A point prevalence survey of antimicrobial therapy use in adult sepsis and septic shock patients in all the critical care units of central and tertiary hospitals in Gauteng Province, South Africa

A mini-dissertation submitted by

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in partial fulfilment of the requirements for the degree of

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DECLARATION

I, Hanneke de Klerk, declare that the mini-dissertation hereby submitted to the Sefako Makgatho Health Sciences University, for the degree of Master of Pharmacy, in the School of Pharmacy, has not previously been submitted by me for a degree at this or any other university; that it is my work in design and execution, and that all material contained herein has been duly acknowledged.

__________________________________   __________________
Surname, Initials (Title)     Date
DEDICATION

This masters is dedicated to my fiancé, Kevin Botha, for your patience, unwavering encouragement and love. You supported my decisions, despite knowing that they normally involved sacrifices on your behalf. You help me to see things in perspective, by supporting me through my failures and successes. Thank you for always being there in all ways possible. Your input and support are invaluable to me.

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# TABLE OF CONTENTS

**ACKNOWLEDGEMENTS** ........................................................................................................ iv  
**LIST OF TABLES** ...................................................................................................................... v  
**LIST OF FIGURES** .................................................................................................................. vi  
**LIST OF APPENDICES** ........................................................................................................... vii  
**ABBREVIATIONS AND ACRONYMS** .................................................................................. viii  
**ABSTRACT** ............................................................................................................................... ix  
**CHAPTER 1** ............................................................................................................................... 1  
**INTRODUCTION** ....................................................................................................................... 1  
  
1.1 INTRODUCTION ..................................................................................................................... 1  
1.2 BACKGROUND AND RATIONALE FOR THE STUDY ......................................................... 1  
1.3 RESEARCH QUESTION ........................................................................................................ 2  
  
1.3.1 Primary research question .............................................................................................. 2  
1.3.2 Secondary research questions ....................................................................................... 2  
1.4 AIM OF THE STUDY ............................................................................................................. 3  
1.5 OBJECTIVES OF THE STUDY ............................................................................................. 3  
1.6 IMPORTANCE OF THE STUDY ............................................................................................ 3  
1.7 OUTLINE OF THE DISSERTATION ...................................................................................... 5  
1.8 SUMMARY ............................................................................................................................ 6  
**CHAPTER 2** ............................................................................................................................... 7  
**LITERATURE REVIEW** ............................................................................................................. 7  
  
2.1 INTRODUCTION ..................................................................................................................... 7  
2.2 SEPSIS AND SEPTIC SHOCK ............................................................................................... 7  
2.3 INFECTION IN THE SEPTIC PATIENT ............................................................................... 8  
2.4 ANTIMICROBIALS USE IN SEPSIS AND SEPTIC SHOCK ................................................. 8  
2.5 THE ROLE OF SEPSIS BIOMARKERS IN DIAGNOSING SEPSIS ................................. 9  
2.6 RECOMMENDATIONS AND GUIDELINES FOR TREATING SEPSIS AND SEPTIC SHOCK ......................................................................................................................... 10
<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.7</td>
<td>THE BURDEN OF SEPSIS AND SEPTIC SHOCK IN DEVELOPING COUNTRIES</td>
<td>18</td>
</tr>
<tr>
<td>2.8</td>
<td>SEPSIS IN SOUTH AFRICA</td>
<td>18</td>
</tr>
<tr>
<td>2.9</td>
<td>DRUG CLASSIFICATION SYSTEMS</td>
<td>20</td>
</tr>
<tr>
<td>2.9.1</td>
<td>Anatomic Therapeutic Chemical Classification System</td>
<td>20</td>
</tr>
<tr>
<td>2.9.2</td>
<td>Access, Watch, or Reserved antibiotic groups</td>
<td>21</td>
</tr>
<tr>
<td>2.9.3</td>
<td>Defined Daily Dose</td>
<td>21</td>
</tr>
<tr>
<td>2.10</td>
<td>SUMMARY</td>
<td>22</td>
</tr>
</tbody>
</table>

CHAPTER 3 .......................................................................................................................... 23

METHODOLOGY .................................................................................................................. 23

<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.1</td>
<td>INTRODUCTION</td>
<td>23</td>
</tr>
<tr>
<td>3.2</td>
<td>STUDY SITES</td>
<td>23</td>
</tr>
<tr>
<td>3.3</td>
<td>STUDY DESIGN</td>
<td>24</td>
</tr>
<tr>
<td>3.3.1</td>
<td>Quantitative research</td>
<td>24</td>
</tr>
<tr>
<td>3.3.2</td>
<td>Descriptive research design</td>
<td>24</td>
</tr>
<tr>
<td>3.4</td>
<td>STUDY POPULATION AND SAMPLE</td>
<td>25</td>
</tr>
<tr>
<td>3.4.1</td>
<td>Study population</td>
<td>25</td>
</tr>
<tr>
<td>3.4.2</td>
<td>Study selection</td>
<td>25</td>
</tr>
<tr>
<td>3.4.3</td>
<td>Sample size</td>
<td>25</td>
</tr>
<tr>
<td>3.4.4</td>
<td>Inclusion criteria</td>
<td>26</td>
</tr>
<tr>
<td>3.4.5</td>
<td>Exclusion criteria</td>
<td>27</td>
</tr>
<tr>
<td>3.5</td>
<td>DATA COLLECTION</td>
<td>27</td>
</tr>
<tr>
<td>3.5.1</td>
<td>Data collection period</td>
<td>27</td>
</tr>
<tr>
<td>3.5.2</td>
<td>Data collection training</td>
<td>28</td>
</tr>
<tr>
<td>3.5.3</td>
<td>Data collection instruments</td>
<td>28</td>
</tr>
<tr>
<td>3.6</td>
<td>PILOT STUDY</td>
<td>30</td>
</tr>
<tr>
<td>3.7</td>
<td>DATA capture AND ANALYSIS</td>
<td>30</td>
</tr>
<tr>
<td>3.7.1</td>
<td>Data capture</td>
<td>30</td>
</tr>
<tr>
<td>3.7.2</td>
<td>Data analysis</td>
<td>30</td>
</tr>
<tr>
<td>3.8</td>
<td>RELIABILITY AND VALIDITY</td>
<td>31</td>
</tr>
</tbody>
</table>
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LIST OF TABLES

Table 2.1: Terminology regarding the recommendations for treating sepsis and septic shock .............................................................. 14

Table 2.2: Classification of amoxicillin according to the ATC classification system .... 20

Table 2.3: DDD examples ............................................................................. 21

Table 3.1: Gauteng Tertiary and Central hospital characteristics .................. 24

Table 3.2: Inclusion criteria ........................................................................... 26

Table 3.3: Exclusion criteria .......................................................................... 27

Table 3.4: Threats to internal validity (Hungler and Polit, 1997) ...................... 32

Table 1: Patients with sepsis or septic shock per hospital ................................ 44

Table 2: Antimicrobials which were administered to septic patients ................ 45

Table 3: Overall compliance to the SSC guidelines for each hospital ............. 50
LIST OF FIGURES

Figure 1.1: Layout of dissertation ................................................................. 6

Figure 1: Outcome of the systemic review ................................................. 43

Figure 2: Antimicrobial combinations prescribed to patients ..................... 46

Figure 3: Distribution of antimicrobial agents consumption in Central and Tertiary hospitals, expressed in DDD per ATC-subclass and compared to WHO recommended values ................................................................. 48

Figure 4: Number of antibiotics in their AWaRe groups per hospital ............. 49
# LIST OF APPENDICES

<table>
<thead>
<tr>
<th>Appendix</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Data collecting instrument</td>
<td>70</td>
</tr>
<tr>
<td>2</td>
<td>SMUREC Clearance certificate</td>
<td>73</td>
</tr>
<tr>
<td>3</td>
<td>Ethical clearance for Steve Biko Academic Hospital</td>
<td>75</td>
</tr>
<tr>
<td>4</td>
<td>Ethical clearance for Chris Hanie Baragwanath Academic Hospital</td>
<td>76</td>
</tr>
<tr>
<td>5</td>
<td>Ethical clearance for Dr. George Mukhari Academic Hospital</td>
<td>77</td>
</tr>
<tr>
<td>6</td>
<td>Ethical clearance for Charlotte Maxeke Johannesburg Academic Hospital</td>
<td>78</td>
</tr>
<tr>
<td>7</td>
<td>Ethical clearance for Kalafong Hospital</td>
<td>79</td>
</tr>
<tr>
<td>8</td>
<td>Ethical clearance for Thembisa Hospital</td>
<td>80</td>
</tr>
<tr>
<td>8</td>
<td>Ethical clearance for Helen Joseph</td>
<td>81</td>
</tr>
</tbody>
</table>
# ABBREVIATIONS AND ACRONYMS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMR</td>
<td>Antimicrobial resistance</td>
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<td>AMS</td>
<td>Antimicrobial Stewardship</td>
</tr>
<tr>
<td>ATC</td>
<td>Anatomic Therapeutic Classification</td>
</tr>
<tr>
<td>AWaRe</td>
<td>Access, Watch, or Reserved</td>
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<tr>
<td>CDC</td>
<td>Centre for Disease Control and Prevention</td>
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<tr>
<td>CEO</td>
<td>Chief executive officer</td>
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<tr>
<td>CI</td>
<td>Confidence Interval</td>
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<tr>
<td>CMJAH</td>
<td>Charlotte Maxeke Johannesburg Academic Hospital</td>
</tr>
<tr>
<td>CRP</td>
<td>C-reactive protein</td>
</tr>
<tr>
<td>DDD</td>
<td>Defined Daily Dose</td>
</tr>
<tr>
<td>DGMAH</td>
<td>Doctor George Mukhari Academic Hospital</td>
</tr>
<tr>
<td>ENAABLERs</td>
<td>Enhancing Appropriate Antimicrobial and Vaccine Use via Mobile Health and Other Techniques in the Republic of South Africa</td>
</tr>
<tr>
<td>ESBL</td>
<td>Extended-spectrum beta-lactamase</td>
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<tr>
<td>HIV</td>
<td>Human Immunodeficiency Virus</td>
</tr>
<tr>
<td>ICU</td>
<td>Intensive Care Unit</td>
</tr>
<tr>
<td>IV</td>
<td>Intravenous</td>
</tr>
<tr>
<td>MIC</td>
<td>Minimum Inhibitory Concentration</td>
</tr>
<tr>
<td>MRSA</td>
<td>Methicillin-resistant <em>Staphylococcus aureus</em></td>
</tr>
<tr>
<td>MURIA</td>
<td>Medicine Utilisation Research in Africa</td>
</tr>
<tr>
<td>NHRDB</td>
<td>National Health Research Data Base</td>
</tr>
<tr>
<td>PCT</td>
<td>Procalcitonin</td>
</tr>
<tr>
<td>PPS</td>
<td>Point Prevalence Survey</td>
</tr>
<tr>
<td>SA</td>
<td>South Africa</td>
</tr>
<tr>
<td>SD</td>
<td>Standard Deviation</td>
</tr>
<tr>
<td>SIRS</td>
<td>Systemic inflammatory response syndrome</td>
</tr>
<tr>
<td>SMUREC</td>
<td>Sefako Makgatho University Research and Ethics Committee</td>
</tr>
<tr>
<td>SOFA</td>
<td>Sequential Organ Failure Assessment</td>
</tr>
<tr>
<td>SOPRC</td>
<td>School of Pharmacy Research Committee</td>
</tr>
<tr>
<td>SSC</td>
<td>Surviving Sepsis Campaign</td>
</tr>
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<td>US</td>
<td>Unites States</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organisation</td>
</tr>
</tbody>
</table>
ABSTRACT

Introduction:

Sepsis is a global burden and is one of the top ten most common causes of death in developing countries, but in SA infectious diseases is the second most common cause of death. Studies revealed that 30-60% of the antibiotics prescribed in the ICU are inappropriate, suboptimal, or unnecessary, which lead to antimicrobial resistance. Currently, there are no guidelines included in the STG and EML for the treatment of sepsis and septic shock.

Objectives:

The aim of this study was to assess antimicrobial therapy utilisation in patients treated for sepsis or septic shock in the ICUs of all central and tertiary hospitals of Gauteng. The objectives of the study was to list the antimicrobials used in adult patients diagnosed with sepsis and/or septic shock, to describe antimicrobial therapy use pertaining to defined daily dose (DDD), route of administration, length of therapy, days in ICU and Anatomical Therapeutic Chemical (ATC) classification and to assess adherence of prescribers to the SSC guideline regarding antimicrobial therapy.

Method:

The study was a descriptive, cross-sectional point prevalence survey (PPS), with a quantitative study design. The study was conducted in four Central and three Tertiary hospitals in Gauteng. All adult patients admitted to an ICU with sepsis were included.

Results:

In the Central and Tertiary Hospitals, the total number of patients surveyed in the adult ICUs were 118, whereof 18 (15.25%) patients were diagnosed with sepsis. 20 ICU wards were surveyed across 7 hospitals, whereof only two (10%) ICU wards had a protocol for the management or treatment of sepsis and septic shock in place, although 17 (85%) collect data form septic patients. All 18 patients, diagnosed with sepsis or septic shock, were on antimicrobial therapy. The total number of antimicrobials prescribed for these patients was 30, on average 1.67 (±0.69) antimicrobials were prescribed per patient. None of the hospitals were fully compliant with the SCC guidelines.


Conclusion:

This study shows that guidelines are not begin adhered to and unnecessary and inappropriate antibiotics and dosages are being prescribed to patients with no cultures to support this treatment – all these leads to antimicrobial resistance.
1.1 INTRODUCTION

This chapter provides an introduction to the study and emphasises the impact of sepsis on global health and although many studies have been conducted, the global mortality rate continues to increase in patients with sepsis and septic shock. This chapter further highlights the differences between sepsis and septic shock in developing and developed countries, as well as the limited research that is currently available on sepsis and septic shock in developing countries. This is followed by the research question, aim and objectives of the study, as well as a description of the importance and significance of the study. The chapter ends with a short overview of the dissertation’s outline.

1.2 BACKGROUND AND RATIONALE FOR THE STUDY

Sepsis is considered a medical emergency that affects public health globally (Chehade, Chebl, Majzoub and Dagher, 2015). Sepsis remains the leading cause of increased mortality in Intensive Care Units (ICU) (Kübler, Adamik, Ciszewicz-Adamiczka, Ostrowska, 2015), with a mortality rate of one in four people and sometimes even more (Rhodes, Evans, Alhazzani, Levy, Antonelli, Ferrer, Kumar, Sevransky, Sprung, Nunnally, Rochwerg, Rubenfeld, Ang, Annane, Beale, Bellinghan, Bernard, Chiche, Coopersmith, De Backer, French, Fujishima, Gerlach, Hidalgo, Hollenberg, Jones, Karnad, Kleinpell, Koh, Lisboa, Machado, Marini, Marshall, Mazuski, McIntyre, McLean, Mehta, Moreno, Myburgh, Navalesi, Nishida, Osborn, Perner, Plunkett, Ranieri, Schorr, Seckel, Seymour, Shieh, Shukri, Simpson, Singer, Thompson, Townsend, Van der Poll, Vincent, Wiersinga, Zimmerman and Dellinger, 2017). The World Sepsis Declaration estimates that there are about 20 – 30 million sepsis cases annually, with an increased rate of 13 – 18% per annum (Kübler et al., 2015).

The epidemiology of sepsis differs between developed and developing countries. In developed countries gram-positive bacteria commonly causes sepsis, while in developing countries sepsis is more commonly caused by gram-negative bacteria (Chehade et al., 2015; Martin, 2012). Developed countries are resource rich which makes the treatment of sepsis more accessible, whereas developing countries, like South Africa (SA), struggle to achieve basic healthcare. Resources are limited in a developing country and therefore a
greater portion of the burden is borne by developing countries (Chehade et al., 2015). Most of the research is being conducted in developed countries, which leads to an unrealistic picture of the impact of sepsis around the world (Martin, 2012).

The significant differences in the epidemiology of sepsis between developed and developing countries will influence the treatment approaches (Mayr, Yende and Angus, 2014). The usage of appropriate antibiotic therapy in an ICU is crucial. Studies revealed that 30-60% of the antibiotics prescribed in the ICU are inappropriate, suboptimal, or unnecessary, which lead to antimicrobial resistance (Luyt, Bréchet, Trouillet and Chastre, 2014). There is no assessment to estimate whether appropriate antibiotic therapy was given after blood cultures were collected (Yokota, Marra, Martino, Victor, Dura˜o, Edmond and dos Santos, 2014). According to Yokota et al (2014), the mortality rate decreased with 46% after the implementation of the appropriate use of antibiotics (Yokota et al., 2014). Limited research has been conducted regarding the appropriate use of antimicrobial therapy in critical care patients diagnosed with sepsis and septic shock. There is also limited literature on whether clinicians are following the recommendations of the Surviving Sepsis Campaign (SSC) guideline, with regards to antimicrobial therapy within tertiary and central hospitals in SA. This study aimed to describe the use of antimicrobials in septic ICU patients in Gauteng, SA.

Limited literature is available regarding the utilisation of antimicrobials in septic patients and whether clinicians are adhering to these SSC recommendations in SA. Therefore, this study aims to describe whether clinicians adhere to the recommendations of the SSC, regarding the appropriate use of antimicrobials in septic ICU patients.

1.3 RESEARCH QUESTION

1.3.1 Primary research question

Were antimicrobial therapy utilised in ICU patients treated for sepsis or septic shock in all of Gauteng’s central and tertiary hospitals?

1.3.2 Secondary research questions

- Were clinicians adhering to the recommendations of the SSC regarding the appropriate use of antimicrobials in septic ICU patients?
- What antimicrobial therapy are used in the treatment of adult septic patients?
- What is the defined daily dose of each antimicrobial used?
Chapter 1: Introduction

- What was the most frequent route of administration?
- Which organism was cultured?
- Was treatment de-escalated after culture results were available?

1.4 AIM OF THE STUDY

To assess antimicrobial therapy utilisation in patients treated for sepsis or septic shock in the ICUs of all central and tertiary hospitals of Gauteng.

1.5 OBJECTIVES OF THE STUDY

The objectives of the study were as follows:

- To list the antimicrobials used in adult patients diagnosed with sepsis and/or septic shock.
- To describe antimicrobial therapy use pertaining to defined daily dose (DDD), route of administration, length of therapy, days in ICU and Anatomical Therapeutic Chemical (ATC) classification.
- To assess adherence of prescribers to the SSC guideline regarding antimicrobial therapy.

1.6 IMPORTANCE OF THE STUDY

Sepsis goes back to the times of Hippocrates (Angus and van der Poll, 2013), but today sepsis is a global burden (Chehade, Chebl, Majzoub and Dagher, 2015). According to the World Health Organisation (WHO), sepsis affects more than 30 million patients globally every year, leading to 6 million deaths each year (World Health Organisation, 2018). In 2014, Mayr et al. (2014) found sepsis to be the leading cause of death in the Unites States (US) within ICUs, with a prevalence of 300 in every 100 000 patients. More than half of these patients were found outside of an ICU setting. The simplest means to define the epidemiology of sepsis in ICU is through a point prevalence survey (PPS) (Mayr et al., 2014).

The epidemiology of sepsis differs between developed and developing countries. In developed countries gram-positive bacteria commonly causes sepsis, while in developing countries sepsis is more commonly caused by gram-negative bacteria (Chehade et al., 2015; Martin, 2012). The likelihood of gram-negative bacterial infections progressing to
Chapter 1: Introduction

Septic shock is increasing (Rhodes et al., 2017). The significant differences in the epidemiology of sepsis between developed and developing countries will influence the treatment approaches (Mayr, Yende and Angus, 2014). The usage of appropriate antibiotic therapy in an ICU is crucial. Studies revealed that 30-60% of the antibiotics prescribed in the ICU are inappropriate, suboptimal, or unnecessary, which lead to antimicrobial resistance (Luyt et al., 2014).

Developed countries are resource rich, which makes the treatment of sepsis more accessible, whereas developing countries, like SA, struggle to achieve basic healthcare. Resources are limited in a developing country and therefore a greater portion of the burden is borne by developing countries (Chehade et al., 2015).

Selection of the appropriate empiric therapy depends on intricate issues related to local epidemiology factors, the patient’s history and clinical status. Patient factors play a key role in the choice of antimicrobials. Factors to consider when choosing the appropriate antimicrobial regime include the site of infection; whether the patient was part of the community at the time of infection or in a care institution or hospital location; chronic organ failure; form of immunocompromised; indwelling devices; underlying diseases; medications; known recent infection; receipt of antimicrobials within the past three months; the prevalence of local pathogens and their susceptibility patterns within the community and hospital; resistance patterns and toxicity. Due to the aforementioned factors, the empiric treatment for sepsis and septic shock is complex and cannot be summarised into a simple table (Rhodes et al., 2017).

Sepsis kills more than one in four patients (Rhodes et al., 2017) and despite 87% of the world’s population living in developing countries (Reinhart, Daniels, Kissoon, Machado, Schachter and Finfer, 2017), only 10% of the 655 references which supports the new 2016 SSC guidelines, pertain to studies that have been conducted in developing countries (Rhodes et al., 2017). Due to insufficient resources within developing countries, most recommendations from the SSC cannot be implemented (Tupchong, Koyfman and Foran, 2015), leading to an urge in priority to develop sustainable models for diagnosis and treatment of sepsis in developing countries (Papali, McCurdy and Calvello, 2015).

A PPS done in 2009 in SA included 248 septic patients. Of the administered antibiotic, 28% were inappropriate and only 12% were appropriate. Antimicrobials were only changed in 24% of the patients to targeted treatment after culture sensitivity was available and the
Chapter 1: Introduction

duration of treatment was correct in 28% of the incidents (Bhagwanjee, Scribante, Paruk, and Richards, 2009).

Due to ongoing reports of limited research being conducted in developing countries such as SA and outdated statistics regarding antimicrobial utilisation in septic patients, it is necessary for further studies to be conducted on this subject, to assess the adherence of clinicians towards the SSC guidelines in SA and the effect it has on sepsis and septic shock patients in SA.

1.7 OUTLINE OF THE DISSERTATION

This dissertation consists of five chapters. This first chapter serves as an introduction into the study by providing the reader with a background and rational of this study together with the aims, objectives and significance of this study.

Chapter two consists of the literature review and research done on the topic, which includes literature from other studies conducted in this field of practice. The following main headings are discussed: sepsis and septic shock, infection in the septic patient, antimicrobials used in sepsis and septic shock, recommendations and guidelines for treating sepsis and septic shock and the burden of sepsis and septic shock on developing countries.

Chapter three consists of a detailed descriptive methodology for this study, starting with discussion of the study site, study design, study population and sample followed by description of the data collection, pilot study and data capture and analysis. Reliability, validity and bias are explained. The chapter concludes with a discussion of this study’s ethical considerations.

Chapter four is written in the form of an article that provides all the results of the study together with a discussion on the findings, a description of the limitation of the study with recommendations and finally, a conclusion.

Chapter five gives a summary of all the results, concludes the dissertation and discusses all the limitations of the study together with recommendations. Figure 1.1 provides a short illustration of the outline of this dissertation.
1.8 SUMMARY

This chapter emphasised the impact of sepsis not only on global health, but also on developing countries like SA. Although many studies have been conducted in developed countries, the global mortality rate continues to increase in patients with sepsis and septic shock. The chapter outlined the significances of this study as there as limited research available about sepsis and septic shock in developing countries and also list the aims and objects that were covered during this study. Chapter two will follow with the emphasis being on a fully comprehensive literature review done on the study topic.
2.1 INTRODUCTION

In this chapter, an overview of published literature on the study topic as well as previous research done in this particular field are provided. The chapter starts with a review of the literature covered and is discussed under the following main headings: definitions of sepsis and septic shock, infection in septic patients, antimicrobials used in sepsis and septic shock, recommendations and guidelines used for treating sepsis and septic shock and the burden of sepsis and septic shock on developing countries. The chapter concludes with a summary of the findings of the literature review.

2.2 SEPSIS AND SEPTIC SHOCK

In ancient times, sepsis was defined by Hippocrates as: ‘the process by which swamps releasing revolting airs, rotting flesh and wounds becoming septic’ (Angus and van der Poll, 2013). Sepsis was seen ‘as a systemic host response to an infection’ in the past century. William Osler, an American physician, made the observation that patients are dying from the body’s response to an infection instead of the infection itself (Martin, 2012). In 1972, this concept was confirmed by Thomas stating that ‘it is our response that makes the disease’ (Thomas, 1972).

Singer et al. (2016), have updated the definition for sepsis as a ‘life-threatening organ dysfunction caused by a dysregulated host response to infection’. Organ dysfunction can occur if there is an increase of more than two points in the Sequential Organ Failure Assessment (SOFA) score. In-hospital mortality is more than 10% (Singer, Deutschman, Seymour, Shankar-Hari, Annane, Bauer, Bellomo, Bernard, Chiche, Coopersmith, Hotchkiss, Levy, Marshall, Martin, Opal, Rubenfeld, der Poll, Vincent and Angus, 2016). Septic shock is defined as ‘a subset of sepsis in which particularly profound circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone’ (Singer et al., 2016), with the highest mortality, approaching 50% (Mayr et al., 2014).
2.3 INFECTION IN THE SEPTIC PATIENT

Although the aetiology of sepsis can be of fungal, viral or bacterial origin, the majority of the cases is due to bacterial infections (Vincent, 2016). Immune suppression is induced by sepsis, which leads to an increase in susceptibility to secondary infections, leading to a correlation with late mortality (Hutchins, Unsinger, Hotchkiss and Ayala, 2014). In a study done by van Vught et al. (2016), it was found that the risk of acquiring an ICU-infection increased in patients that were diagnosed with sepsis, especially if the patients were connected to a central venous line, catheter and mechanical ventilator (van Vught, Klein Klouwenberg, Spitoni, Scicluna, Wiewel, Horn, Schultz, Nürnberg, Bonten, Cremer and van der Poll, 2016). If patients with sepsis are not treated effectively and rapidly, septic shock and multiple organ failure will follow. With a mortality rate of about 30%, sepsis management relies on infection control and support of organ function. Since there is no specific therapy for these patients, it is important to remove the source and to provide them with effective antibiotics (Vincent, 2016). Many studies have shown the correlation between early treatment and an improved outcome in patients with sepsis. The importance of an early diagnosis is crucial. The sooner sepsis is diagnosed, the sooner treatment can start, to prevent sepsis becoming progressively worse. However, it remains a major challenge for clinicians (Vincent, 2016).

The percentage of sepsis incidents will vary between different countries, depending on the number of ICU beds. If the availability of ICU beds is low in a country, the percentage of patients with sepsis in ICU will be high and for countries with more ICU beds, the percentage of sepsis will be lower (Kübler et al., 2015). Therefore, an estimation that is based on the percentage of patients with sepsis in ICUs can be misleading (Kübler et al., 2015). The number of sepsis incidents in ICUs is not a true reflection of sepsis among the population, since not all patients with sepsis are treated in an ICU (Mayr et al., 2014).

2.4 ANTIMICROBIALS USE IN SEPSIS AND SEPTIC SHOCK

Gram-positive, gram-negative and mixed bacterial microorganisms commonly cause sepsis (Rhodes et al., 2017). It was initially thought that sepsis was caused by gram-negative bacteria, but over the last years, research has shown that the majority of organisms that currently causes sepsis are gram-positive bacteria in developed countries (Ramachandran, 2014), and gram-negative bacteria in developing countries (Chehade et al., 2015).
When sepsis is suspected, a broad-spectrum antibiotic has to be administered to cover all the likely pathogens, such as a carbapenem, an extended-range penicillin/β-lactamase inhibitor combination, cephalosporin (third generation or higher) or when methicillin-resistant *Staphylococcus aureus* (MRSA) exist, teicoplanin, vancomycin or any other anti-MRSA agent. Once an organism has been cultured and identified, therapy should be de-escalated by changing the broad-spectrum therapy to more targeted treatment (Rhodes *et al.*, 2017).

A study done by Kumar *et al.* (2006) was the first to find that a delay in initiation of effective antibiotics following the onset of hypotension is a critical therapeutic variable associated with septic shock mortality. They found a 79.9% survival rate if effective antibiotics are administered within the first hour following onset of septic shock related hypotension. The survival rate drops with an average of 7.6% in the first 6 hours for every additional hour that the antibiotic treatment was delayed (Kumar, Roberts, Wood, Light, Parrillo, Sharma, Suppes, Feinstein, Zanotti, Taiberg, Gurka, Kumar and Cheang, 2006). In one cohort, 20% of ICU patients diagnosed with infection and systemic inflammatory response syndrome (SIRS) progressed to severe sepsis and septic shock within six days of delay in antimicrobials. Statistics show that 18.6% of sepsis patients presenting to emergency department of hospitals, progress to severe sepsis or septic shock (Whiles, Deis and Simpson, 2017).

Due to all the variables that have to be considered, no definitive recommendations of any specific regimens are possible for sepsis and septic shock. There are only general guidelines and recommendations for consideration, to provide potential regimens that are based on specific immune defects of anatomic site of infections (Rhodes *et al.*, 2017).

### 2.5 THE ROLE OF SEPSIS BIOMARKERS IN DIAGNOSING SEPSIS

Accurate sepsis biomarkers can help facilitate the diagnosis of sepsis, taking into consideration the difficulties in diagnosing sepsis. There are more than 170 biomarkers. Some of them can be used to assist with an early initiation of antibiotic treatment, optimising the chances of survival. Biomarkers include receptors, cell surface markers, numerous cytokines, coagulation factors, acute phase reactants, complement factors and much more, but not one works 100% specifically for sepsis. C-reactive protein (CRP) is the most studied sepsis biomarker in the world, as this biomarker increases with every inflammatory disorder,
making it sensitive but not very specific. A more specific biomarker, Procalcitonin (PCT), was discovered in 1993. (Vincent, 2016).

According to Vincent (2016) sepsis biomarkers can help with the following:

- Ruling out an infection;
- Evaluating the severity of a disease; and
- Monitoring the patient’s response to treatment.

The biomarkers PCT and CRP can be used in sepsis to guide early discontinuations of antibiotic treatment, if there is a progressive decrease in their concentrations (Oliveria et al., 2013). Re-evaluation of the antibiotic therapy can be suggested after the first 48 hours of treatment if there is an increase in the concentration of CRP, since it may suggest that the antibiotic is ineffective (Vincent, 2016). Although PCT levels were used as a guidance for antibiotic treatment, it is not wise to use as an antibiotic-escalation strategy since it can lead to a worse outcome (Schuetz et al., 2009; Heyland et al., 2011). Clinicians should not diagnose or make clinical decisions that is only based on the concentrations of biomarkers. To make a clinical decision, other hemodynamic and laboratory parameters but also the clinical status of the patient must be included (Vincent, 2016).

There is never going to be only one ideal biomarker to can be used for sepsis. The future research focus should be on using combinations of markers, since the response in sepsis involves multiple players that are present at different times during the development of the disease (Vincent, 2016).

By using the correct combination of biomarkers, the diagnostic accuracy and the outcome of the patient can be improved, which will limit unnecessary treatment and tests, a reduction in time to treat effectively, improvement of antibiotic stewardship and reducing antibiotic resistance (Vincent, 2016).

2.6 RECOMMENDATIONS AND GUIDELINES FOR TREATING SEPSIS AND SEPTIC SHOCK

Recommendations, according to the SSC, for the use of antimicrobial therapy in patients with sepsis and septic shock are described below (Rhodes et al., 2017):
• Intravenous (IV) antimicrobials should be administrated as soon as possible after recognition and within one hour for both septic shock and sepsis.

The largest and highest-quality studies show a significant increase in mortality rate in sepsis and septic shock for every hour delay in administrating the appropriate antimicrobial (Amaral, Fowler, Pinto, Rubenfeld, Ellis, Bookatz, Marshall, Martinka, Keenan, Laporta, Roberts, and Kumar, 2016). Quality improvement initiatives can be used to overcome the most issues. To ensure early administration, antimicrobials can be premixed to be administered in urgent situations, if efficient preparation and delivery are not possible. Drugs that can be administered as a rapid infusion or bolus can offer an advantage to reach therapeutic levels faster, in cases where vascular access is limited (Rhodes et al., 2017).

Another possibility in cases of limited vascular access is intraosseous access. Intraosseous administrations can be used to rapidly administer any antimicrobials dosages (Petitpas, Guenezan, Vendeuvre, Scepi, Oriot, and Mimoz, 2016). If IV access nor intraosseous access is unavailable, intramuscular preparations can be administered, which consist of several β-lactams, including cefepime, ertapenem, imipenem/cilastatin and ceftriaxone (Rhodes et al., 2017).

• To cover all pathogens, empiric broad-spectrum therapy should be used for patients that present with sepsis or septic shock.

Choosing the appropriate empiric antimicrobial is one of the most crucial steps to determine a favourable outcome. Empiric therapy which fails to cover the causing organism in septic patients, decreases the patient’s survival five times (Paul, Shani, Muchtar, Kariv, Robenshtok, and Leibovici, L., 2010).

Selection of the appropriate empiric therapy depends on intricate issues related to local epidemiology factors, the patient’s history and clinical status. Patient factors play a key role in the choice of antimicrobials. Factors to consider when choosing the appropriate antimicrobial regime include the site of infection; if at the time of infection the patient was from the community; in a care institution or in hospital location; chronic organ failure; form of immunocompromised; indwelling devices; underlying diseases; medications; known recent infection; receipt of antimicrobials within the past three months; the prevalence of local pathogens and their susceptibility patterns within the community and hospital; resistance patterns, and toxicity. Due to the aforementioned empiric treatment
for sepsis and septic shock is complex and cannot be summarised into a simple table (Rhodes et al., 2017).

Healthcare professionals should individualise each patient’s therapy according to their patient factors and anatomic site of infection. To ensure a sufficient empiric broad-spectrum coverage, a multidrug therapy is often required (Rhodes et al., 2017).

In high risk patients who is critically ill, with possible multidrug-resistant pathogens, a supplemental gram-negative agent can be added to the empiric regimen (Micek, Welch, Khan, Pervez, Doherty, Reichley and Kollef, 2010). If risk factors for MRSA exist, teicoplanin, vancomycin, or another anti-MRSA drug can be used. A fluoroquinolone or macrolide can also be added to the regime if a patient whose risk is increase of infections with *Legionella* species (Rhodes et al., 2017). Antifungal drugs can also be added to the regimen if the patient is at high risk for infection with *Candida* species (Pappas, Kauffman, Andes, Clancy, Marr, Ostrosky-Zeichner, Reboli, Schuster, Vazquez, Walsh, Zaoutis and Sobel, 2016).

- De-escalate empiric antimicrobial therapy once the pathogen is identified.

  Empiric broad-spectrum therapy should be continued until the causative organism with its antimicrobial susceptibility is identified, thereafter all unnecessary antimicrobials should be eliminated and treatment should be narrowed towards the susceptibility of the organisms. Stop all antimicrobials when no infection is found to decrease the patient’s risk of becoming infected with a resistant pathogen (Guo, Gao, Yang, Ma and Sui, 2016).

- Sustained systemic antimicrobial prophylaxis should be avoided in patients with extreme inflammatory states of non-infectious origin.

  Antimicrobial treatment is not necessary in patients with a systemic inflammatory response without infection, to decrease the patient’s risk of becoming infected with a resistant pathogen or developing drug-related adverse effects. Such conditions include extensive burn injuries or severe pancreatitis (Working Group IAP/APA Acute Pancreatitis Guidelines, 2013).

  Despite this recommendation, if there is a strong suspicion of concurrent sepsis or septic shock in patients with extreme inflammatory state without infection, antimicrobial treatment is indicated (Rhodes et al., 2017).
In patients with sepsis and septic shock, the dosing strategies of antimicrobials should be based on pharmacodynamic or pharmacokinetic principles and specific drug properties.

The outcome of septic patients improved with early optimisation of antimicrobial pharmacokinetic. Septic patients differs from the typical infected patient, which affects the optimal antimicrobial treatment strategy. These differences include a high prevalence of unrecognised immune dysfunction, susceptible to infection with resistant pathogens, an increase in frequency of renal and hepatic dysfunction and an increased volume of distribution due to fluid resuscitation (Blot, Koulenti, Akova, Dimopoulos, Kaukonen, Martin, Montravers, Rello, Rhodes, Starr, Wallis, Lipman, and Roberts, 2014).

Every drug requires a specific peak targeted plasma concentration to achieve their optimal outcome. Clinical failure with aminoglycosides occurs if there is a failure to achieve the drug’s specific peak plasma concentration with initial dosing. Serious MRSA infections occur with inadequate early vancomycin trough plasma concentration levels (Men, Li, Zhai, and Zhao, 2016). The clinical success rate with fluoroquinolone (Drusano, Preston, Fowler, Corrado, Weisinger, and Kahn, 2004) and aminoglycoside therapy in serious infections correlates with higher peak concentration levels in the blood, in relation to the minimum inhibitory concentration (MIC) of the pathogen (Rhodes et al., 2017).

Optimal dosing strategies, when administering fluoroquinolones or aminoglycosides include to optimise the peak drug concentrations. Aminoglycosides can be administered as once-daily dosing, which will decrease the risk for renal toxicity. Aminoglycosides can be used in patients with preserved renal function but should be avoided in patients with severe renal dysfunction (Rhodes et al., 2017).

Vancomycin is partially concentration-dependent, with a recommended trough level of 15 – 20mg/L. This concentration is necessary to achieve appropriate pharmacodynamic targets, increases tissue penetration and optimised clinical outcomes (Steinmetz, Eliakim-Raz, Goldberg, Leibovici, and Yahav, 2015). Vancomycin needs an IV loading dose of 25 – 30mg/kg to reach the therapeutic range quicker in septic patients (Kumar, 2014).

The pharmacodynamics of beta-lactams is the time the plasma concentration of the drug is above the MIC of the pathogen, relevant to the dosing interval (Time > MIC). To
achieve a sufficient clinical response in patients with sepsis or septic shock the Time > MIC needs to be 100% and not just 60%, which is generally required for moderate illness (McKinnon, Paladino, and Schentag, 2008). An easy way to achieve this is to increase the dosing frequency. To achieve the therapeutic range faster with beta-lactams, the initial dose can be given as a rapid infusion or a bolus, following an extended infusion over several hours, which also increases Time > MIC (Yost, Cappelletty, and RECEIPT Study group, 2011).

Patients with sepsis or septic shock have a variety of physiologic perturbations which changes the pharmacokinetics of antimicrobials. These patients are hemodynamic unstable, have an increased cardiac output, their kidney and liver functions are altered, have an increased volume of distribution due to an increase in the extracellular volume and reduced serum albumin causing a change in the binding of drug (Roberts, Abdul-Aziz, Lipman, Mouton, Vinks, Felton, Hope, Farkas, Neely, Schentag, Drusano, Frey, Theuretzbacher and Kuti, 2014).

- The initial management of septic shock should be with empiric combination therapy for the most likely bacterial pathogen(s). Two antibiotics of different antimicrobial classes should be used.

Table 2.1 provides general terminology regarding different types of therapies that are being used.

<table>
<thead>
<tr>
<th>Empiric therapy</th>
<th>Can be defined as the initial therapy that is started in the absence of a definitive identification of a microbiologic pathogen. Empiric therapy may be given as mono-, combination, broad spectrum, and/or multidrug treatment (Rhodes et al., 2017).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Targeted / definitive Therapy</td>
<td>This treatment is usually given after identification of the pathogen to target a specific pathogen. This therapy may be mono- or combination, but should not be broad spectrum (Rhodes et al., 2017).</td>
</tr>
<tr>
<td>Broad spectrum therapy</td>
<td>Is usually used during empiric therapy and can be defined as the usage of one or more antimicrobial agents with the intention of broadening the antimicrobial covering range of potential pathogens (e.g., piperacillin/tazobactam, vancomycin, and anidulafungin; each one is used to cover a different group of pathogens). If multiple pathogens are identified, the broad spectrum therapy may be continued into the targeted therapy phase (Rhodes et al., 2017).</td>
</tr>
</tbody>
</table>
### Multidrug therapy

In this therapy, multiple antimicrobials are used to provide a broad spectrum treatment for empiric therapy or to potentially advance pathogen clearance of specific pathogen(s) where the pathogen(s) is known or suspected. This term therefore includes combination therapy (Rhodes et al., 2017).

### Combination therapy

In this therapy, multiple antimicrobials that have different mechanisms are used with the intention of covering the known or suspected pathogen(s) (e.g., piperacillin/ tazobactam and an aminoglycoside or fluoroquinolone for gram-negative pathogens). Combination therapy are used to advance pathogen clearance rather than to broaden antimicrobial coverage. Other indications of combination therapy include potential immune modulatory effects or inhibition of bacterial toxin production (Rhodes et al., 2017).

- Avoid using a combination therapy routinely for ongoing treatment of other serious infections, such as sepsis without shock.
- Avoid combination therapy for the routine treatment of neutropenic sepsis/bacteraemia.
- Referring to targeted and empiric initial combination therapy, de-escalation with discontinuation of the combination therapy should transpire within the first few days in response to clinical improvement and/or evidence of infection resolution. This recommendation concerns both culture-positive infections as well as empiric therapy.

Due to an increase in the frequency of pathogen resistance, initial multi-drug empiric treatment is often required to ensure an appropriate broad-spectrum coverage. Combination therapy is the combination of two antimicrobials with different mechanisms of actions used to treat a pathogen which is suspected to be sensitive towards both antimicrobials, with the main purpose of accelerated pathogen clearance (Rhodes et al., 2017). Some studies have shown an increase in survival when treating septic patients with a mortality of greater than 25% with combination therapy (Díaz-Martín, Martínez-González, Ferrer, Ortiz-Leyba, Piacentini, Lopez-Pueyo, Martín-Loeches, Levy, Artigas, Garnacho-Montero, 2012).

Although many studies have evidence which show a favourable outcome for combination therapy in septic patients, direct evidence from randomised clinical trials are not available to validate this approach definitively (Kumar, 2014). This recommendation is weak and is based on low quality evidence (Rhodes et al., 2017). Combination therapy is only useful in circumstances where the pathogen(s) is identified and treatment can be specific, however, in most cases the causative pathogen is not
known at the time of presentation (Bass, Bauer, Neuner, and Lam, 2015). Evidence also shows that combination therapy is not effective for ongoing treatment (includes ongoing empiric treatment for culture negative infections and ongoing targeted treatment for culture positive infections) in patients with bacteraemia and sepsis without shock (Rhodes et al., 2017).

- A duration of 7-10 days of antimicrobial treatment is suggested to be sufficient for most serious infections related to sepsis and septic shock.

- If the patient has a slow clinical response, undrainable infection, S. areus bacteraemia, some fungal and viral infections or neutropenia, a longer course of antimicrobial treatment is suggested.

- Patients with a quick clinical resolution, following effective source control of intra-abdominal or urinary sepsis, as well as those with anatomically uncomplicated pyelonephritis, should receive shorter courses of treatment.

- Patients with sepsis and septic shock should be monitored on a daily basis for de-escalation of antimicrobial therapy.

An adequate treatment duration for antimicrobials (without source control problems) is between 7 to 10 days, but patient factors may influence the length (Kalil, Metersky, Klompas, Muscedere, Sweeney, Palmer, Napolitano, O'Grady, Bartlett, Carratalà, El Solh, Ewig, Fey, File, Restrepo, Roberts, Waterer, Cruse, Knight, and Brozek, 2016). A study conducted by Sawyer et al. (2015), showed that certain serious infections can be treated with a shorter course antimicrobials if needed or if successful source control is implemented. No significant difference in the outcome based on the duration of treatment was demonstrated (Sawyer, Claridge, Nathens, Rotstein, Duane, Evans, Cook, O'Neil, Mazuski, Askari, Wilson, Napolitano, Namias, Miller, Dellinger, Watson, Coimbra, Dent, Lowry, Cocanour, West, Banton, Cheadle, Lipsett, Guidry and Popovsky, K;STOP-IT Trial Investigators. 2015). Similar studies shown that the efficacy of 3 to 5 day treatment duration is as adequate as a treatment duration lasting up to 10 days or longer (Eliakim-Raz, Yahav, Paul, and Leibovici, 2013). There are a few conditions which require more prolonged antimicrobial therapy, e.g. infections with a slow clinical response, MRSA infection, undrainable foci (Rhodes et al., 2017), candida infections (Pappas et al., 2016), viral infections, other fungal infections and immunologic deficiencies. The duration of treatment should be based on patient factors and the nature of the causative pathogen (Rhodes et al., 2017).
Administration of extended unnecessary antimicrobials is harmful to both patient and society. Antimicrobial resistance (AMR) is driven by prolonged usage of antimicrobials, which is a burden on society. Patients using prolonged unnecessary antimicrobials have an increased risk of mortality (Garnacho-Montero, Gutiérrez-Pizarraya, Escoresca-Ortega, Corcia-Palomo, Fernández-Delgado, Herrera-Melero, Ortiz-Leyba, and Márquez-Vácaro, 2014) and also an increased risk of developing Clostridium difficile colitis (Stevens, Dumyati, Fine, Fisher, and van Wijngaarden, 2011).

In conclusion, due to the harmful effects of prolonged unnecessary antimicrobial therapy, patients with sepsis or septic shock should be assessed on a daily basis for de-escalation of antimicrobial therapy based on clinical presentation (Rhodes et al., 2017).

- In sepsis patients, the measurement of PCT levels can be used to shorten the duration of antimicrobial therapy.
- The SSC also suggests that PCT levels can be used to support the discontinuation of empiric antibiotics for patients who were initially diagnosed with sepsis, but have subsequently no or few clinical evidence of infection.

Around the world, serum PCT is used as a biomarker to help diagnosing acute infections and assist with the duration of antimicrobial therapy. Different procalcitonin-based algorithms are used. These algorithms measure serum PCT, to assist in the de-escalation of antimicrobial treatment in sepsis (Westwood, Ramaekers, Whiting, Tomini, Joore, Armstrong, Ryder Stirk, Severens, and Kleijnen, 2015). Literature recommends PCT measurement since it assists with quicker and safer de-escalation of antimicrobial therapy, compared to a standard clinical approach with reduced antimicrobial consumption without an adverse effect on mortality (Rhodes et al., 2017).

Recent literature show that PCT assist in shortening the duration of antimicrobial therapy, reducing the DDD of antimicrobials (de Jong, van Oers, Beishuizen, Vos, Vermeijden, Haas, Loev, Dormans, van Melsen, Kluiters, Kemperman, van den Elsen, Schouten, Streekerk, Krabbe, Kieft, Kluge, van Dam, van Pelt, Bormans, Otten, Reidinga, Endeman, Twisk, van de Garde, de Smet, Kesecioglu, Girbes, Nijsten and de Lange, 2016) and a decreased mortality rate, however another study failed to show similar survival advantages. Other studies suggest the use of PCT to differentiate between infective and non-infective conditions (Rhodes et al., 2017).
The SSC advise that PCT and other biomarkers should only be used as supportive and supplemental data to clinical assessments and that decisions pertain to initiating, changing, or de-escalating any antimicrobial therapy should never solely be made on the basis of changes in biomarkers (Rhodes et al., 2017).

2.7 THE BURDEN OF SEPSIS AND SEPTIC SHOCK IN DEVELOPING COUNTRIES

Developing countries consist of 87% of the world’s population (Reinhart et al., 2017) and yet only 10% of the supporting references of the SSC pertain to studies in developing countries (Rhodes et al., 2017). According to the WHO, the burden of sepsis on developing countries are probably the highest (World Health Organisation, 2018). Most of the management of fungal and bacterial sepsis, which guidelines focus on, were collected in developed countries. This leads to concerns that problems and challenges addressed in developing countries remain insufficient. Most of the SSC guideline recommendations cannot be implemented in developing countries, due to inadequate resources (Tupchong et al., 2015).

For all the reasons outlined above and the relative paucity in scientific literature on the use of antimicrobial therapy in SA, this study sets out to assess antimicrobial therapy in patients with sepsis and septic shock.

2.8 SEPSIS IN SOUTH AFRICA

The development and implementation of sepsis protocols in developed countries have contributed to the identification and management of sepsis, in order to decline mortality rates (Kaukonen, Bailey, Suzuki, Pilcher and Bellomo, 2014). Certain factors make it very difficult to implement protocols from developed countries within developing countries. These factors include cost restraints, access to healthcare, lack of resources and the delayed presentations of septic patients (Bhikoo, Versfeld, Basson, and Oosthuizen, 2017).

A retrospective study was done by Bhikoo et al. (2017) in a large district hospital in Cape Town, with a study population of 70 septic patients. Their main objectives were to determine the adequacy of sepsis identification and management by clinicians within the hospital. The most common diagnosis causing sepsis, by the emergency personnel, was lower respiratory tract infections following by acute gastroenteritis. Ceftriaxone was the most commonly prescribed antibiotic for sepsis during this study. The correct antibiotics for the particular infection were prescribed for 78.5% of the septic patients. They also noted that
10% of the septic patients did not receive antibiotics within the first 24 hours after presentation. The average time passed for a patient being diagnosed with sepsis in casualties to receiving an antibiotic was 3.63 hours. The association between sepsis management principals and in-hospital mortality were as follow:

- The rate of survival decreases with 7% for every hour delay in antibiotic administration, which is similar to the findings of Kumar et al. (2006), stating that the survival rate drops with an average of 7.6% within the first 6 hours for every additional hour that the antibiotic treatment was delayed (Kumar et al., 2006) (Bhikoo et al., 2017).
- The mortality rate decreased by 83% if the patients received antibiotics that have been changed to target the specific organisms causing the infection (Bhikoo et al., 2017).

One of the concerns within their study was regarding the inadequate evidence of prescribing the correct antibiotic for a specific infection in an environment with a high prevalence of human immunodeficiency virus (HIV) infections. They recommended a septic check sheet which could lead to improve the management of sepsis, since their results clearly showed that education is necessary for all healthcare providers to help with the identification and management of sepsis. It is therefore apparent that additional research on sepsis in developing countries should be conducted (Bhikoo et al., 2017).

A nationwide study conducted by Bhagwanjee et al., looked at whether physicians in the ICUs of SA were capable of making effective diagnosis and implementing the correct therapy for sepsis. A PPS done in 2009 in SA included 248 septic patients. Of the perceived antibiotic, 28% were inappropriate and only 12% were appropriate. Antimicrobials were only changed in 24% of the patients to targeted treatment after culture sensitivity were available and the duration of treatment was correct in 28% of the incidents (Bhagwanjee, Scribante, Paruk, and Richards, 2009).

During a study on neonatal sepsis, conducted in Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), it was found that the most common gram-positive organism causing sepsis in the neonates is MRSA and coagulase-negative Staphylococcus. The predominant cultured gram-negative organisms were Escherichia coli, Acinetobacter baumannii and Klebsiella pneumonia. High levels of resistance towards commonly used antibiotics such as gentamicin, ampicillin and ceftazidime were found. The organisms cultured in this study differs from the organisms cultured in another study obtained in the same unit at CMJAH a
few years ago. They confirmed that organisms causing neonatal sepsis change over a period of time and gram-negative organisms were the predominate cause of neonatal sepsis (Lebea & Davies, 2017).

2.9 DRUG CLASSIFICATION SYSTEMS

2.9.1 Anatomic Therapeutic Chemical Classification System

In the 1970s, the anatomic therapeutic chemical (ATC) classification system was initiated and since 1982, it is organised by the WHO Collaborating Center for Drug Statistics Methodology. The ATC system is the most used classification system around the world to express drug utilisation. The ATC codes are revised by the WHO and are maintained as an inline database and published index (Hutchinson, Patrick, Marra, Ng, Bowie, Heule, Muscat, and Monnet, 2004).

The ATC codes divides drugs according to the system or organ which they act on and/or their therapeutic and chemical characteristics. At least one ATC code is assigned for each drug. The ATC code is classified into groups at five different levels. Table 2.2 shows an illustration of amoxicillin being classified according to the ATC classification (Hutchinson et al., 2004).

<table>
<thead>
<tr>
<th>ATC classification</th>
<th>ATC category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>J</td>
<td>General anti-infective for systemic use</td>
<td>1st level: anatomical main group</td>
</tr>
<tr>
<td>J01</td>
<td>Antibacterial for systemic use</td>
<td>2nd level: therapeutic main group</td>
</tr>
<tr>
<td>J01C</td>
<td>Beta-lactam antibacterial, penicillin’s</td>
<td>3rd level: therapeutic/pharmacological subgroup</td>
</tr>
<tr>
<td>J01C A</td>
<td>Penicillin with extended spectrum</td>
<td>4th level: chemical/therapeutic/ pharmacological subgroup</td>
</tr>
<tr>
<td>J01C A04</td>
<td>Amoxicillin</td>
<td>5th level: subgroup for chemical substance</td>
</tr>
</tbody>
</table>
2.9.2 Access, Watch, or Reserved antibiotic groups

The 2017 WHO EML for adults classifies antibiotics into three groups: Access, Watch, or Reserved (AWaRe). Antibiotics used as first- or second-line treatment for important infections fall under the Access antibiotics group. High-quality formulations of these antibiotics should be available universally at a low cost. Antibiotics which have a higher potential for selecting antibiotic resistance are grouped as a Watch antibiotic. Reserved antibiotics are the last resort antibiotics and should be used under guidance of a specialist with specific monitoring (Hsia, Sharland, Jackson, Wong, Magrini, and Bielicki, 2018).

2.9.3 Defined Daily Dose

The Defined Daily Dose (DDD) is a technical unit of measurement which was designed to use in comparison with the ATC classification system, to compare consumption data across geography and time. The DDD is assigned to every drug at the 5th ATC level classification (Hutchinson et al., 2004).

DDD can be defined as "The assumed average maintenance dose per day for a drug used for its main indication in adults" (World Health Organisation, 2018). DDD of drugs may differ depending on the different drug formulations (e.g. oral formulations versus parenteral formulations) (Hutchinson et al., 2004). Examples of DDD can found in Table 2.3.

<table>
<thead>
<tr>
<th>ATC classification</th>
<th>ATC drugs</th>
<th>DDD</th>
</tr>
</thead>
<tbody>
<tr>
<td>J01C A04</td>
<td>Amoxicillin</td>
<td>1g (parenteral or oral)</td>
</tr>
<tr>
<td>J01M A06</td>
<td>Norfloxacin</td>
<td>0.8g (oral)</td>
</tr>
<tr>
<td>J01M A02</td>
<td>Ciprofloxacin</td>
<td>1g (oral)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.5g (parenteral)</td>
</tr>
<tr>
<td>J01F F01</td>
<td>Clindamycin</td>
<td>1.2g (oral)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.8g (parenteral)</td>
</tr>
<tr>
<td>J01C A12</td>
<td>Piperacillin</td>
<td>14g (parenteral)</td>
</tr>
</tbody>
</table>


2.10 SUMMARY

In conclusion, this chapter gives an overview on the evolution of sepsis and septic shock definitions. The chapter also emphasises the importance of infection control and administering effective antimicrobials. The epidemiology of sepsis and septic shock are explained and the lack of literature pertaining to developing counties regarding management of sepsis, followed by recommendations from the SCC regarding the treatment of sepsis and septic shock. Chapter three will focus on the methodology employed during this study.
Chapter 3: Methodology

CHAPTER 3

METHODOLOGY

3.1 INTRODUCTION

This chapter presents a detailed description of the study and consists of an outline of the study site and design. The study population is described followed by the sample selection according to the inclusion and exclusion criteria that were used. An explanation of the pilot study and data capture and analysis are provided. The data collection is also discussed, providing an overview of the data collection period, data collection instruments, data collectors as well as data collection training. A discussion follows on the methods used to ensure reliability and validity throughout the study. The chapter concludes with a discussion on ethical consideration and finally a summary of the chapter.

3.2 STUDY SITES

The study was conducted in all the tertiary and central hospitals in Gauteng, SA. These sites were selected based on their classification according to the regulations relating to the categories of hospitals, in terms of Section 35, read together with Section 90 of the National Health Act, 2003, (Act No. 61 of 2003) (Department of Health, 2012). The requirement for both tertiary and central hospitals in SA, according to the regulations, is to provide intensive care services under the supervision of a specialist or an intensivist. The latter provides the reasoning for the proposed study sites. See Table 3.1 for hospital characteristics.
### Table 3.1: Gauteng Tertiary and Central hospital characteristics

<table>
<thead>
<tr>
<th>Level of care</th>
<th>Hospital</th>
<th>Total number or beds</th>
<th>Total number of adult ICU beds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tertiary</td>
<td>Helen Joseph</td>
<td>485</td>
<td>10</td>
</tr>
<tr>
<td>Hospitals</td>
<td>Tembisa</td>
<td>840</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Kalafong</td>
<td>857</td>
<td>6</td>
</tr>
<tr>
<td>Central</td>
<td>Steve-Biko Academic Hospital</td>
<td>832</td>
<td>10</td>
</tr>
<tr>
<td>Hospitals</td>
<td>Chris Hani Baragwanath Academic Hospital,</td>
<td>2888</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>Dr George Mukhari Academic Hospital</td>
<td>1652</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>Charlotte Maxeke Academic Hospital</td>
<td>1018</td>
<td>79</td>
</tr>
<tr>
<td>7 Hospitals</td>
<td></td>
<td>8,472</td>
<td>155</td>
</tr>
</tbody>
</table>

#### 3.3 STUDY DESIGN

The study was a descriptive, cross-sectional point prevalence survey (PPS), with a quantitative study design. Point prevalence pertains to a number of people who has a specific disease over a specified period of time or at a particular point in time (PubMed Health, 2018). For this study, the number of adult sepsis patients in the ICU was counted on a particular day at a specific hospital.

#### 3.3.1 Quantitative research

Quantitative research emphasises objective measurements. A quantitative research method was used to measure the number of septic patients per hospital and the number of antimicrobials per patient.

#### 3.3.2 Descriptive research design

This study had a descriptive research design, with the purpose of providing a presentation of the study environment and the characteristics of the study population, including the demographics of each patient.
3.4 STUDY POPULATION AND SAMPLE

3.4.1 Study population

This study included ICU patients of 18 years and older presenting with sepsis and/or septic shock, admitted to the adult ICU during the data collection period.

3.4.2 Study selection

The PPS design of the study require that all the patients in the ICUs be surveyed to determine the denominator. The patients included in the study, according to the inclusion criteria, will then be surveyed and serve as the numerator. Data will be collected through convenient, purposive sampling. Convenience sampling is a type of non-random or non-probability sampling, where people who meet the specific criteria are selected out of the targeted population and included in the study, due to their convenient accessibility to the researcher (Etikan, 2016).

3.4.3 Sample size

The researcher visited seven hospitals, totalling 155 beds. The sample comprised of the total number of patients in the adult ICU on the day of sampling. The calculated sample size was 96, with a two-sided 95% confidence interval (CI) for the proportion of patients with sepsis/septic shock. This was within ± 10% of the proportion percentage, assuming that the proportion is around 0.5 (50%). Sample size calculation was done in nQuery Advisor (Statistical solutions Ltd, Cork, Ireland). Release 7.0, and was based on the large sample normal approximation of the binomial distribution.
3.4.4 Inclusion criteria

Table 3.2 indicates the inclusion criteria that was applied:

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Justification</th>
<th>Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients 18 years and older</td>
<td>All patients aged 18 years and older were surveyed, as the study focus on septic patients in the adult ICU.</td>
<td>All patients aged 18 years and older were included in the survey. No informed consent from patients were necessary, as only the patients files were used.</td>
</tr>
<tr>
<td>All patients in the adult ICU with a written diagnoses of sepsis, septic shock and suspected or confirmed sepsis.</td>
<td>The study aimed at identifying patients with sepsis, septic shock and suspected or confirmed sepsis.</td>
<td>Patients files with the written suspected or confirmed sepsis were surveyed.</td>
</tr>
<tr>
<td>The following written keyword/s was identified on the medical file for inclusion; sepsis, severe sepsis, septic shock, septicaemia, septic, bloodstream infection.</td>
<td>These written keywords on the patients' file were used to identify patients with suspected or confirmed sepsis.</td>
<td>All adult patients' files were thoroughly checked for the written keywords as diagnosis, to help identify the patients needed to be included in the sepsis survey.</td>
</tr>
</tbody>
</table>
3.4.5 Exclusion criteria

Table 3.3 indicates the exclusion criteria that was applied.

Table 3.3: Exclusion criteria

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Justification</th>
<th>Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any patients admitted after 08:00 on the day of data collection for the specific hospital ICU.</td>
<td>A PPS looks at a particular point in time. The cut of pint was 08:00 and patients who were admitted to the ICU after 08:00 on that particular day were not surveyed.</td>
<td>Patients admitted to the ICU after 08:00 on that particular day were not included in the survey.</td>
</tr>
<tr>
<td>Patients diagnosed of treated for sepsis outside the ICU for sepsis or septic shock.</td>
<td>The main focus of this study is the utilization of antimicrobial in an ICU, as the SSC guidelines are based on an ICU setting.</td>
<td>This was done according to the SSC guidelines and patients diagnosed outside the ICU were excluded from the survey.</td>
</tr>
</tbody>
</table>

3.5 DATA COLLECTION

This section provides an overview of the data collection period, data collection instruments, data collectors as well as data collection training.

3.5.1 Data collection period

Data was collected prospectively from March 2018 to September 2018. The data was collected during weekdays, over a period of seven months. One hospital was surveyed in March 2018, two hospitals in May 2018, two hospitals in June 2018 and two hospitals in September 2018. Data collection was unable to be completed during a period of four months, since the process by which ethical clearance needed to be obtained from each hospital was time consuming. Each hospital was assigned one day where data was collected from each adult ICU. Data collection started from 08:00 until all sepsis cases in the unit were surveyed. All the patients in the ICU were surveyed to determine the denominator as well as the total number of beds.
and the total number of patients admitted. Patients who met the inclusion criteria served as the numerator of the research. The mobile application Knack® was used to capture all the data.

3.5.2 Data collection training

In 2018, the School of Pharmacy at Sefako Makgatho Health Sciences University hosted a workshop on Antimicrobial Stewardship (AMS) for tertiary, districts and community healthcare centers, which the researcher attended. The aim of the Enhancing Appropriate Antimicrobial and Vaccine Use via Mobile Health and Other Techniques in the Republic of South Africa (ENAABLERS) workshop was to teach health care professionals about the AMS principles, introducing the nationwide study and to give training pertaining to the usage of Knack®.

3.5.3 Data collection instruments

The PPS are well established surveillance methods for the monitoring of antimicrobial prescribing in hospitals. In the Global Point Prevalence Survey of Antimicrobial Consumption and Resistance (Global PPS), a web-based application was used for data-entry, validation and reporting. The web-based application allowed the global PPS to stretch over 53 countries and included 335 hospitals in 2015.

For the purpose of ongoing PPS’s, a web-based application was developed in SA, as part of the ENAABLERS project. The web-application allows for anonymous patient data entry directly into the application via any mobile device connected to the web. The data encryption is done with both secure hash algorithm-256 (SHA-256) and Advance Encryption standard-265 (AES-256); these are the strongest encryption available and the same level of encryption used by international banks.

The data backups consist of both active and manual backups and both the active back-up and archives use the same encryption as the database. To minimize the risk of data mitigation failure, the data is stored in different geographic locations. The infrastructure is powered by Amazon Web Services (AWS), the industry leader in cloud services and is trusted by organizations like DOW Jones, Pfizer and the Centres for Diseases Control and Prevention (CDC). Every access to the data is logged and time-stamped and a log-file can be provided in the unlikely case.

Only authenticated users can access the database, various passwords protect the application, and passwords are protected by double encrypted password technology.
Chapter 3: Methodology

The raw data can be exported as comma separated values (.csv), text (.txt), a JavaScript object notation (.json) formats to Microsoft Excel for data analysis and statistical purposes.

Data collection within the ENAABLERS application consists of the following fields.

- Hospital code, ward code, patient code, admission date, age, sex, employed, transferred
- Hospitalisation in past 90 days, Antimicrobial use past 90 days, duration and names of antibiotics in past 90 days
- Catheterisation, Intubation
- Pre-existing medical conditions
- Prescriber classification, Antimicrobial prescribed, indication, dose, frequency, route
- Date, missed doses, out of stock
- CST results, Bacterium name, sensitivity, IV to oral switch
- Prescribed in INN, according to SEDL
- Unrelated surgery, prophylaxis
- Hospital Questionnaire

Furthermore, no patient sensitive data was stored directly within the ENAABLERS application and patient confidentiality is maintained through the use of an anonymous coding system build directly into the application.

In February 2016, the MURIA instruments were developed in Botswana by the main shareholders (Massele, Tiroyakgosi, Matome, Desta, Muller, Paramadhas, Malone, Kurusa, Didimalang, Moyo, and Godman, 2017 ECDC, 2013) and piloted in June 2016 (Paramadhas, Tiroyakgosi and Godman, 2016). Afterwards, the MURIA instruments were refined by academics from all over Africa, as well as relevant contribution from the WHO. See Appendix 1 for the complete data collection instrument that will be used for the proposed research. The data collection instrument comprises of different sections that will be captured in the mobile application:

- Section A: ICU data
- Section B: Patient data
- Section C: Diagnosis
- Section D: Antimicrobial therapy
- Section E: Supportive therapy
- Section F: SSC bundle data
Chapter 3: Methodology

The medical files were used as the main data collection source. All missing data was noted. Appendix A was the data collection instrument for the entire research project. For the purpose of this master’s degree, only Sections A, B and D were used for data collection and analysis.

3.6 PILOT STUDY

A pilot study can be defined as a trial study that is conducted before finalising the research design to help test the reliability, validity and feasibility of the proposed study design (Thabane, Ma, Chu, Cheng, Ismaila, Rios, Robson, Thabane, Giangregorio and Goldsmith, 2010).

The findings of the pilot study conducted prior to March 2017 by an SMU researcher (Dlamini, 2016), were discussed during a planned workshop in Scotland in May 2017. These findings were used to refine the data collection instruments for this study. The pilot study further tested the use of the PPS forms in an electronic format using the mobile health application, Knack®, developed specifically for this purpose.

The results from the pilot study were used to assist to ensure the feasibility, reliability and validity of the data collection tools, allowing for additional corrections and refinement of the application before roll-out across all public sector health facilities.

Another pilot study was conducted in order to test the reliability and validity of the final PPS data collection instrument (see Appendix 1). The pilot study took place after ethical clearance was obtained and this protocol was approved by SMUREC and the Chief Executive Officer (CEO) of the Dr. George Mukhari Academic Hospital (DGMAH).

3.7 DATA CAPTURE AND ANALYSIS

3.7.1 Data capture

Knack®, a mobile application, was used to capture all the data, thereafter the data was exported to a Microsoft Excel™ spreadsheet. The data was verified for accuracy and also cleaned. The clean data was exported to SAS (SAS Institute Inc., Carey, NC, USA, Release 9.4 or higher) and analysed accordingly.

3.7.2 Data analysis

Demographic and clinical characteristics (e.g. comorbidities and medication related variables etc.) of patients was summarised descriptively by mean, standard deviation (SD), median, interquartile range, minimum and maximum values for continuous variables (e.g. age) and by
frequency counts and percentage calculations for categorical variables (e.g. gender, diagnosis).

A 95% CI was calculated for prevalence. Clinical outcomes (e.g. mortality, length of stay, infection related length of stay etc.) was summarised. Comparisons of subgroups of patients was performed if the comparisons were of clinical interest. All the results were presented in text, tables and graphs. Statistical analysis was performed in SAS (SAS Institute Inc., Carey, NC, USA, Release 9.4 or higher). All statistical tests were two-sided and p-values \( \leq 0.05 \) (5%) were considered significant.

3.8 RELIABILITY AND VALIDITY

In a quantitative study, the validity and reliability of an instrument must be measured. Validity refers to determining how accurate an instrument measures what it is supposed to measure. Reliability measures the accuracy of an instrument, or to what extent a research instrument gives consistent results in the same situation on repeated occasions (Heale and Twycross, 2015).

There are two types of validity, namely internal and external validity. External validity refers to generalisation and applying the conclusion of the study outside of the setting of the study. Population validity is a type of external validity, indicating the extent to which the findings can be generalised to another population. Ecological validity refers to whether or not the results can be generalised throughout different settings (Hungler and Polit, 1997).

Internal validity refers to whether the results are valid within a study. Internal validity can be increased when the chance for confounding decreases. For this study, construct and face validation is relevant. Construct validity refers to the degree to which the instrument measures the intended hypothetical construct (Peter, 1981) and by adhering to the study’s objectives, content validity will be obtained. The questionnaires in Knack ® are selected, adapted and included only if they adhere to the criteria they intended to measure. Face validity refers to whether or not the instrument measures what it aimed to measure (Peter, 1981) and was ensured by piloting the questionnaire in Jubilee District Hospital.
Table 3.4: Threats to internal validity (Hungler and Polit, 1997)

<table>
<thead>
<tr>
<th>Threat.</th>
<th>Definition.</th>
<th>Applicability to current study.</th>
<th>What was done to minimize the effect?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effect size.</td>
<td>The failure to define the statistical and interval significance of the study.</td>
<td>Due to an incorrect sample size a misinterpretation of the calculated study variables, e.g. P-values (over or under the correct value) can occur.</td>
<td>A statistician assisted to express the statistical significance of the obtained data.</td>
</tr>
<tr>
<td>Researcher bias.</td>
<td>Occurs when the researcher follows his or her own favourite techniques.</td>
<td>The researcher influenced the study to portray his or her prearranged hypothesis.</td>
<td>Knack®, a mobile application, was used as a data collecting tool.</td>
</tr>
</tbody>
</table>

Table 3.5: Threats to external validity (Hungler and Polit, 1997)

<table>
<thead>
<tr>
<th>Threat.</th>
<th>Definition.</th>
<th>Applicability to the current study.</th>
<th>What will be done to minimize the effect?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ecological validity.</td>
<td>Refers to whether the results can be generalised throughout different settings.</td>
<td>The variables, conditions, content and settings in which the data is collected, influence the collected data and study conclusions.</td>
<td>Data was collected from 08:00 in all the adult ICUs of each hospital.</td>
</tr>
<tr>
<td>Population validity.</td>
<td>Refers to how a sample group is generalised to represent a larger population.</td>
<td>Due to external factors, the available sample might not represent the whole group. No sampling was conducted.</td>
<td>In each hospital, every patient’s file in the adult ICU were reviewed.</td>
</tr>
</tbody>
</table>

Testing the instrument for reliability and validity increases the possibility that the results are representative of what was intended to measure; this makes the data more dependable and useful (Bartlett, 2013). The pilot study was used to ensure reliability, as well as validity of the data collection and data capturing, since there was no previous validated data collection form and instruments that are used to assess antimicrobial therapy utilisation in septic ICU patients. The researcher, together with the supervisor and co-supervisor, developed the questionnaire in the mobile application.
3.9 BIAS

Bias is defined as a propensity that prevents unprejudiced consideration for a question (Pannucci and Wilkins, 2010). Bias can occur in the data collection, data analysis and interpretation phases, which could lead to false conclusions (Simundic, 2013). In research, bias occurs when systemic errors are introduced into testing or sampling by encouraging or selecting one outcome over others (Pannucci and Wilkins, 2010) and it can either be unintentional or intentional (Simundic, 2013).

Bias was eliminated in this study through appropriate study design and data analysis. The researcher collected the data, therefore minimising inter-observer variability and bias in the study design. Selection bias was eliminated by selecting patients using a rigorous criteria (Pannucci and Wilkins, 2010). Bias that can occur during the data analysis phase was eliminated through the use of the cell phone application that recorded the information of patients with sepsis in the ICU (Simundic, 2013).

3.10 ETHICAL CONSIDERATIONS

Ethical clearance was obtained from SMUREC (SMUREC/P/342018: PG) before the commencement of the study. See Appendix 2 for the SMUREC certificate.

3.10.1 Permission

Permission from the CEO of each hospital was obtained prior to research commencement. Permission was sought from the National Health Research Data Base (NHRDB). Approval from the Provincial health research committee of the Gauteng province was also received.

3.10.2 Informed consent

No informed consent from the patient was needed as no personal information was obtained during this study - only the patient’s medical file was reviewed.

3.10.3 Anonymity

Each patient was allocated a unique identification number for identification. No patient name or personal information was recorded and no patient was known or contacted. A password was required on Knack® that was only known by the trained data collector. The data was kept safe and secure and was only accessible to the researcher and supervisors for the purpose of this study, thus confidentiality and anonymity was maintained.
3.10.4 Confidentiality

By allocating identification numbers to each patient, confidentiality was maintained by not recoding any patient names or personal information. No patient was contacted or identified, thus confidentiality and anonymity were maintained.

3.11 SUMMARY

In conclusion, this chapter focuses on the methodology that was used to conduct this study. This was a descriptive, cross-sectional PPS study done on adult ICU patients admitted to central and tertiary hospitals in Gauteng. A mobile application, Knack®, was used to capture relevant data from the patients’ files. The data was exported to a Microsoft Excel™ spreadsheet from Knack®, where it was analysed. Validity and reliability of the mobile application were measured in a pilot study at Jubilee District Hospital and bias was eliminated. No inform consent was necessary, since no personal information were recorded and the data was only collected from the patients’ medical files. Anonymity and confidentiality were kept through the entire study. Permission was sought form SMUREC and the CEOs of each hospital before the studies were conducted.
CHAPTER 4

MANUSCRIPT

4.1 INTRODUCTION

This chapter is presented in the form of a manuscript and consists of a letter to the editor, the results of the study, and a discussion thereof. The manuscript will be submitted for publication to the International Journal Of Infectious Diseases with the title: ‘Antimicrobial utilization in the treatment of septic patients of Central and Tertiary hospitals in Gauteng Province, South Africa’. A draft letter to the editor appears, followed by the manuscript.
LETTER TO THE EDITOR

30 December 2018

Professor Eskild Petersen
Department of Infectious Diseases
Institute of Clinical Medicine
Aarhus University Hospital
Aarhus
Denmark
E-mail: eskild.petersen@clin.au.dk.

Dear Professor Eskild Petersen

Please consider the abovementioned manuscript for publication in the International Journal of Infectious Diseases (IJID). The authors (H de Klerk, N Schellack, JC Meyer and Q Labuschagne) have consented to publish in your journal. This article has not been submitted to nor published in any other journal.

Infectious diseases is the second most common cause of death in South Africa, yet there are no guidelines included in the STG/EML for the treatment of sepsis and septic shock. This study was conducted in 2018 in the Central and Tertiary hospitals of Gauteng Province, South Africa, using a web-based application. Antimicrobial utilization in the treatment of septic patients was surveyed and adherence of prescribers towards the Surviving Sepsis Campaign guideline was measured.

We believe that the results of this study will give insight into the treatment of sepsis and septic shock regarding antimicrobial utilization. Results can also be used to identify gaps for further studies. IJID is the journal of choice for publication because it is open-access and widely read by South Africans in the field of clinical pharmacy.

Yours faithfully,

Hanneke de Klerk

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MANUSCRIPT FOR PUBLICATION

The manuscript, which will be submitted to the IJID for consideration of publication, is included in this section.

Antimicrobial utilization in treatment of septic patients of Central and Tertiary Hospitals in Gauteng Province, South Africa

Hanneke de Klerk*, Natalie Schellack, Johanna C. Meyer and Quinten Labuschagne

School of Pharmacy, Sefako Makgatho Health Sciences University, Garankuwa, South Africa

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Keywords: antibiotic utilization, treatment, sepsis, adherence, ICU, South Africa

Abstract

Introduction

Sepsis is a global burden and is one of the top ten most common causes of death in developing countries, but in SA infectious diseases is the second most common cause of death. Studies revealed that 30-60% of the antibiotics prescribed in the intensive care unit (ICU) are inappropriate, suboptimal or unnecessary, which lead to antimicrobial resistance. Currently there are no guidelines included in the STG and EML for the treatment of sepsis and septic shock.

Methods

The study was a descriptive, cross-sectional point prevalence survey (PPS), with a quantitative study design. The study was conducted in four Central and three Tertiary hospitals in Gauteng. All adult patients with sepsis admitted to an ICU were included.

Results

In the Central and Tertiary Hospitals, the total number of patients surveyed in the adult ICUs were 118, whereof 18 (15.25%) patients were diagnosed with sepsis. From the seven hospitals, 20 ICU wards were surveyed, whereof only two (10%) ICU wards had a protocol for
the management or treatment of sepsis and septic shock in place, although 17 (85%) collected data from septic patients. All 18 patients, diagnosed with sepsis or septic shock, were on antimicrobial therapy. The total number of antimicrobials prescribed for these patients was 30, on average 1.67 (±0.69) antimicrobials were prescribed per patient. None of the hospitals were fully compliant with the SCC guidelines.

**Conclusion**

This study shows that guidelines are not begin adhered to. Unnecessary and inappropriate antibiotics and dosages are being prescribed to patients with no cultures to support this treatment, which leads to antimicrobial resistance. Incomplete documentation of patient files leads to a misleading picture of the reality within Central and Tertiary hospitals in Gauteng.

**Introduction**

Sepsis can be defined as ‘a life threatening organ dysfunction caused by a dysregulated host response to infection’ (Rhodes *et al.*, 2017). Sepsis goes back to the time of Hippocrates (Angus and van der Poll, 2013), but today sepsis is a global burden (Chehade, Chebl, Majzoub and Dagher, 2015) and remains the leading cause of increased mortality in an Intensive Care Unit (ICU) (Kübler, Adamik, Ciszewicz-Adamiczka, Ostrowska, 2015).

According to the World Health Organization (WHO), infectious diseases is one of the top ten most common causes of death in developing countries (World Health Organization, 2018), but according to statistics released in 2018, infectious diseases was the second most common underlying cause of death in South Africa (SA) in 2016, responsible for 18.2% of deaths (Statistics South Africa, 2018).

Today, antimicrobial resistance is a considerable global health challenge (Van den Honert, Gouws and Hoffman, 2018) and is escalating to a pandemic. Due to selection pressure from undiscriminating and irrational antimicrobials use in human health, resistance is emerging (Essack, Desta, Abotsi and Agoba, 2016). The usage of appropriate antibiotic therapy in an ICU is crucial. Studies revealed that 30-60% of the antibiotics prescribed in the ICU are inappropriate, suboptimal, or unnecessary, which lead to antimicrobial resistance (Luyt *et al.*, 2014).

The epidemiology of sepsis differs between developed and developing countries. In developed countries, gram-positive bacteria commonly causes sepsis, while in developing countries sepsis is more commonly caused by gram-negative bacteria (Chehade *et al.*, 2015; Martin,
The likelihood of gram-negative bacterial infections progressing to septic shock is increasing (Rhodes et al., 2017). The significant differences in the epidemiology of sepsis between developed and developing countries will influence the treatment approaches (Mayr, Yende and Angus, 2014).

Not only is SA a developing country, but also caters for a public and private healthcare sector. The public healthcare sector caters for the majority, approximately 84%, of the SA population, while the private sector is the minority, comprising approximately 16%. In the private sector, prescribers can select any antimicrobial they feel is most appropriate, making prescribing unrestricted. The Standard Treatment Guidelines (STGs) is the guideline for prescribing in the public sector, driven by the availability and inclusion of medicines on the Essential Medicines List (EML) (Schellack et al., 2017). Currently, there are no guidelines included in the STG and EML (STGs/EML) for the treatment of sepsis and septic shock (Gov.za, 2018).

Research shows an improved patient outcome when adhering to the recommendations of the Surviving Sepsis Campaign (SSC) guideline (Rhodes et al., 2017) (Kaukonen, Bailey, Suzuki, Pilcher and Bellomo, 2014). There are 655 references that support this; however, only 10% of these references pertain to studies that have been conducted in developing countries (Rhodes et al., 2017). Currently, 87% of the world’s population is living in developing countries (Reinhart, Daniels, Kissoon, Machado, Schachter and Finfer, 2017), however, limited research is being conducted in developing countries. Due to insufficient resources within developing countries, most recommendations from the SSC cannot be implemented (Tupchong, Koyfman and Foran, 2015) leading to an urge in priority to develop sustainable models for diagnosis and treatment of sepsis in developing countries (Papali, McCurdy and Calvello, 2015).

For all the reasons outlined above and the relative paucity in scientific literature on the use of antimicrobial therapy in SA, this study sets out to assess antimicrobial therapy in patients with sepsis and septic shock.

**Methods**

**Systematic Review**

A systematic review of literature pertaining to antimicrobial use in ICU settings and of the global as well as South African prevalence of sepsis in ICUs was performed, with literature published between January 2010 and December 2017 being included. The primary outcomes had to relate to either antimicrobial treatment of sepsis in adult ICU patients and compliance to SSC guidelines. The following search terms were used: sepsis, sepsis globally, intensive
care medicine, antimicrobials used in sepsis, drug utilization, epidemiology of sepsis, sepsis in developing countries, sepsis in SA, sepsis in Gauteng. Review articles as well as articles pertaining to neonatal sepsis and sepsis outside the ICU settings were excluded. The principal researcher (H.d.K.) read the articles along with the research team and developed the final list of relevant papers.

**Study Design, Setting and Study Period**

The study was a descriptive, cross-sectional point prevalence survey (PPS), with a quantitative study design. The study was conducted in four Central and three Tertiary hospitals in the Gauteng Province of SA. These sites were selected based on their classification according to the regulations relating to the categories of hospitals, in terms of Section 35, read together with Section 90 of the National Health Act, 2003 (Act No. 61 of 2003) (Department of Health, 2012). The requirement for both tertiary and central hospitals in SA, according to the regulations, is to provide intensive care services, under the supervision of a specialist or an intensivist. The total number of hospital beds for all seven hospitals were 8 472, of which 158 beds belonged to the ICUs. Data collection took place over a period of seven months, from March 2018 to September 2018.

**Study Population and Sample**

The reviewed patients were all 18 years of age or older and were admitted to the hospitals’ ICUs. Patients whose files contained written keywords such as suspected or confirmed sepsis, severe sepsis, septic shock, septicaemia, septic or bloodstream infection were surveyed.

**Compliance to the Guidelines**

Compliance of prescribing to the South African STGs/EML could not be evaluated, as these guidelines do not contain any recommendations nor guidelines for the treatment of sepsis and septic shock in adults. Therefore, antimicrobial prescribing compliance was evaluated with regards to the SSC guidelines (Rhodes *et al*., 2017). The recommendations in the SSC guideline are graded from strong to weak recommendations, based on the level of quality of evidence. To determine the strength of the recommendations, the SSC assessed the evidence according to risk of bias, inconsistency, indirectness, imprecision, publication bias, and other criteria (Rhodes *et al*., 2017).

The following recommendations from the SSC guidelines were used to assess adherence of prescribers towards these recommendations (Rhodes *et al*., 2017):
• Obtaining blood cultures before administering an antimicrobial.
• Obtaining blood cultures to identify the pathogen.
• Administering intravenous (IV) antimicrobials within one hour after recognition of both sepsis and septic shock.
• To cover all pathogens, empiric broad-spectrum therapy should be used for patients that present with sepsis or septic shock.
• De-escalate empiric antimicrobial therapy once the pathogen is identified.
• Measuring procalcitonin (PCT) levels.
• Measuring C-reactive protein (CRP) levels.

Data Collection and Analysis

Data collection started from 08:00 until all sepsis cases in the unit were surveyed. A web-based application (App), referred to as Knack®, was used to capture all the data on a mobile phone, after which the data was exported automatically to a Microsoft Excel™ spreadsheet.

The data was verified for accuracy, cleaned and exported to SAS (SAS Institute Inc., Carey, NC, USA, Release 9.4) for statistical analysis. All statistical tests were two-sided and p-values ≤ 0.05 (5%) were considered significant.

The antimicrobials were analysed according to their Defined Daily Dose (DDD) and their Anatomic Therapeutic Classification (ATC) code. The ATC classifications divides drugs according to the system or organ which they act on and/or their therapeutic and chemical characteristics. The DDD provides a unit of measurement which was used in comparison with the ATC codes.

Antibiotics are also grouped into three groups: Access, Watch, or Reserved (AWaRe). The 2017 WHO EML for adults classifies antibiotics into these AWaRe groups. Antibiotics used as first- or second-line treatment for important infections fall under the Access antibiotics group. High-quality formulations of these antibiotics should be available universally at a low cost. Antibiotics which have a higher potential for selecting antibiotic resistance are grouped as a Watch antibiotic. Reserved antibiotics are the last resort antibiotics and should be used under guidance of a specialist with specific monitoring (Hsia, Sharland, Jackson, Wong, Magrini, and Bielicki, 2018).
**Ethical Considerations**

Before the commencement of the study, ethical clearance was obtained from Sefako Makgatho University Research Ethics Committee (SMUREC/P/342018: PG). Permission was received from the chief executive officer of each hospital, the National Department of Health as well as from the Provincial Health Research Committee of the Gauteng province. The study was also registered on the National Health Research Data Base.

No patient name nor personal information was recorded. A password was required on Knack® that was only known by the trained data collector. All data was kept safe and secure, thus confidentiality and anonymity were maintained.

**Results**

**Systemic Review**

Database searches identified a total number of 598,000 papers. Through adding additional search terms, the number was refined to 17,100 (Figure 1). Ten final papers remained for review, after the review for eligibility of papers was completed.
In the Central and Tertiary Hospitals, the total number of patients surveyed in the adult ICUs were 118, of whom 18 (15.25%) patients were diagnosed with sepsis. The majority of the septic patients (16; 88.89 %) were identified in Central Hospitals. Two tertiary hospitals had no septic patients (Table 1). Half (9; 50%) of the patients whom presented with sepsis, were male and the mean age (± standard deviation (SD)) of patients whom presented with sepsis was 42.5 (±16.59). The mean number of days these patients spent in the ICU on that specific day was 16.18 (±12.53).

From the seven hospitals, 20 ICU wards were surveyed, whereof only two (10%) ICU wards had a protocol for the management or treatment of sepsis and septic shock in place, although 17 (85%) ICU wards collected data from septic patients.
A total of 32 organisms were cultured for the 18 patients, with an average of 1.78 (±1.44) organisms per patient. Gram negative organisms (81.25%) were the most profound organisms causing sepsis or septic shock. The predominant gram negative organisms were *Escherichia coli* (15.63%) followed by *Klebsiella pneumonia* (12.5%), while the most common gram positive organisms were *Enterococcus spp.* (9.38%) and *Streptococcus spp.* (6.25%).

### Table 1: Patients with sepsis or septic shock per hospital

<table>
<thead>
<tr>
<th>Hospital</th>
<th>Total number of beds per hospital</th>
<th>Beds in ICU</th>
<th>Beds occupied in ICU</th>
<th>Number of patients with sepsis or septic shock (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central Hospital A</td>
<td>832</td>
<td>41</td>
<td>32 (78.05%)</td>
<td>4 (12.5%)</td>
</tr>
<tr>
<td>Tertiary Hospital B</td>
<td>840</td>
<td>10</td>
<td>8 (80%)</td>
<td>2 (25%)</td>
</tr>
<tr>
<td>Central Hospital C</td>
<td>1652</td>
<td>26</td>
<td>16 (61.54%)</td>
<td>4 (25%)</td>
</tr>
<tr>
<td>Central Hospital D</td>
<td>1018</td>
<td>45</td>
<td>32 (71.11%)</td>
<td>4 (12.5%)</td>
</tr>
<tr>
<td>Central Hospital E</td>
<td>2888</td>
<td>18</td>
<td>15 (83.33%)</td>
<td>4 (26.66%)</td>
</tr>
<tr>
<td>Tertiary Hospital F</td>
<td>857</td>
<td>8</td>
<td>7 (87.5%)</td>
<td>0</td>
</tr>
<tr>
<td>Tertiary Hospital G</td>
<td>485</td>
<td>10</td>
<td>8 (80%)</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>8 472</td>
<td>158</td>
<td>118 (74.68%)</td>
<td>18 (15.25%)</td>
</tr>
</tbody>
</table>

**Antimicrobials used**

All 18 patients diagnosed with sepsis or septic shock, were on antimicrobial therapy. The total number of antimicrobials prescribed for these patients was 30; on average 1.67 (±0.69) antimicrobials were prescribed per patient. Ten patients received more than one antimicrobial simultaneously.

Of all the antimicrobials prescribed for sepsis, the most frequently prescribed antibacterials were meropenem (9; 30%), followed by piperacillin with an enzyme inhibitor (6; 20%). Antifungals were also prescribed with fluconazole being the most frequent (7; 23.33%), always in combination with an antibacterial. Dose and frequency were not documented for two patients; one patient received vancomycin orally and another patient received IV administered piperacillin with an enzyme inhibitor (Table 2).
Table 2: Antimicrobials which were administered to septic patients

<table>
<thead>
<tr>
<th>System</th>
<th>ATC* classification</th>
<th>International name</th>
<th>Number of patients (n=18)</th>
<th>Mean length of therapy in days (standard deviation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>J Anti-infective for systemic use</td>
<td>J01 CR 02</td>
<td>Amoxicillin and enzyme inhibitor</td>
<td>2</td>
<td>2.5 (±2.12)</td>
</tr>
<tr>
<td>J01 CR 05</td>
<td></td>
<td>Piperacillin and enzyme inhibitor</td>
<td>6</td>
<td>8.2 (±5.02)</td>
</tr>
<tr>
<td>J01 DH 02</td>
<td></td>
<td>Meropenem</td>
<td>9</td>
<td>5.33 (±4.21)</td>
</tr>
<tr>
<td>J01 DH 03</td>
<td></td>
<td>Ertapenem</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>J01 DD 04</td>
<td></td>
<td>Ceftriaxone</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>J01 XA 01</td>
<td></td>
<td>Vancomycin (parenteral)</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>J01 XA 09</td>
<td></td>
<td>Vancomycin (oral)</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>J01 XB 01</td>
<td></td>
<td>Colistin (injection/infusion)</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>J02 AC 01</td>
<td></td>
<td>Fluconazole</td>
<td>7</td>
<td>8.14 (±5.01)</td>
</tr>
<tr>
<td>J02 AA 01</td>
<td></td>
<td>Amphotericin B</td>
<td>1</td>
<td>4</td>
</tr>
</tbody>
</table>

The total antimicrobials prescribed will not equate to 18, as one patient can be on more than one antimicrobial.

*Anatomic Therapeutic Classification (ATC)
Antimicrobials used

Route of administration

All antimicrobials were administered via IV, except for one patient who received vancomycin orally.

Multi-drug antimicrobial therapy

Ten different types of antimicrobials were prescribed and co-administered to ten patients (55.56%) as multi-drug antimicrobial therapy. The combinations used in this multi-drug therapy consisted of either antibiotic combinations or antibiotics with an antifungal. Combinations which included three antimicrobials were administered to two (11.11%) patients. The most frequently prescribed multi-drug combinations were fluconazole with meropenem (2; 11.11%) and fluconazole with amoxicillin and an enzyme inhibitor (2; 11.11%). See Figure 2 for more detail pertaining to the co-administered multi-drug antimicrobial therapy.

![Figure 2: Antimicrobial combinations prescribed to patients](image-url)
Length of therapy and days in ICU

The average number of days a patient spent in the ICU was 16.23 (±12.53) and the average number of days per patient receiving antimicrobials was 5.6 (±4.54), as on the date of data collection. See Table 2 for the average length of therapy for each antimicrobial classified according to the Anatomic Therapeutic Classification (ATC) code.

Defined Daily Dose and Anatomic Therapeutic Classification

The average Defined Daily Dose (DDD) of fluconazole prescribed to a patient (0.57g; ±0.29) was almost three times more than the DDD of the WHO (Who.cno, 2018). Meropenem’s average DDD was 3.78g (±1.79) and piperacillin with an enzyme inhibitor was 12.6g (±4.93). The DDD of amphotericin B was five times greater than the value recommended by the WHO and colistin three times the value. See Figure 3 for the average DDD per ATC classification per hospital and compared to WHO recommended values.
Colistin was given in million units (mu), Average (Avg).

Figure 3: Distribution of antimicrobial agents consumption in Central and Tertiary hospitals, expressed in DDD per ATC-subclass and compared to WHO recommended values

**WHO: the AWaRe antibiotic groups**

Within the five hospitals, antibiotics were prescribed 22 times. The only access antibiotic used across the five hospitals was amoxicillin with an enzyme inhibitor. Amoxicillin with an enzyme inhibitor was prescribed in half (50%) of the cases in Central hospital E, but was only prescribed two out of the 22 times leading to access antibiotics being prescribed less than 10% (9.09%). Colistin was the only Reserve drug prescribed across all the hospitals. Although
colistin was prescribed in 20% of the cases within Central hospital A, the overall percentage for all five hospitals was 4.55%. All the antibiotics prescribed within Tertiary hospital B, Central hospital C and Central Hospital D came from the Watch group, causing the Watch group to be the most (86.36%) prescribed antibiotics across all five hospitals. Watch group antibiotics included meropenem, ertapenem, vancomycin, ceftriaxone and piperacillin with an enzyme inhibitor. See Figure 4 for the AWaRe index for each hospital.

![Figure 4: Number of antibiotics in their AWaRe groups per hospital](image)

**Assessment of prescribers adherence towards the SSC guideline regarding antimicrobial therapy**

Not one hospital complied fully to all seven criteria (blood cultures obtained before administering antimicrobials, blood culture results to identify the causative pathogen, broad-spectrum antibiotics used, IV antimicrobial started within the first hour of diagnosing sepsis, de-escalation of antimicrobials, PCT levels and CRP levels). Central Hospital E was the most compliant (78.57%) by complying fully to four of the seven criteria. On average, 59.29% of the seven criteria were met across the five hospitals (Table 3). For every patient admitted to Central Hospital E, CRP and PCT were measured, the causative organisms were identified through blood cultures and they were all started on a broad-spectrum antibiotic.

Compliance in terms of starting an IV antibiotic within the first hour of diagnosis was not fully met in any of the hospitals (5%). The average compliance of the hospitals for obtaining blood
cultures before administering antimicrobials was just over a third (35% (± 25.5%)). All hospitals complied with the criteria of administering a broad-spectrum antibiotic and measuring CRP levels. Compliance toward antimicrobial de-escalation was 30% (± 25%) across the five hospitals.

Table 3: Overall compliance to the SSC guidelines for each hospital

<table>
<thead>
<tr>
<th>Hospital</th>
<th>Overall (%) compliance to SSC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central Hospital A</td>
<td>57.14%</td>
</tr>
<tr>
<td>Tertiary Hospital B</td>
<td>42.86%</td>
</tr>
<tr>
<td>Central Hospital C</td>
<td>53.57%</td>
</tr>
<tr>
<td>Central Hospital D</td>
<td>64.29%</td>
</tr>
<tr>
<td>Central Hospital E</td>
<td>78.57%</td>
</tr>
<tr>
<td>Average compliance</td>
<td>59.29%</td>
</tr>
<tr>
<td>Standard Deviation</td>
<td>13.27%</td>
</tr>
</tbody>
</table>

Discussion

The primary purpose of this study was to assess antimicrobial therapy utilization in patients treated for sepsis or septic shock in adult ICUs and to assess the adherence of prescribers to the SSC guideline regarding antimicrobial use, in Central and Tertiary Hospitals in the Gauteng Province.

The results showed that sepsis and septic shock were predominantly caused by gram negative organisms (81.25%), which is supported by similar findings from other studies such as Chehade et al. (2015) and Martin (2012). The most prescribed antimicrobial was meropenem, a broad-spectrum carbapenem, largely covering gram negative organisms. According to the STGs/EML, the dosage of fluconazole for prophylaxis is normally 200 milligrams (mg) per day, whereas treatment dosages can go up to 800mg per day for invasive fungal infections such as *Cryptococcal meningitis*. Four of the seven patients treated with fluconazole received a DDD of 800mg without any positive blood cultures for fungal infections. In these cases, the DDD for fluconazole was four times more the DDD as recommended by the WHO.

Colistin’s DDD was three times higher than the WHO’s recommended DDD. The increase in the DDD of colistin is in line with the findings from the 2016 South African colistin guideline (Labuschagne et al., 2016). Labuschagne et al. (2016) reported that the clinical cure rates improved from 51% to 70% when the DDD of two million units (MU) is increased to nine MU (Labuschagne et al., 2016). These results suggest that the WHO’s DDD of colistin may be inadequate to treat infections and can emerge in resistance.
The results showed that antibiotics from the Watch antibiotic group were prescribed 19 times within Central and Tertiary Hospital ICUs. According to Hsia et al. (2018), this grouping creates an opportunity to review country-level antibiotic consumption and a potential for antimicrobial stewardship (Hsia et al., 2018).

Due to the increase in the frequency of pathogen resistance, multi-drug therapy is often required to ensure appropriate broad-spectrum coverage (Rhodes et al., 2017), which is seen in the results of this study. More than half (55.56%) of the patients received co-administered multi-drug antimicrobial therapy. An average number of 1.66 organisms were cultured per patient, with five organisms being the most cultured for one patient.

One of the strongest recommendations by the SCC guidelines is the administration of an IV antimicrobial within the first hour of diagnosing sepsis or septic shock (Rhodes et al., 2017). Kumar et al. (2011) showed that within the first six hours after diagnosis, survival decreases by 7.6% with every hour delay in antimicrobial therapy (Kumar et al. 2011), yet only one patient (5.55%) received IV antibiotics within the first hour, as this was either not done or not documented in the patients’ files. Broad-spectrum antimicrobials were administered in all the hospitals of either empiric or targeted treatment. One of the most crucial steps to determine a favorable outcome is to initiate an empiric broad-spectrum antimicrobial as soon as possible. Empiric therapy which fails to cover the causing organism in septic patients can decrease the patient’s survival five times (Paul et al., 2010).

The results of this study indicated that the adherence of prescribers to the SCC guidelines pertaining to prescribing of antimicrobials was poor in both Central and Tertiary Hospitals. Since the burden of sepsis is the highest in developing countries (WHO, 2018), the development and implementation of sepsis protocols could be beneficial to reduce mortality rates in developing countries. Kaukonen, Bailey, Suzuki, Pilcher and Bellomo (2014) showed that the development and implementation of sepsis protocols in developed countries have contributed to the identification and management of sepsis, with subsequent decline in mortality rates (Kaukonen, Bailey, Suzuki, Pilcher and Bellomo, 2014).

Limitations

We are aware that this study had a number of limitations. The survey was conducted in Central and Tertiary Hospitals in the Gauteng Province only, therefore these results cannot be generalized across SA. Only patients treated for sepsis and septic shock in an adult ICU setting were included, hence septic patients admitted to other wards were omitted. Incomplete diagnosis pertaining to no written diagnosis of sepsis in the patient’s file, lead to possible
exclusion of septic patients. Due to some patients’ prolonged stay in ICU, their previous charts were locked away in storerooms, leading to incomplete files and restricted access to their information and previous treatment. Incomplete patient files were found in all the hospitals. Patient files did not contain the time blood cultures were drawn or the time of prescribing of an antimicrobial, which made it extremely difficult to determine whether blood cultures were drawn before administration of antimicrobials and whether antimicrobials were given within the first hour of diagnosing sepsis or septic shock. The dose and frequency of the antimicrobials being administered to two of the patients were not recorded in their files and therefore altered the results, as they could not be included. Despite these limitations, we believe that the results provide a basis for improving the future management of sepsis and septic shock in hospitals in South Africa, ultimately preventing the development of antimicrobial resistance.

**Recommendations**

We recommend that a guideline for the treatment of sepsis or septic shock is developed and implemented in all hospitals, as studies have shown that doing so improves patient outcomes in developed countries (Kaukonen, Bailey, Suzuki, Pilcher and Bellomo, 2014). Annual studies should be conducted to determine whether the guidelines that were initially developed and implemented are adhered to and to determine whether these are sufficient in improving patients’ outcomes.

Patients’ files should be completed thoroughly and should always be accessible. If charts get removed from the patient’s bedside to a storeroom, the hospital should ensure that these can still be accessed to be reviewed.

We recommend the involvement of clinical pharmacists in the management of septic patients in the ICU to assist with the following activities:

- To monitor adherence towards the hospital’s guidelines.
- To ensure de-escalation of antimicrobials according to sensitivity reports.
- To ensure the most appropriate empiric antimicrobials are prescribed.
- To ensure antimicrobial therapy is administered within the first hour of diagnosing sepsis.
- To assist with the dosing strategies of antimicrobials, as they should be based on pharmacodynamics or pharmacokinetic principles and specific drug properties.
Chapter 4: Manuscript

Conclusions

This is the first study to date classifying antibiotics used in a South African adult ICU setting according to the WHO’s AWaRE antibiotic groups. De-escalation occurred in only 30% of the times, leading to antibiotics within the Watch group to be the most prescribed group. Watch antibiotics are more toxic and have higher resistant potentials which could lead to safety concerns for patients and higher resistance rates. The DDDs recommended by the WHO cannot be implemented in septic patients, because the septic patients differ from the typical infected patient. Therefore the dosing strategies of antimicrobials should be based on pharmacodynamics and pharmacokinetic principles and specific drug properties in septic patients. Not one hospital complied fully to all seven criteria. On average, 59.29% of the seven criteria were met across the five hospitals This indicates that adherence of prescribers to the SCC guidelines pertaining to antimicrobials and treatment of sepsis are poor in both Central and Tertiary Hospitals. This study showed that guidelines are not begin adhered to, unnecessary and inappropriate antibiotics and dosages are being prescribed to patients with no cultures to support this treatment. All of these factors leads to antimicrobial resistance. Incomplete documentation of patient files leads to a misleading picture of the reality within Central and Tertiary hospitals in Gauteng.

Acknowledgments

The doctors and nurses of all the ICUs for receiving me into their ICUs and assisting me where necessary and D. Kruger, for assisting in data collection training and providing the Knack®.

Conflict of Interest

None.

Funding Sources

ENAABLERS
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CHAPTER 5

LIMITATIONS, RECOMMENDATIONS AND CONCLUSIONS

5.1 INTRODUCTION

This chapter discusses the limitations of the study such as the restriction of locations, ethical clearance from the hospitals and documentation. The chapter ends off with recommendations and conclusions.

5.2 LIMITATIONS OF THE STUDY

5.2.1 PPS in Gauteng Province

This study was conducted in Central and Tertiary Hospitals of Gauteng, therefore these results cannot be generalised across SA.

5.2.2 Only ICU admissions

Only patients treated for sepsis and septic shock in an adult ICU setting were included. Septic patients admitted to other wards outside of the ICU were excluded.

5.2.3 Ethical clearance from hospitals

Data collection was intended to be collected within a period of four months, due to this study being season sensitive, but the data collecting period continued for seven months. Data collection was unable to be obtained during a period of four months since the process by which ethical clearance needed to be obtained from each hospital was very time consuming.

5.2.4 Documentation

5.2.4.1 No diagnosis of sepsis

In some instances, the diagnosis of sepsis was not written on the patient’s file. The blame shifted to the nurses, whom were responsible for writing secondary diagnosis such as septic on a patient’s file. Another argument was raised that sepsis is a secondary diagnosis and therefore it was not necessary to be written down, since everyone could see the patient is septic. The limitation is therefore that these patients cannot be included in the study as certain terminology of sepsis was necessary to be written on their files.
5.2.4.2 Restricted access to files

Due to some patients’ prolonged stay in the ICU, their previous charts were locked away in storerooms, leading to incomplete files and restricted access to their information and previous treatment.

5.2.4.3 Incomplete documentation

Incomplete patients’ files were found in all the hospitals. The files did not contain the time blood cultures were drawn, time of diagnosis or the time of prescribing the antimicrobial, which made it extremely difficult to see whether blood cultures were drawn before administration of antimicrobials and whether antimicrobials were given within the first hour of diagnosing sepsis or septic shock.

The dose and frequency of the antimicrobials being administered to two patients were not written in their files and therefore altering results as they could not be included.

5.3 RECOMMENDATIONS

We recommend that a guideline for the treatment of sepsis or septic shock is developed and implemented in all hospitals, as studies have shown that by doing so it improves patient outcomes in developed countries. Yearly studies should be conducted to see whether the guidelines that were initially developed and implemented are adhered to and to determine whether they are sufficient in improving patients’ outcomes.

Patients’ files should be completed thoroughly and should always be accessible. If charts get removed from the patient’s bedside to a storeroom, the hospital should ensure they can still be accessed to be reviewed.

We recommend the involvement of clinical pharmacists in the management of septic patients in the ICU to assist with the following:

- To monitor adherence towards the hospital’s guidelines.
- To ensure de-escalation of antimicrobials according to sensitivity reports.
- To ensure the most appropriate empiric antimicrobials are prescribed.
- To ensure antimicrobial therapy is administered within the first hour of diagnosing sepsis.
• To assist with the dosing strategies of antimicrobials, as they should be based on pharmacodynamics or pharmacokinetic principles and specific drug properties.

5.4 CONCLUSIONS

This is the first study to date classifying antibiotics used in a South African adult ICU setting according to the WHO’s AWARE antibiotic groups. De-escalation only occurred in 30% of the times, leading to antibiotics within the Watch group to be the most prescribed group. Watch antibiotics are more toxic and have higher resistant potentials which could lead to safety concerns for patients and higher resistance rates. The DDD’s from the WHO cannot be implemented in septic patients, since septic patients differ from the typical infected patients. Therefore the dosing strategies of antimicrobials should be based on pharmacodynamics and pharmacokinetic principles and specific drug properties in septic patients. Not one hospital complied fully to all seven criteria. On average, 59.29% of the seven criteria were met across the five hospitals. This indicates that adherence of prescribers to the SCC guidelines pertaining to antimicrobials and treatment of sepsis are poor in both Central and Tertiary Hospitals. This study shows that guidelines are not begin adhered to, unnecessary and inappropriate antimicrobials and dosages are being prescribed to patients with no cultures to support this treatment, which leads to antimicrobial resistance. Incomplete documentation of patient files leads to a misleading picture of the reality within Central and Tertiary hospitals in Gauteng.
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## APPENDICES

### Appendix 1: Data collecting instrument

**PROVISIONAL DATA COLLECTION CAPTURE SHEET**

<table>
<thead>
<tr>
<th>SECTION A: HOSPITAL ICU DATA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date:</td>
</tr>
<tr>
<td>Name of Hospital:</td>
</tr>
<tr>
<td>Hospital Name:</td>
</tr>
<tr>
<td>Hospital Category:</td>
</tr>
<tr>
<td>Type of ICU:</td>
</tr>
<tr>
<td>Total ICU beds:</td>
</tr>
<tr>
<td>Total beds occupied by a patient at point of data collection:</td>
</tr>
<tr>
<td>Does this ICU have a protocol for the management of sepsis in place?</td>
</tr>
<tr>
<td>Does this ICU collect compliance data for the management of sepsis?</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SECTION B: PATIENT DATA</th>
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</thead>
<tbody>
<tr>
<td>Patient code:</td>
</tr>
<tr>
<td>Admission date:</td>
</tr>
<tr>
<td>Current no of days in ICU:</td>
</tr>
<tr>
<td>Age:</td>
</tr>
<tr>
<td>Sex:</td>
</tr>
<tr>
<td>Employment:</td>
</tr>
<tr>
<td>Prior Hospitalization:</td>
</tr>
<tr>
<td>Admission to ICU:</td>
</tr>
<tr>
<td>Intubated (Mechanically ventilated):</td>
</tr>
<tr>
<td>On HAART:</td>
</tr>
<tr>
<td>Blood/urea/unknown:</td>
</tr>
<tr>
<td>CD4 count:</td>
</tr>
<tr>
<td>eGFR/mm3:</td>
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</table>

<table>
<thead>
<tr>
<th>SECTION C: DIAGNOSIS</th>
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</thead>
<tbody>
<tr>
<td>Sepsis:</td>
</tr>
<tr>
<td>Severe Sepsis:</td>
</tr>
<tr>
<td>Septic Shock:</td>
</tr>
<tr>
<td>Septicemia:</td>
</tr>
<tr>
<td>Bloodstream infection:</td>
</tr>
<tr>
<td>Other:</td>
</tr>
<tr>
<td>Is infection:</td>
</tr>
<tr>
<td>Suspected:</td>
</tr>
<tr>
<td>Confirmed:</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Where blood cultures obtained?</th>
</tr>
</thead>
<tbody>
<tr>
<td>YES</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>If yes, when were cultures obtained:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before antibiotic administration</td>
</tr>
<tr>
<td>After antibiotic administration</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Time (hms):</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Where two or more sets of blood cultures obtained:</th>
</tr>
</thead>
<tbody>
<tr>
<td>YES</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>From which sites where cultures obtained:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood</td>
</tr>
<tr>
<td>CSF</td>
</tr>
<tr>
<td>Urine</td>
</tr>
<tr>
<td>Wounds</td>
</tr>
<tr>
<td>Respiratory secretions:</td>
</tr>
<tr>
<td>Other:</td>
</tr>
<tr>
<td>Not applicable:</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Was invasive procedures used to sample blood cultures:</th>
</tr>
</thead>
<tbody>
<tr>
<td>YES</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>If yes:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchoscopy</td>
</tr>
<tr>
<td>Invasive surgery</td>
</tr>
<tr>
<td>Other:</td>
</tr>
</tbody>
</table>
## Appendices

### This question pertains to a patient initiated of a new antibiotic

Where two or more sets of blood cultures taken before initiation of new antibiotic.

<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
<th>N/A</th>
</tr>
</thead>
</table>

### This question pertains to a patient with an intravascular catheter in place for >48 hours

Was at least one blood culture obtained from the catheter along with peripheral blood cultures?

<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
<th>N/A</th>
</tr>
</thead>
</table>

Was the intravascular device removed after a positive blood culture?

<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
<th>N/A</th>
</tr>
</thead>
</table>

Was at least one from the two or more blood cultures drawn peripherally?

<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
<th>N/A</th>
</tr>
</thead>
</table>

From which sites where the second or more blood cultures obtained?

- Peripherally via venipuncture:
- Each separate intravascular device but not through the lumens of the same IVD
- Multiple lumens in an IVD

### What criteria was used to diagnose sepsis?

Select appropriate option(s):

- Solely based on physician suspicion
- SIRS Criteria
- SOFA Score

### The following questions pertain to patients with septic shock

Is the patient on a vasopressor to maintain a MAP of 60mmHg or greater?

<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
</table>

Does the patient have a persisting lactate of greater than 2 mmol/L after fluid resuscitation?

<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
</table>

What is the MAP?

<table>
<thead>
<tr>
<th>mmHg</th>
</tr>
</thead>
</table>

What is the lactate level?

<table>
<thead>
<tr>
<th>mmol/L</th>
</tr>
</thead>
</table>

Is there an IC850 code for diagnosis?

<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
</table>

If yes, what is the IC850 code?

### SECTION D: ANTIBIOTIC THERAPY

Was the time of diagnosis/suspicion recorded?

<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
</table>

Was IV antibiotics started within 1 hour after recognition of sepsis/septic shock?

<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
<th>N/A</th>
</tr>
</thead>
</table>

Which empiric broad spectrum antibiotics coverage was used to cover all likely pathogens?

<table>
<thead>
<tr>
<th>Bacterial</th>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fungal</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>Viral</td>
<td>YES</td>
<td>NO</td>
</tr>
</tbody>
</table>

If yes, which empiric broad spectrum antibiotic where prescribed (include dose and duration)?

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Dose</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial</td>
<td>PO/Bid</td>
<td>PO/Bid</td>
</tr>
<tr>
<td>Fungal</td>
<td>PO/Bid</td>
<td>PO/Bid</td>
</tr>
<tr>
<td>Viral</td>
<td>PO/Bid</td>
<td>PO/Bid</td>
</tr>
</tbody>
</table>

Where blood cultures sensitivities done?

<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
</table>

If yes, was antibiotics deescalated according to pathogen identification and sensitivities?

<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
</table>

If cultures were obtained, which pathogens where identified? (Include sensitivities)

<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
</table>

Was antibiotic therapy stopped after no pathogen/s where identified?

<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
</table>
The following question should be answered if the patient is on an amphotericin, vancomycin, fluoroquinolones, in infections, catheter.

Was dosing strategies of the above-mentioned antibiotics optimized for the individual? [physician to answer]

| YES | NO |

What is the current antibiotic regimen for the patient?

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Frequency</th>
<th>Starting date</th>
<th>Current no of therapy days</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| YES | NO |

Is the procalcitonin measured?  
Is the C-reactive protein (CRP) measured?

| YES | NO |

SECTION I: SUPPORTIVE THERAPY

| Is the patient receiving fluid therapy? | YES | NO |

If yes, what fluid is administered?
Insert list of all fluids.

| YES | NO |

Is the patient on any vasopressor medication?
If yes, what vasopressor medication and dose?
Insert list of vasopressor medication

| YES | NO |

Does the patient have an arterial catheter in place to measure arterial pressure?

| YES | NO |

Did the patient receive RBC transfusion when the hemoglobin was below 7 g/dL?

| YES | NO |

Was enoxaparin used during anemia associated with sepsis?

| YES | NO |

| YES | NO | Date: |

| YES | NO |

Is continuous or intermittent sedation minimized in patients who are mechanically ventilated?

| YES/NO |

| YES | NO |

If the patient is receiving an insulin infusion, continue with following questions:

| YES | NO |

| YES | NO |

| YES | NO |

| YES | NO |

How is blood glucose measured?

<table>
<thead>
<tr>
<th>Arterial blood</th>
<th>Capillary blood</th>
</tr>
</thead>
</table>

| YES | NO |

Which VTE prophylaxis is/are being used?

| UFH | LMWH |

| Mechanical | UFH | Mechanical | LMWH |

| Does this patient have any risk factors for gastrointestinal bleed? | YES | NO |

| Coagulopathies | YES | NO |

| Mechanical ventilation >48 hours | YES | NO |

| YES | NO |

Was stress ulcer prophylaxis initiated in this patient?
If yes

| YES | NO |

| EPI | AG/A |
Appendices

Appendix 2: SMUREC Clearance certificate

SEFAKO MAGATHO
HEALTH SCIENCES UNIVERSITY

Research & Postgraduate Studies Directorate
Sefako Makgatho University Research Ethics Committee
(SMUREC)

APPROVAL NOTICE - NEW APPLICATION

01 February 2018

Miss H de Klerk
Department of Pharmacy
P.O Box 218
Medunsa 5004

MEETING: 01/2018

SMUREC Ethics Reference Number: SMUREC/04/2018: PG

The new application received on 18 January 2018, was reviewed by members of Sefako Makgatho University Research Ethics Committee on 01 February 2018 and was provisionally approved on 01 February 2018.

Title: A point prevalence survey of antimicrobial therapy use in adult septic and septic shock patients in all the critical care units of central and tertiary hospitals in Gauteng Province

Researcher: Miss H de Klerk
Supervisor: Prof N Schellack
Co-supervisor: Prof JC Meyer

Department: Pharmacy
School: Pharmacy
Degree: M Pharma

Please note the following information about your approved research protocol:

Approval Period: 01 February 2018 – 01 February 2019

Please remember to use your protocol number (SMUREC/04/2018: PG) on any documents or correspondence with the REC concerning your research protocol. Please note that the REC has the prerogative and authority to seek further questions, seek additional information, require further modification, or monitor the conduct of your research and the consent process.

After Ethical Review: Please note a template of the progress report is obtainable in the Research Office and should be submitted to the Committee before the year has expired. The Committee will then consider the continuation of the project for a further year (if necessary). Annually a number of projects may be selected randomly for an external audit. Translation of the consent document in the language applicable to the study participants should be submitted.
Appendices
Appendix 3: Ethical clearance for Steve Biko Academic Hospital

Permission to do Research and access Records / Files / Data base at the Hospital

To: Chief Executive Officer/Information Officer
   Hospital
   Hospital

From: The Investigator

Dr.________________________

Re: Permission to do the following research at Hospital

Dr. Hannette Smymy and I are researchers working at the Hospital. I am requesting permission on behalf of all of us to conduct a study on the Hospital grounds that involves access to patient records.

The title of the study is: A point prevalence survey of antimicrobial therapy use in surgical and emergency patients in all the critical care units of tertiary hospitals in Gauteng Province.

We intend to publish the findings of the study in a professional journal and/or at professional meetings like symposia, congresses, or other meetings of such a nature.

We furthermore request in terms of the requirements of the Promotion of Access to Information Act No. 2 of 2000 that we be granted access to clinical records, files and databases.

We undertake not to proceed with the study until we have received approval from the Faculty of Health Sciences Research Ethics Committee, University of Pretoria.

Yours sincerely,

[Signature]

Investigator of the Principal Investigator

Permission to do the research study at this hospital and to access the information as requested, is hereby approved.

Chief Executive Officer

[Signature]

Hospital Official Stamp
Appendix 4: Ethical clearance for Chris Hani Baragwanath Academic Hospital

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

MEDICAL ADVISORY COMMITTEE
CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL

PERMISSION TO CONDUCT RESEARCH

Date: 14 Feb 2018

TITLE OF PROJECT: Appropriate antimicrobial and vaccine use via mobile health and other techniques in the Republic of South Africa (ENAABLERS Project)

UNIVERSITY: Sehako Makgatho Health Sciences University

Principal Investigator: N Schellack

Department: School of Pharmacy

Supervisor (If relevant):

Permission Head Department (where research conducted): N/A

Date of start of proposed study: Feb 2018
Date of completion of data collection: Dec 2019

The Medical Advisory Committee recommends that the said research be conducted at Chris Hani Baragwanath Hospital. The CEO/management of Chris Hani Baragwanath Hospital is accordingly informed and the study is subject to:

- Permission having been granted by the Human Research Ethics Committee of the University of the Witwatersrand.
- The Hospital will not incur extra costs as a result of the research being conducted on its patients within the hospital.
- The MAC will be informed of any serious adverse events as soon as they occur.
- Permission is granted for the duration of the Ethics Committee approval.

Recommended
(On behalf of the MAC)
Date: 14 February 2018

Approved/Not Approved
Hospital Management
Date: 19/02/18
Appendices

Appendix 5: Ethical clearance for Dr. George Mukhari Academicc Hospital

Dr. George Mukhari Academic Hospital

Office of the Director Clinical Services
Enquiries: Dr. C Holm
Tel: (012) 529 3691
Fax: (012) 560 0999
Email: Christene.Holm@gauteng.gov.za
keltumetse.mongale@gauteng.gov.za

To Miss H de Klerk
Department of Pharmacy
University of Sefako Makgatho Health Sciences
Internal Box 216
MEDUNSA
0204

Date: 14 May 2018

PERMISSION TO CONDUCT RESEARCH

The Dr. George Mukhari Academic Hospital hereby grants you permission to conduct research on "A point prevalence survey of antimicrobial therapy use in adult sapsic and septic shock patients in all the critical care units of central and tertiary hospitals in Gauteng Province" at Dr George Mukhari Academic Hospital

This permission is granted subject to the following conditions:

☑ That you obtain Ethical Clearance from the Human Research Ethics Committee of the relevant University

☑ That the Hospital incurs no cost in the course of your research

☑ That access to the staff and patients at the Dr George Mukhari Hospital will not interrupt the daily provision of services.

☑ That prior to conducting the research you will liaise with the supervisors of the relevant sections to introduce yourself (with this letter) and to make arrangements with them in a manner that is convenient to the sections.

☑ Formal written feedback on research outcomes must be given to the Director: Clinical Services

☑ Permission for publication of research must be obtained from the Chief Executive Officer.

Yours sincerely,

DR. C. HOLM
ACTING DIRECTOR CLINICAL SERVICES
DATE: 14/5/18
Appendices

Appendix 6: Ethical clearance for Charlotte Maxeke Johannesburg Academic Hospital

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL

Enquiries:
Ms. N. Mella
Office of the Clinical Director
Tel: (011) 485-4812
Email: NotAvail/Mella@gauteng.gov.za
18th April 2018

GP_201802_005

Dear Natalie Schellack

STUDY TITLE: Appropriate Microbial and Vaccine Use via Mobile Health and Other Techniques in the Republic of South Africa (Easabiers Project).

Permission is granted for you to conduct the above recruitment activities as described in your request provided:

1. Charlotte Maxeke Johannesburg Academic Hospital will not anyway incur or inherit costs as result of the said study.
2. Your study shall not disrupt services at the study sites.
3. Strict confidentiality shall be observed at all times.
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.

[Signature]

Dr. M.I. Motokieng
Clinical Director
DATE: 17/04/2018

[Signature]

Ms. G. Bogoshi
Chief Executive Officer
Date: 04.04.2018
Appendices

Appendix 7: Ethical clearance for Kalafong Hospital

KALAFONG HOSPITAL
PRIVATE BAG X396
PRETORIA
0001

TO: HANNEKE DE KLERK

RE: PERMISSION TO CONDUCT RESEARCH

TITLE: A POINT PREVALENCE SURVEY OF ANTIMICROBIAL THERAPY USE IN ADULT SEPSIS AND SEPTIC SHOCK PATIENTS IN ALL THE CRITICAL CARE UNITS OF CENTRAL AND TERTIARY HOSPITALS IN GAUTENG PROVINCE

Permission is hereby granted for the research to be conducted at Kalafong Provincial Tertiary Hospital. This is done in accordance to the "Promotion of Access to Information Act, No 2 of 2000".

Please note that in addition to receiving approval from the hospital research committee, you are still required to seek permission from the relevant departments.

Furthermore, collecting of data and consent for participation remains the responsibility of the researcher.

You are also required to submit your final report or summary of your findings and recommendations to the office of the CEO.

Approved:

[Signature]

DR K.E LETEBELE-HARTELL
SENIOR MANAGER: MEDICAL SERVICES
DATE: 11/05/2018
Appendices

Appendix 8: Ethical clearance for Thembisa Hospital

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

TEMBISA PROVINCIAL TERTIARY HOSPITAL
PR NO: 5002791
Cnr Finl Mazibuko Dr & Rev Nkana, Olifantsfontein, 1565
Private bag X 97, Olifantsfontein, 1565
Tel: 011 923 2329 | Fax: 011 926 2719
Inquiries: Dr. LM Mogaladi
E-mail: Telephone.Mogaladi@gauteng.gov.za

To: Natalie Schellack

Subject: Acknowledgement of request to conduct research at Tembisa Provincial Tertiary Hospital

From: Dr LM Mogaladi, Chief Executive Officer, Tembisa Provincial Tertiary Hospital

Date: 19 February 2018

Mr/Ms/Dr/Prof: N. Schellack

We received your request to conduct research in our institution on 06 February 2018 for the study entitled: Appropriate Antimicrobial and Vaccine Use via mobile Health and other Techniques in the Republic of South Africa (ENAABLERS PROJECT).

We have realised that the above protocol is an overarching and that there are various sub-studies that will be performed by different researchers.

We will only be able to review and give permission for individual studies.

Please note that in order for our research committee to grant you permission the following documents are required:

<table>
<thead>
<tr>
<th>Documents</th>
<th>Received</th>
<th>N/A</th>
<th>Pending</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Study Protocol for each individual study</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>2. Faculty approval of research (if applicable)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Ethics Clearance Certificate for each individual protocol</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>4. NHRD Registration Number for each individual study</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>5. GDor/Ekurhuleni Research Committee Approval or proof of submission</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Your request will be reviewed and a response sent to you following receipt of the outstanding items above.

Please send outstanding items or enquiries to Ms L Mazzi: Linda.Mazzi@gauteng.gov.za (Personal Assistant of the CEO)

Dr Mathabane J. Mathabane
Clinical Manager for Surgery and Pharmacy

Tembisa Provincial Tertiary Hospital
Appendix 8: Ethical clearance for Helen Joseph

Gauteng Department of Health
Helen Joseph Hospital
Enquiries: Dr. M.R. Billa
Chief Executive Officer
Tel.: (011) 489-0306/1087
Fax.: (011) 726-5425
E-mail: Raymond.Billa@gauteng.gov.za
Date: 22 May 2018

Dr. M.R. Billa
Chief Executive Officer
Helen Joseph Hospital

Dear Dr. M.R. Billa

STUDY: Appropriate antimicrobial and vaccine use via mobile health and other techniques in the republic of South Africa (enablers Project)

RESEARCHERS: Natalie Schellack

Ethic No: SMREC/P233/2017:IR

Above the study was discussed at the Research Committee Meeting. We recommend that permission be granted for Helen Joseph Hospital to be used as a site for the above research. However, since this is Individual / patients.

Upon completion of the study, a copy thereof should be submitted to Helen Joseph Hospital.

It is the duty of the researcher to collect the data to the relevant department after the Research Committee approved the study.

Thank you

Dr. Murimisi Mukansi
CHIEF PERSON

Approved

Dr. M.R. Billa
CHIEF EXECUTIVE OFFICER

Date:

2018