but rather empiric therapy for a critical ill patient. Vancomycin stopped following the identification of *K. pneumoniae*.
36	Ertapenem	Y	Blood culture	*K. pneumoniae* (CRE)	-	-	Empiric – patient from within hospital. MIC low enough to continue with ertapenem.
46	Augmentin	Y	Fluid / Aspirate	*P. aeruginosa*	Piperacillin - Tazobactam	Y	Empiric – patient from community.

Patient number	Empiric treatment ★	Appropriate Yes (Y) or No (N)	Specimen type(s)	Isolated ESKAPE pathogen(s)	Subsequent or definitive treatment ■	Appropriate Yes (Y) or No (N) or Inconclusive (I) or Clinical data not available (CDNA)	Comment
47	Imipenem + Amikacin	Y	Blood culture	*K. pneumoniae* (CRE)	-	-	Empiric – patient from within hospital. MIC low enough to continue imipenem.
49	Piperacillin - Tazobactam	N	Blood culture	*A. baumannii* (CR & ESBL, Piptaz resistant)	-	CDNA	Empiric – patient from within hospital. Central venous catheter removed or patient deceased before directed therapy.
50	Imipenem	N	Fluid / Aspirate	1) *E. faecium* 2) *K. pneumoniae* (ESBL & CRE) 3) *P. aeruginosa*	1) Meropenem + Tigecycline 2) Ertapenem + Tigecycline	Y	Empiric – patient from within hospital. Escalation & directed therapy.
53	Ertapenem + Amikacin	Y	Blood culture	*K. pneumoniae*	Piperacillin - Tazobactam	Y	Empiric – patient from within hospital. Appropriate de-escalation of therapy.

Patient number	Empiric treatment ★	Appropriate Yes (Y) or No (N)	Specimen type(s)	Isolated ESKAPE pathogen(s)	Subsequent or definitive treatment ■	Appropriate Yes (Y) or No (N) or Inconclusive (I) or Clinical data not available (CDNA)	Comment
54	Ertapenem + Amikacin	N	1) Tracheal aspirate 2) Blood culture	1) *A. baumannii* (ESBL & CR) 2) *K. pneumoniae* (ESBL & CRE)	1) Cloxacillin + Cefazolin 2) Ertapenem + Cefazolin	CDNA	Empiric – patient from within hospital. MIC low enough to continue with ertapenem. Cefazolin – concern for staphylococcal infection.
57	Piperacillin - Tazobactam + Amikacin	Y	1) Blood culture 2) IV Catheter tip	1) *K. pneumoniae* 2) *E. faecalis*	Imipenem + Piperacillin - Tazobactam	Y	Empiric – patient from within hospital. Don't use both agents together - Piptaz alone would have covered for the *K. pneumoniae*. Potential change of therapy during the day. Catheter tip ignored (catheter removed).

Patient number	Empiric treatment ★	Appropriate Yes (Y) or No (N)	Specimen type(s)	Isolated ESKAPE pathogen(s)	Subsequent or definitive treatment ■	Appropriate Yes (Y) or No (N) or Inconclusive (I) or Clinical data not available (CDNA)	Comment
60	Piperacillin - Tazobactam + Amikacin	Y	Blood culture	*S. aureus*	Vancomycin + Cloxacillin + Gentamicin	Y	Empiric – patient from within hospital. Gentamicin – concern for endocarditis. Use of vancomycin – whilst waiting for MRSA result.
61	Augmentin	N	1) Blood culture 2) Sputum	1) *K. pneumoniae* (ESBL &CRE) 2) *P. aeruginosa*	1) Ertapenem + Amikacin 2) Colistin + Imipenem 3) Imipenem + Azithromycin	Y	Empiric – community infection. Escalation & directed therapy. Azithromycin – quorum sensing.
62	Augmentin + Azithromycin	N	Blood culture	*K. pneumoniae*	1) Piperacillin - Tazobactam + Amikacin 2) Meropenem + Amikacin	CDNA	Empiric – CAP. Meropenem – broader spectrum, possible to cover for possible CRE.
67	Piperacillin - Tazobactam	Y	Blood culture	*K. pneumoniae*	-	-	Empiric – patient from within hospital.

Patient number	Empiric treatment ★	Appropriate Yes (Y) or No (N)	Specimen type(s)	Isolated ESKAPE pathogen(s)	Subsequent or definitive treatment ■	Appropriate Yes (Y) or No (N) or Inconclusive (I) or Clinical data not available (CDNA)	Comment
68	Piperacillin - Tazobactam	N	Blood culture	*E. coli* (Resistant to ampicillin & Piperacillin-tazobactam)	-	CDNA	Empiric – patient from within hospital. Patient discharged before directed therapy started.
70	Tigecycline + Gentamicin	Y	Blood culture	*K. pneumoniae* (ESBL & CRE, meropenem Intermediate)	Tigecycline + Meropenem	Y	Gentamicin – amikacin not available. Appropriate directed therapy.
74	Meropenem + Amikacin	N	Blood culture	*E. faecalis*	-	CDNA	Possible line related sepsis and line was removed, with clinical improvement on treatment.

Patient number	Empiric treatment ★	Appropriate Yes (Y) or No (N)	Specimen type(s)	Isolated ESKAPE pathogen(s)	Subsequent or definitive treatment ■	Appropriate Yes (Y) or No (N) or Inconclusive (I) or Clinical data not available (CDNA)	Comment
77	Ertapenem + Vancomycin	N	Tracheal aspirate	*K. pneumoniae* (ESBL & CRE)	1) Meropenem + Vancomycin 2) Linezolid + Tigecycline 3) Colistin + Tigecycline	CDNA	Empiric – patient from within hospital. Linezolid & Vancomycin due to concern for Gram-positive pathogen. Resistant CRE – escalation to colistin & tigecycline.
81	Imipenem	Y	Blood culture	1) *A. baumannii* (ESBL & CR) 2) *E. faecium* (VRE)	-	-	Empiric – patient from within hospital. Continued imipenem due to clinical response. *E. faecium* – low concern.

Patient number	Empiric treatment ★	Appropriate Yes (Y) or No (N)	Specimen type(s)	Isolated ESKAPE pathogen(s)	Subsequent or definitive treatment ■	Appropriate Yes (Y) or No (N) or Inconclusive (I) or Clinical data not available (CDNA)	Comment
84	Ertapenem + Vancomycin	Y	Tracheal aspirate	1) *P. aeruginosa* 2) *S. aureus*	Meropenem	Y	Empiric – patient from within hospital. Escalation to cover the *P. aeruginosa*.
85	Augmentin + Clindamycin	N	1) Wound aspirate 2) Blood culture	1) *A. baumannii* (ESBL & CR) 2) *K. pneumoniae* (ESBL & CRE)	-	CDNA	Empiric – possible SSI. Directed therapy not initiated – patient discharged before results.
87	Augmentin	Y	Wound aspirate	*E. coli* (Augmentin resistant)	-	-	Empiric – community infection. Isolated pathogen not deemed to be invasive.
91	Piperacillin - Tazobactam	Y	1) Blood culture 2) Tracheal aspirate	1) *K. pneumoniae* 2) *E. cloacea*	1) Ertapenem + Vancomycin 2) Cefepime 3) Ertapenem	Y	Empiric – patient from within hospital. Ertapenem – final directed therapy for ESBL pathogens.

Patient number	Empiric treatment ★	Appropriate Yes (Y) or No (N)	Specimen type(s)	Isolated ESKAPE pathogen(s)	Subsequent or definitive treatment ■	Appropriate Yes (Y) or No (N) or Inconclusive (I) or Clinical data not available (CDNA)	Comment
92	Augmentin + Clindamycin	N	Tissue	1) *A. baumannii* (ESBL & CR) 2) *E. faecium*	Cefepime	CDNA	Empiric – community infection. Isolated pathogens not deemed to be invasive.
94	Piperacillin - Tazobactam	Y	Blood culture	*E. coli*	Ertapenem	Y	Empiric – patient from within hospital. Possible concern for ESBL, or patient not clinically improving.
95	Piperacillin - Tazobactam + Vancomycin	N	Blood culture	*K. pneumoniae* (ESBL & CRE)	1) Meropenem + Tigecycline + Azithromycin 2) Imipenem + Colistin + Tigecycline + Amikacin	Y	Empiric – patient from within hospital. Escalation & directed therapy – high MICs.

Patient number	Empiric treatment ★	Appropriate Yes (Y) or No (N)	Specimen type(s)	Isolated ESKAPE pathogen(s)	Subsequent or definitive treatment ■	Appropriate Yes (Y) or No (N) or Inconclusive (I) or Clinical data not available (CDNA)	Comment
96	Piperacillin - Tazobactam	N	Blood culture	*K. pneumoniae* (ESBL & CRE)	1) Ertapenem + Vancomycin + Amikacin 2) Meropenem + Colistin	Y	Empiric – patient from within hospital. Escalation & directed therapy – high MICs.
97	Meropenem + Amikacin + Vancomycin	Y	Blood culture	1) *K. pneumoniae* (ESBL & CRE) 2) *S. aureus* (MRSA)	Colistin + Tigecycline	Y	Empiric – patient from within hospital. Escalation & directed therapy. Tigecyclin – cover ESBL & *Staphylococcus*.
100	Piperacillin - Tazobactam + Azithromycin	Y	Sputum	*P. aeruginosa*	1) Ertapenem + Amikacin 2) Ciprofloxacin	Y	Empiric – patient from within hospital. Ciprofloxacin susceptible.

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101	Ertapenem	N	1) Tissue 2) Blood culture 3) Swab (superficial)	1) *E. faecium* (VRE) & *E. faecalis* 2) *A. baumannii* (ESBL & CR) 3) *E. cloacae* (ESBL)	1) Colistin + Meropenem 2) Augmentin	Y	Empiric – patient from within hospital. Escalation & directed therapy. Augmentin – subsequent infection after blood stream infection.
105	Meropenem + Amikacin	Y	Blood culture	1) *A. baumannii* (ESBL & CR) 2) *P. aeruginosa* (ESBL & CR)	Colistin + Meropenem	Y	Empiric – patient from within hospital. Escalation & directed therapy.
107	Augmentin + Azithromycin	Y	Fluid / Aspirate	*E. faecium*	-	-	Empiric – severe CAP. Isolated pathogen not deemed to be invasive.
108	Ertapenem + Amikacin	N	Fluid / Aspirate	*A. baumannii* (ESBL & CR)	1) Tigecycline + Meropenem 2) Colistin	Y	Empiric – patient from within hospital. Escalation & directed therapy.
109	Piperacillin - Tazobactam	Y	Wound aspirate	1) *K. pneumoniae* 2) *E. coli*	-	-	Empiric – patient from within hospital.

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110	Ertapenem + Amikacin + Azithromycin	N	Blood culture	*E. faecium*	-	-	Empiric – patient from within hospital. Patient deceased before directed therapy.
111	Piperacillin - Tazobactam + Augmentin	N	Midstream urine	*E. cloacae* (ESBL)	Meropenem	Y	Possible transcription missing from chart for change to Piptaz from Augmentin. Escalation to meropenem due to concern for UTI.
112	Piperacillin - Tazobactam	N	Catheter urine	*E. faecium*	-	CDNA	Empiric – patient from within hospital. Isolated pathogen not deemed to be invasive.
113	Vancomycin + Amikacin	N	Urine	*K. pneumoniae* (ESBL & CRE)	Ertapenem + Erythromycin	Y	Ertapenem to cover the ESBL, and the CRE if MICs are low enough. Erythromycin – prokinetic effect.

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116	Augmentin + Clindamycin	Y	Tissue	1) *E. cloacae* 2) *K. aerogenes* (both resistant to Augmentin)	-	-	Empiric – possible SSI. Isolated pathogens not deemed to be invasive.
117	Colistin + Meropenem	Y	Blood culture	*K. pneumoniae* (ESBL & CRE)	-	-	Empiric – patient from within hospital; already on directed therapy.
123	Augmentin	Y	Swab (superficial	*E. coli* (ESBL)	-	-	Empiric – community infection. Isolated pathogen not deemed to be invasive.
124	Piperacillin - Tazobactam + Amikacin	N	1) Blood culture 2) Tracheal Aspirate	1) *A. baumannii* & *K. pneumoniae* (ESBL & CRE) 2) *P. aeruginosa* (ESBL & CR)	1) Meropenem + Tigecycline 2) Colistin + Tigecycline 3) Ceftazidime-Avibactam + Colistin	Y	Empiric – patient from within hospital. Escalation & directed therapy. Colistin – high MIC or NDM component
126	Piperacillin - Tazobactam + Vancomycin	Y	Blood culture	*E. coli*	-	-	Empiric – patient from within hospital.

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127	Augmentin	N	Urine	*K. aerogenes* (ESBL)	1) Erythromycin 2) Piperacillin – Tazobactam 3) Ertapenem	CDNA	Empiric – community infection. Escalation of therapy.
128	Piperacillin - Tazobactam	Y	Blood culture	*K. pneumoniae* (ESBL)	Ertapenem	Y	Empiric – patient from within hospital. Escalation of therapy.
129	Piperacillin - Tazobactam	N	1. Urine 2. Tracheal aspirate	1. *K. pneumoniae* (ESBL & CRE) 2. *S. aureus*	Cefepime	CDNA	Empiric – patient from within hospital. Isolated pathogens not deemed to be invasive.
131	Augmentin	N	1. Blood culture 2. Fluid / Aspirate	1. *K. aerogenes* 2. *K. pneumoniae* (ESBL & CRE) & *E. cloacae* (ESBL & CRE) & *A. baumannii* (ESBL & CR) & *P. aeruginosa*	1) Piperacillin – Tazobactam + Vancomycin 2) Meropenem + Amikacin 3) Colistin + Tigecycline 4) Cefepime	Y	Empiric – community infection. Escalation & directed therapy.

Patient number	Empiric treatment ★	Appropriate Yes (Y) or No (N)	Specimen type(s)	Isolated ESKAPE pathogen(s)	Subsequent or definitive treatment ■	Appropriate Yes (Y) or No (N) or Inconclusive (I) or Clinical data not available (CDNA)	Comment
132	Piperacillin - Tazobactam + Amikacin	Y	Tracheal aspirate	1. *K. pneumoniae* 2. *E. coli*	Piperacillin - Tazobactam + Ertapenem	Y	Empiric – patient from within hospital.
134	Piperacillin - Tazobactam	N	1. Tissue 2. Fluid / Aspirate	1. *S. aureus* (MRSA) 2. *A. baumannii* (ESBL, CR, colistin) & *K. pneumoniae* (ESBL, CRE & colistin)	1) Ertapenem 2) Meropenem + Tigecycline + Azithromycin 3) Imipenem + Tigecycline + Azithromycin	Y	Empiric – patient from within hospital. Combination of imipenem & colistin for MDR pathogens. Azithromycin – quorum sensing.
138	Piperacillin - Tazobactam + Amikacin	Y	1. Sputum 2. Blood culture 3. Tracheal aspirate	1. *K. aerogenes* 2. *K. pneumoniae* (ESBL) 3. *P. aeruginosa*	1) Cefepime 2) Ertapenem	Y	Empiric – patient from within hospital. Cefepime – Piptaz out of stock. Ertapenem – directed therapy.
140	Augmentin + Azithromycin	N	Blood culture	*E. faecium* (amoxicillin resistant	1) Ceftriaxone 2) Ertapenem + Amikacin	CDNA	Empiric – CAP. Possible line related infection.

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141	Augmentin + Clindamycin	N	Abscess swab	*E. coli* (Augmentin resistant)	-	CDNA	Empiric – possible SSI. Isolated pathogen not deemed to be invasive.
142	Gentamicin	N	Blood culture	*K. pneumoniae* (ESBL & CRE)	-	CDNA	Empiric – from within hospital.
144	Ertapenem + Amikacin + Vancomycin	Y	1. Sputum 2. Tracheal aspirate 3. Blood culture	1. *K. pneumoniae* (ESBL) 2. *E. coli* & *P. aeruginosa* 3. *E. faecalis*	1) Imipenem + Colistin 2) Imipenem + Vancomycin	Y	Empiric – patient from within hospital. Escalation & directed therapy in critically ill patient.
145	Augmentin	N	1. Sputum 2. Blood culture	*1. E. coli* (ESBL & CR) & *E. cloacae* 2. *P. aeruginosa* (ESBL & CR)	1) Ertapenem + Amikacin 2) Piperacillin – Tazobactam 3) Colistin + Cefepime	CDNA	Empiric – community infection. Escalation & directed therapy once full susceptibility reports. Combination to cover CRE.

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147	Ertapenem + Amikacin + Vancomycin	N	1. Blood culture 2. Tracheal aspirate 3. Catheter urine	1. *A. baumannii* & *K. pneumoniae* 2. *P. aeruginosa* (ESBL & CR) 3. *K. aerogenes* (ESBL & CRE)	Colistin + Tigecycline	Y	Empiric – patient from within hospital. Escalation & directed therapy.
149	Piperacillin - Tazobactam + Amikacin	Y	1. Blood culture 2. Tracheal aspirate 3. Unknown	1. *E. faecalis* & *E. cloacae* & *A. baumannii* (ESBL & CR) 2. *K. aerogenes* 3. *P. aeruginosa*	1) Ertapenem + Vancomycin 2) Colistin + Tigecycline	Y	Empiric – patient from within hospital. Escalation & directed therapy.
150	Augmentin	N	Blood culture	*K. pneumoniae* (ESBL, CRE & Piptaz resistant)	Piperacillin - Tazobactam + Amikacin + Vancomycin	CDNA	Empiric – community infection. Changed to Piptaz before full susceptibility report.
153	Piperacillin - Tazobactam	Y	1. Blood culture 2. Unknown	1. *A. baumannii* (ESBL & CR) 2. *P. aeruginosa*	1) Ertapenem 2) Colistin + Tigecycline + Amikacin	Y	Empiric – patient from within hospital. Escalation & directed therapy.

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154	Ertapenem + Amikacin + Vancomycin	Y	Tracheal aspirate	1. *E cloacae* 2. *K. pneumoniae* (ESBL & CRE)	-	-	Empiric – patient from within hospital. Vancomycin – Gram positive cover.
156	Meropenem + Amikacin + Vancomycin	Y	1. Urine 2. Blood culture	1. *E. cloacae* (ESBL) 2. *K. pneumoniae* (ESBL & CRE) & *P. aeruginosa*	Colistin + Tigecycline	Y	Empiric – patient from within hospital. Escalation & directed therapy.
158	Piperacillin - Tazobactam + Amikacin	Y	Blood culture	*K. pneumoniae*	-	-	Empiric – patient from within hospital.
160	Piperacillin - Tazobactam + Amikacin + Vancomycin	N	Blood culture	*A. baumannii*	Imipenem	Y	Empiric – patient from within hospital. Directed therapy.

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162	Augmentin + Clindamycin	N	1. Tissue 2. Tracheal aspirate 3. Blood culture 4. Sputum	1. *E. faecium* & *E. cloacae* 2. *E. coli* (Augmentin resistant) 3. *A. baumannii* 4. *P. aeruginosa* (ESBL & CR)	Cefepime + Vancomycin	Y	Empiric – possible SSI. Directed therapy.
163	Piperacillin - Tazobactam	N	1. Superficial swab 2. Bile 3. Fluid / Aspirate	1. *E. cloacae* 2. *A. baumannii* 3. *K. pneumoniae* & *P. aeruginosa*	1) Ertapenem + Amikacin 2) Imipenem + Colistin	Y	Empiric – patient from within hospital. Escalation & directed therapy.
164	Augmentin	N	Blood culture	*A. baumannii*	-	CDNA	Empiric – community infection. Patient discharged before culture result.

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168	Piperacillin - Tazobactam	N	1. Blood culture 2. Fluid / Aspirate	1. *E. coli* 2. *K. pneumoniae* (ESBL & CRE)	1) Ertapenem + Amikacin 2) Cloxacillin + Vancomycin 3) Cloxacillin + Imipenem	CDNA	Empiric – patient from within hospital. Imipenem – directed therapy for CRE. Cloxacillin – possible phlebitis?
169	Imipenem	Y	Blood culture	*E. coli* (amoxicillin resistant)	-	-	Empiric – patient from within hospital.
171	Piperacillin - Tazobactam + Cloxacillin	N	Tracheal aspirate	*P. aeruginosa* (ESBL, CR & Piptaz resistant)	-	CDNA	Empiric – patient from within hospital. Isolated pathogen not deemed to be invasive.

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172	Piperacillin - Tazobactam	Y	1. Tracheal aspirate 2. Blood culture	1. *A. baumannii* (ESBL, CR & Piptaz resistant) 2. *E. faecalis* & *E. coli* (ESBL) & *K. aerogenes* (ESBL, CRE & Piptaz) & *K. pneumoniae* (ESBL, CRE & Piptaz)	1) Imipenem 2) Piperacillin – Tazobactam + Amikacin 3) Colistin + Meropenem 4) Colistin + Imipenem	Y	Empiric – patient from within hospital. Escalation & directed therapy – identification of the CRE MICs of the bloodstream pathogens.
173	Augmentin	Y	Tissue	*E. coli*	Ertapenem	Y	Empiric – community infection. Escalation of therapy.
174	Piperacillin - Tazobactam	Y	1. Tracheal aspirate 2. Blood culture	1. *A. baumannii* & *P. aeruginosa* 2. *K. aerogenes* (all ESBL, CR & Piptaz resistant)	1) Tigecycline 2) Colistin + Amikacin 3) Meropenem + Amikacin	Y	Empiric – patient from within hospital. Colistin for the CRE – swop to meropenem once MICs are shown to be favourable.

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175	Augmentin + Clindamycin	N	Blood culture	*E. cloacae* (Augmentin resistant)	-	-	Empiric – possible SSI. Patient deceased before culture results.
178	Ertapenem	Y	Blood culture	*K. pneumoniae*	-	-	Empiric – patient from within hospital.
180	Piperacillin - Tazobactam	N	Fluid / Aspirate	1. *K. pneumoniae* (ESBL, CRE & Piptaz resistant) 2. *E. faecium* (amoxicillin resistant)	-	CDNA	Empiric – patient from within hospital. Isolated pathogens not deemed to be invasive.
182	Augmentin + Clindamycin	N	1. Wound aspirate 2. Tracheal aspirate 3. Fluid / Aspirate	1. *E. coli* & *P. aeruginosa* & *E. faecium* 2. *A. baumannii* (ESBL & CR) 3. *K. pneumoniae* (ESBL & CRE)	1) Piperacillin - Tazobactam + Amikacin 2) Azithromycin 3) Ceftazidime + Gentamicin 4) Imipenem + Amikacin	Y	Empiric – possible SSI. Piptaz – broader spectrum. Azithromycin – quorum sensing. Agents broadened based on microbiological results & discussion with the microbiology team.

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183	Augmentin + Piperacillin - Tazobactam	N	Blood culture	*A. baumannii* (ESBL, CR & Piptaz resistant)	Piperacillin - Tazobactam	CDNA	Empiric – possible switch from Augmentin to Piptaz on same day missing from chart. Possible catheter removal and patient clinically improved.
184	Ceftriaxone	N	1. Blood culture 2. Tracheal aspirate	1. *E. faecalis* & *E. cloacae* (ESBL) & *K. pneumoniae* (ESBL & CRE) 2. *A. baumannii* (ESBL & CR) & *P. aeruginosa* (ESBL)	1) Piperacillin – Tazobactam + Amikacin 2) Imipenem	Y	Empiric – ceftriaxone used in some wards due to broader spectrum than Augmentin. Escalation & directed therapy.
187	Augmentin	N	Blood culture	*A. baumannii* (ESBL, CR, Piptaz & Colistin resistant)	-	-	Empiric – community infection. Patient discharged before culture results.

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190	Meropenem + Amikacin + Vancomycin	N	Urine	*E. faecium*	-	CDNA	Empiric – patient from within hospital. Isolated pathogen not deemed to be invasive.
191	Piperacillin - Tazobactam	Y	1. Tracheal aspirate 2. Blood culture	1. *K. pneumoniae* (ESBL & Piptaz resistant) 2. *K. aerogenes* (ESBL & Piptaz resistant) & *P. aeruginosa*	-	-	Empiric – patient from within hospital. Patient deceased before culture results.
193	Augmentin	N	Sputum	*K. pneumoniae* (ESBL & CRE)	1) Imipenem + Amikacin 2) Clindamycin	CDNA	Empiric – community infection. Isolated pathogens not deemed to be invasive.

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196	Ceftriaxone	Y	1. Blood culture 2. Urine 3. IV catheter tip 4. Unknown	1. *A. baumannii* (ESBL) & *K. pneumoniae* (ESBL & CRE) 2. *E. faecium* 3. *E. coli* (ESBL) 4. *P. aeruginosa*	1) Ceftazidime + Amikacin 2) Colistin + Imipenem	Y	Initial empiric treatment. Subsequent escalation & directed therapy.
197	Augmentin + Clindamycin	N	Blood culture	1. *K. aerogenes* (Augmentin & Piptaz resistant) 2. *E. faecium*	-	-	Empiric – possible SSI. Patient discharged before culture results.
199	Augmentin	N	1. Tracheal aspirate 2. Superficial swab 3. Urine	1. *E. coli* (Augmentin resistant) & *P. aeruginosa* 2. *S. aureus* 3. *K. pneumoniae* (ESBL & CRE)	1) Piperacillin – Tazobactam 2) Amikacin	Y	Empiric – community infection. Escalation & directed therapy.

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203	Augmentin	N	Blood culture	1. *E. coli* (Augmentin & Piptaz resistant) 2. *K. pneumoniae* (ESBL, CRE & Piptaz resistant) 3. *P. aeruginosa*	1) Piperacillin – Tazobactam 2) Imipenem + Amikacin + Ceftazidime 3) Colistin + Imipenem + Amikacin 4) Imipenem 5) Piperacillin – Tazobactam	Y	Empiric – community infection. Piptaz – broader spectrum. Escalation & directed therapy. Piptaz continued for longer to treat the *P. aeruginosa*.
204	Augmentin	N	1. Blood culture 2. Fluid / Aspirate	1. *E. faecalis* & *E. cloacae* (Augmentin resistant) 2. *K. pneumoniae* (ESBL, CRE & Piptaz resistant)	1) Piperacillin – Tazobactam 2) Ertapenem 3) Cefepime + Amikacin	Y	Empiric – community infection. Escalation & directed therapy. Cefepime (de-escalation) – cover the blood culture pathogens.
205	Augmentin + Azithromycin	N	Tracheal aspirate	*P. aeruginosa*	-	CDNA	Empiric – severe CAP. Isolated pathogen not deemed to be invasive.

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206	Piperacillin - Tazobactam	Y	Blood culture	*A. baumannii* (ESBL & Piptaz resistant)	1) Cefepime 2) Ceftriaxone	CDNA	Empiric – patient from within hospital. Possible removal of central venous catheter & de-escalation of therapy.
208	Meropenem + Amikacin	Y	Blood culture	1. *K. pneumoniae* (ESBL & CRE) 2. *A. baumannii* (ESBL, CR & Colistin resistant) 3. *P. aeruginosa*	1) Tigecycline 2) Meropenem + Amikacin	CDNA	Empiric – patient from within hospital. Possible low MICs.
209	Cloxacillin	Y	Blood culture	*S. aureus*	Piperacillin - Tazobactam	CDNA	Piptaz – to cover possible an additional problem.

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210	Piperacillin - Tazobactam + Amikacin	Y	1. Gastric aspirate 2. Fluid / Aspirate 3. Blood culture	1. *A. baumannii* (ESBL & CRE) 2. *E. cloacae* 3. *K. pneumoniae* (ESBL) & *P. aeruginosa* (CRE)	-	-	Empiric – patient from within hospital.
214	Ertapenem + Amikacin	Y	Catheter urine	*K. pneumoniae* (ESBL & CRE)	-	-	Empiric – from within hospital. Low MIC for CRE & use of dual therapy. Catheter changed and clinical response.
218	Augmentin	N	Tracheal aspirate	*K. pneumoniae* (ESBL, CRE & Augmentin resistant)	Colistin + Imipenem	Y	Empiric – community infection. Escalation & directed therapy.

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225	Piperacillin - Tazobactam + Amikacin	Y	Blood culture	*A. baumannii* (ESBL, CR, Piptaz & Colistin resistant)	Ertapenem	CDNA	Empiric – patient from within hospital. Ertapenem – broader cover. Possible removal of central venous catheter, as likely the source of infection, therefore escalation of therapy not needed.

Patient number	Empiric treatment ★	Appropriate Yes (Y) or No (N)	Specimen type(s)	Isolated ESKAPE pathogen(s)	Subsequent or definitive treatment ■	Appropriate Yes (Y) or No (N) or Inconclusive (I) or Clinical data not available (CDNA)	Comment
226	Ceftriaxone	N	1. Blood culture 2. CSF	1. *A. baumannii* & *K. pneumoniae* & *P. aeruginosa* (previous 3 all ESBL, CR & Piptaz resistant) & *E. faecium* 2. *E. faecalis*	1) Moxifloxacin + Amikacin 2) Ertapenem + Amikacin 3) Colistin + Imipenem 4) Colistin + Meropenem 5) Meropenem + Tigecycline	CDNA	Empiric – from within hospital. Ceftriaxone – meningitis cover Moxifloxacin – concern for TB. After the culture results – Carbapenem & Colistin combination. Antimicrobial regimen suggested following infectious diseases and microbiology consultation.
227	Piperacillin - Tazobactam	Y	1. Sputum 2. Fluid / Aspirate	1. *E. coli* 2. *K. pneumoniae* (ESBL & CRE)	-	-	Empiric – patient from within hospital.
229	Augmentin	N	Blood culture	*E. coli* (Augmentin resistant / ESBL)	Imipenem	Y	Empiric – community infection. Escalation of therapy due to ESBL.

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231	Augmentin	N	Blood culture	1. *A. baumannii* (Colistin resistant) 2. *K. pneumoniae* (both ESBL, CR & Piptaz resistant)	1) Piperacillin – Tazobactam 2) Ertapenem + Amikacin	CDNA	Empiric – community infection. Escalation of therapy. Patient discharged before culture results.
232	Piperacillin - Tazobactam + Amikacin	Y	1. Blood culture 2. Fluid / Aspirate	1. *A. baumannii* 2. *K. pneumoniae* (Colistin resistant) (both ESBL, CR & Piptaz resistant)	Meropenem	N	Empiric – patient from within hospital. Escalation of treatment. Patient deceased before culture results.
234	Piperacillin - Tazobactam	Y	1. Blood culture 2. Abscess aspirate 3. Superficial swab	1. *E. cloacae* 2. *A. baumannii* & *K. pneumoniae* (ESBL & Piptaz resistant) 3. *P. aeruginosa* (CR)	Imipenem + Vancomycin	Y	Empiric – patient from within hospital. Escalation & directed therapy, with clinical response.

Patient number	Empiric treatment ★	Appropriate Yes (Y) or No (N)	Specimen type(s)	Isolated ESKAPE pathogen(s)	Subsequent or definitive treatment ■	Appropriate Yes (Y) or No (N) or Inconclusive (I) or Clinical data not available (CDNA)	Comment
235	Vancomycin	N	1. Tracheal aspirate 2. Blood culture	1. *A. baumannii* (ESBL, CR & Piptaz resistant) & *P. aeruginosa* (CR) 2. *E. coli & K. pneumoniae* (ESBL, CRE & Piptaz resistant)	Colistin + Imipenem	Y	Escalation & directed therapy.
236	Augmentin	N	Tracheal aspirate	*E. coli* (Augmentin resistant)	-	CDNA	Empiric – community infection. Isolated pathogen not deemed to be invasive.
237	Augmentin	N	1. Urine 2. Tracheal aspirate	1. *K. pneumoniae* 2. *K. aerogenes* (Augmentin resistant) & *P. aeruginosa* (CR)	-	CDNA	Empiric – community infection. Isolated pathogens not deemed to be invasive.

Patient number	Empiric treatment ★	Appropriate Yes (Y) or No (N)	Specimen type(s)	Isolated ESKAPE pathogen(s)	Subsequent or definitive treatment ■	Appropriate Yes (Y) or No (N) or Inconclusive (I) or Clinical data not available (CDNA)	Comment
240	Augmentin	N	1. Sputum 2. Blood culture	1. *A. baumannii* (ESBL, CR & Piptaz resistant) 2. *E. faecium* & *K. pneumoniae* (ESBL, CRE & Piptaz resistant)	1) Ciprofloxacin + Amikacin 2) Imipenem + Amikacin 3) Meropenem + Amikacin 4) Colistin + Meropenem	Y	Empiric – community infection. Ciprofloxacin – some isolates susceptible. Escalation & directed therapy. Colistin – high MICs. Clinical response.
243	Ceftriaxone + Gentamicin + Vancomycin	Y	Blood culture	*E. coli*	1) Cefepime 2) Imipenem	Y	Empiric – patient from within hospital. Likely ESBL – directed therapy.

Patient number	Empiric treatment ★	Appropriate Yes (Y) or No (N)	Specimen type(s)	Isolated ESKAPE pathogen(s)	Subsequent or definitive treatment ■	Appropriate Yes (Y) or No (N) or Inconclusive (I) or Clinical data not available (CDNA)	Comment
244	Piperacillin - Tazobactam	Y	1. Tracheal aspirate 2. Blood culture	1. *A. baumannii* (ESBL, CR & Piptaz resistant) & *P. aeruginosa* 2. *E. faecium* & *E. coli* & *K. pneumoniae* (ESBL, CRE & Piptaz resistant)	Imipenem + Vancomycin	Y	Empiric – patient from within hospital. Escalation & directed therapy – low MIC for imipenem use.
246	Meropenem	N	Tracheal aspirate	*A. baumannii* (ESBL, CR & Piptaz resistant)	Piperacillin - Tazobactam	Y	Isolated pathogen not deemed to be invasive, thus de-escalation of therapy. Clinical decision based on the fact that the specimen was a tracheal aspirate only.

Patient number	Empiric treatment ★	Appropriate Yes (Y) or No (N)	Specimen type(s)	Isolated ESKAPE pathogen(s)	Subsequent or definitive treatment ■	Appropriate Yes (Y) or No (N) or Inconclusive (I) or Clinical data not available (CDNA)	Comment
250	Piperacillin - Tazobactam	N	Superficial swab	*E. faecium* (Piptaz resistant)	-	CDNA	Empiric – patient from within hospital. Isolated pathogen not deemed to be invasive.
251	Cloxacillin + Ciprofloxacin + Amikacin	Y	Blood culture	1. *S. aureus* 2. *K. pneumoniae* (ESBL)	Moxifloxacin + Amikacin	Y	Empiric – patient from within hospital. Ciprofloxacin used until moxifloxacin was available. Moxifloxacin – TB concern. Directed therapy.
252	Piperacillin - Tazobactam	Y	1. Blood culture 2. Superficial swab	1. *A. baumannii* (ESBL, CR & Piptaz resistant) 2. *P. aeruginosa*	Imipenem + Amikacin	Y	Empiric – patient from within hospital. Escalation & directed therapy – low MIC for imipenem use.
258	Augmentin	N	Fluid / Aspirate	*E. cloacae*	Piperacillin – Tazobactam + Amikacin	Y	Empiric – community infection. Escalation & directed therapy.

Patient number	Empiric treatment ★	Appropriate Yes (Y) or No (N)	Specimen type(s)	Isolated ESKAPE pathogen(s)	Subsequent or definitive treatment ■	Appropriate Yes (Y) or No (N) or Inconclusive (I) or Clinical data not available (CDNA)	Comment
262	Piperacillin - Tazobactam	Y	1. Sputum 2. Blood culture	1. *K. aerogenes* (ESBL, CRE & Piptaz resistant) 2. *P. aeruginosa* (Piptaz intermediate)	Ceftazidime + Amikacin	Y	Empiric – patient from within hospital. Escalation & directed therapy. Dual initial therapy for critically ill patient until susceptibility is available.
264	Piperacillin - Tazobactam	Y	Fluid / Aspirate	1. *E. faecium* 2. *E. coli* 3. *K. pneumoniae*	-	-	Empiric – patient from within hospital.
268	Augmentin	N	1. Tracheal aspirate 2. Urine	1. *P. aeruginosa* 2. *K. pneumoniae* (ESBL, CRE, Augmentin & Piptaz resistant)	-	CDNA	Empiric – community infection. Isolated pathogens not deemed to be invasive.
269	Augmentin	N	Blood culture	*A. baumannii* (ESBL, CR, Piptaz & Colistin resistant)	-	-	Empiric – community infection. Patient deceased before culture results.

Patient number	Empiric treatment ★	Appropriate Yes (Y) or No (N)	Specimen type(s)	Isolated ESKAPE pathogen(s)	Subsequent or definitive treatment ■	Appropriate Yes (Y) or No (N) or Inconclusive (I) or Clinical data not available (CDNA)	Comment
271	Meropenem	Y	Fluid / Aspirate	*E. cloacae*	-	-	Empiric – patient from within hospital.
272	Ceftriaxone	Y	Blood culture	*A. baumannii* (ESBL, CR, Piptaz & Colistin resistant)	-	-	Empiric – patient from within hospital. Patient deceased before culture results.
273	Piperacillin - Tazobactam + Clindamycin	Y	1. Blood culture 2. Tissue	1. *A. baumannii* & *K. pneumoniae* (both ESBL, CR & Piptaz resistant) 2. *E. faecium* & *E. coli* (ESBL)	Imipenem	Y	Empiric – patient from within hospital & SSI. Directed therapy – low MIC for imipenem use.

◆ Y = Appropriate for the isolated ESKAPE pathogens, N = Not appropriate for the isolated ESKAPE pathogens, I = Inconclusive – multiple antimicrobial regimens or multiple ESKAPE pathogens.

★ Empiric treatment was taken as the first antimicrobial treatment administered during the patient's admission to the ICU.

■ If there is no treatment noted under subsequent or definitive treatment, this means that the empiric treatment was not changed.

All resistance mechanisms have been documented in the above table and throughout the document for completeness; however, it is convention to utilize highest level of resistance documented in the laboratory.

Table 4.10: A summary of the empiric antimicrobial treatment prescribed in the ICU

Empiric antimicrobial treatment ★	**Number of patients (*n* = 132)**
Piperacillin + tazobactam	27 (20.5%)
Amoxicillin + clavulanic acid	25 (18.9%)
Piperacillin + tazobactam & Amikacin	13 (9.8%)
Amoxicillin + clavulanic acid & Clindamycin	8 (6.1%)
Amoxicillin + clavulanic acid & Azithromycin	7 (5.3%)
Ertapenem & Amikacin	7 (5.3%)
Ceftriaxone	4 (3%)
Ertapenem	3 (2.3%)
Ertapenem & Amikacin & Vancomycin	3 (2.3%)
Imipenem	3 (2.3%)
Meropenem & Amikacin	3 (2.3%)
Meropenem & Amikacin & Vancomycin	3 (2.3%)
Amoxicillin + clavulanic acid & Piperacillin + tazobactam	2 (1.5%)
Ertapenem & Vancomycin	2 (1.5%)
Imipenem & Amikacin	2 (1.5%)
Meropenem	2 (1.5%)
Piperacillin + tazobactam & Azithromycin	2 (1.5%)
Piperacillin + tazobactam & Vancomycin	2 (1.5%)
Cefazolin & Clindamycin	1 (0.76%)
Ceftriaxone & Gentamicin & Vancomycin	1 (0.76%)
Cloxacillin	1 (0.76%)
Cloxacillin & Ciprofloxacin & Amikacin	1 (0.76%)
Colistin & Meropenem	1 (0.76%)
Ertapenem & Amikacin & Azithromycin	1 (0.76%)
Gentamicin	1 (0.76%)
Piperacillin + tazobactam & Amikacin & Vancomycin	1 (0.76%)
Piperacillin + tazobactam & Clindamycin	1 (0.76%)
Piperacillin + tazobactam & Cloxacillin	1 (0.76%)
Piperacillin + tazobactam & Erythromycin	1 (0.76%)
Tigecycline & Gentamicin	1 (0.76%)
Vancomycin	1 (0.76%)
Vancomycin & Amikacin	1 (0.76%)

★ Empiric treatment was taken as the first antimicrobial treatment administered during the patient's admission to the ICU.

Of the 132 patients, 64 patients (48.5%) received appropriate empiric antimicrobial therapy. The most common empiric antimicrobial treatment was piperacillin with tazobactam (37.9%), followed by amoxicillin-clavulanic acid (31.8%). Of the 132 patients, 82 patients (62.1%)

received different antimicrobial treatment relative to the primary prescribed empiric treatment. The most common definitive antimicrobial treatment was ertapenem (19%), followed by piperacillin-tazobactam (17%). The definitive or subsequent antimicrobial treatment was appropriate for 61 patients (74.4%) and not appropriate or clinical data missing, that could account for the appropriateness, for 21 patients (25.6%). When considering the final antimicrobial treatment received by the patient, whether it was empiric or definitive, the following results can be found: 87 patients (66%) received appropriate antimicrobial treatment, 6 patients (4.5%) did not receive appropriate treatment, and 39 patients (29.5%) had clinical data not available and thus appropriateness could not be determined.

4.4 Rectal swabs

Rectal swab screening for carbapenem-resistant Enterobacterales was performed in 91 (69%) patients, from whom ESKAPE pathogens were subsequently isolated (n=132). Of the 91 patients for whom rectal swab screening was performed, 10 of the rectal swabs tested positive for CRE (10.98%). Figure 4.6 illustrates the rectal swab screening results for the 91 patients.

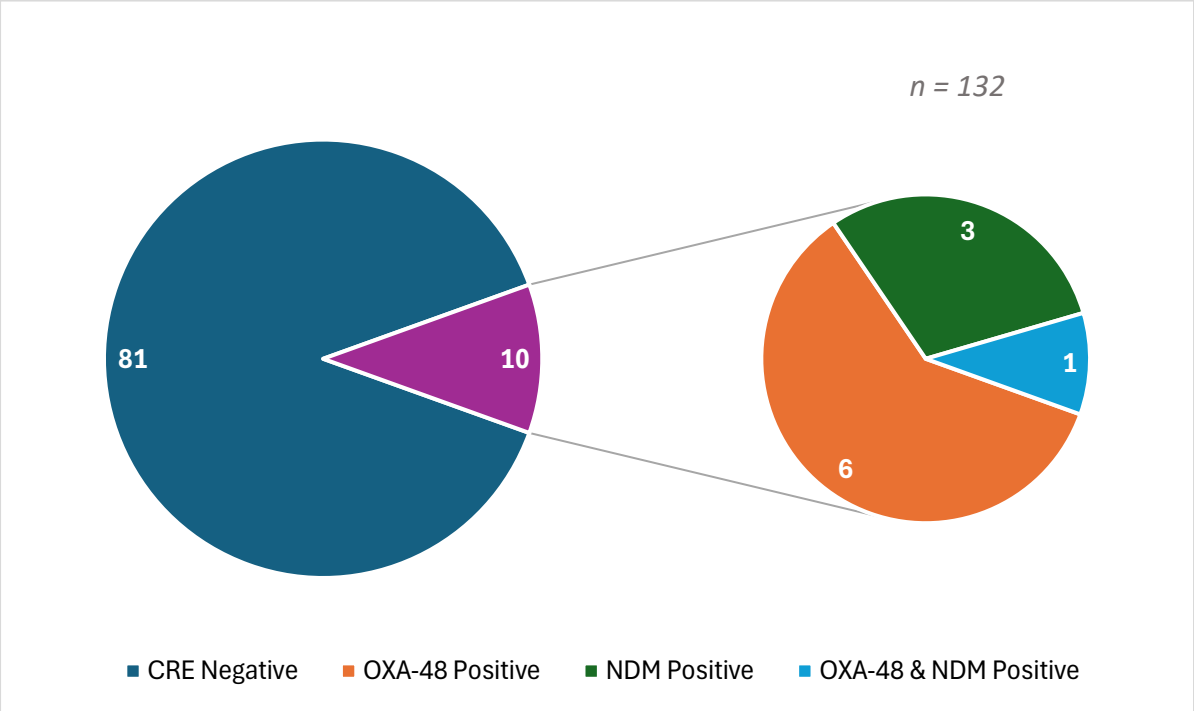

Figure 4.6: Rectal swab screening results (*n* = 91).

The most common carbapenemase was OXA-48 and variants (63.6%), followed by NDM (New Delhi metallo β lactamase) (36.4%). One of the rectal swabs screened positive for both OXA-48 and NDM. Table 4.11 summarizes the patient information for the patients whose rectal swabs tested positive for CRE.

Table 4.11: Patients who screened positive for CRE

Patient number	Age	Gender	Point of referral (within or outside of CMJAH)	Length of ICU stay (days)	Subsequent CRE infection
5	61	F	Outside	25	Yes
9	25	M	Outside	19	Yes
14	34	M	Outside	7	Yes
53	45	F	Outside	9	No
74	51	F	Within	3	No
95	65	M	Within	31	Yes
153	28	F	Within	22	No
156	45	M	Outside	14	Yes
208	32	M	Within	32	Yes
214	67	M	Within	2	Yes

For the patients who screened positive for CRE, the length of the ICU stay varied and half of the patients were referred from outside of CMJAH. Of the ten patients who screened positive for CRE, seven subsequently developed a CRE infection. Table 4.12 below compares the length of stays for patients who received pre-admission rectal swab screening and those who did not during the study period.

Table 4.12: Comparing length of stay for patients who received pre-admission rectal swab screening and those who did not receive screening.

Rectal swab screening	Average length of stay in days (SD)	p-value
Screened	20.7 (±21.4)	0.31
Not Screened	16.8 (±19.7)	
CRE Positive	16.4 (±10.5)	0.27
CRE Negative	21.3 (±22.4)	

The difference in length of stay for patients with and without rectal swab screening was not statistically significant (p = 0.31). The difference in length of stay for patients who screened positive for CRE versus negative for CRE was not statistically significant (p = 0.27).

CHAPTER 5
DISCUSSION

5.1 Introduction

This chapter discusses the study findings regarding patient demographics, ESKAPE pathogens, antimicrobial treatment and rectal swab screening.

5.2 Patient demographics

Of the 690 patients, 273 patients (39.6%) received antimicrobial treatment, of which one or more of the ESKAPE pathogens were isolated from 132 patients (48.35%). A study on the prevalence of infection in South African ICU's, found that 73.5% of patients admitted to the ICU received antimicrobial treatment (Paruk et al., 2012). Another study looking at antimicrobial treatment across all the ICUs at CMJAH, found that 55.2% of patients received antimicrobial treatment during their admission to an ICU (Johnston et al., 2018). In comparison to the previous two studies, the ICU at CMJAH uses antimicrobial treatment more conservatively. The lower use of antimicrobial treatment could be due to several reasons. The study period was during the COVID19 pandemic, and thus a higher number of patients were admitted to the ICU during that period. Another reason could be better prescribing practices by the healthcare practitioners and a greater knowledge regarding the negative effects of overuse of antibiotics (Ayukekbong et al., 2017).

The average patient age was 43.2 years, with more male patients (60.6%) than female patients (39.4%) admitted. Male patients also had a longer average length of stay 21 days. It has been noted that compared to female patients, male patients are admitted to the intensive care unit and utilize its resources more frequently (Lat et al., 2021). Possible reasons for this are that female patients are often subjected to gender bias during the triage process and that oestrogen is thought to have an immunoprotective effect (Lat et al., 2021).

5.3 ESKAPE pathogens

Specimens for microbiological testing were collected from various sites from patients in the study sample. The most common specimen type was blood cultures (44.9%), followed by tracheal aspirates (16.3%) and fluid aspirates (13.6%). For specimens not from blood cultures, the ICU team raised a point regarding colonisation and invasive infection, as a factor that affects

the choice of antimicrobial treatment. ESKAPE pathogens isolated from blood cultures are deemed to be causative of invasive infection, whereas ESKAPE pathogens isolated from the other specimen types could purely be colonizers (Wohrley and Bartlett, 2018). Colonization is when microorganisms are present within a host, but not causing disease (Wohrley and Bartlett, 2018).Positive blood cultures are an indication of bacteraemia, which can help aid in the diagnosis of suspected sepsis (Chela et al., 2019). Positive tracheal aspirates are useful indicators of potential ventilator associated pneumonia, or pathogens isolated from tracheal aspirates could be colonizers of the respiratory tract (Jelic et al., 2023). Only the first isolate per microbial species per patient was included. Where a microbial species was isolated in a variety of specimen types, preference was given to the blood cultures, which could be the reason for the much higher number of blood cultures in comparison to the other specimen types.

The most frequently isolated ESKAPE pathogen from blood cultures was *K. pneumoniae* followed by *A. baumannii* and *E. coli*. This data is consistent with data collected from the public sector in South Africa for the period 2018-2022, where the most isolated. ESKAPE pathogens from blood cultures were, *K. pneumoniae, S. aureus*, *E. coli,* and *A. baumannii* (South Africa Department of Health, 2024). A study conducted by the European CDC found that the most common causative pathogens in bloodstream infections were coagulase-negative staphylococci, *Enterococcus* spp., *Klebsiella* spp. and *S. aureus* (European Centre for Disease Prevention and Control, 2019b). A review on the most common nosocomial pathogens in ICUs in lower-middle income countries, found *A. baumannii*, *P aeruginosa* and *K. pneumoniae* (Saharman et al., 2021*).* A study in Mexico City regarding the incidence of bacteraemia caused by Gram-negative ESKAPE pathogens, also found that the most common isolated ESKAPE pathogens were *A. baumannii, K. pneumoniae* and *P. aeruginosa* (Alcántar-Curiel et al., 2023). These findings reveal that *A. baumannii* infections are more extensive in the lower-middle income countries compared to that in Europe, which align with the findings of this study.

The most frequently isolated ESKAPE pathogen from respiratory specimens was *P. aeruginosa*, followed by *A. baumannii, E. coli and K. pneumoniae*, consistent with a study in the ICUs of a Dutch hospital and a study by the European CDC, where the most commonly isolated ESKAPE pathogens from endotracheal aspirates and most common causative pathogens in ICU-acquired pneumonia were *P. aeruginosa, S. aureus, E. coli*, and *K. pneumoniae* (Scholte et al., 2015, European Centre for Disease Prevention and Control, 2019a). A five-year study in public sector facilities in Kwa Zulu Natal, South Africa, found that *K.*

pneumonia, A. baumannii and *P. aeruginosa,* were the most isolated organisms associated with nosocomial respiratory tract infections (Ramsamy et al., 2018). Once again, there is a discrepancy between higher income country and lower-middle income countries, where *A. baumannii* is much more prevalent.

The most frequently isolated ESKAPE pathogen from fluids or aspirates was *K. pneumoniae*, followed by *E. faecium* and *A. baumannii*. The most frequently isolated ESKAPE pathogen from other specimen types was *K. pneumoniae* and *E. faecium*, followed by *E. cloacae, E. coli,* and *P. aeruginosa*. The high prevalence of *E. faecium* in these two groups of specimens, is due to its frequent association with infections of the urinary system, the bloodstream, surgical wounds, as well as endocardial, intra-abdominal and intrapelvic infections (Raza et al., 2018). These results, when compared to a study conducted in Kwa-Zulu Natal during 2011-2015, showed similar findings (Ramsamy et al., 2018). This study found that in urinary specimens the most prevalent ESKAPE pathogen was *K. pneumoniae*, followed by *A. baumannii* and *P. aeruginosa* (Ramsamy et al., 2018). *Klebsiella pneumoniae* is commonly the causative pathogen for healthcare-associated urinary tract infections (Chapelle et al., 2021). Urinary specimens were included under the "other" specimen group, and this could help to explain the high levels of *K. pneumoniae* isolated from these specimens.

5.3.1 Susceptibility of ESKAPE pathogens in blood cultures

For the ESKAPE pathogens isolated from blood cultures, the following results were found. The *A. baumannii* isolates (*n* = 29) showed 82.8% CR, 90% resistance to ceftazidime and/or cefepime and 41.4% were non-susceptible to tigecycline. The resistance to carbapenems is like the findings from the SA surveillance report (80%); however, a higher resistance to tigecycline is seen (4%) (South Africa Department of Health, 2024). The higher levels of tigecycline resistance could be due to the limited treatment options that are available for MDR *A. baumannii,* with main options in the public sector being colistin or tigecycline (South Africa Department of Health, 2021, South Africa Department of Health, 2024). Thus, the usage of tigecycline for the CR *A. baumannii,* could have contributed to higher levels of tigecycline resistance. The findings from study in Mexico City, found 100% ESBL, with only colistin remaining as a viable antimicrobial agent (Alcántar-Curiel et al., 2023). The lower levels of resistance to ceftazidime and/or cefepime in *A. baumannii*, could be due to lower usage of β-lactam antibiotics for empiric treatment of potential healthcare-associated infections or implementation of AMS principles (Ashiru-Oredope et al., 2022). From table 4.9, patients with

potential healthcare associated infections are mostly started empirically on piperacillin-tazobactam instead of amoxicillin-clavulanic acid.

For *K. aerogenes* (*n* = 6), it was found that 33.3% of the isolates were CRE and 50% ESBL-producing. None of the *E. cloacae* isolates (*n* = 6) were CRE; however, 16.7% were ESBL-producing. The findings on *Enterobacter* spp. in Mexico City, showed 56% ESBL and 6% CRE (Alcántar-Curiel et al., 2023). Comparing the two studies, it is seen that in this study there were higher levels of CRE, yet lower levels of ESBL-producing *Enterobacter* spp. This could be due to higher usage of carbapenems versus penicillins or cephalosporins for empiric treatment of potential healthcare-associated infections or implementation of AMS principles (Baughman, 2009, Ashiru-Oredope et al., 2022)

None of the *E. coli* isolates (*n* = 12) were CRE; however, 25% were ESBL-producing and 41.7% were non-susceptible to fluoroquinolones. The resistance to β-lactams is like the findings from the SA surveillance report (28%); however, a higher resistance to fluoroquinolones is observed (33%) (South Africa Department of Health, 2024). The higher resistance to fluoroquinolones is potentially due to a higher proportion of the infections being healthcare-associated versus community-acquired (South Africa Department of Health, 2021, South Africa Department of Health, 2024). Fluoroquinolones are no longer being used as first-line treatment for urinary tract infections, but rather being preserved for when truly indicated, due to the rise in fluoroquinolone resistance in *E. coli* and the risk of long-lasting side effects involving the tendons, nervous system, joints and muscles (European Medicines Agency, 2019, Thompson et al., 2024).

The *K. pneumoniae* isolates (*n* = 38) demonstrated 71.1% CRE and 81.6% ESBL-producing, which are higher than what was found in the SA surveillance report, 36% CRE and 70% ESBL-producing (South Africa Department of Health, 2024). The findings from Mexico City showed similar resistance to β-lactam antibiotics (84%); however, a much lower incidence of CRE (6%) (Alcántar-Curiel et al., 2023). When comparing the results two both studies, it is seen that the *K. pneumoniae* isolates demonstrated much higher levels of CRE than what would be expected. This could be due to the use of carbapenems for empiric treatment, as described in table 4.10 where 22.7% of patients received a carbapenem as part of their empiric treatment, leading to increased levels of resistance (McLaughlin et al., 2013).

The *P. aeruginosa* isolates (*n* = 10) demonstrated 60% CR, 40% resistance to ceftazidime and/or cefepime, and 60% non-susceptible to piperacillin-tazobactam. These findings are also higher than what was found in the SA surveillance report, namely 60% versus 23% resistance to carbapenems, and 60% non-susceptible to piperacillin-tazobactam versus 15% (South Africa Department of Health, 2024). The findings from Mexico City showed levels below 30% for resistance of *P. aeruginosa*, notably only 19% CRE (Alcántar-Curiel et al., 2023). As for the *K. pneumoniae* isolates, the *P. aeruginosa* isolates also demonstrated much higher levels of CR than what would be expected. A possible explanation could be the overuse of carbapenems for empiric treatment, leading to increased levels of resistance (Llor and Bjerrum, 2014).

Enterococcus faecalis (*n* = 6) demonstrated susceptibility to ampicillin, linezolid, and vancomycin. The *E. faecium* isolates (*n* = 7) showed 100% non-susceptibility to ampicillin and 57.1% non-susceptibility to vancomycin (VRE). Dissimilarly, the SA Surveillance report noted an incidence of 1% and 2% in 2020 and 2022, respectively (South Africa Department of Health, 2021, South Africa Department of Health, 2024). This could be due to a larger proportion of infections being healthcare-associated versus community-acquired, as VRE is more commonly found in healthcare settings (Orsi and Ciorba, 2013).

The *S. aureus* isolates (*n* = 4) showed 0% VRSA; however, 25% MRSA. This is like the findings in the SA surveillance report of 23% and 16% in 2016 and 2022, respectively (South Africa Department of Health, 2024). Similarly, Ramsamy et al (2018) noted a 24% incidence (Ramsamy et al., 2018, South Africa Department of Health, 2021). In contrast, MRSA was found in more than 50% of the *S. aureus* isolates in a review of lower-middle income countries (Saharman et al., 2021).

5.3.2 Susceptibility of ESKAPE pathogens in respiratory specimens and the other specimen categories

There is a lack of studies reporting on ESKAPE pathogens isolated from the other specimen groups. The reason for this is that, unlike blood cultures, where the isolated micro-organisms are invasive pathogens, for the other specimen types, the isolated micro-organisms could be colonizers and not the causative pathogen. For studies reporting on laboratory-based data, such as this study, it is thus difficult to draw accurate conclusions on the causative pathogens for other specimen types without taking into consideration the clinical presentation of the patient.

For the ESKAPE pathogens isolated from respiratory specimens, the following results were found. The *A. baumannii* isolates (*n* = 12) showed 91.7% CR, resistance to ceftazidime and/or cefepime and non-susceptibility to tigecycline. The *A. baumannii* isolates show a higher level of resistance in the respiratory specimens than the blood cultures. This would mean that for infections caused by *A. baumannii* in the respiratory tract, there will be fewer appropriate antimicrobial treatment options, an increase in usage of last resort antimicrobials, and adverse effects on clinical outcomes, such as longer hospitalization and even treatment failure (Chinemerem Nwobodo et al., 2022). For *K. aerogenes* (*n* = 5), it was found that 20% of the isolates were CRE and ESBL-producing. The *K. aerogenes* isolates show a lower level of resistance in the respiratory specimens than the blood cultures. This could imply that for infections in the respiratory tract caused by *K. aerogenes*, there are more appropriate antimicrobial treatment options and potentially better clinical outcomes.

The *K. pneumoniae* isolates (*n* = 7) showed 57% CRE and 86% ESBL-producing. The *K. pneumoniae* isolates show lower levels of CRE, but higher levels of ESBL-producing isolates than the isolates in the blood cultures. Thus, for respiratory infections caused by *K. pneumoniae*, carbapenems remain a better treatment option than for example amoxicillin-clavulanic acid. The reason for the higher levels of ESBL-producing isolates in the respiratory specimens, could be due to the overuse of β-lactam antibiotics for respiratory tract infections (de Sécurité and des Produits de Santé, 2003).

The *P. aeruginosa* isolates (*n* = 17) showed 57% CR, 86% resistance to ceftazidime and/or cefepime, and 52.9% non-susceptible to piperacillin-tazobactam. The *P. aeruginosa* isolates in the respiratory specimens show lower levels of CRE and non-susceptibility to piperacillin-tazobactam, but higher levels of resistance to ceftazidime and/or cefepime in the isolates. The reason for the higher levels of resistance to ceftazidime and/or cefepime in the respiratory specimens, could be due to the overuse of β-lactam antibiotics for respiratory tract infections (de Sécurité and des Produits de Santé, 2003). None of the *S. aureus* isolates (*n* = 4) from respiratory specimens showed non-susceptibility to methicillin or vancomycin; however, the first line agents for *S. aureus* infections are still an effective antimicrobial treatment option (Pendleton et al., 2013).

5.4 Antimicrobial treatment

One may assume that the provided antimicrobial susceptibilities might be viewed as appropriateness of the antimicrobial treatment, when empiric treatment is started regardless of culture results or knowledge of prior antibiotic use (Scholte et al., 2015). Only 48.5% of patients received empiric antimicrobial therapy that was appropriate for the subsequently isolated ESKAPE pathogen. Of the 132 patients, 62.1% received subsequent antimicrobial treatment, different to what was given empirically. This indicates that 37.9% of patients either received appropriate empirical treatment and showed clinical improvement, or that these patients demised or were discharged before subsequent treatment was initiated.

A study on the prevalence of infection in South African ICU's, found that 54.9% of patients admitted to the ICU received inappropriate antimicrobial treatment (Paruk et al., 2012). This study found that fewer (34%) patients colonized with an ESKAPE pathogen received inappropriate empiric therapy. Notably, the study by Paruk *et al* (2012) predates the publication of the South African AMR framework (South Africa Department of Health, 2018a) and the focus on implementing AMS protocols. (Ha et al., 2019).

Effective antimicrobial treatment selection has become even more difficult considering the high infection burden among ICU patients. This is due in part to the direct relationship between the intervention and outcome, as well as the need to consider the issue of AMR, which is a global concern (Paul et al., 2010, Nanao et al., 2023). Selecting empiric antimicrobial treatment can be based off several different factors. These factors include severity of the patient's illness, suspected aetiology and resistance patterns, prior antimicrobial usage or hospitalization of the patient, as well as other patient features, for example potential site of infection and neutropenia (Baughman, 2005, Leekha et al., 2011). Empiric antimicrobial treatment selection will also be based on whether the infection is community- or hospital-acquired (Leekha et al., 2011).

Upon analysis of the results, it was evident that clinical input was required to draw the necessary conclusions. The ICU team provided clinical insight into the decision-making process, and these insights are explained in table 4.9. For the patients where the ESKAPE pathogens were isolated from sources other than blood cultures, these pathogens were likely colonizing pathogens. The susceptibility data for the ESKAPE pathogen did not necessitate changes to the empiric antimicrobial treatment for patients with clinical improvement, as it was deemed that these pathogens were not the source of infection, but rather colonising the sample

site. Thus, the ICU team was targeting the infection and not the organism isolated. For the empiric treatment, amoxicillin-clavulanic acid is generally prescribed for patients with community-acquired infections, less likely to be infected with a MDR pathogen. For patients referred from a different hospital or ward, the piperacillin-tazobactam is usually given as empiric treatment. This is because piperacillin-tazobactam has a broader spectrum of antimicrobial activity. Patients already on empiric treatment on referral to the ICU were managed on the same treatment unless the patient status required re-evaluation, whilst they are awaiting culture results.

The most common empiric antimicrobial treatment was piperacillin-tazobactam, amoxicillin-clavulanic acid and carbapenems, such as ertapenem or meropenem. A study conducted on the antibiotic usage across the various ICUs at CMJAH in 2016, found that the most common antimicrobial treatment prescribed was amoxicillin-clavulanic acid, piperacillin-tazobactam and cefazolin (Johnston et al., 2018). The findings of this study are similar, apart from the usage of carbapenems. Carbapenems are typically used as empiric antimicrobial treatment for healthcare-associated infections caused by Enterobacterales (Hoo et al., 2022). This study found a high prevalence of infections caused by ESBL-producing Enterobacterales, especially *K. pneumoniae*, which could account for the high usage of carbapenems, as carbapenems and piperacillin-tazobactam are considered the preferred treatments for ESBL-producing Enterobacterales (Lee et al., 2012b).

Amoxicillin-clavulanic acid will typical be used treat suspected community-acquired infections where patients are unlikely to have been exposed to prior antimicrobial treatment or MDR pathogens (Huttner et al., 2020). Piperacillin-tazobactam and carbapenems are used to treat suspected nosocomial infections or if there are signs of sepsis (Munch et al., 2023). Of the three most used empiric treatments, only amoxicillin-clavulanic acid forms part of the Access group of antimicrobial agents. Piperacillin-tazobactam and the carbapenems, namely ertapenem and meropenem, are part of the Watch group of antimicrobial agents (World Health Organization, 2022, World Health Organization, 2023).

Piperacillin-tazobactam is an effective antimicrobial treatment option for a variety of infections, such as skin and soft tissue, respiratory tract, and urinary tract infections, and is used as an empiric treatment for moderate to severe infections (Gin et al., 2007, Munch et al., 2023). As a

carbapenem-sparing treatment, piperacillin/tazobactam can be used to stop the spread of MDR bacteria (Munch et al., 2023).

Ertapenem and meropenem exhibit a wide range of activity against Gram-positive, and Gram-negative pathogens, including ESBL Enterobacterales (Keating and Perry, 2005, Baldwin et al., 2008). Thus, for the empirical treatment of serious bacterial infections in hospitalized patients, ertapenem and meropenem remain valuable treatment options (Keating and Perry, 2005, Baldwin et al., 2008).

The use of azithromycin as part of the empiric antimicrobial treatment might not be due to its antimicrobial effect, but due to its ability to inhibit biofilm formation, specifically, the biofilms formed by *P. aeruginosa* (Kaplan, 2011, Imperi et al., 2014). Additionally, subminimal inhibitory concentrations (sub-MIC) levels of azithromycin can inhibit quorum sensing (Kaplan, 2011, Imperi et al., 2014). Thus, the addition of azithromycin as part of the empiric antimicrobial treatment is appropriate.

5.5 Rectal swab screening

Rectal swab screening was performed in 69% of the patients. Of the 91 patients screened, 10.98% were positive for CRE. In contrast, a study conducted at a hospital in London (Otter et al., 2016). found CRE rectal swab screening to be positive in only 0.1% of patients. (Otter et al., 2016, Foschi et al., 2019). However, the aforementioned study investigated the rectal swab screening of all admissions, whereas this study only describes patients who had ESKAPE pathogens isolated from. The two carbapenemases isolated were OXA-48 (63.6%) and NDM (36.4%), similar to other studies (Otter et al., 2016, Thomas and Duse, 2018, Foschi et al., 2019). One rectal swab screened positive for both OXA-48 and NDM carbapenemases. There was no statistically significant difference in the length of stay for patients who received rectal swab screening and those who did not, as well as patients who screened positive for CRE and patients who screened negative. A larger sample of patients would allow for more effective comparisons to be drawn. Data captured did not allow for synchronisations between rectal swab screening and the subsequently isolated CRE pathogen, thus a study determining the link between these two factors could be valuable.

CHAPTER 6
CONCLUSIONS & RECOMMENDATIONS

6.1 Introduction

This chapter describes the recommendations for future research. This chapter will also highlight the key findings and study conclusions.

6.2 Limitations of the study.

One of the limitations of this study is that it was retrospective. Data was extracted from the CMJAH database, where the patient files are scanned and kept digitally. Some of the scanned pages were not clear, whereas some of the pages had sections cut off, leading to obscured information. To determine if the antimicrobial treatment was appropriate, it is necessary to refer to the diagnosis of the patient and clinical investigations. This was not always possible as, in some instances, this information was omitted or not available in the digital archive. This precluded the use of hang time, dose and dosing frequency as measures of appropriateness, as increased or reduced doses could not be linked to patient factors such as renal clearance and liver function. Antimicrobial treatment was hence described as appropriate where the ESKAPE pathogen isolated and the presenting infection was treated with the correct agent.

Another limitation is that the microbiological data was not self-obtained, but rather supplied by the NHLS. This means that there was no means to correlate or double-check any possible discrepancies. For example, the ideal MIC testing method for colistin broth microdilution. The colistin MICs supplied by the NHLS is from Vitek and, thus, not as reliable as the broth microdilution (Tan and Ng, 2007). No discussion or conclusions regarding colistin resistance were made due to this limiting factor.

6.3 Recommendations

A recommendation can be made for a prospective study to be conducted using a multi-disciplinary team, involving pharmacists, clinicians, and microbiologists. This will allow for more clinical data to be included and better analysis and understanding of the treatment of infections by the ESKAPE pathogens. Another recommendation is for the clinical diagnosis of patients to be updated and noted clearly on the ICU charts to facilitate easier identification of the necessary clinical data for any future retrospective studies. Lastly, a recommendation can

be made for the review of the ICU guidelines on the selection of empiric antimicrobial treatment, based on the findings of this study.

6.4 Key findings and Conclusion

This study investigated the extent and treatment of infections caused by ESKAPE pathogens in an ICU at CMJAH, and the screening for bacterial colonization using rectal swabs. Of the total patients admitted to the ICU during the study period, one or more of the ESKAPE pathogens were isolated from 132 patients (19%). The most common specimen type was blood cultures (44.9%), and the most frequently isolated ESKAPE pathogen from blood cultures was *K. pneumoniae* followed by *A. baumannii* and *E. coli*. These findings are similar to findings from studies in other lower-middle income countries. There was a lack of other studies on the ESKAPE pathogens found in the other specimen types, indicating a need for future studies on the prevalence and resistance of ESKAPE pathogens across the various specimen types.

Most patients, 66% of the 132 patients, received appropriate antimicrobial treatment. Common antimicrobial treatments were piperacillin-tazobactam, amoxicillin-clavulanic acid and carbapenems. This study found a high prevalence of infections caused by ESBL-producing Enterobacterales, especially *K. pneumoniae*, which could account for the higher usage of carbapenems, than found in other studies.

For the rectal swab screening, 10.98% of the rectal swabs screened positive for CRE. A longer study period may be valuable to determine the extent of CRE infections and to draw meaningful conclusions regarding the impact of rectal swab screening.

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Appendix A – Data Collection Tool

Data collection tool

PATIENT DEMOGRAPHICAL INFORMATION				
PATIENT IDENTIFIER				
AGE (in years)				
GENDER (tick appropriate)	MALE		FEMALE	

WARD LOCATION AND INFORMATION								
FROM WHERE THE PATIENT WAS REFERRED TO THE ICU (i.e. other ward or from outside the hospital)								
LENGTH OF STAY IN ICU (days)								
INFECTION THE PATIENT PRESENTED WITH (tick appropriate)	BJ		BSI		CNS		CVS	
	EENT		GI		LRI		NPS	
	PNEU		REPR		SSI		SST	
	SYS		UTI		VAE		OTHER	
	If other, specify:							

KEY: BJ: bone and joint infection; BSI: bloodstream infection; CNS: central nervous system infection; CVS: cardiovascular system infection; EENT: eye, ear, nose, throat infection; GI: gastrointestinal system infection; LRI: lower respiratory infection (except pneumonia); NPS: Neutropenic sepsis; PNEU: pneumonia; REPR: reproductive tract infection; SSI: surgical site infection; SST: skin and soft tissue infection; SYS: systemic infection; UTI: urinary tract infection; VTE: ventilator associated event

ADMISSION SWAB INFORMATION						
WAS A RECTALSWAB DONE UPON ADMISSION? (Y or N)						
MICROBIAL ISOLATE(S)						
SUSCEPTIBILITY TESTING (tick only where resistant)	Ampicillin / Amoxicillin		Clindamycin		Aztreonam	
	Amoxicillin-Clavulanate		Erythromycin		Ertapenem / Meropenem	
	Cloxacillin / Flucloxacillin		Telithromycin		Imipenem - cilastatin	
	Piperacillin-Tazobactam		Cotrimoxazole		Levofloxacin / Moxifloxacin	
	Cefepime		Fucidic acid		Tetracycline / Doxycycline	
	Ceftazidime		Teicoplanin		Linezolid	
	Gentamicin		Vancomycin		Tigecycline	
	Amikacin		Daptomycin		Colistin	
	If other, specify:					

EMPIRIC ANTIMICROBIAL THERAPY								
ANTIBIOTIC PRESCRIBED								
TIME BETWEEN ADMISSION AND ADMINISTRATION OF ANTIBIOTIC								
METHOD OF ADMINISTRATION (PO, IV, IM)			DOSE (mg)					
DOSING FREQUENCY (tick appropriate)	Daily		Every 12 hours		Every 8 hours			
	Every 6 hours		Every 4 hours		Other			
ADDITIONAL ANTIBIOTIC PRESCRIBED								
METHOD OF ADMINISTRATION (PO, IV, IM)			DOSE (mg)					
DOSING FREQUENCY (tick appropriate)	Daily		Every 12 hours		Every 8 hours			
	Every 6 hours		Every 4 hours		Other			
ADDITIONAL ANTIBIOTIC PRESCRIBED								
METHOD OF ADMINISTRATION (PO, IV, IM)			DOSE (mg)					
DOSING FREQUENCY (tick appropriate)	Daily		Every 12 hours		Every 8 hours			
	Every 6 hours		Every 4 hours		Other			

MICROBIAL RELATED LABORATORY TESTS												
MICROBIAL ISOLATE(S)												
SAMPLE SOURCE (tick appropriate)	Blood		Urine		Catheter		Sputum		Stool		Other	
	If other, specify:											
	If catheter, specify:											
	Urinary		Pleural		CVP		CVE		Other			
EXTENT OF RESISTANCE (tick where appropriate)	ESBL		MRSA		MRSE		VRE		VISA			
	CRKP		MDR		XDR		PDR		Other			
SUSCEPTIBILITY TESTING (tick only where resistant)	Ampicillin / Amoxicillin		Clindamycin		Aztreonam							
	Amoxicillin-Clavulanate		Erythromycin		Ertapenem / Meropenem							
	Cloxacillin / Flucloxacillin		Telithromycin		Imipenem - cilastatin							
	Piperacillin-Tazobactam		Cotrimoxazole		Levofloxacin / Moxifloxacin							
	Cefepime		Fucidic acid		Tetracycline / Doxycycline							
	Ceftazidime		Teicoplanin		Linezolid							
	Gentamicin		Vancomycin		Tigecycline							
	Amikacin		Daptomycin		Colistin							
	If other, specify:											

MICROBIAL RELATED LABORATORY TESTS														
ADDITIONAL MICROBIAL ISOLATE(S)														
SAMPLE SOURCE (tick appropriate)	Blood		Urine		Catheter		Sputum		Stool		Other			
	If other, specify:													
	If catheter, specify:													
	Urinary		Pleural		CVP		CVE		Other					
EXTENT OF RESISTANCE (tick where appropriate)	ESBL		MRSA		MRSE		VRE		VISA					
	CRKP		MDR		XDR		PDR		Other					
SUSCEPTIBILITY TESTING (tick only where resistant)	Ampicillin / Amoxicillin		Clindamycin		Aztreonam									
	Amoxicillin-Clavulanate		Erythromycin		Ertapenem / Meropenem									
	Cloxacillin / Flucloxacillin		Telithromycin		Imipenem - cilastatin									
	Piperacillin-Tazobactam		Cotrimoxazole		Levofloxacin / Moxifloxacin									
	Cefepime		Fucidic acid		Tetracycline / Doxycycline									
	Ceftazidime		Teicoplanin		Linezolid									
	Gentamicin		Vancomycin		Tigecycline									
	Amikacin		Daptomycin		Colistin									
	If other, specify:													

ANTIBIOTIC THERAPY FOLLOWING SUSCEPTIBILITY TESTING						
ANTIBIOTIC PRESCRIBED						
TIME BETWEEN ADMISSION AND ADMINISTRATION OF ANTIBIOTIC						
METHOD OF ADMINISTRATION (PO, IV, IM)			DOSE (mg)			
DOSING FREQUENCY (tick appropriate)	Daily		Every 12 hours		Every 8 hours	
	Every 6 hours		Every 4 hours		Other	
ADDITIONAL ANTIBIOTIC PRESCRIBED						
METHOD OF ADMINISTRATION (PO, IV, IM)			DOSE (mg)			
DOSING FREQUENCY (tick appropriate)	Daily		Every 12 hours		Every 8 hours	
	Every 6 hours		Every 4 hours		Other	
ADDITIONAL ANTIBIOTIC PRESCRIBED						
METHOD OF ADMINISTRATION (PO, IV, IM)			DOSE (mg)			
DOSING FREQUENCY (tick appropriate)	Daily		Every 12 hours		Every 8 hours	
	Every 6 hours		Every 4 hours		Other	

APPROPRIATENESS OF ANTIBIOTIC THERAPY				
WAS SUSCEPTIBILITY TESTING PERFORMED?	**YES**		**NO**	
WAS THE INITIAL ANITBIOTIC THERAPY APPROPRIATE FOR THE INDICATION?	**YES**		**NO**	
WAS ANTIBIOTIC THERAPY CHANGED FOLLOWING THE SUSCEPTIBILITY RESULTS?	**YES**		**NO**	
WAS APPROPRIATE ANTIBIOTICS PRESCRIBED BASED ON THE RESISTANCE PATTERNS OF THE BACTERIAL ISOLATE?	**YES**		**NO**	
TIME BETWEEN ADMISSION AND THE START OF APPROPRIATE ANTIMICROBIAL THERAPY (hours)				

Appendix B – Ethics certificate

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

2023/05/05

Ms B Naude
School of Therapeutic Sciences
Department of Pharmacy and Pharmacology
Medical School
University

Sent by e-mail to: 2614122@students.wits.ac.za

Dear Ms Naude

Re: **Protocol Ref No:** M220872
Protocol Title: *Investigating the extent and treatment of infections caused by ESKAPE pathogens in an intensive care unit*
Principal Investigators: Ms B Naude

Thank you for your letter of 2023/04/24.

I can confirm that we have noted and approve of your proposal to acquire patient data directly from the NHLS, subject to whatever requirements they may have of you.

Thank you for keeping us informed.

Yours Sincerely

J. Burns

.....

Mr I Burns
For the Human Research Ethics Committee (Medical)

CB Penny

.....

Dr CB Penny, Chairperson, Human Research Ethics Committee (Medical)

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG	HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

Office of the Deputy Vice-Chancellor (Research and Innovation)

TO: Ms B Naude
School of Therapeutic Sciences
Department of Pharmacy and Pharmacology
Medical School
University

E-mail: 2614122@students.wits.ac.za

CC: Supervisor: Professor M Mer; Dr A Orchard; Mr M Vally; Ms R Khan <Muhammed.Vally@wits.ac.za>
and <HREC-Medical Research Office@wits.ac.za>

FROM: Mr Iain Burns
Human Research Ethics Committee (Medical)
Tel: 011 717 1252

E-mail: Iain.Burns@wits.ac.za

DATE: 2023/01/03

REF: R14/49

PROTOCOL NO: **M220872** (This is your ethics application reference number. Please quote it in all enquiries, oral or written, relating to this study.)

PROJECT TITLE: *Investigating the extent and treatment of infections caused by ESKAPE pathogens in an intensive care unit*

Please find attached the Clearance Certificate for the above project. I hope it goes well and that an article in a recognized publication comes out of it. This will reflect well on your professional standing and contribute to Government funding of the University.

MSWorks2000/Iain0007/Clearscan.wps

Appendix C – Approval from CMJAH

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL (CMJAH)
OFFICE OF THE CLINICAL DIRECTOR

Enquiries: *Ms N. Mzila*
Email: Nolwazi.Mzila@gauteng.gov.za
Tel: *011 488 3365*
Ref: *1/7/2*
Date: 04 January 2023

GP_202209_055

Dear Mrs Bianka Naude

RE: FINAL APPROVAL OF STUDY

TITLE: INVESTIGATING THE EXTENT AND TREATMENT OF INFECTIONS CAUSED BY ESKAPE PATHOGENS IN AN INTENSIVE CARE UNIT.

Permission is granted for you to conduct the above-mentioned study as described in your request provided:

1. Charlotte Maxeke Johannesburg Academic Hospital will not in any way incur or inherit costs as a result of the said study.
2. Your study shall not disrupt services at the study sites.
3. Strict confidentiality shall always be observed.
4. Informed consent shall be solicited from patients participating in your study.

Please liaise with the HOD and Unit Manager or Sister in charge to agree on the dates and time that would suit all parties.

Kindly forward this office with the results of your study on completion of the research.

Approved/~~Not Approved~~

Signed by:Jayshina Punwasi
Signed at:2023-01-04 14:27:35 +02:00
Reason:Witnessing Jayshina Punwasi

Dr J. Punwasi
Clinical Director and Acting Chief Executive Officer: CMJAH

Appendix D – Approval from ICU

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

FACULTY OF HEALTH SCIENCES

Request for permission to conduct research in the intensive care unit at Charlotte Maxeke Johannesburg Academic Hospital

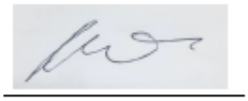
To whom it may concern,

My name is Bianka Naude and I am currently completing my MPharm degree at the University of Witwatersrand. The research I want to conduct is for the fulfilment of my MPharm requirement. The title of the study is "Investigating the extent and treatment of infections caused by ESKAPE pathogens in an intensive care unit". This project will be conducted under the supervision of Mrs Khan (Wits University), Dr Orchard (Wits University), Mr Vally (Wits University) and Prof Mer (Charlotte Maxeke Johannesburg Academic Hospital).

I hereby request permission for access to patient records in the intensive care unit for the collection of data for the study. I will provide a copy of the research proposal which includes copies of the data collection tool.

If you require any further information, please do not hesitate to contact me on 2614122@students.wits.ac.za .Thank you for your time and consideration in this matter.

Yours sincerely,
Bianka Naude



Prof Mervyn Mer (Head of ICU department)

Appendix E – Research Protocol Approval

UNIVERSITY OF THE
WITWATERSRAND,
JOHANNESBURG

Private Bag 3 Wits, 2050
Fax: 027117172119
Tel: 02711 7172076

Reference: Mrs Sandra Benn
E-mail: sandra.benn@wits.ac.za

02 July 2022
Person No: 2614122
PAG

Miss B Naude
1105 Kent Place South
41 St Andrew's Str
Birdhaven
2196
South Africa

Dear Miss Bianka Naude

Master of Pharmacy: Approval of Title

We have pleasure in advising that your proposal entitled *Investigating the extent and treatment of infections caused by ESKAPE pathogens in an intensive care unit* has been approved. Please note that any amendments to this title have to be endorsed by the Faculty's higher degrees committee and formally approved.

Yours sincerely

Mrs Sandra Benn
Faculty Registrar
Faculty of Health Sciences

Appendix F – Turnitin report

BNaude Dissertation 28122024

ORIGINALITY REPORT

13%	9%	10%	2%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	wiredspace.wits.ac.za Internet Source	2%
2	pmc.ncbi.nlm.nih.gov Internet Source	1%
3	Ankita Agrawal, Amiya Kumar Patel. "Chapter 2 Antibiotic Resistance Profile and Detection in ESKAPE Pathogens", Springer Science and Business Media LLC, 2024 Publication	1%
4	"13th European Congress of Clinical Microbiology and Infectious Diseases", Clinical Microbiology and Infection, 2003 Publication	<1%
5	"Posters", Clinical Microbiology and Infection, 4/2007 Publication	<1%
6	www.ncbi.nlm.nih.gov Internet Source	<1%
7	www.frontiersin.org Internet Source	<1%