Antimicrobial prescribing in the surgical and medical wards at a private hospital in KwaZulu-Natal

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DECLARATION

In fulfilment of the requirements of the coursework degree of Master of Pharmacy, in the Discipline of Pharmacy, University of KwaZulu-Natal, Durban, South Africa, I, Valencia Jacob, declare as follows:

i. That the work described in this thesis has not been submitted to UKZN or other tertiary institution for purposes of obtaining an academic qualification, whether by myself or any other party.

ii. The research reported in this dissertation, except where referenced, is my original work.

iii. This dissertation does not contain other person's text, tables, data, graphs or other information, unless specifically acknowledged as being sourced from other persons.

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PREFACE

This is a mini dissertation comprising of 50% research project component. The University of KwaZulu-Natal CR13 (c) directs that a dissertation "*may comprise one or more papers of which the student is the prime author, published or in press in peer-reviewed journals approved by the relevant college academic affairs board or in manuscripts written in a paper format, accompanied by introductory and concluding integrative material*". As such a standalone methodology is not required, as it forms part of the submitted paper/manuscript chapter. The outline of each chapter is presented at the end of Chapter 1.

DEDICATION

This thesis is dedicated to my beloved grandmother, Parvathiamma Naidoo, my greatest cheerleader.

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ABBREVIATIONS AND ACRONYMS

EML	Essential Medicines List
ICU	Intensive care unit
NHI	National Health Insurance
SA	South Africa
SAP	Surgical antibiotic prophylaxis
SSI	Surgical site infection
STG	Standard Treatment Guidelines
WHO	World Health Organisation

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ABSTRACT

Background: Appropriate antimicrobial use is imperative due to the misuse of antimicrobials that has resulted in a growing burden of antimicrobial resistance. Evidence-based guidelines should be adhered to in order to ensure the sustainability of effective antimicrobials.

Objectives: To assess the appropriateness of antimicrobial prescribing at a private hospital in Durban, KwaZulu-Natal.

Methods: The records of patients admitted to the surgical and medical wards from June 2019 to July 2019 were reviewed to assess the choice of antimicrobials prescribed, dose and duration. The guidelines used to determine appropriateness were the Standard Treatment Guidelines and the Essential Medicines List for South Africa (hospital level for adults, 2015 edition), the South African Medicines Formulary (13th edition, 2019), the South African Antibiotic Stewardship Programme guidelines (2014 edition) and the evidence-based surgical prophylaxis guidelines (2017 edition) developed by the hospital group where the research was conducted.

Results: During the study period, 466 patients were admitted and prescribed an antimicrobial, of which 220 (47.2%) were admitted to the surgical ward and 246 (52.8%) were admitted to the medical wards. A total of 779 antimicrobials were prescribed. Of the 660 antimicrobials prescribed for empiric treatment, 305 (46.2%) antimicrobials were appropriately prescribed based on drug choice, dose and duration. Of the 38 antimicrobials that were classified as targeted, 36 (94.7%) were prescribed according to the correct dose and 33 (86.8%) were prescribed according to the correct duration. Of the 81 antimicrobials prescribed for surgical prophylaxis, only 32 (39.5%) met the criteria for appropriateness in terms of drug choice, dose and duration.

Conclusion: Our findings suggest that compliance with evidence-based guidelines for the use of antimicrobials is not optimal in hospitals in the private sector. Antimicrobials are prescribed inappropriately both for empiric treatment and for surgical prophylaxis. Private hospital groups should consider adopting antimicrobial prescribing guidelines that are mandatory for doctors to adhere to in order to promote rational antimicrobial prescribing and thereby reduce the burden of antimicrobial resistance.

Chapter One: Introduction

This chapter describes the problem of antimicrobial resistance and highlights the need for rational antimicrobial use in both the private and public health sectors. The background, need for this research, study objectives and format of the dissertation are presented.

1.1 Background

Antimicrobial stewardship refers to systematic interventions that are initiated to develop and ascertain the appropriate use of antimicrobials with the aim of improving overall patient outcomes. [1] The use of antimicrobials has led to a reduction in morbidity and mortality in seriously ill patients, but antimicrobial misuse has caused the gradual development of antimicrobial-resistant bacteria, which is now a significant public health problem. [2] By 1968, it was estimated that 50% of antimicrobial use was either unwarranted or inappropriate. [3] The decrease in the development and approval of new antimicrobials supports the notion that there will be fewer treatment options for infections in the imminent future. [4]

Existing methods to combat antimicrobial resistance should be supported to protect the efficacy of antimicrobials that are presently available. Infection prevention and control practices should be amplified as this can help to regulate the spread of resistance. [4] The judicious use of antimicrobials is vital to preserve what limited treatment is available for future generations. In 2015, the World Health Assembly approved a global action plan to combat antimicrobial resistance. To accomplish this goal, the global action plan established five strategic objectives. These included enhancing awareness and understanding of antimicrobial resistance, reinforcing knowledge through surveillance and research, reducing the incidence of infection, augmenting the use of antimicrobials and developing the economic case for sustainable investment that considers the needs of all countries. [5]

1.2 Antimicrobial stewardship efforts in South Africa

A globally recognized antimicrobial stewardship effort that South Africa (SA) partakes in is the World Antibiotic Awareness Week which is an initiative by the World Health Organization (WHO). This initiative promotes rational antimicrobial practices among the public, health workers and policymakers to prevent a further increase in antimicrobial resistance. [6, 7] Various antimicrobial stewardship programs exist in SA. National efforts to

moderate antimicrobial prescribing include the South African Antibiotic Stewardship Programme, whose main aim is to provide leadership, advocacy for, and strengthening of, antimicrobial stewardship in SA. [8] The National Antimicrobial Resistance Strategy Framework in South Africa was developed to provide critical interventions to manage antimicrobial resistance, limit additional increases in resistant bacterial infections and improve patient prognoses. [9] This framework focuses on communication with the public to create antimicrobial awareness and provide education to improve patients' knowledge of the dangers associated with the inappropriate use of antimicrobials. [9]

Antimicrobial resistance is a global problem however it is of particular concern in developing countries where the infectious disease burden is high. The Global Antibiotic Resistance Partnership (GARP) aims to outline policy solutions and opportunities. Despite poor health status, SA has had the most active surveillance for antimicrobial resistance of any African country. [10] The Group for Enteric, Respiratory and Meningeal Disease Surveillance in South Africa is a national laboratory-based surveillance program that publishes quarterly reports on antimicrobial resistance in the public and private sectors. [11]

National antimicrobial prescribing guidelines are available electronically in SA. However, these are only utilised in the public sector where not all antimicrobials are available at all levels of care. In the private sector, prescribing is based on the clinical opinion of the physician, and there are no restrictions placed on antimicrobial prescribing. Higher rates of antimicrobial prescribing have been reported in the private sector in SA, compared to the public sector. [12] There is a need for antimicrobial stewardship to be implemented proficiently in both the public and private sectors.

1.3 The importance of using antimicrobials appropriately

Inappropriate antimicrobial use has created a significant challenge to public health by increasing antimicrobial resistance which results in an increase in morbidity and mortality and greater economic implications. [13] Inappropriate empiric treatment with a broad-spectrum antimicrobial can also lead to secondary complications such as subjecting patients to the risk of *Clostridium difficile* infection. [5] Poor patient outcomes in intensive care units (ICU) in the public and private sectors in SA have been shown with inappropriate antimicrobial prescribing. [12] Appropriate prescribing means selecting the correct antimicrobial agent based on the patient's diagnosis, at the correct dose and duration. In a South African study

conducted in the public and private health sector, an appropriate antimicrobial choice was associated with an 11% mortality compared to a 27% mortality where the antimicrobial was considered inappropriate. It was also found that antimicrobial duration was inappropriate in most of the cases. [12] Since insufficient exposure to an antimicrobial can lead to an increase in resistant bacteria at a site of infection, the dose and duration of the antimicrobial treatment can have an impact on the emergence of resistance. [14] Restricting the duration of antimicrobial treatment has been targeted by antimicrobial stewardship efforts in recent years to minimise the emergence of antimicrobial resistance and drug toxicity. [15] The appropriate use of antimicrobials has been linked to a reduced length of stay, which may translate to reduced healthcare costs. [16]

Globally, there are numerous reports on the gaps in antimicrobial prescribing across the spectrum of high, middle, and low-income countries. [17, 18, 19, 20] In a country such as SA, where antimicrobial stewardship programs are evolving, and vast differences exist between the public and private sector, it is important to evaluate current practice and determine the need for improvement.

1.4 The empiric use of antimicrobials and their de-escalation

De-escalation is a strategy to unite the competing aims of prescribing empiric treatment that is appropriate and covers the likely pathogens, and restricting antimicrobial exposure, which can increase the risk of resistant pathogens emerging. [21] The concept of de-escalation involves replacing the empiric antimicrobial with one that is efficacious and exhibits a narrower spectrum of activity or discontinuing the antimicrobial if it is not required. [22] The process involves submitting a suitable patient specimen (e.g. blood, urine, faeces, and cerebrospinal fluid) for microscopy, culture and sensitivity testing before administering a broad-spectrum antimicrobial that is effective for the suspected clinical diagnosis. If negative culture results are obtained, this could necessitate the cessation of the empiric treatment depending on the clinical symptoms of the patient. De-escalation allows targeted treatment of the identified pathogen, reducing cost, and a conceivable decrease in the development of antimicrobial resistance. [21] The empiric antimicrobial should be selected rationally, and de-escalation should occur as soon as possible or resistant micro-organisms may develop. Antimicrobials are often prescribed empirically in hospitalised patients, and it has been shown that often clinicians do not reassess the choice of the antimicrobial after reviewing the patient's clinical and laboratory data, including microscopy, culture and sensitivity results. [20]

1.5 The prescription of antimicrobials for surgical prophylaxis

Surgical antibiotic prophylaxis (SAP) is defined as "the administration of systemic antibiotics before or during a surgical procedure". [23] The WHO recommends a single pre-operative dose and advises against extended SAP after completion of the surgical procedure because of the risk of antimicrobial resistance. [24] Additional intra-operative doses of SAP are recommended for prolonged procedures when using drugs with short half-lives e.g. cephalosporins and penicillins. Additional doses are also recommended for procedures with major intra-operative blood loss (>1500ml in adults). Certain surgical procedures do not require SAP, such as specific clean orthopaedic procedures or low-risk elective laparoscopic procedures. [24] Evidence-based guidelines should be followed to prevent surgical site infections while also avoiding the emergence of antimicrobial resistance. Healthcare providers should be conscious of their role in decreasing the excessive use of unwarranted antimicrobials, especially in the case of surgical patients. If inappropriate SAP can increase the risk of antimicrobial resistance, then prophylaxis may cause overall harm. [25]

1.6 Problem statement

On the 11th of August 2011, SA took a bold stance with its National Health System subsequent to the publication of the policy on the National Health Insurance (NHI). [26] The intention of the NHI is to facilitate reform within the health sector in order to enhance the provision of services for all South Africans. It is designed to promote equity and efficiency to provide all South Africans with access to cost-effective, quality healthcare irrespective of their socio-economic status. There needs to be standardization and integration between the public and private sectors when the NHI becomes fully functional. While the public health sector is guided by the Essential Medicines List/ Standard Treatment Guidelines (EML/STG) when prescribing antimicrobials, the private sector is unrestricted with a vast availability to various antimicrobials. There is a need to determine how closely guidelines are followed to determine the level of uniformity between the public and private sectors.

There are very few studies in SA that assess the appropriateness of antimicrobial prescribing in the private healthcare sector. The private sector utilises a formulary that is developed at the discretion of the hospital management or the hospital group management. However, this formulary is not enforced as stringently as the EML/STG is in the public sector. Due to the rapid escalation of antimicrobial resistance globally, appropriate antimicrobial prescribing is

critical now more than ever. This study is important because it will evaluate how judiciously antimicrobials are being used in a private hospital setting. This study will provide valuable information to hospital management and doctors that can direct antimicrobial stewardship initiatives. The findings will also act as a baseline on which to measure improvement in antimicrobial prescribing in future studies.

1.7 Purpose

The purpose of this study was to assess the appropriateness of antimicrobial prescribing in the surgical and medical wards at a private hospital in KwaZulu-Natal.

1.8 Objectives

The specific study objectives were:

1) To investigate the appropriateness of antimicrobial prescribing in terms of dose, duration and frequency in a private hospital in Durban;
2) To determine whether antimicrobial prescribing is adjusted based on microscopy, culture and sensitivity results; and
3) To assess the appropriateness of antimicrobials used for surgical prophylaxis.

1.9 General methodology

1.9.1 Study setting

The study was conducted at a private hospital in Durban, KwaZulu-Natal, SA. The hospital consists of 215 beds and serves a middle-income population.

1.9.2 Study population and sample frame

Patients admitted to the surgical or medical wards, who were prescribed an antimicrobial during their hospital admission from June to July 2019, were considered for inclusion in this study. Each ward comprises of 27 beds. The surgical ward includes patients with general surgical conditions, gastrointestinal, urology, dental/maxillofacial, orthopaedic and plastic surgery. Patients prescribed antimicrobials for tuberculosis or for the eradication of *Helicobacter pylori* were excluded, with the exception of Oseltamivir since the patient sample was taken during the influenza season. Patients below the age of 18 years, patients with incomplete or missing data, and patients that were admitted for

gynaecological conditions were also excluded. For patients that were readmitted during the study period, only the first admission was included.

1.9.3 Sample size

Approximately 150-170 patients are admitted to the surgical and medical wards per month. Based on previous admissions, 40% to 65% of patients are prescribed an antimicrobial per month. A sample size of 385 was estimated to be effective for this study. This sample size produces a two-sided 95% confidence interval with a precision of ±7.5% where variability is unknown. The calculation is based on normal distribution and the assumption that there would be more than 30 patients.

1.9.4 Study design

This was an observational, analytic cross-sectional study.

1.9.5 Data collection and analysis

Electronic patient records were assessed. Variables such as age, gender, the ward type (surgical or medical), discipline, and length of hospital stay were collected. The clinical variables collected included diagnosis, whether a patient had a comorbidity or not and the following inflammatory markers: procalcitonin, C-reactive protein, erythrocyte sedimentation rate, and white cell count. The variables related to antimicrobial prescription included antimicrobial choice, route of administration, the reason for prescribing, the dose and duration of antimicrobial and microscopy, culture and sensitivity testing. Whether the antimicrobial was necessary or not was determined when measuring the appropriateness of the choice of antimicrobial, taking into consideration the diagnosis and inflammatory markers. The duration was considered appropriate using a fixed duration for specific infections. All patient data were anonymised, and no patient identifiers were collected.

A distinction was made between patients prescribed antimicrobials for prophylaxis and those who were prescribed antimicrobials as treatment for an infection. In terms of therapeutic use, antimicrobials were further classified as empiric or targeted. An antimicrobial was classified as targeted if the antimicrobial was prescribed according to microscopy, culture and sensitivity results. Antimicrobials were classified as prophylactic if the medical records reflected that the antimicrobial was used for prophylaxis or if administered one hour prior to the start of the surgical procedure.

Antimicrobial prescriptions were assessed for compliance of drug choice, dose, and duration using the Standard Treatment Guidelines and the Essential Medicines List for South Africa (hospital level for adults, 2015 edition), the South African Medicines Formulary, and The South African Antibiotic Stewardship Programme guidelines called A Pocket Guide to Antibiotic Prescribing for adults in South Africa, 2015. [27, 28, 29] The antimicrobials that were prescribed for empiric and targeted treatment were assessed according to the Standard Treatment Guidelines and the Essential Medicines List for South Africa (hospital level for adults, 2015 edition) and The South African Antibiotic Stewardship Programme guidelines. The South African Medicines Formulary was used to verify the dose and duration of the antimicrobials stated in the guidelines. The antimicrobials prescribed for prophylaxis were assessed according to the surgical prophylaxis guidelines adopted by the hospital group where the research was conducted.

Antimicrobial therapy was only classified as appropriate if the drug choice, the dose, and the duration were in accordance with the guidelines. The assessment of appropriateness was performed by the senior pharmacist. Any inconsistencies were discussed with the clinical practice pharmacist at the hospital to reach a consensus. A sample of 47 (10%) of the electronic data collected was assessed by a research assistant to verify the accuracy of the data entry and the assessment of appropriateness according to the guidelines.

Data from the electronic patient records were entered onto the data collection sheet (Appendix 1), and captured into Microsoft Excel for descriptive analysis. The data was exported into Stata 15.1 for statistical analysis. Quantitative data were summarised using the mean and standard deviation. Categorical variables were presented using proportions. The odds ratio was calculated to assess for any associations between length of hospital stay and the presence of microscopy, culture and sensitivity testing. The chi-square test was used to assess for the significance of associations between categorical variables. A nonparametric test, the Kruskal-Wallis test, was used to assess differences between three or more groups. A p-value of <0.05 was considered statistically significant.

1.9.6 Ethical considerations

Gate-keeper permission was obtained from the research committee of the private hospital group (Appendix 2). Ethics approval for the study was granted by the Biomedical Research Ethics Committee at the University of KwaZulu-Natal (BE457/19) (Appendix 3).

1.10 Format of dissertation

This dissertation is presented in four chapters:

- Chapter 1 describes the background of the problem of antimicrobial resistance and the importance of the rational use of antimicrobials, provides a framework for the research problem and includes the research objectives, and an overview of the methodology used;

- Chapter 2 contains a literature review critically appraising research pertaining to the rational and judicious use of antimicrobials globally and nationally;

- Chapter 3 presents the journal manuscript that has been accepted to the South African Medical Journal; and

- Chapter 4 discusses additional results, limitations, and recommendations that are not presented in the journal manuscript.

1.11 Summary

This chapter provided the context and structure of the study. The challenge of antimicrobial resistance and the concepts of appropriate de-escalation and surgical prophylaxis have been outlined, highlighting the need for a study investigating the rational use of antimicrobials in the South African private healthcare setting.

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Chapter 2: Literature review

2.1 Introduction

The purpose of this chapter is to critically evaluate the existing research on the appropriateness of antimicrobial prescribing, antimicrobial surgical prophylaxis, and antimicrobial de-escalation. The literature search was conducted using the electronic databases Pubmed, Google Scholar, EBSCOhost and the Cochrane Library. Key search terms included *'appropriate antimicrobial', 'appropriateness of antimicrobial', 'microbiology', 'de-escalation', 'antimicrobial surgical prophylaxis'* and *'narrowing of spectrum'.* Studies wrote in English, not older than ten years, and those based in a hospital or primary health care setting were considered for inclusion in this literature review.

2.2 Appropriateness of antimicrobial prescribing

Many countries have developed guidelines to ensure that the correct antimicrobial is prescribed for specific conditions, at the correct dose, and for an appropriate duration. Numerous studies have shown that the appropriateness of antimicrobial prescribing according to guidelines varies, and there have been no published reports of 100% adherence to antimicrobial prescribing guidelines in any healthcare setting. A flowchart developed in the Netherlands by a multi-disciplinary team led by Professor Gyssens, an infectious disease specialist, to assess antimicrobial prescribing, has been used frequently by researchers in other countries. This flowchart includes criteria such as antimicrobial indication, whether there is a more effective or less toxic alternative and whether there is an alternate antimicrobial with a narrower spectrum of activity. [1]

In a systematic review of 57 studies on the effectiveness of appropriate or inappropriate antimicrobial therapy for gram-negative bacterial infections, appropriate antimicrobial therapy was associated with a decreased risk of mortality and treatment failure, and inappropriate antimicrobial therapy was linked to adverse patient outcomes. [2] A retrospective study conducted at a private hospital in KwaZulu-Natal, South Africa, found that 28.8% of patients admitted to the ICU had antimicrobials administered. [3] Antimicrobial prescribing patterns were assessed over a two-month period according to local and international guidelines. The accuracy of the dose, frequency and duration of administration of the antimicrobial was evaluated, as well as whether treatment was microbiologically informed, and the practice of

de-escalation. An indication for the prescription of an antimicrobial agent was found in 58.5% of the patients, of whom 70.2% were prescribed treatment in accordance with the guidelines. Doses were assessed as correct for 91.1% of the patients. The lack of microscopy, culture and sensitivity guided therapy in 38.8% of patients, and the incorrect choice of drug in 29.8% of patients highlighted a need for better adherence to treatment guidelines.

In a South African study to examine the antimicrobial prescribing patterns of general practitioners for the treatment of acute bronchitis, the medical aid claims for members of 11 schemes were assessed. An antimicrobial was prescribed in 52.9% of patients. [4] Penicillins, cephalosporins and other beta-lactams made up almost 72% of the antimicrobials prescribed. [4] Each acute bronchitis instance was classified as either viral, bacterial or unknown. It was more probable for a patient with viral bronchitis to be prescribed an antimicrobial than a patient diagnosed with bacterial bronchitis (odds ratio 1.17). Previous studies have shown that antimicrobials are frequently prescribed for patients with acute bronchitis even though this condition is self-limiting and usually of viral origin. [4] This study found that a large proportion of patients with acute bronchitis are prescribed antimicrobials, and interventions need to be put in place to address this practice.

In a retrospective study conducted at Brits hospital and 6 primary health care clinics in the North West Province of South Africa, 775 (32.7%) out of 2370 prescriptions with information available were non-complaint to the STG/EML for PHC facilities. [5] In Brits, among the 9058 prescriptions that were assessed, at least one antibacterial medicine was recorded in 2313 (25.5%) of the prescriptions. In total, 2970 antibacterial agents were prescribed however, drugs prescribed for tuberculosis were included in this study. This study forms part of a more extensive study that includes 5 pilot projects which focuses on the surveillance of antimicrobial use in the community and antimicrobial resistance in resource-constrained settings. The proportion of antimicrobials prescribed in public health care facilities varied between Vellore, India (41.9%), Mumbai, India (48.6%), Brits, South Africa (25.5%) and Durban, South Africa (16.1%). [5]

In a retrospective medical record review conducted to evaluate antimicrobial prescribing in primary health care facilities in Cape Town, 68.7% out of 654 patients were prescribed an antimicrobial. [6] The sample was taken using all patients seen over 2 days in 8 representative primary care facilities. Patients who had antimicrobials prescribed for surgical antimicrobial

prophylaxis and tuberculosis treatment were excluded. The STG/EML for South Africa was used to assess the antimicrobials that were prescribed. In total, 45.1% of the antimicrobials prescribed were in line with the guidelines. The absence of a diagnosis (30.5%), the unnecessary use of an antimicrobial (21.6%), incorrect drug choice (11.5%), incorrect dose (12.9%) and the incorrect duration of treatment (9.5%) were the highest reasons for the guidelines not being adhered to. [6] This study adds to the evidence of poor compliance to antimicrobial prescribing guidelines in the public sector in SA.

A study conducted in public and private sector ICUs in SA showed that antimicrobials were prescribed in 73.5% of patients, of which 54.9% were inappropriately prescribed. [7] Antimicrobial prescribing was assessed by two intensivists. The information collected included the number of patients that had therapeutic antimicrobials prescribed, the appropriateness of the choice of antimicrobial, whether de-escalation and duration of administration were appropriate, and the hospital mortality. Inappropriate antimicrobial prescribing in ICUs in the public and private sectors in South Africa are frequent and are related to poor patient outcomes. [7]

In a prospective study conducted at a tertiary hospital in Malaysia, only 26.4% of patients received appropriate antimicrobial therapy. [8] The study included all surgical patients who were prescribed antimicrobials from November 2012 – July 2013. The outcome measures were appropriateness of the antimicrobials prescribed, the pattern of antimicrobial use, the antimicrobial resistance pattern, and clinical outcomes. The common causes of inappropriate antimicrobials used for prophylaxis were inappropriate timing (36.4%) and inappropriate duration of prophylaxis (34.5%). For therapeutic antimicrobials, 42.1% were an inappropriate choice and 40.7% were inappropriately indicated.

Compliance of antimicrobial prescriptions with standards such as the Standard Treatment Guidelines and the Essential Medicines List is an area of concern. [9] In Namibia, prescribing practices were assessed using the Namibia Standard Treatment Guidelines and it was found that 38% of prescriptions were not in accordance with the treatment guidelines. [10] In a study conducted in Zambia, the clinical indication, dose, frequency, route and duration of antimicrobials prescribed, and collection of culture samples before initiation of antimicrobial treatment were assessed using the flowchart developed by Gyssens *et al*, and the Zambian Standard Treatment Guidelines (STG). It was found that 70.1% of the 385 admitted patients

were prescribed antimicrobials. The prescriptions that complied with Gyssens *et al.* flowchart varied across disciplines: 24.3% in obstetrics and gynaecology, 12.4% in internal medicine, and 22.2% in surgery. Only 31.9% of patients who were prescribed an antimicrobial had microscopy, culture and sensitivity tests ordered. This study highlighted the deficiencies in the use of microscopy, culture and sensitivity testing, which is meant to guide antimicrobial therapy and ensure that patients receive the correct antimicrobial for their specific indication.

A study undertaken at a hospital in Addis Ababa, Ethiopia, showed that ceftriaxone was used inappropriately in 87.9% of the cases assessed. [11] The study investigated the use of ceftriaxone in the emergency and medical wards. Ceftriaxone is a commonly used antimicrobial because it has a broad spectrum of activity. However, global trends indicate that ceftriaxone has been misused. [11] In this study, the treatment guideline was prepared by specialists from the School of Medicine and School of Pharmacy by collaborating existing evidence-based recommendations from multiple sources, including the Ethiopian STG (2010). Of the 314 medical records assessed, 58% contained a prescription for ceftriaxone. Ceftriaxone was used empirically in 87.3% of cases. Only 10.5% of patients had microscopy, culture and sensitivity tests done, of which only 8 cases (24.2 %) had an organism isolated. The inappropriate use of antimicrobials can contribute to decreased patient safety and lead to increased antimicrobial resistance.

Another study that assessed antimicrobial prescribing using the flowchart by Gyssens et al. also found a high rate of inappropriate antimicrobial prescribing (73.3%) for patients admitted to the ICU, gynaecology, internal medicine, surgery, trauma, or paediatric ward at a hospital in Kyrgyzstan. [12] The antimicrobials were assessed according to the choice of antimicrobial, the dosage, route, and intervals of administration. The most common cause for inappropriateness was drug choice, as it was found that in 143 (48.6%) of the cases, there was no indication for the antimicrobial.

The issues with inappropriate antimicrobial prescribing are not limited to adult patients. In a point prevalence survey conducted in 12 paediatric hospitals in Turkey, 46.7% of the 711 patients receiving an antimicrobial were prescribed at least one drug that was inappropriate. [13] The appropriateness of the antimicrobial prescribed was compared between the indications, types of antimicrobials prescribed, wards, and discussion with an infectious disease specialist. Antimicrobial prescriptions were evaluated as inappropriate if the choice or the dose of the antimicrobial was incorrect based on the recommendations of the American

Academy of Paediatrics. The surgical wards had the highest proportion of inappropriate use (80.2%).

2.3 De-escalation of empiric antimicrobial treatment

Many antimicrobial stewardship programmes advocate for improved antimicrobial de-escalation. In a systematic review and meta-analysis to assess the safety and consequences of de-escalation, 16 observational studies found that de-escalation guided by culture results was associated with fewer deaths in patients with pneumonia, sepsis or bacteraemia. [14] On the contrary, 3 small randomised controlled trials were included in this systematic review that showed increased mortality with de-escalation however, this finding was non-significant.

In a retrospective cohort study conducted in Idaho, 9319 patients were considered for outcomes associated with antimicrobial de-escalation of treatment for pneumonia. [15] The endpoints were length of stay, 30-day readmission rate, and 30-day *Clostridium difficile* infection rate confirmed by laboratory detection. The results demonstrated that de-escalation was not associated with 30-day *Clostridium difficile* infection nor 30-day readmission; however, de-escalation was associated with decreased length of stay. This study found that de-escalation is a rational, safe option and can modestly reduce the length of hospital stay.

In a study conducted at a public, academic hospital in Brazil, it was found that out of 224 patients, de-escalation was warranted in 66 patients (29.4%) but only executed in 44 of these patients (66.7%). In this study, the prevalence of antimicrobial de-escalation, the adequacy of antimicrobial treatment, and the rates of culture positivity in patients diagnosed with severe sepsis or septic shock were evaluated. [16] Data was collected for all microbiological tests and antimicrobials prescribed using an electronic system. Antimicrobial de-escalation was executed by narrowing the antimicrobial spectrum in 24 (54.5%) patients, decreasing the number of antimicrobials in 17 (38.5%) patients, and discontinuing the antimicrobial early in only 3 (7%) patients. The hospital in which this study was conducted had a system to monitor the local profile of antimicrobial resistance and develop and amend protocols for the empiric use of antimicrobials. The empiric antimicrobials prescribed was appropriate in 200 (89.3%) patients. This study found high rates of empirical antimicrobial adequacy, suboptimal de-escalation rates, and low rates of positive blood cultures. The study concluded that de-escalation should be promoted more actively to aid the reduction in antimicrobial consumption and provide more precise antimicrobial therapy.

A retrospective study, conducted from January to December 2011, at a tertiary care medical centre in the United States of America found that 63% of the 240 patients assessed had their antimicrobial treatment de-escalated. [17] The study determined the frequency of antimicrobial de-escalation in randomly selected patients who received simultaneous piperacillin/tazobactam and vancomycin. The patient characteristics that were evaluated included the duration, indication, antimicrobial regimen, culture results, length of hospital stay, and hospital mortality. However, the appropriateness of either the empiric or de-escalated antimicrobial treatment was not assessed. It was found that in patients who had their antimicrobial treatment de-escalated, the median length of stay was 4 days shorter. The authors did not find a difference in adjusted mortality between patients who had their treatment de-escalated and those who did not.

In a South African study conducted in an adult ICU at a private hospital in KwaZulu-Natal, de-escalation was observed in only 13.1% of the 70.8% of patients where de-escalation was warranted. [3] A prospective study conducted in both the public and private sector in SA showed that out of 248 patients, de-escalation was practised in 33.3% of patients in the public sector and 19.7% of patients in the private sector. [7] The study was conducted in 3 parts and included a 1-day point-prevalence study. If de-escalation was done within 72 hours of empiric antimicrobial initiation or within 24 hours of detection of the micro-organism and the susceptibility result, this was considered appropriate. Inappropriate antimicrobial prescribing in ICUs in the public and private sectors in South Africa are frequent. [7] There were inconsistencies that were evident with the practice of de-escalation. This could be due to the access to laboratory services, the available healthcare resources, and whether an antimicrobial stewardship committee exists.

2.4 Appropriateness of antimicrobial surgical prophylaxis

Surgical site infections can be associated with considerably longer hospital stays and higher treatment costs. A systematic review that included 20 studies showed that surgical site infection rates ranged from 0 to 71.1%. [18] Out of 7 studies, 24 bacteria were identified as the agents causing the surgical site infections, most of which were gram-negative. The most commonly reported bacterial isolate was *Escherichia coli*, contributing to 6.7% to 50% of incidence in caesarean sections, orthopaedic, cardiothoracic, and general surgery. *Staphylococcus aureus* was the second most prominent bacterial isolate and contributed to most of the surgical site infections caused by gram-positive bacteria. It is imperative that

rational, standardised guidelines are adhered to in order to prevent antimicrobial resistance and to reduce the prevalence of multidrug-resistant bacteria.

The appropriate use of SAP has been shown to decrease the rate of surgical site infections. In 2015, a systematic review was conducted according to the Cochrane Collaboration methodology in Brazil. [19] There were 859 articles recovered, with 18 studies selected for the review. The outcomes that were analysed in the articles were the appropriate indication of SAP, administration of antimicrobial at the correct time, correct antimicrobial choice, adequate discontinuation of antimicrobial, and adequate antimicrobial prophylaxis. Significant discrepancies were seen in all the outcomes that were evaluated however, all the studies showed that there is a need for better compliance to guidelines for SAP.

A study in Iran found that out of 8586 patients, 44% received SAP that was not required. [20] The study evaluated the use of prophylactic antimicrobials to determine appropriateness of antimicrobial surgical prophylaxis. In this study, cefazolin was the antimicrobial that was chosen for cardiac, orthopaedic, vascular, and neurosurgery operations. Where *Methicillin-resistant Staphylococcus aureus* was suspected, vancomycin was the drug of choice. In the case of the presence of anaerobic pathogens, metronidazole was required. The dose of the antimicrobial was defined as appropriate if the infusion of one to two grams of cefazolin, one gram of vancomycin or, 500 mg of metronidazole was started 60 minutes before incision and repeated three to five hours for cefazolin, six to eight hours for metronidazole, or 12 hours for vancomycin after the first dose. The duration of prophylaxis was considered sufficient if it lasted less than 24 hours or less than 48 hours in cardiac surgery. There were 4815 patients who received prophylaxis of which, 13.1% received it inappropriately, 8.2% received an inappropriate dosage, and 9.5% received an antimicrobial for more than 24 hours. Even though the use of antimicrobials to prevent surgical site infection has been successful, the inappropriate use of antimicrobials for surgical prophylaxis can lead to major complications.

A prospective study conducted in Malaysia found that the choice of SAP was consistent with the guideline in 78.2% of the 87 cases assessed. [21] The study was conducted in a surgical ward of a general hospital. Adherence to the national antimicrobial guideline was assessed in terms of antimicrobial usage in surgical prophylaxis and incidences of surgical site infection. Every patient was assessed post-operatively for up to 30 days to establish the incidence of a surgical site infection. Approximately 80% of the antimicrobials that were used for

prophylaxis were administered within one hour before the operation, and intraoperative re-dosing was omitted in 27.6% of the antimicrobials. In 77% of patients, antimicrobials used for prophylaxis were discontinued within 24 hours post-operatively. Of those antimicrobials that were continued for more than 24 hours, 60% were administered for unknown reasons. Surgical site infections were recorded in 13.8% of the patients studied. [21]

A study conducted at a referral hospital in Ethiopia found that none of the drug choices for SAP conformed to the Ethiopian Standard Treatment Guidelines. [22] The selection, timing and duration of prophylactic antimicrobial administration among surgical patients were assessed. The study found that 76% of the prophylactic antimicrobials were administered for longer than 24 hours. The drug choice was in accordance with the American Society of Health-System Pharmacists guideline in 10.6% of antimicrobials. In a study conducted at a referral hospital for cardiac patients in Jordan, SAP in cardiac surgery was evaluated. Only 2% of patients had the correct antimicrobial chosen, 40% of patients received antimicrobial prophylaxis for 48 hours or less in accordance with the guidelines at the time, and 28% of patients received an appropriate dose. [23] It is important that surgical prophylaxis is assessed according to proper guidelines to elucidate where antimicrobial stewardship efforts should be directed.

2.5 Summary

Studies conducted in high, middle and low-income countries have highlighted the problem of inappropriate antimicrobial prescribing. Based on the majority of studies, de-escalation is not widely practiced, with many patients receiving broad-spectrum antimicrobials unnecessarily. Surgical site infection rates vary substantially, and all the studies on surgical prophylaxis showed the need for better adherence to SAP prescribing guidelines. The literature has highlighted the paucity of data on antimicrobial prescribing in SA, particularly in the private sector.

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Chapter 3: Submitted Paper

This chapter presents the manuscript that has been submitted to the South African Medical Journal as per the stipulated format [http://www.samj.org.za/index.php/samj/about/submissions#authorGuidelines] and limitations in terms of graphs, tables and word count. The manuscript has been accepted for publication (Appendix 4).

VTJ was responsible for proposal development, data collection and analyses (with the assistance of a statistician), and the write-up. SM served as supervisor.

Antimicrobial prescribing in the surgical and medical wards at a private hospital in KwaZulu-Natal, South Africa, 2019

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Background: Appropriate antimicrobial use is imperative due to the misuse of antimicrobials that has resulted in a growing burden of antimicrobial resistance. Evidence-based guidelines should be adhered to in order to ensure the sustainability of effective antimicrobials.

Objectives: To assess the appropriateness of antimicrobial prescribing at a private hospital in Durban, KwaZulu-Natal.

Methods: The records of patients admitted to the surgical and medical wards over a 2-month period were reviewed to assess the choice of antimicrobials prescribed, dose and duration. The guidelines used to determine appropriateness were the Standard Treatment Guidelines and the Essential Medicines List for South Africa (hospital level for adults, 2015 edition), the antimicrobial indications and prescribing instructions in the South African Medicines Formulary, the South African Antibiotic Stewardship Programme guidelines and the evidence-based surgical prophylaxis guidelines adopted by the hospital group where the research was conducted.

Results: During the study period, 466 patients were admitted and prescribed an antimicrobial, of which 220 (47.2%) were admitted to the surgical ward, and 246 (52.8%) were admitted to the medical wards. A total of 779 antimicrobials were prescribed. Of the 660 antimicrobials prescribed for empiric treatment, 305 (46.2%) antimicrobials were appropriately prescribed based on drug choice, dose and duration. Of the 38 antimicrobials that were classified as targeted, 36 (94.7%) were prescribed according to the correct dose and 33 (86.8%) were prescribed according to the correct duration. Of the 81 antimicrobials prescribed for surgical prophylaxis, only 32 (39.5%) met the criteria for appropriateness in terms of drug choice, dose and duration.

Conclusion: Our findings suggest that compliance with evidence-based guidelines for the use of antimicrobials is not optimal in hospitals in the private sector. Antimicrobials are prescribed inappropriately both for empiric treatment and for surgical prophylaxis. Private hospital groups should consider adopting antimicrobial prescribing guidelines that are mandatory for doctors to adhere to in order to promote rational antimicrobial prescribing and thereby reduce the burden of antimicrobial resistance.

Introduction

The threat of antimicrobial resistance is paramount in the area of infectious diseases due to its rapid spread on a global scale. The occurrence of multidrug-resistant microorganisms in hospitals is linked to an increased risk of patient morbidity and mortality, and longer hospital

stays. [1] The continuing emergence of antimicrobial-resistant bacteria resulting from the misuse and abuse of antimicrobials has become a major public health problem, with over one in three antimicrobial prescriptions in the emergency department being prescribed inappropriately. [2,3] Without coordinated and immediate action on a global scale, the world is moving towards a post-antibiotic era in which common infections could once again kill. [4]

The profuse use of broad spectrum antimicrobials is influenced by the lack of the timely detection of causative microorganisms and their antimicrobial susceptibility patterns. This has subsequently caused rapid increases in emerging bacterial resistance. [5] Antimicrobial de-escalation, which refers to narrowing of the antimicrobial spectrum based on the sensitivity of the pathogen, is a commonly accepted management strategy in critically ill patients. [6] The antimicrobial spectrum should be narrowed as soon as possible, based on the clinical condition of the patient, the pathogen identified and the sensitivity profile obtained from the antibiogram. When no evidence of bacterial infection is present, antimicrobial therapy should be suspended. [7] However, de-escalation has not been widely adopted. This could be due to the doctor's hesitancy to change an antimicrobial that has demonstrated effectiveness, an inadequate understanding of how to de-escalate appropriately, lack of microbiological data, and the different opinions about the safety and usefulness of de-escalation. [6]

Antimicrobial surgical prophylaxis forms part of a collection of processes that aims to decrease the incidence of surgical site infections (SSI). One of the fundamental goals of surgical prophylaxis is to reduce the bacterial load in the wound in order to assist the natural defences of the host to prevent the occurrence of infection. [8] The World Health Organization (WHO) has developed a Surgical Safety Checklist intended to improve the safety of patients undergoing surgical procedures because safety measures are often not appropriately applied. [9] The suitable use of surgical prophylaxis can significantly decrease the rate of SSI by up to 50%. [9] Evidence based guidelines can be followed in order to prevent SSI while also avoiding the emergence of antimicrobial resistance. Research has shown that better compliance to guidelines for antimicrobial surgical prophylaxis is required. [10]

In 2015, South Africa responded to the WHO's request to raise awareness about the preservation of antimicrobials through appropriate and rational use by implementing World Antibiotic Awareness Week initiatives. [11] The development of the Essential Medicines List (EMLs) and Standard Treatment Guidelines (STGs) forms part of a plan to minimize the unnecessary prescription of antimicrobials in the public sector. In the private sector, formularies are developed according to hospital management or the hospital group protocols however antimicrobial prescribing is rarely standardised in practice. The use of formularies can be used to regulate the choice of antimicrobials thereby reducing expenses to the patient, the hospital and the government. [12] Antimicrobial prescription practices can only be improved when there is evidence to show that there are deficiencies in practices. Therefore the objectives of this study were to investigate the appropriateness of antimicrobial prescribing in terms of dose, duration and frequency; to determine whether antimicrobial prescribing is adjusted based on microscopy, culture and sensitivity results and to assess the appropriateness of antimicrobials used for surgical prophylaxis.

Methods

Study setting

The study was conducted at a private hospital in Durban, Kwa-Zulu Natal, South Africa (SA). The hospital consists of 215 beds and serves a middle income population.

Study population and sample frame

Patients admitted to the surgical and medical wards who were prescribed an antimicrobial during their hospital admission over a 2 month period in 2019 were considered for inclusion in this study. Each ward is a 27 bed unit. The surgical ward includes patients with general surgical conditions, plastic surgery, urology, orthopaedic surgery as well as other disciplines.

Patients with antimicrobials prescribed for tuberculosis or for the eradication of *Helicobacter pylori* were excluded, with the exception of Oseltamivir since the patient sample was taken during the influenza season. Patients below the age of 18 years, patients with incomplete or missing data and patients that were admitted for gynaecological conditions were also excluded. Patients that were readmitted during the study period had only the first admission included.

Sample size

Approximately 150-170 patients are admitted to the surgical and medical wards per month. Based on previous admissions, 40% to 65% of patients are prescribed an antimicrobial per month. A sample size of 385 was estimated to be effective for this study. This sample size produces a two-sided 95% confidence interval with a precision of ±7.5% where variability is unknown. The calculation is based on normal distribution and the assumption that there would be more than 30 patients.

Study design

This was an observational, analytic cross-sectional study.

Data collection and analysis

Electronic patient records were used to collect clinical data and patient data such as age and gender. The clinical variables included diagnosis, whether a patient had a co-morbidity or not, length of hospital stay, the ward type (surgical or medical) and discipline. The variables related to antimicrobial prescription included antimicrobial choice, route of administration, dose and duration of antimicrobial and microscopy, culture and sensitivity testing results. The infection markers assessed were procalcitonin (PCT), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and white cell count (WCC). All patient data was anonymized and no patient identifiers were collected.

A distinction was made between patients who were prescribed antimicrobials for prophylaxis and those who were prescribed antimicrobials as treatment for an infection. In terms of therapeutic use, antimicrobials were further classified as empiric or targeted. An antimicrobial was classified as targeted if the antimicrobial was prescribed according to antibiogram results. Antimicrobials were classified as prophylactic if the patient records reflected that the antimicrobial was used for prophylaxis or if it was administered one hour prior to the start of a surgical procedure.

Antimicrobial prescriptions were assessed according to drug choice, dose and duration to see if it complied with the Standard Treatment Guidelines and the Essential Medicines List for South Africa (hospital level for adults, 2015 edition), [13] the South African Medicines Formulary [14] and the South African Antibiotic Stewardship Programme guidelines called A Pocket Guide to antibiotic prescribing for adults in South Africa, 2015. [15] The antimicrobials that were prescribed for surgical prophylaxis were assessed according to the surgical

prophylaxis guidelines adopted by the hospital group where the research was conducted. Antimicrobial therapy was only classified as appropriate if the drug choice, the dose and the duration were consistent with the guidelines. The assessment of appropriateness was performed by the senior pharmacist. Any inconsistencies between the guidelines were discussed with the clinical practice pharmacist at the hospital to reach a consensus. There were no queries that required further input from a clinician.

Quantitative data were summarised using the mean and standard deviation. Categorical variables were presented using proportions. The odds ratio was calculated to assess for any associations between length of hospital stay and the presence of microscopy, culture and sensitivity testing. The chi-square test was used to assess for significance of associations between categorical variables. The Kruskal-Wallis test was used to assess differences between three or more groups. A p-value of <0.05 was considered statistically significant.

Ethical considerations

Gate-keeper permission was obtained from the hospital manager and pharmacy manager at the facility. Permission was also obtained from the health research ethics committee of the hospital group. Ethics approval for the study was granted by the Biomedical Research Ethics Committee at the University of KwaZulu-Natal (BE457/19).

Results

There were 1051 patients admitted over the 2 month period of which 601 (57.2%) patients were prescribed antimicrobials. After applying the exclusion criteria, 466 patients were included in this study, of which 246 (52.8%) were from the medical wards, and 220 (47.2%) patients were from the surgical ward.

Profile of patients

Just over half of the study population (n= 253, 54.3%) were female (Table 1). Of the 246 patients admitted to the medical wards, there were more females (n=154, 62.6%) than males. The converse was seen in the surgical ward where only 99 of 220 patients (45%) were female, $p<0.001$. Overall, the mean age of females was 51.8 years (SD: 16.6) and the mean age of males was 52.8 years (SD: 17.3), $p=0.56$. In the medical ward, the mean age for females was 53.2 years (SD: 15.4) compared to 50.0 years (SD: 17.6) for males, $p=0.14$. In the surgical ward, the mean age for females was 49.8 years (SD: 16.8) compared to 54.8 years (SD: 16.7) for males, $p=0.03$.

Infection markers were requested for 278 (59.7%) patients, of which 127 (45.7%) were from the medical ward. More than half of these patients (n=162, 58.3%) had elevated infection markers. Two-hundred and seventy-six patients (59.2%) had a co-morbidity recorded. The median length of stay was 4 days with a range of 1 to 41 days. More than a third of patients (n=160, 34.3%) had a length of stay of greater than 4 days.

Table 1: Profile of patients in the surgical and medical wards at a private hospital in KwaZulu-Natal, 2019

Age	**Frequency (%)**
18 – 20	12 (2.6)
21 – 30	49 (10.5)
31 – 40	59 (12.7)
41 – 50	87 (18.6)
51 – 60	108 (23.2)
61 – 70	80 (17.2)
>70	71 (15.2)
Gender	**Frequency (%)**
Female	253 (54.3)
Male	213 (45.7)
Length of stay	**Frequency (%)**
1-2 days	122 (26.2)
3-4 days	184 (39.5)
> 4 days	160 (34.3)

Antimicrobial prescribing

A total of 779 antimicrobials were prescribed over the two-month period of which 660 (84.7%) were prescribed empirically, 81 (10.4%) were prescribed for surgical prophylaxis and 38 (4.9%) were targeted. More than half the antimicrobials (n=422, 54.2%) were prescribed in the medical ward, and the most frequent antimicrobial prescribed in this ward was Amoxicillin/Clavulanic acid (n=80, 19%). In the surgical ward, the most frequent antimicrobial prescribed was Cefuroxime (n=75, 21%). Just less than a third of the antimicrobials were prescribed by a physician (n= 142, 30.8%) and 92 (19.7%) were prescribed by a general practitioner (Table 2). Among all the patients, the most common antimicrobials prescribed empirically were Amoxicillin/Clavulanic acid (n=126, 19%), Ceftriaxone (n=106, 16%) and Cefuroxime (n=82, 12.4%). The most common antimicrobials prescribed for surgical prophylaxis were Amoxicillin/Clavulanic acid (n=21, 25.9%), Cefazolin (n=17, 21%) and Cefuroxime (n=13, 16%). Of the 71 patients who were prescribed Oseltamivir, only 27 were tested for the influenza virus, of which 11 tested positive for a strain of influenza.

Appropriateness of antimicrobial prescribing

Of the total 779 antimicrobials prescribed, 407 (52.3%) met the criteria for appropriate drug choice, 734 (94%) were prescribed using the appropriate dose and 560 (71.9%) were prescribed using the appropriate duration. There was no significant difference in the appropriateness of antimicrobial prescribing between the surgical and medical wards. (p=0.5) (Figure 1). Of the 81 antimicrobials prescribed for surgical prophylaxis, 42 (51.9%) met the criteria for appropriate drug choice, 77 (95%) were prescribed according to the correct dose and 45 (55.6%) were prescribed for the correct duration. Overall, 32 (39.5%) of these antimicrobials met the criteria for appropriateness in terms of drug choice, dose and duration.

Table 2: Antimicrobials prescribed in the surgical and medical wards at a private hospital in KwaZulu-Natal, 2019

Antimicrobial	**Frequency (%)**
Amikacin	25 (3.2)
Amoxicillin	2 (0.3)
Amoxicillin/Clavulanic acid	153 (19.6)
Azithromycin	30 (3.9)
Cefazolin	17 (2.2)
Cefpodoxime	7 (0.9)
Ceftazidime	2 (0.3)
Ceftriaxone	116 (14.9)
Cefuroxime	99 (12.7)
Ciprofloxacin	35 (4.5)
Clarithromycin	16 (2)
Clindamycin	23 (3)
Doxycycline	2 (0.3)
Ertapenem	16 (2)
Fosfomycin	2 (0.3)
Levofloxacin	81 (10.4)
Linezolid	2 (0.3)
Meropenem	6 (0.8)
Metronidazole	33 (4.2)
Moxifloxacin	28 (3.6)
Nitrofurantoin	2 (0.3)
Norfloxacin	1 (0.1)
Oseltamivir	71 (9.1)
Piperacillin/Tazobactam	5 (0.6)
Teicoplanin	2 (0.3)
Trimethoprim/Sulphamethoxazole	1 (0.1)
Vancomycin	2 (0.3)
Route of administration	**Frequency (%)**
Oral	275 (35.3)
Intravenous	504 (64.7)
Discipline	**Frequency (%)**
Medical	142 (30.8)
General practitioner	92 (19.7)
Urology	76 (16)
General surgery	57 (12.2)
Gastrointestinal	38 (8.1)
Other	19 (4)
Plastic surgery	17 (3.6)
Orthopaedic	12 (2.6)
Ear/Nose/Throat	10 (2.1)
Dental/Maxillofacial	3 (0.6)

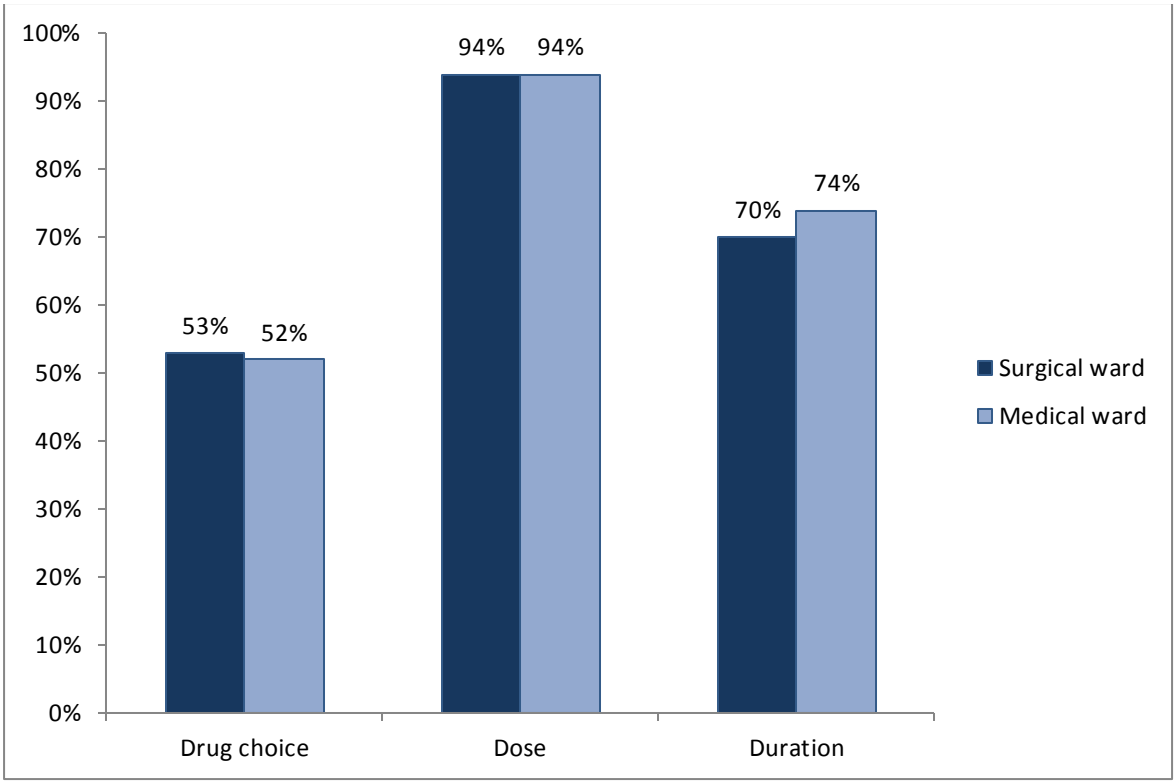

Figure 1: Appropriateness of antimicrobial prescribing in the surgical and medical wards at a private hospital in KwaZulu-Natal in 2019

De-escalation

Microscopy, culture and sensitivity tests were ordered for 159 (34.1 %) patients of which, 77 (48.4%) had a pathogen cultured. Of these 77 patients, only 28 (36.4%) were de-escalated appropriately. Patients with a length of stay > 4 days were significantly more likely to have a microscopy, culture and sensitivity test done compared to patients with a length of stay of 1-2 days (OR = 2.4: $p<0.05$) or 3-4 days (OR = 1.8: $p<0.05$).

Discussion

This is the first reported study of antimicrobial prescribing in the surgical and medical wards at a private hospital in KwaZulu-Natal. More than half of the patients in this study were prescribed an antimicrobial during their hospital stay. Whilst there are no other published reports to compare our findings to, it is lower than 61% reported in a study conducted in an intensive care unit (ICU) setting in a hospital in the private sector in SA. [16] In our study, 94% of antimicrobials were prescribed using the appropriate dose. This is similar to findings from the aforementioned study where 91% of antimicrobials were prescribed using the appropriate dose. [16]

An alarming 52.6% of antimicrobials were inappropriately prescribed according to drug choice, dose and duration. A study conducted in eight primary care facilities in the Cape Town Metro District also showed that non-adherence to national guidelines was 54.9%. [17] The guideline used was the Standard Treatment Guidelines and Essential Medicines List for South Africa, Primary Healthcare Level, 2014 edition. The most common reason for non-adherence in this study was because a diagnosis was not specified in the medical records. In

our study, all the relevant information was collected electronically and the diagnosis was always noted as it is a requirement that the ICD-10 coding system is used for all patients. In an Australian study that evaluated the appropriateness of antimicrobial prescribing in private hospitals, it was found that 48% of antimicrobials were assessed as inappropriate. [18] The proportion of inappropriately prescribed antimicrobials in our study is also similar to previous studies conducted in Turkey (47%) and Namibia (38%). [19, 20] In our study, 52.3% of antimicrobials met the criteria for appropriate drug choice. This is lower than the results from the WHO pilot study in Brits, North West Province, where 67% of 2370 prescriptions complied with STG/EML guidelines for appropriate drug choice. [21] This pilot study was conducted in the public sector therefore the difference in appropriateness of drug choice could be due to the private sector having an array of antimicrobials to choose from with poor adherence to formularies by doctors.

Only 34% of patients in our study had microscopy, culture and sensitivity tests ordered and only 36% of patients who had a pathogen cultured were de-escalated appropriately. In a South African study commonly known as the prevalence of infection in South African intensive care units (PISA) study, de-escalation was practised in 33.3% and 19.7% of the public and private sector patients, respectively. [22] The difference in proportion between the public and the private sector can be attributed to the presence of 'open' ICUs in the private sector where each patient is managed by the admitting doctor who may prescribe antimicrobials indiscriminately, often without appropriate knowledge of the epidemiology of the unit. [22] In a study conducted in a private hospital in South Africa in 2015, de-escalation was noted in only 13.1% of cases in the ICU. [16] The higher proportion of patients who had their antimicrobial de-escalated in our study compared to findings from other private hospitals in SA may be due to the incorporation of a regional clinical pharmacist to guide the antimicrobial stewardship programme at our hospital. Since the aforementioned study was conducted in 2015, it is possible that de-escalation in the private sector has improved since antimicrobial stewardship efforts have developed over the last few years. Further studies in the private sector are required in order to determine if this is true. In a study that measured de-escalation in a private acute care hospital in North Carolina, in the United States of America, 63% of patients had their antimicrobial regimens de-escalated. [23] This high proportion of patients who are de-escalated may be attributed to the establishment of antimicrobial stewardship programmes at this hospital more than a decade prior to the study being conducted. In contrast, the antimicrobial stewardship programme in our study setting was established 5 years ago and is still facing challenges. Antimicrobial stewardship meetings are meant to be held quarterly with representation from at least one doctor. It is also preferable for a microbiologist to attend these meetings; however the attendance of doctors and microbiologists is a rare occurrence.

We found that less than 40% of the antimicrobials prescribed for surgical prophylaxis met the criteria for appropriateness in terms of drug choice, dose and duration. In a systematic review of 18 studies that evaluated the adherence to guidelines for antimicrobial surgical prophylaxis, substantial differences were observed in all the outcomes that were assessed. [10] These outcomes included administration of antimicrobial at the correct time (12.7% to 100%), correct antimicrobial choice (22% to 95%), and adequate antimicrobial prophylaxis (0.3% to 84.5%). [10] The findings from the systematic review and our study indicate that greater adherence to guidelines for surgical prophylaxis is necessary. The correct dose was prescribed in 95% of the antimicrobials prescribed for surgical prophylaxis indicative that the drug choice and the duration contributed to the overall high level of inappropriate prescribing. In our study setting, surgical prophylaxis is monitored and audited regularly and doctors should

be contacted when patients are maintained on the antimicrobial prophylaxis for a prolonged period. The inappropriate duration of antimicrobials prescribed for surgical prophylaxis is due to doctors not stopping the antimicrobial timeously. The hospital hosts an aging population of doctors and it is plausible that there is a reluctance to change prescribing habits. Factors such as age, gender, educational status, specialty and work experience have been noted to influence doctors' prescription patterns. [24] In a study that investigated prescription patterns in Chinese county hospitals, it was found that doctors under 45 years of age prescribed fewer antimicrobials than those over the age of 45 years. [24] In a study in Ethiopia, 76% of antimicrobials prescribed for surgical prophylaxis were administered for greater than 24 hours, only 10.6% of the drug choices complied with the American Society of Health-System Pharmacists guideline and none of the selections were compliant to the national Standard Treatment Guidelines of the country. [25] The failure to comply with the guidelines is the result of prolonged surgical prophylaxis administration beyond the recommended timeframe. Although the guidelines state that administration of the antimicrobial used for surgical prophylaxis should be stopped within 24 hours, 44.4% of the antimicrobials were administered for up to five days. [25] A study in Johannesburg that assessed anaesthetists' knowledge of surgical prophylaxis found that overall knowledge was poor with few anaesthetists reporting to follow any guideline. [26] The mean knowledge score was 56.2%, and only 36.3% of participants were aware that most guidelines state that prophylaxis should only be continued for the duration of the surgery. [26]

In a study to describe South African prescribers' knowledge of, attitudes to and perceptions of antimicrobial resistance; it was found that prescribers of antimicrobials in the private sector in SA felt pressure from patients to prescribe antimicrobials even though they are conscious of the problem of antimicrobial resistance. [27] This may be a contributing factor to the high proportion (52.6%) of antimicrobials that were inappropriately prescribed in our study. In a review that included 33 studies, the factors that influenced the prescribing decisions of physicians were evaluated, and many factors related to the working and external environment were identified. These included physicians' personal attributes, cost of the medicine and pharmaceutical industries' marketing and promotion strategies. [28] These factors showed that prescribing is not always purely for the benefit of the patient, but can also be guided by individual interest. The use of suitable and reliable practice guidelines could decrease the harmful impact of certain factors and endorse rational prescribing. [28]

Our study was only conducted in one private hospital which limited the generalisability of the findings. However, in the private sector in SA, doctors often admit and manage patients at more than one hospital; therefore our findings are likely to reflect the practices at other hospitals in the private sector, particularly in Durban. Data was collected retrospectively using an electronic surveillance program; therefore clinical data such as the patient's temperature and radiological findings could not be assessed. It was only noted whether a patient had a co-morbidity or not and the type of co-morbidity was not recorded. It is possible that the presence of co-morbidities may have affected the choice, dose and duration of an antimicrobial. Furthermore, the assessment of infection markers was based on only whether or not the patient had a raised PCT, CRP, ESR or WCC, with no alignment of the patient's clinical condition. The appropriateness of antimicrobial selection was based on the assumption that the electronically recorded diagnosis was accurate. A prospective study with the collection of more clinical data and inclusion of clinicians may provide better insight as to reasons for the antimicrobial choices, doses and duration.

Conclusion

Our findings suggest that compliance with evidence-based guidelines for the use of antimicrobials is not optimal in hospitals in the private sector. Antimicrobials are prescribed inappropriately both for empiric treatment and for surgical prophylaxis. There is an urgent need to cascade antimicrobial prescribing guidelines using innovative educational strategies that target all prescribing doctors working in the private sector. Private hospital groups should consider adopting antimicrobial prescribing guidelines that are mandatory for doctors to adhere to. Doctors should be informed of the antimicrobial and surgical prophylaxis prescribing guidelines when applying to work at a private hospital, and sign an agreement to adhere to these guidelines. Restrictions on the empiric use of certain antimicrobials, and regular audits of antimicrobial prescribing with feedback to prescribers should also be implemented to promote rational antimicrobial prescribing.

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Conflicts of Interest. None

Author Contributions. VTJ conceptualized the research, collected and analysed the data, and wrote all versions of the manuscript. SM supervised all aspects of the research and reviewed all versions of the manuscript.

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Chapter 4: Synthesis, Conclusion and recommendations

The purpose of this chapter is to present additional results, synthesis, limitations, and recommendations that were not included in the journal manuscript.

4.1 Additional results

4.1.1 Empiric antimicrobial prescribing

Of the 660 antimicrobials prescribed empirically, 330 (50%) met the criteria for appropriate drug choice, 621 (94%) were prescribed using the appropriate dose, and 482 (73%) were prescribed for the appropriate duration. Of the 382 patients prescribed empiric antimicrobials; only 132 (34.6%) had microscopy, culture and sensitivity tests done. A fifth of the sample (n=132, 20%) were prescribed fluoroquinolones, and four patients were prescribed linezolid (n=2) and teicoplanin (n=2) empirically (Table 3).

Table 3: Empiric antimicrobials prescribed in the surgical and medical wards at a private hospital in KwaZulu-Natal, 2019

Antimicrobial	Frequency (%)
Amikacin	17 (2.6)
Amoxicillin/Clavulanic acid	126 (19.1)
Azithromycin	30 (4.5)
Cefpodoxime	7 (1.1)
Ceftriaxone	106 (16)
Cefuroxime	82 (12.4)
Ciprofloxacin	28 (4.2)
Clarithromycin	14 (2.1)
Clindamycin	19 (2.9)
Doxycycline	1 (0.2)
Ertapenem	11 (1.67)
Fosfomycin	2 (0.3)
Levofloxacin	76 (11.5)
Linezolid	2 (0.3)
Meropenem	4 (0.6)
Metronidazole	29 (4.4)
Moxifloxacin	28 (4.2)
Nitrofurantoin	2 (0.3)
Norfloxacin	1 (0.2)
Oseltamivir	66 (10)
Piperacillin/Tazobactam	4 (0.6)
Teicoplanin	2 (0.3)
Trimethoprim/Sulphamethoxazole	1 (0.2)
Vancomycin	3 (0.3)

4.1.2 Antimicrobial surgical prophylaxis

Cefazolin was prescribed in 17 (21%) of the 81 antimicrobials prescribed for surgical prophylaxis. Twelve (70.6%) of the prescriptions for cefazolin met the criteria for appropriateness in terms of drug choice, dose and duration. Two patients were prescribed intravenous ertapenem (n = 1) and ciprofloxacin (n = 1). The top three disciplines for the prescribing of antimicrobials for surgical prophylaxis were urology (n = 25, 35.7%), general surgery (n = 11, 15.7%) and orthopaedic surgery (n = 10, 14.3%).

Table 4: Antimicrobials prescribed for surgical prophylaxis in the surgical and medical wards at a private hospital in KwaZulu-Natal, 2019

Antimicrobial	Frequency (%)
Amikacin	7 (8.6)
Amoxicillin	1 (1.2)
Amoxicillin/Clavulanic acid	21 (26)
Cefazolin	17 (21)
Ceftriaxone	9 (11.2)
Cefuroxime	13 (16)
Ciprofloxacin	1 (1.2)
Clindamycin	3 (3.7)
Ertapenem	1 (1.2)
Levofloxacin	5 (6.2)
Metronidazole	3 (3.7)

4.1.3 Appropriateness of prescribing according to the discipline of prescriber

The majority (n = 142) of antimicrobials were prescribed by a physician (Table 5). The overall appropriateness of the antimicrobials prescribed differed across disciplines: 60.6% by a physician, 57.9% by a general surgeon, 29.3% by a general practitioner, and 26.3% by an urologist. There was a significant association between the discipline of the prescriber and appropriateness of drug choice ($p<0.001$) and duration of antimicrobial ($p=0.001$), but no significant association with the dose of antimicrobial ($p=0.3$). Physicians and general surgeons were significantly more likely to prescribe an antimicrobial appropriately in comparison to general practitioners (OR = 0.27: $p<0.001$; OR = 0.3: $p<0.001$, respectively) or urologists (OR = 0.23: $p<0.001$; OR = 0.26: $p<0.001$, respectively). There was no statistical difference in the appropriateness of prescribing between physicians and general surgeons.

Table 5: Appropriateness of antimicrobial prescribing according to discipline at a private hospital in KwaZulu-Natal, 2019

Appropriateness category	Prescriber			
	Physician (n = 142)	General practitioner (n = 92)	Urologist (n = 76)	General surgeon (n = 57)
Drug choice	89 (62.7%)	31 (33.7%)	21 (27.6%)	34 (59.6%)
Dose	137 (96.5%)	83 (90.2%)	72 (94.7%)	55 (96.5%)
Duration	114 (80.3%)	54 (58.7%)	45 (59.2%)	44 (77.2%)

4.2 Synthesis

The findings of this study indicate that antimicrobials are prescribed inappropriately both for empiric treatment and for surgical prophylaxis in the surgical and medical wards at a private hospital in SA. The majority of prescriptions for empiric treatment included the correct antimicrobial dose (94%), but only 52.3% of antimicrobials were chosen appropriately. Adherence to guidelines was poor, particularly for surgical prophylaxis, where only 39.5% of antimicrobials met the criteria for appropriateness in terms of drug choice, dose and duration.

Empiric antimicrobials should be broad-spectrum and chosen with the intention of covering the most likely pathogens that are associated with the suspected diagnosis and are therefore based on local prescribing guidelines. [1] Linezolid and teicoplanin were used as empiric treatment however, these antimicrobials should ideally be used as targeted treatment, following microscopy, culture and sensitivity results. In a prospective study conducted at a tertiary hospital in Iran, 256 patients were randomly selected and assessed according to appropriateness of teicoplanin indication, dose and duration. It was found that teicoplanin was prescribed appropriately according to treatment protocols and guidelines in only 21.9% of cases. [2] The susceptibility of *Staphylococcus aureus* to teicoplanin using 100 randomly selected bacterial isolates showed an increasing trend of *Methicillin-resistant Staphylococcus aureus* to teicoplanin in comparison with previous studies conducted in Iran. [2] There is therefore concern that the inappropriate use of teicoplanin will further increase the prevalence of resistant strains of *Staphylococcus aureus*.

In our study, there was a high proportion of fluoroquinolones prescribed as empiric treatment however these antimicrobials are not indicated as first-line treatment for any of the diagnoses in the STG/EML. In 2020, the South African Health Products Regulatory Authority issued a medicine safety information warning in conjunction with various pharmaceutical companies, alerting healthcare professionals to the risk of mitral and aortic regurgitation associated with fluoroquinolones. [3] The European Medicines Agency (EMA) and The Food and Drug Administration (FDA) in the USA have also issued warnings about the adverse effects of Fluoroquinolones. This class of antimicrobial should not be used for common bacterial infections unless there are no other alternative agents. [4]

Our findings have shown that more than half the antimicrobials prescribed for surgical prophylaxis are not aligned to the hospital-specific guidelines. Carbapenems are not indicated as prophylaxis for any type of surgical procedure in the hospital-specific guideline; however ertapenem was prescribed. Ciprofloxacin ear drops are indicated for surgical prophylaxis in the case of grommet insertion; however intravenous ciprofloxacin was used for surgical prophylaxis in this study, and this is not indicated.

We found higher levels of appropriate antimicrobial prescribing among physicians and surgeons compared to general practitioners and urologists. In Iran, general surgery had the highest proportion of appropriate antimicrobial prescribing (73.3%) compared to internal medicine, and the ICUs. [5] A South African study also reported the highest proportion of antimicrobials prescribed appropriately was in general surgery (94%), followed by cardiology (89%), nephrology (80%), pulmonology (70%), and trauma (67%). Only 50% of antibiotics prescribed by gastroenterologists were appropriate and 33% by endocrinologists. [6] Just over a quarter of the antimicrobials prescribed by urologists (26.3%) in this setting were appropriate. The low proportion of appropriate antibiotic prescribing among urologists was also reported in a study conducted in Cape Town in which only 16.3% of antimicrobials prescribed by urologists were appropriately prescribed. [7]

4.3 Additional limitations

Certain study limitations were presented in the journal manuscript in chapter three. Additional limitations with particular focus on systematic sources of error and the methods employed to mitigate them are deliberated here.

4.3.1 Information bias

Information bias occurs as a result of misclassification of exposure or disease status. Recording and coding errors could contribute to the inaccurate assessment of the prescribed antimicrobial. Since all data was collected retrospectively from an electronic patient information system, there may have been some inaccuracies. Firstly, there may have been errors in the patient's demographic or clinical details. This information is unlikely to have affected the results of this study but may have underestimated the proportion of patients with co-morbidities. Secondly, patients may have had inflammatory markers measured prior to their admission, and this would not have been reflected on their current admission record. Thirdly, the data for antimicrobials was obtained from the prescriptions. It is possible that changes to the dose and duration may have been made during ward rounds that would not have been reflected on the original prescription.

Data collection was conducted exclusively by the principal investigator as stipulated by the hospital group's ethics committee. Human error could have affected the accuracy of the data collected however, segments of the data were reviewed and verified at regular intervals. A sample of 47 (10%) of the consolidated dataset was assessed for accuracy to ensure that the data was captured correctly. Confirmation bias is the tendency to interpret information and make a decision according to preconceived ideas, beliefs, values or preferences. Although the decision on appropriateness was made according to evidence-based guidelines, and systems were in place to verify the assessment, there is still a slight possibility of confirmation bias. Differentiation between colonisation and infection was not ascertained. Whether a patient had their antimicrobial de-escalated or not was measured however, de-escalation time was not.

4.3.2 Selection bias

Patients were chosen according to purposive sampling rather than a random sampling method. This can lead to selection bias however, inclusion and exclusion criteria were applied to all participants, thereby limiting selection bias.

4.3.3 Confounding

Patients' recent use of antimicrobials at home, and any microscopy, culture and sensitivity testing that might have been done prior to hospital admission, are possible confounders that were not assessed in this study. For some patients, it may not have been possible to obtain a specimen to send for microscopy, culture and sensitivity testing. The renal function of a

patient, allergies, and co-morbidities may have affected the choice of the antimicrobial prescribed. Loading doses, continuous infusions, off-label dosing and the spectrum of cover of the antimicrobial agent were not considered when determining appropriateness. Since the research was retrospective in nature, blood loss could not be taken into account when assessing patients for the appropriateness of surgical prophylaxis.

4.4 Conclusion

There was a high prevalence of inappropriately prescribed antimicrobials for empiric treatment and for surgical prophylaxis in the medical and surgical wards in a private hospital setting. The choice of drug was not in line with the recommendations from the STG/EML in the majority of cases. Prescribers did not adhere to the surgical prophylaxis guideline specific to the hospital group, particularly with regards to drug choice and duration. The use of microscopy, culture and sensitivity tests to guide antimicrobial prescribing was not commonly practiced, and de-escalation was not practiced efficiently even when it was warranted.

4.5 Additional recommendations

The manuscript included some of the recommendations based on the findings of this study. This section expands on some these recommendations and includes additional recommendations.

4.5.1 Initiatives to improve antimicrobial prescribing at the hospital level

a) A designated, multi-disciplinary antimicrobial stewardship committee should be nominated to:
- meet regularly to provide updates on the hospital's antimicrobial consumption data with a link to microbiological data generated from the hospital; and
- include de-escalation as a measurable objective, and monitor whether de-escalation is being practiced;
- Hospital management should incorporate attendance of antimicrobial stewardship meetings into the service agreement between the hospital and the doctor.

b) Interventions to improve drug choice should specifically target prescribers and should include the provision of information in the form of webinars, continuing professional development talks and lectures from microbiologists and infectious disease specialists;

c) The clinical pharmacist should participate in ward rounds routinely, and conduct audits of antimicrobials prescribed for surgical prophylaxis.

4.5.2 Initiatives to improve antimicrobial prescribing within the hospital group

a) A 'traffic-light system' should be considered to preserve the efficacy of available antimicrobials. Antimicrobials are classified as green, orange or red. Green antimicrobials have no explicit restrictions on their use. Orange antimicrobials are restricted and can only be prescribed if specific criteria are met, and red antimicrobials are highly restricted and require discussion with an infectious disease physician or clinical microbiologist before commencement;

b) Ensure that all relevant healthcare workers (surgeon, anaesthetist and surgical and theatre nurses) have read the surgical prophylaxis guidelines and sign an agreement to adhere to these guidelines;

c) Review and update antimicrobial prescribing guidelines regularly. A multi-disciplinary team should be involved, with at least one representative from each hospital.

4.5.3 Initiatives to improve antimicrobial prescribing at a national level

a) National awareness should be created for healthcare workers in the public and private sectors on the importance of adhering to antimicrobial guidelines and the long term repercussions of antimicrobial resistance;

b) Educational initiatives during World Antibiotic Awareness Week should be standardised between the public and private sectors;

c) A national antimicrobial stewardship committee should be established in response to national guidelines that includes representation from both the public and the private sectors to ensure appropriate antimicrobial prescribing and limit the emergence of resistant bacteria.

4.5.4 Recommendations for further research

- A similar study with a prospective study design and more detailed clinical data may provide better evidence on the appropriateness of antimicrobial prescribing.
- Audits of antimicrobial prescribing in other wards should be conducted to assess whether antimicrobials are prescribed appropriately in other patient cohorts and paediatric patients.

- Qualitative studies may provide a better understanding of prescribers' choice of drugs.
- Similar studies should be conducted in the public sector to draw comparisons between the public and private sectors with regards to antimicrobial prescribing practices.

4.6 Summary

The last chapter highlighted additional results, synthesis, additional limitations, underlined the conclusions drawn from the study, and provided recommendations for corrective action as well as for future research.

References: Synthesis, Conclusions and Recommendations

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APPENDICES

Appendix 1 – Data collection tool

Ward							Additional notes			
Medical or surgical discipline										
Gender										
Age										
Diagnosis										
Length of hospital stay										
Co-morbidities										
Discharged on antibiotics (Y/N)										
Name of antibiotic prescribed	Date started	Date stopped	Dose	Frequency	Duration	Surgical prophylaxis (S) Empiric treatment (E) Targeted treatment (T)	Signs of infection present: Yes (Y) No (N) Not Applicable (N/A) Unable to determine from the records (U)	Specimen source	Type of microorganism/s cultured	De-escalated: (Y/N)

Appendix 2 – Gatekeeper permission

National Health Research Ethics Committee registration: REC 251015-048

REF: 11122019/2

11 December 2019

Dear Valencia Jacob

RE: APPLICATION TO CONDUCT RESEARCH:

Title of study: Antibiotic prescribing in the medical and surgical ward at a private hospital in KwaZulu-Natal

The Health Research Ethics Committee of [redacted] hereby grants permission with no conditions for your study to be conducted at [redacted] **Hospital.**

1. If patient or institutional confidentiality is breached, [redacted] is entitled to withdraw this permission immediately. The Higher Education institution under which the research is taking place will be notified, and [redacted] reserves the right to take legal action against you, should the company feel that this is warranted.

2. An electronic copy of the research report must be submitted to the [redacted] Research Ethics Committee prior to publication. Failure to do this may result in permission to continue to examination being withdrawn. The Higher Learning institution will be notified of this withdrawal.

3. No direct reference may be made to [redacted] its subsidiaries or any of its facilities or institutions in the research report or any publications thereafter. The Company and its facilities, patients and staff must be de-identified in the study, and remain so for any other studies which may utilise this information.

4. The research must be completed within the time allotted by the Higher Learning institution. If the research is being done in an individual capacity by an employee of the [redacted] the research must be conducted within one year of permission being given by the Company, OR the proposed time period must be specified in the proposal, and approved. Permission may be withdrawn if the research extends beyond the approved time period.

5. [redacted] will not take responsibility for any unforeseen circumstances within its institutions which may materially change the context and potential outcomes of a student's research. Should this occur, the student will be required to approach their Higher Learning institution for guidance around alternatives.

6. Placement of the electronic research report and any publications on the Company's research register after approval by the associated Higher Education Institution.

7. [redacted] will not be liable for any costs incurred during or related to this study.

Yours sincerely,

On behalf of the Health Research Ethics Committee

Appendix 3 – Ethical approval from the Biomedical Research and Ethics Committee

UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI

18 December 2019

Ms VT Jacob
School of Health Sciences
College of Health Sciences
Valjacob14@gmail.com

Dear Ms Jacob

Protocol: Antibiotic prescribing in the medical and surgical ward at a private hospital in KwaZulu-Natal
Degree: Masters in Pharmacy Practice
BREC reference number: BE457/19

EXPEDITED APPLICATION: APPROVAL LETTER

A sub-committee of the Biomedical Research Ethics Committee has considered and noted your application received on 05 July 2019.

The study was provisionally approved pending appropriate responses to queries raised. Your response received on 12 December 2019 to BREC letter dated 17 July 2019 has been noted by a sub-committee of the Biomedical Research Ethics Committee. The conditions have been met and the study is given **full ethics approval** and may begin as from 18 December 2019. **Please ensure that outstanding site permissions are obtained and forwarded to BREC for approval before commencing research at a site.**

This approval is valid for one year from **18 December 2019.** To ensure uninterrupted approval of this study beyond the approval expiry date, an application for recertification must be submitted to BREC on the appropriate BREC form 2-3 months before the expiry date.

Any amendments to this study, unless urgently required to ensure safety of participants, must be approved by BREC prior to implementation.

Your acceptance of this approval denotes your compliance with South African National Research Ethics Guidelines (2015), South African National Good Clinical Practice Guidelines (2006) (if applicable) and with UKZN BREC ethics requirements as contained in the UKZN BREC Terms of Reference and Standard Operating Procedures, all available at http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx.

BREC is registered with the South African National Health Research Ethics Council (REC-290408-009). BREC has US Office for Human Research Protections (OHRP) Federal-wide Assurance (FWA 678).

The sub-committee's decision will be **noted** by a full Committee at its next meeting taking place on **11 February 2020.**

Yours sincerely

Prof V Rambiritch
Chair: Biomedical Research Ethics Committee

cc: Postgraduate Admin: nenep1@ukzn.ac.za Supervisor: mahomeds@ukzn.ac.za

Biomedical Research Ethics Committee
Professor V Rambiritch (Chair)
Westville Campus, Govan Mbeki Building
Postal Address: Private Bag X54001, Durban 4000
Telephone: +27 (0) 31 260 2486 **Facsimile:** +27 (0) 31 260 4609 **Email:** brec@ukzn.ac.za
Website: http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx

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UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI

20 October 2020

Ms VT Jacob
School of Health Sciences
College of Health Sciences
Valjacob14@gmail.com

Dear Ms Jacob

Protocol: Antibiotic prescribing in the medical and surgical ward at a private hospital in KwaZulu-Natal
Degree: Masters in Pharmacy Practice
BREC reference number: BE457/19
New title: ***Antibiotic prescribing in the surgical and medical wards at a private hospital in KwaZulu-Natal"***

We wish to advise you that your response received on 16 October 2020 to BREC letter dated 16 September 2020 has been noted by a subcommittee of the Biomedical Research Ethics Committee.
Your correspondence received on 11 September 2020 submitting an application for amendments listed below for the above study has now been **approved** by a subcommittee of the Biomedical Research Ethics Committee.

Amendments noted and approved:

(i) Inclusion of the female medical ward.
(ii) Change in title to the new title above.
(iii) Change period of study from 3 months to 2 months.

The committee will be advised of the above at its next meeting to be held on 10 November 2020.

Yours sincerely

.....
Ms A Marimuthu
(for) Prof D Wassenaar
Chair: Biomedical Research Ethics Committee

UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI

20 November 2020

Ms VT Jacob
School of Health Sciences
College of Health Sciences
Valjacob14@gmail.com

Dear Ms Jacob

Protocol: Antibiotic prescribing in the surgical and medical wards at a private hospital in KwaZulu-Natal"
Degree: Masters in Pharmacy Practice
BREC reference number: BE457/19
New title: ***"Antimicrobial prescribing in the surgical and medical wards at a private hospital in KwaZulu-Natal"***

We wish to advise you that your correspondence received on 17 November 2020 submitting an application for amendments to change the title to the above new title for the above study has been **noted and approved** by a subcommittee of the Biomedical Research Ethics Committee.

The committee will be advised of the above at its next meeting to be held on 08 December 2020.

Yours sincerely

.....
Ms A Marimuthu
(for) Prof D Wassenaar
Chair: Biomedical Research Ethics Committee

Appendix 4 – South African Medical Journal acceptance for publication

Ref.: SAMJ15403
Antimicrobial prescribing in the surgical and medical wards at a private hospital in KwaZulu-Natal, South Africa, 2019
South African Medical Journal

Dear Miss Jacob,

We are pleased to tell you that your work has now been accepted for publication in South African Medical Journal. Before we send to the production team however, please could you attend to the following technical issues:

1. Please provide DOIs where possible. Please refer to the SAMJ author guidelines for details
2. Figures to be provided in pdf format.

Please send your amended manuscript to claudian@samedical.org

Please find payment form attached herewith. As soon as proof of payment and the completed form have been received, we will send your article into production. (Please note that we are unable to process American Express card payments). Please send proof of payment to claudian@samedical.org
Thank you for submitting your work to the journal.

Best wishes

Bridget Farham, PhD
Editor
South African Medical Journal

Appendix 5 – Turnitin report

Valencia_dissertation_28012021_for_turnitin.docx

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3	Dipika Chunnilall, Abdool Peer, Indirani Naidoo, Sabiha Essack. "An evaluation of antibiotic prescribing patterns in adult intensive care units in a private hospital in KwaZulu-Natal", Southern African Journal of Infectious Diseases, 2015 Publication	1%
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