

https://dspace.org/

The usage of antibiotics in paediatric patients while admitted to the intensive care unit at a public tertiary hospital

Sinyela, Nkhumiseni

2018
https://hdl.handle.net/10539/25449

Downloaded from a DSpace repository. https://dspace.org/



The Usage of Antibiotics in Paediatric Patients while Admitted to the Intensive Care Unit at a Public Tertiary Hospital

Research report by:

Nkhumiseni Sinyela

Student Number 336759

Supervisor:

Deanne Johnston

Department of Pharmacy and Pharmacology

A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, in partial fulfillment for the degree of Masters of Science in Medicines: Pharmaceutical Affairs

June 2018

Declaration

I, Nkhumiseni Sinyela declare that this research is my own work. It is being submitted for the degree of Master of Science in Medicine: Pharmaceutical affairs at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

Signature ……..

Date……

Acknowledgement

I would like to acknowledge my Supervisor, Deanne Johnston as well as ICU and record retention room staff of Charlotte Maxeke Hospital for their assistance.

Table of Content **Page Number**

DECLARATION ii

ACKNOWLEDGEMENT iii

LIST OF FIGURES vii

LIST OF TABLES viii

LIST OF ABBREVIATIONS ix

ABSTRACT x - xi

CHAPTER 1: INTRODUCTION

1.1 Introduction 1

1.2 Background 1

1.3 Antibiotics Use in Paediatrics 1 - 2

1.4 Antibiotics Availability in Hospital 3 - 4

1.5 Aim and Objectives 5

1.6 Conclusion 5

CHAPTER 2: LITERATURE REVIEW

2.1 Introduction 6

2.2 Antibiotics Resistance 6 - 8

2.3 Antibiotics Usage in Paediatrics 8 - 9

2.4 Antibiotic Resistance in Paediatrics 9 - 10

2.5 Antibiotic Stewardship 10 - 12

2.6 Antibiotic Stewardship in South Africa 12

2.7 Conclusion 13

CHAPTER 3: METHODOLOGY

3.1 Introduction 14

3.2 Purpose of the Study 14

3.3 Study Site 14 - 15

3.4 Study Design 15

3.5 Study Period 15

3.6 Study Population and Sample Selection 16

3.7 Data Collection 16
3.8 Statistical Analysis 17
3.9 Reliability and Validity of Data 17
3.10 Ethical Considerations 17
3.11 Conclusion 18
CHAPTER 4: RESULTS
4.1 Introduction 19
4.2 Demographic Data Comparison 19 - 20
4.3 Antibiotics Prescribed and Frequency 20 - 21
4.4 Number of Antibiotics Prescribed Per Patient 22
4.5 Concurrent Use of Antibiotics 23 - 24
4.6 Indications of Prescribed antibiotics in terms of it being either Prophylactic (P), empiric (E) or definitive (D) 24
4.7 Calculations of Dosages 25 - 29
4.8 Average duration of Antibiotics 30 - 31
4.9 Missed Doses 32
4.10 Hang Time 32 - 33
4.11 Blood Cultures 33- 34
4.12 Infection Markers 34
4.13 Summary of Diagnosis 34 - 35
4.14 Conclusion 35
CHAPTER 5: DISCUSSION
5.1 Introduction 36
5.2 Antibiotics Prescribed and Doses 36 - 39
5.3 Duration of Antibiotics 39 - 40
5.4 Antibiotics Dosing 40 - 41
5.5 The importance of hang Time 41 - 42
5.6 Culture ordering Practice 42
5.7 The value of Infection Marker (CRP) 42 - 43
5.8 Conclusion 43

CHAPTER 6: STUDY LIMITATION, RECOMMENDATIONS AND CONCLUSION

6.1 Introduction	44
6.2 Study Limitations	44
6.3 Recommendations	44 - 45
6.4 Conclusion	45
6.5 Conflict of interest	45
6.6 Funding	45
REFERENCES	46 – 52
APPENDICES	
Appendix 1: Modified version of the South African Antibiotics Prescription Chart	53
Appendix 2: Hang time	54
Appendix 3: Diagnosed conditions	55 - 56
Appendix 4: Protocol Approval	57
Appendix 5: Ethical Clearance letter	58
Appendix 6: Hospital approval letter	59
Appendix 7: Doses given versus calculated SAMF doses for 2016	60 - 61
Appendix 8: Doses given versus calculated SAMF doses for 2017	62 – 64

List of Figures:

Figure 1: Ordering process followed for antibiotics 4

Figure 2: Patients admission process flow 14

Figure 3: Number of antibiotics patients received during Admission to ICU 21

Figure 4: Duration of prescribed antibiotics (days) 30

List of Tables:

Table 1: CMJAH Pediatric ICU empiric antibiotics treatment Guideline 14

Table 2: Demographic data comparison 18

Table 3: Age sub categorization 19

Table 4: Antibiotics prescribed and frequency 20

Table 5: Antibiotics administered concurrently in 2016 22

Table 6: Antibiotics administered concurrently in 2017 23

Table 7: Doses lower than calculated SAMF doses in 2016 25

Table 8: Doses higher than SAMF calculated doses in 2016 26

Table 9: Doses lower than calculated SAMF doses in 2017 27

Table 10: Doses higher than SAMF calculated doses in 2017 28

Table 11: Average duration of prescribed antibiotics in 2016 and 2017 29

Table 12: Number of doses missed 31

Table 13: Hang time 32

Table 14: Culture specimen ordered

Table 15: Summary of diagnosed condition 33

List of Abbreviations

ASPs: Antibiotics Stewardship Programmes

CMJAH: Charlotte Maxeke Johannesburg academic hospital

CoNS: Coagulase-negative Staphylococci

CRP: C- Reactive Protein

EOS: Early Onset Sepsis

EML: Essential Medicine List

ESBL: Extended-Spectrum Beta Lactamase

FDA: Food and Drug Administration

ICU: Intensive Care Unit

LOS: Late Onset Sepsis

MDR: Multi Drug-Resistant

WHO: World Health Organization

SAASP: The South African Antibiotic Stewardship Programme

STGs: Standard Treatment Guidelines

Abstract

Background: The overuse and misuse of antibiotics decreases their effectiveness and results in increasing bacterial resistance which is considered an international public health crisis. Antibiotics are one of the most commonly used groups of medicines in peadiatric patients however there are limited data available on the usage of antibiotics in paediatrics globally but especially in South Africa. The aim of this study was to conduct a retrospective review of antibiotics used in paediatric patients in intensive care.

Method: This study reviewed antibiotic therapy from patient charts in the Intensive Care Unit at Charlotte Maxeke Johannesburg Academic hospital. The review was done from 15 January 2016 to 15 February 2016 and 15 January 2017 to 15 February 2017.

Results: There were 40 files reviewed for 2016 and 55 files for 2017. Most patients (2016: 78% and 2017: 60%) were neonates aged between 0 -3 months. There were 15 antibiotics prescribed in 2016 and 2017 that differed between the two study periods. The most frequently prescribed antibiotics in 2016 were: vancomycin (19%), imipenem (18%), ampicillin (11%) and gentamycin (11%). In comparison in 2017, the most frequently prescribed antibiotics were meropenem (21.7%) vancomycin (20.8%) and co-amoxiclav (11.7%). In both periods majority of patients received two antibiotics as therapy during their ICU stay, 47.5% in 2016 and 40% in 2017. The average numbers of days in ICU were 5 days in 2016 and 4 days in 2017. Diagnosis classifications were similar between the two study periods. Cultures (blood) were ordered in 73% (2016) compared to 75% (2017). C-reactive protein samples were taken from 85% of patients in 2016 and 82% in 2017. In 2017, there were 46.2% (n=36) of doses with a hang time less than 60 minutes and 32.5% (n=26) in 2016.

Conclusion: This study showed that most antibiotics were prescribed empirically with imipenem and vancomycin the most used combination antibiotic therapy in 2016, meropenem and vancomycin in 2017. Majority of patients received two antibiotic therapies during their ICU stay.

CRP and cultures (blood) were frequently ordered and hang time mostly documented. Prescription of antibiotics was mostly compliant with the unit antibiotic prescription guidelines.

Chapter 1

INTRODUCTION

1.1 Introduction

This chapter will provide an overview of the importance of antibiotics, global concerns related to overuse and inappropriate use of antibiotics as well as concerns related to antimicrobial resistance. It also briefly discusses antibiotic use in paediatric patients, challenges associated with antibiotic use in paediatrics, serious adverse events, antimicrobial stewardship programme and availability of antibiotics in hospital as well as outlining the aim and objectives of this study.

1.2 Background

Antibiotics, discovered in the early 20th century, considerably changed healthcare and improved medicine globally. They reduced morbidity and mortality from infectious diseases. Optimal utilisation of the existing and recently developed antibiotics is important in ensuring continuous benefits and provision of effective care to patients (Barlam *et al,* 2016).

Antibiotics are important for the treatment of very sick patients such as those admitted in the Intensive Care Units (ICUs), those with weakened immune systems due to transplantation, chemotherapy or HIV, and those with bacterial infections. Antibiotics are frequently prescribed to critically ill patients worldwide and have significantly improved patient's management by improving clinical outcomes of infections (Paruk *et al,* 2012 Magsarili *et al,* 2015). Recent evaluation suggests that the discovery and use of antibiotics have brought about an additional 20 years of life expectancy (Mendelson, 2015).

1.3 Antibiotic use in Paediatrics

Antibiotics are lifesaving therapy for children with bacterial infections and are the most commonly recommended treatment to children (Rogawaski *et al,* 2017). Antibiotics are also the most frequently prescribed medications in neonatal ICU with nearly 1% of neonates receiving antibiotic therapy in developed countries (Tzialla *et al,* 2015).

There are challenges associated with the use of antibiotics within the paediatric population (Magsarili *et al,* 2015). Those challenges include the fact that children have special medical needs which include the need for different antibiotic dosing requirements and they may react

differently to treatment. Furthermore, there are also difficulties with regards to confirmation of diagnosis in infants and children since they frequently present with non-specific signs and symptoms.

There is increasing evidence that improper or excessive usage of antibiotics in neonatal ICU leads to serious adverse event (Cantey and Patel, 2014). Those serious adverse outcomes include the emergence of multidrug-resistance (MDR) organisms linked to endemic or epidemic infections, increased rates of invasive candidiasis, necrotising enterocolitis, late onset sepsis or death. Infection with antibiotic resistant organisms is associated with several challenges such as: delay in commencing with effective antibiotic therapy, limited alternative treatment options, increased morbidity and death rate, lengthen hospital stay and increased costs of hospitalization (Ballot *et al,* 2012).

Most antibiotics used in infants do not have Food and Drug Administration (FDA) labelling resulting in clinicians often prescribing these antibiotics "off-label" to infants without clinical trial data to support dose selection. Ampicillin and clindamycin are examples of commonly used antibiotics in infants even though the FDA label has no specific dosing for infants and does not address dosing in premature infants and infants less than one month old (Pineda and Watt, 2016).

Few registered medications have dosing indications for children and infants and therefore understanding of the usage or drug administration in children and infants becomes important to the practice of medicines in peadiatrics (Mabila *et al,* 2016). There is also a lack of data on antibiotics utilisation in children (Palcevski *et al,* 2003). In addition, both Shipp *et al (*2016) and Patel and Saiman (2012) pointed out the fact that there are limited guidelines on antibiotic stewardship in neonatal ICU. They further suggested that antibiotic stewardship principles can be implemented in the neonatal ICU as well. Those principles include correctly selecting patients who requires antibiotic treatment, use of locally available epidemiology data to assist with choice of empiric therapy, not prescribing antibiotics with overlapping activity, using culture results to modify antibiotics dosing, monitoring adverse events and optimising dosage, appropriate administration route and treatment duration. Despite positive results associated with antibiotics stewardship programmes (ASPs) in adult patients, there is a lack of data related to experiences of ASPs in neonatal settings (Tzialla *et al,* 2015).

1.4 Description of antibiotic availability in the hospital

The hospital in which the study was conducted is a public tertiary hospital. As a public institution with limited financial resources, not all antibiotics registered in South Africa are available for prescription in the hospital. Prescribers are generally required to adhere to the Essential Medicine List (EML, 2014 edition) while prescribing. The process of prescribing antibiotics in the unit is illustrated in Figure 1. Antibiotics are prescribed on the ICU chart by the attending physician. For those antibiotics that are available in ICU stock, dosing can occur immediately. Antibiotics not available from ICU stock are ordered from the pharmacy on a per patient basis, accompanied by appropriate documentation. The hospital has a list of specific antibiotics, for example colistin, where the prescriber needs permission from a specialist or the head of the unit to prescribe the antibiotic, furnished with supporting documentation such as culture results. The antibiotics ordered are recorded manually when dispensed by the pharmacy.

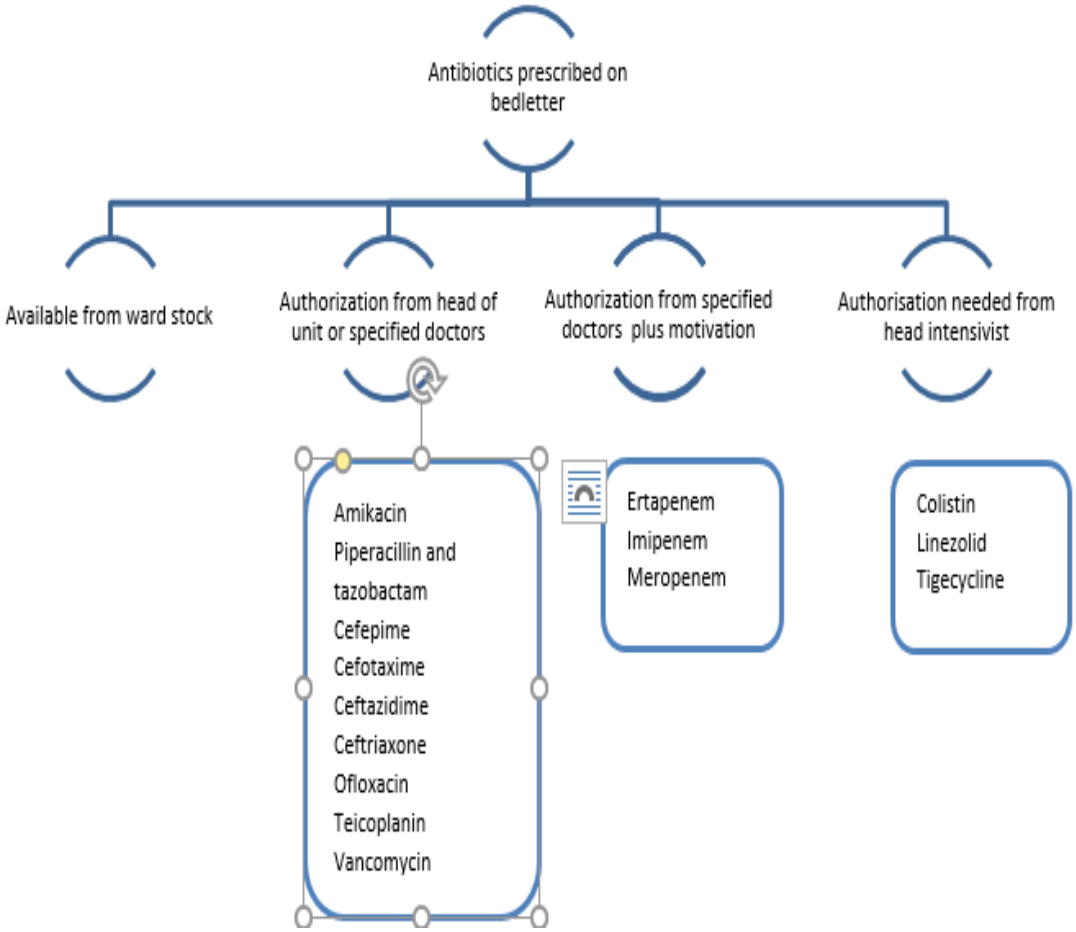


Figure 1: Ordering process followed for antibiotics

There is limited information regarding the usage of antibiotics in paediatric patients, especially in South Africa. This study will help fill this gap by documenting the usage of antibiotics in a paediatric ICU.

1.5 Aim and Objectives

Therefore, the aim of the study was to conduct a retrospective record review of antibiotics utilised in paediatric patients in the ICU. To achieve this aim, the following objectives were outlined:

a. To record the antibiotics prescribed in terms of frequency, dosage and duration.
b. To categorise the prescribed antibiotic indications in terms of it being prophylactic (P), or empiric (E) or definitive (D).
c. To document if cultures and specific infection markers such as C-reactive protein (CRP) were ordered in relation to antibiotic prescribed.
d. To calculate the hang time of antibiotics prescribed.
e. To compare the two study periods in 2016 and 2017.

1.6 Conclusion

This chapter provided a short introduction to the study and described the process in which antibiotics are available in the hospital. The chapter concludes with the stating of the problem statement and the outlining to the study's aim and objectives.

The next chapter provides an in-depth review of the literature.

Chapter 2

LITERATURE REVIEW

2.1 Introduction

This chapter reviews the literature relating to the emergence of antimicrobial resistance, mechanisms of resistance as well global concerns of increasing antimicrobial resistance. It will also discuss the importance of global interventional strategies such as antimicrobial stewardship programmes to curb the emergence of antimicrobial resistance.

2.2 Antibiotic Resistance

Antibiotic use comes with toxicities and adverse events, the most critical being antibiotic resistance (Magsarili *et al,* 2015). As a result of the overuse of antibiotics, there is a need for effective control and regulation of antibiotics to avert antibiotic resistance (Chunnilall *et al,* 2015). Processes and procedures should be in place to ensure that antibiotics are properly prescribed, dispensed and that an appropriate route of administration is selected.

There is an existing worldwide apprehension that there is a drive towards the post antibiotic era brought about by several years of imprudent antibiotic use which is causing the emergence of multi drug resistant bacterial infections (Boyles *et al,* 2013).

There is a global worry regarding overuse, misuse and inappropriate use of antibiotics which has resulted in an international growth in bacterial resistance to antibiotics. Recently, the worldwide surge in bacterial resistance to antibiotics has led to a concerning situation where normal infections that were previously easy to treat have become difficult to treat, requiring second line or third line antibiotics. Some of the common infections have become incurable (Boyles *et al,* 2017).

Resistance to antibiotics is considered to be the greatest current public health threat. It has been estimated that if the rate of increase in drug resistance is not slowed, deaths associated with drug resistance will increase to 10 million annually globally by 2050 (Goff *et al,* 2017). There are also

cost implications to health care systems related to antibiotics resistance. This is due to the excessive cost of second and third line antibiotics and additional hospital stay by patients.

The mechanisms in which bacteria have become resistant to antibiotics vary and are multifaceted. Currently, bacteria have developed resistance to numerous categories of available antibiotics. The most frequent form of resistance is the one which is acquired and conveyed horizontally through the conjugation of a plasmid. Novel mechanisms of resistance have resulted in concurrent development of resistance to various antibiotic classes producing dangerous MDR bacteria strains, also known as "superbugs" (Alanis, 2005). Selective pressure by antimicrobial drugs is by far the most central cause for the growth of microbial resistance (Shankar *et al*, 2003).

There is concern related to the increasing spread of colistin resistance. Sprenger and Fukuda (2016) indicated that resistance to colistin develops through two mechanisms. The first one is triggered by increased colistin usage, resulting in emergence and spreading of colistin-resistant mutants normally related to chromosomal mutation. The second one is associated with the discovered plasma-mediated polymixin resistance gene, mcr-1, in *Escherichia coli* isolated from animals in Shanghai.

Bacterial resistance continues to evolve, leading to some pathogens that were considered routine to treat becoming resistant to almost all antimicrobial agents There are great concerns related to the emergence of vancomycin resistance in *Staphylococcus aureus* and carbapenems resistance in strains of *Enterobacter* and *Klebsiella pneumoniae* (Brink, 2005).

Clinical practice has shown that broad spectrum antibiotics predispose patients for resistant bacteria than narrow spectrum antibiotics (Isaacs, 2006). Multi-resistant bacteria are causing several challenges in neonatal ICUs. There are concerns that the use of ampicillin and third generation cephalosporin selects for Gram-negative bacilli which increases extended spectrum β-lactamases (ESBL) production. ESBLs render microorganism resistant to many antibiotics. Similarly, carbapenems, such as imipenem and meropenem are used in laboratories to promote the production of β-lactamases. Therefore the over usage of imipenem and meropenem could

select β lactamase- producing organisms, as well as microorganisms which are not susceptible to imipenem.

2.3 Antibiotic usage in paediatrics

It is estimated that at least 40% (3.1 million neonate deaths each year) of under-five deaths globally happens in the neonatal phase (Eman *et al*, 2015). Majority of these deaths, approximately 1 million, are related to infectious causes including neonatal sepsis, meningitis and pneumonia.

Infections are common and significant complications in the paediatric population. Most infants admitted to ICUs are exposed to antibiotics. There is a lack of infant's specific dosing regimens and as such doses are frequently extrapolated from data in adults or older children. This may result in an increased risk of drug adverse events and lack of clinical effectiveness. It is important to determine appropriate dosing regimens for this population (Pineda and Watt, 2016).

Nosocomial infections are one of the most common causes of the increased death rate and morbidity in neonatal ICUs (Mohammed and Seifi, 2014). Mohammed and Seifi pointed out that nosocomial infections include blood stream infections, pneumonia, urinary tract infections, meningitis, secondary skin infections, eye, ear, nose or throat infections. They further noted that the contributing microorganisms could be bacterial, viral, or fungal in origin. Furthermore, they indicated that microorganisms causing neonatal infections are not the same from country to country and they can also differ within different ICUs as well as changing within years in the same setting. This variation requires ongoing effective surveillance to evaluate the epidemiology, associated risk factors and causative organisms in order to understand the epidemiology of nosocomial infection locally.

Strong emphasis should be placed on the importance of optimising the use of the current antibiotics in paediatrics (Doofaeff *et al,* 2016). Antibiotic use can be optimised by making use of data from pharmacokinetic studies. There are several challenges associated with conducting pharmacokinetic studies in critical ill neonate and paediatric patients. These include the small blood volumes in children, limited study consent rates, challenges with the measurement of drug

concentration due low drug volume and limited experience in the field of paediatric modelling. They concluded that current antibiotic doses for critically ill paediatric patients are frequently suboptimal because of poor understanding of different pharmacokinetic properties.

There are other challenges associated with prescribing antibiotics to the paediatric populations such as lack of suitable formulations or doses, which leads to the need for the preparations of extemporaneous formulations and diagnostic uncertainty since infants and children commonly present with non-specific symptoms (Magsarili *et al,* 2015). In addition, they indicated challenges with paediatric patients in ensuring optimal dosing in relation to their age, body size and disease condition.

Leroux *et al* (2015) further pointed out that few antibiotics have validated clinical trials data to get a marketing authorization for neonatal prescription and the majority of them are used off-label. They indicated that there is a shortage of clinical trials data to support and ensure optimal dosing recommendations for almost all antibiotics in neonates. They further pointed out that this is demonstrated by the two examples of amikacin and metronidazole. They showed that they were 19 different neonatal dosing regimens proposed for amikacin in literature. In addition, they observed that there were only 2 population pharmacokinetic clinical trials published with few number of neonates (n=32) even though the drug has been used for several years as a treatment for complicated abdominal infections in neonates.

Brinkman *et al* (2015) pointed out that vancomycin, which is one of the most frequently prescribed antibiotics in paediatric ICU is associated with adverse effects such as nephrotoxicity and ototoxicity at a suboptimal concentration level. They further pointed out that ICU patients have a greater possibility for development of nephrotoxicity than non-ICU patients.

2. 4 Antibiotic Resistance in peadiatrics

Antibiotics resistance in bacteria is continually evolving and presents an increasing burden in all populations, including children. Prolonged duration of antibiotic use in the neonatal population promotes many disease stimulating alterations such as changes in the gut microbiota. Modifications in the gut flora causes reduced gut microbial variety which is associated with early side effects such as necrotizing enterocolitis and possible life-long consequences such as

increased possibility for obesity and inflammatory disease conditions**.** In addition, antibiotic therapy in neonatal phase was connected to reduced wealth of protective commensal anaerobic bacteria which offer colonization resistance against antibiotics resistant bacteria and potentially pathogenic bacteria like Enterobacteriaceae and *Clostridium difficile*. Over usage of antibiotic during neonatal period is generally linked with an added risk of antibiotic resistance development, especially ESBL producing Gram-negative bacteria and other multi drug resistance (MDR) bacteria (Fjalstad *et al,* 2017*).* Medernach and Logan (2017) reported that antibiotic resistant infections are growing in children globally as a result of the selective pressure offered by the inappropriate usage of broad-spectrum antibiotics. They further indicated that there are high cases of adverse events of polymyxins (polymyxin B and colistin) in children such as neurotoxicity and nephrotoxicity.

2.5 Antimicrobial stewardship

The United Nations and the World Health Organization (WHO) have designated antimicrobial resistance as a main health priority. They have developed action plans to reduce antimicrobial resistance in all health settings. They advocated for the establishment of institutional APSs as a key intervention to reduce antibiotic consumption in hospitals and to address high rates of MDR bacteria (da Silver *et al*, 2017). WHO further emphasized the need for coordinated interventions and joint approach. The aim of the approach is to support poor countries in optimizing antibiotic usage through learning and stewardship programs. This will require the need for the formulation of strategies and road map to combat the increase of antibiotic resistance. The plan centred on the need for APS (Goff *et al,* 2017).

Lee *et al* (2016) further pointed out that the primary goal for ASPs is to improve patient outcomes as well as reducing the negative after effect of antibiotic use. The secondary goals of reducing antibiotic purchasing and healthcare cost related to the antibiotic resistance are the expected favourable consequences of appropriate prescribing

Sameer and Saiman (2012) also mentioned that the main aim of antimicrobial stewardship is to optimize clinical outcome while reducing adverse consequence of antimicrobial use, including side effects and the emergence of resistance. They further stated that primary focus of ASPs

should be a continuous assessment of the need for antibiotics, the proper choice of dose regimen, and the selection of appropriate route of administration.

Goff *et al* (2017) discussed several core strategies for implementation of ASPs. Those discussed strategies included prospective audit and feedback, formulary restriction and preauthorisation. Several other supplemental strategies and interventions such as education, guidelines, reassessment of the choice/duration, antibiotic order form, dosage optimisation and selection of oral route of administration were also highlighted.

In addition, Spyridis *et al* (2015) also indicated that important action required to address the problem of antimicrobial resistance is to evaluate and modify the way antibiotics are used. They also emphasized the fact that antimicrobial stewardship programme (ASPs) intend to promote the appropriate use of antibiotics. They further discussed the urgent need for establishment of ASPs in paediatric's departments. They pointed out that one of the most important components of ASPs is the development and implementation of evidence-based antibiotic prescribing guidelines providing a standard approach to the optimal selection, dosage and duration of antibiotic therapy. Few European hospitals participating in their study have comprehensive antibiotic prescribing guidelines for common paediatric infections and majority uses a wide mixture of reference sources. Guidelines most commonly available were those for upper respiratory tract infections, urinary tract infection and normal sepsis.

Ballot *et al* (2012) added that antibiotic stewardship, including appropriate selection and administration of antibiotics, de-escalation of therapy, and a multidisciplinary team approach to managing neonatal sepsis, is recommended to limit inappropriate antibiotic use and prevent the development of antimicrobial resistant organisms.

Cantey and Patel (2014) discussed neonatal ICU antibiotics management strategies which are necessary to optimize clinical outcomes while minimizing the unintended consequences of antibiotic therapy. They pointed out several useful antimicrobial metrics for neonatal ICU including: avoiding unnecessary antibiotic use, reducing broad-spectrum antibiotic use and avoiding inadequate therapy. They further discussed the following suggested strategies for stewardship in neonatal ICU: diagnosis; empiric therapy; dose optimization; prescriber audit and feedback and duration of therapy.

Ensuring that patients receive antibiotics timeously from recognition of onset of infections is part of comprehensive management strategy to ensure timely intervention as part of the antibiotic stewardship strategies. Mok K *et al* (2014) recommended starting of broad-spectrum antibiotics within 1 hour of recognition of severe sepsis or septic shock. They pointed out that there was increasing evidence supporting that promptly and appropriate antibiotic therapy improves morbidity and mortality. This was also supported by Messina *et al* (2015) study which showed that ensuring that patients receive antibiotics timeously is important in the treatment of patients with infections. They indicated that the rate of death of patients increases by 7.6 % for every hour of delay in the administration of antibiotics therapy in patients with sepsis. They further concluded that due to logistics within hospital, the time passed from prescription to the actual administration or "hang time" can frequently be several hours due to possible barriers such as: delay of getting prescription order to the pharmacy, delays in transferring medication from the pharmacy to the wards or reconstitution of intravenous antibiotics by nursing staff.

2.6 Antibiotic Stewardship in South Africa

In South Africa the EML and the standard treatment guidelines (STGs) have been developed to guide prescribers in the public sector. The South African Antibiotic Stewardship Programme (SAASP) has a guideline which is also aligned to the EML and the STGs. This guideline provides an algorithmic approach to prescribing and further information on treatment duration. This guideline does not include paediatric treatment standards. The SAASP developed an antibiotic prescription chart to be used for infection episodes and antibiotic prescriptions (Mendelson, 2015).

An antibiotic prescription chart was designed to focus antibiotic prescribing on distinct infection episodes. The chart requires the prescribing doctor to define the following parameters for each infection episode; the indication for antibiotic, whether antibiotics were being prescribed on prophylactic, empiric or definitive; whether the infection was community or hospital-acquired, diagnosis and whether appropriate specimens had been sent for laboratory culture before or after antibiotics had started (Boyle's *et. al,* 2013).

2.7 Conclusion

This chapter provided an in-depth review of available literature on antibiotic resistance, mechanism of resistance, antibiotic use in paediatrics and antibiotic stewardship programme.

The next chapter will detail the methodology employed in this study. .

Chapter 3

METHODOLOGY

3.1 Introduction

This chapter discusses the methodology of the study. It provides information related to the purpose of the study, study site, ICU empiric antibiotics guidelines, study design, study period, data collection methods, statistical analysis and ethical considerations.

3.2 Purpose of the Study

The purpose of this study was to conduct a retrospective record review of antibiotics utilized in paediatric patients in an ICU at two-time periods. There was however no intervention made between these two study months.

3.3 Study Site

The study was conducted at Charlotte Maxeke Johannesburg Academic Hospital's Paediatric ICU. The hospital is a public academic hospital located in Parktown, Johannesburg, Gauteng Province. This unit has 12 beds which are reserved for any paediatric patient needing this level of care.

It was noted during discussions with the ICU unit that they followed specific admission process flow in the ICU (Figure 2). They indicated that once neonates are admitted in ICU and there is a suspected nosocomial infection, blood culture and CRP samples are taken, and the neonates are immediately started on empiric therapy.

In consultation with the ICU unit, they indicated that the unit's antibiotic treatment guideline/protocol outlines the following empiric treatment algorithm as outlined in Table 1. Regimen A or B is used in neonates depending on the suspected organism. For older children, the ampicillin/cefotaxime/ceftriaxone is the preferred antibiotics to be used empirically. These regimens provide broad-spectrum coverage. It was also confirmed with the unit that amoxicillin was used prophylactically post-operatively.

Table 1: Charlotte Maxeke hospital ICU empiric antibiotics treatment guideline

	Neonates (Empirically)
Regimen:	**A:** Gentamycin plus Ampicillin
	B: Meropenem plus Vancomycin or Amikacin plus Tazocin
	Paediatric (Empiric)
	C: Co-amoxiclav/cefazolin
	D: Ampicillin/cefotaxime/ceftriaxone

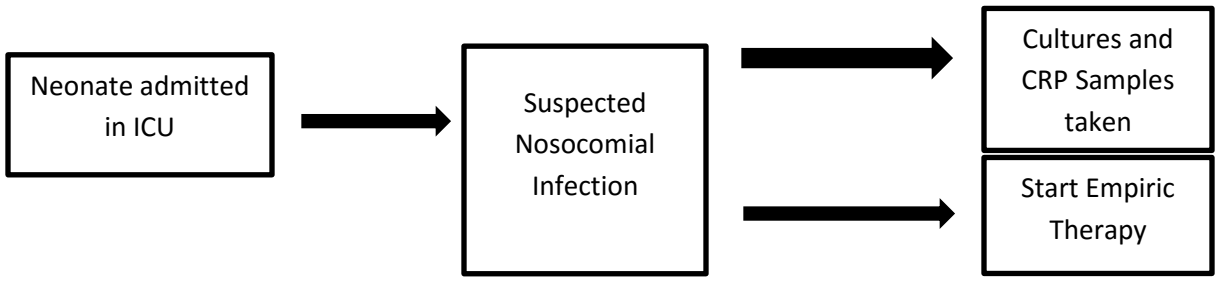


Figure 2: Patients admission process flow

3.4. Study Design

This was a retrospective review of patient ICU charts.

3.5 Study period

Retrospective chart review was done for the following periods: 15 January 2016 to 15 February 2016 and 15 January 2017 to 15 February 2017. There was no intervention made between the two study periods. This study wanted to document utilization of antibiotics in two consecutive years.

3.6 Study Population and Sample Selection

Paediatric patients admitted to paediatric ICU who were prescribed and administered antibiotic during the study dates were included in the study. Patients who were not prescribed antibiotics as well as those whose records were not available were excluded from the study. The sample consisted of 40 patients in 2016 and 55 patients in 2017.

3.7 Data collection

Data was transcribed from the ICU chart onto the data collection tool (Appendix 1). The ICU charts document all the medication prescribed, the amount the patients received and the time the dose was administered. The infection markers and laboratory tests are ordered are recorded on these charts as well. These charts are kept in the ICU until the patient leaves this unit. After which the charts are sent to the record room where they are scanned and stored electronically.

The data collection tool was a modified version of the South African Antibiotic Prescription Chart (Appendix 1). An antibiotic prescription chart focuses the antibiotic prescription on distinct infection episode (Boyles *et al,* 2013). Permission to use this chart was granted by Prof. Mendelson, one of the physicians who designed the chart.

The antibiotic prescription chart captures the antibiotic prescribed; dose, duration, stated indication, microbiology results and the time antibiotics were prescribed and administered for each patient. Laboratory results that were not found on the chart were confirmed using the National Health Laboratory electronic system (LABTRAK).

Records were categorized according to the following age groups; 0-3 months, >3 months – 1 year, >1 – 5 years and older than 5 years. These categories were defined in consultation with the head of the unit as they would best describe the patients within their unit.

Hang time was measured as the time from when the antibiotic was ordered until the dose was administered. This was calculated for each dose where the time of prescribing was indicted on the ICU chart.

3.8 Statistical Analysis

Data was captured on Microsoft Excel (2010) and statistical analyses were performed on SAS (SAS Institute, Carey, NC, USA), Release 9.4. Quantitative data was analyzed using descriptive statistics such as percentages for categorical data and means and standard deviations for numerical data.

3.9 Reliability and Validity of Data

3.9.1 Reliability

The data collection tool for this study, the modified version of the South African Antibiotic Prescription Chart, was used successfully as the data collection tool for the larger study.

3.9.2 Validity

To ensure validity of the study results the researcher collected all the study results for both time periods.

3. 10 Ethical considerations

This was a sub-study of "Situational Analysis of Antibiotic Stewardship in Gauteng Public Hospital" (M141141 – Appendix 5). Hospital approval to conduct this study was obtained (Appendix 7). Permission to conduct this sub-study was received from the Human Research Ethics Committee of the University of Witwatersrand (M1703110- Appendix 6). Management of patient records was as follows:

- Each patient was assigned a study number.
- List of patients and assigned numbers were kept in a locked cupboard which was only accessible to researcher and supervisor.
- No patient was identifiable from the data collection tool (patient's names, hospital numbers and date of birth were not collected).
- Prescribers' details were not recorded.
- No files were copied or removed.

3.11 Conclusion

This chapter described the study methodology including the study design, data collection methods, data analysis and ethical considerations. It also explained the study setting and the guidelines for prescribing antibiotics for empiric and prophylactic use in the ICU.

The next chapter presents the findings of this study.

Chapter 4

RESULTS

4.1 Introduction

This chapter discusses the results of the study and provides data to support the objectives of the study. It documents the antibiotics prescibed, their dosage and frequency, diagnosed conditions and duration of treatment. Also included is culture specimens and CRPs ordered as well as calculating the hang time.

4.2 Demographics data comparison

This study reviewed the usage of antibiotics in 40 patients admitted from 15 January 2016 to 15 February 2016 and 55 patients admitted from 15 January 2017 to 15 February 2017 in the pediatric ICU. There was no significant difference between male and female patients between the two periods (Fisher's exact: p=0.2982). There were 63.6% male patients admitted in 2017 and 47.5% in 2016. There was also no significant difference between median weights of patients for the two periods under review (Fisher's exact; p=0.4813). The average numbers of days in ICU were 5 days in 2016 and 4 days in 2017 (Table 2).

Table 2: Demographic data comparison

	2016 (n=40)	**2017 (n=55)**	**P-value**
Age (months), median (IQR)	0.804 (0.144 - 2.856)	2.004 (0.228 – 11.004)	0.3009*
Weight (grams), median (IQR)	3230 (1465-4555)	3300 (1580-9000)	0.4813*
Number of Days in ICU, mean (Min-Max)	5 (1-16)	4 (1-13)	
Gender: Male n (%)	19 (47.5)	35 (63.6)	0.2982*
Gender: Female n (%)	21 (52.5)	20 (36.4)	

*Fisher's Exact Test

In both study periods majority of the patients were between 0-3 months (2016: 77.5%, 2017: 60%). There was no significant difference between the ages of the children between the two years (Chi ^{2} 5.193; p=0.1582)

Table 3: Age sub categorisation

Age categories	**2016 (n=40)**	**2017 (n=55)**
0- 3months	31 (77.5%)	33(60%)
>3- 12 months	3 (7.5%)	10 (18.2%)
>1- 5 years	2 (5%)	8 (14.6)
>5 years	4 (10%)	4 (7.3%)

4.3 Antibiotics Prescribed and frequency

There were 15 antibiotics prescribed in 2016 and 2017, however these antibiotics differed. The most frequently prescribed antibiotics in 2016 were vancomycin (19%), imipenem (18%), ampicillin (11%), gentamycin (11%), amikacin (8%), co-amoxiclav (6%) and piperacillin/tazobactam (6%). In 2017, the most frequently prescribed antibiotics were meropenem (21.7%) vancomycin (20.8%), co-amoxiclav (11.7%), ampicillin (10%), gentamycin (9.2%), cefotaxime (5.8%), and piperacillin/tazobactam (5.0%). There were differences between the types of antibiotics prescribed during the two review periods. Imipenem (18%), co-trimoxazole (3%), erythromycin (4%) and ertapenem (1%) were only prescribed in 2016. In comparison colistin (2.5%), chloramphenicol (0.8%), and rifampicin (0.8%) were only prescribed in 2017. Three carbapenems (imipenem 18%, meropenem 2% and ertapenem 1%) were prescribed in 2016, however, in 2017 only meropenem (21.7%) was prescribed. The frequency at which vancomycin and gentamycin was similar both in both time periods (Table 4).

Table 4: Antibiotics prescribed and frequency

2016		2017	
Antibiotic Prescribed (n=15)	**Frequency**	**Antibiotic Prescribed (n=15)**	**Frequency**
Amikacin	8	Amikacin	5
Ampicillin	11	Ampicillin	12
Cefazolin	3	Cefazolin	4
Cefotaxime	4	Cefotaxime	7
Ceftriaxone	2	Ceftriaxone	3
Co-amoxiclav	6	Chloramphenicol	1
Co-trimoxazole	3	Cloxicillin	1
Cloxicillin	2	Co-amoxiclav	14
Ertapenem	1	Colistin	4
Erythromycin	4	Doxycycline	1
Gentamicin	11	Gentamicin	11
Imipenem/cilastin	18	Meropenem	26
Meropenem	2	Piperacillin/tazobactam	6
Piperacillin/tazobactam	6	Rifampicin	1
Vancomycin	19	Vancomycin	25

4.4 Number of antibiotics prescribed per patient

There was an observed difference between the percentage of patients that received one antibiotic in 2016 (12.5%) versus 2017 (25.45%). The difference was however not statistically significant (Fisher Exact, p=0.1931). In both periods the majority of patients received two antibiotics as therapy during their ICU stay, 47.5% in 2016 and 40.0% in 2017. Instances when a patient was prescribed three and four antibiotics during ICU stay were similar in both the 2016 and 2017 review period. The highest number of antibiotics prescribed in both time periods was five (2016: n=2) (Figure 3).

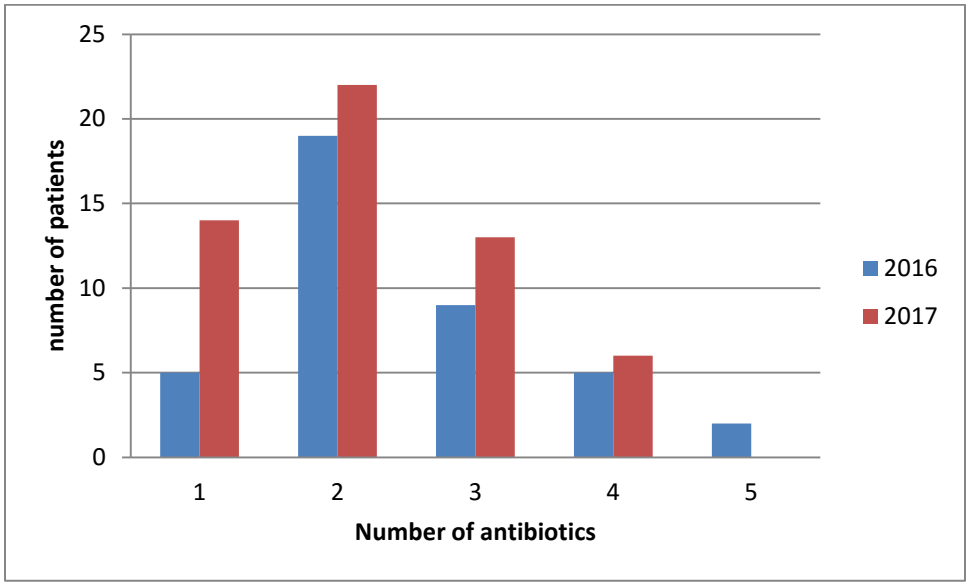


Figure 3: Number of antibiotics patients received during admission to the ICU

4.5 Concurrent use of antibiotics

In 2016, imipenem and vancomycin were concurrently used 12 times, ampicillin and gentamycin concurrently used 9 times and piperacillin/tazobactam and amikacin were concurrently used three times. In 2017, meropenem and vancomycin were concurrently used 19 times, ampicillin and gentamycin concurrently used 11 and piperacillin/tazobactam and amikacin were concurrently used on two occasions. Three antibiotics were concurrently used eight times in 2016, with ampicillin, gentamycin and trimethoprim/sulfamethoxazole concurrent therapy used twice. However, in 2017 three antibiotics were concurrently used six times with meropenem, vancomycin and colistin being used concurrently twice (Table 5 and 6).

Table 5: Antibiotics administered concurrently in 2016

Antibiotic 1	Antibiotic 2	Antibiotic 3	Times used
Ampicillin	Gentamycin		9
Ampicillin	Erythromycin		1
Ampicillin	Gentamycin	Erythromycin	1
Ampicillin	Gentamycin	Trimethoprim/Sulfamethoxazole	2
Cefotaxime	Imipenem	Vancomycin	1
Cefotaxime	Trimethoprim/Sulfamethoxazole		1
Ceftriaxone	Erythromycin		1
Cloxicillin	Cefotaxime		1
Co-amoxiclav	Cefotaxime		1
Ertapenem	Vancomycin	Amikacin	1
Gentamycin	Imipenem	Vancomycin	1
Imipenem	Vancomycin		12
Piperacillin/Tazobactam	Amikacin	Cloxicillin	1
Piperacillin/Tazobactam	Amikacin	Erythromycin	1
Tazocin	Amikacin		3
Vancomycin	Imipenem	Amikacin	1

Table 6: Antibiotics administered concurrently in 2017

Antibiotic 1	Antibiotic 2	Antibiotic 3	Times used
Ampicillin	Gentamycin		11
Ampicillin	Piperacillin/Tazobactam		1
Cefotaxime	Chloramphenicol		1
Cefotaxime	Cloxicillin		1
Cefotaxime	Colistin		1
Cefotaxime	Vancomycin		1
Ceftriaxone	Doxycycline		1
Meropenem	Amikacin		1
Meropenem	Vancomycin		19
Meropenem	Vancomycin	Cefotaxime	1
Meropenem	Vancomycin	Colistin	2
Piperacillin/Tazobactam	Amikacin		1
Piperacillin/tazobactam	Vancomycin		1
Vancomycin	Amikacin	Piperacillin/tazobactam	1

4.6 Indications of Prescribed antibiotics in terms of it being either prophylactic (P), empiric (E) or definitive (D)

It was not indicated in records reviewed whether the prescribed antibiotic was for prophylactic, empirical or definitive purposes. The researcher assigned this classification retrospectively according to the information provided by the unit. However, it could not be confirmed with the prescriber. Most of the doses given in both study periods were classified as presumed empiric. There were two presumed definitive doses in each study period. Five doses in 2016 were presumed empiric initially which changed to definitive after reviewing the culture results. Treatment policy/guideline for the unit is that in general antibiotics are used empirically until sepsis is ruled out. CRP results and culture results are used to direct further treatment action, for example, stopping antibiotics in case of low CRP and negative culture results and changing therapy based on sensitivity pattern.

4.7 Calculation of dosages

Doses of antibiotics given to children in ICU are calculated according to weight. In 2016, there were a total of 94 doses of antibiotics given to children compared to 123 doses in 2017 (Appendix 8 and 9). Doses were recalculated based on dosage guidelines on South African Medicines Formulary (SAMF, 2016) and recorded weight of children. When calculating the doses, it was seldom found that the value calculated was identical to the prescribed dose. Doses where the variation was greater than or equal to 10% are reported in Tables 7 to 10.

The calculated doses showed that 22% (n=21) of doses given in 2016 were lower than calculated doses (Table 7) as compared to 15% (n=19) in 2017 (Table 9) (p=0.2186 Fishers Exact). There was no significant difference between the two periods. There were 3% (n=3) of doses given that were higher than the calculated doses in 2016 (Table 8) as compared to 7% (n=9) doses in 2017 (Table 10)

Table 7: Doses lower that calculated SAMF doses in 2016

Antibiotic	Dose prescribed (mg/kg/dose)	SAMF(2016) calculated dose (mg/kg/dose)
Ampicillin	200	235
Co-amoxiclav	250	380
Co-amoxiclav	100	170
Co-amoxiclav	300	500
Co-amoxiclav	100	170
Co-amoxiclav	60	110
Co-amoxiclav	360	600
Amikacin	280	342
Cefazolin	120	184
Cefazolin	700	1250
Cefazolin	100	120
Vancomycin	30	42
Vancomycin	200	285
Vancomycin	34	51
Vancomycin	22	33
Piperacillin/tazobactam	250	340
Piperacillin/tazobactam	1	2.5
Piperacillin/tazobactam	400	440
Gentamycin	20	38
Imipenem	44	55
Imipenem	75	92

Table 8: Doses higher than SAMF calculated Doses in 2016

Antibiotic	Dose prescribed (mg/kg/dose)	SAMF(2016) calculated dose (mg/kg/dose)
Cefotaxime	270	200
Cefotaxime	250	215
Meropenem	60	46

Table 9: Doses lower than calculated SAMF doses in 2017

Antibiotic	Dose prescribed (mg/kg/dose)	SAMF(2016) calculated dose (mg/kg/dose)
Amikacin	20	43
Co-amoxiclav	120	132
Co-amoxiclav	360	580
Co-amoxiclav	250	450
Co-amoxiclav	145	240
Co-amoxiclav	120	185
Co-amoxiclav	180	280
Co-amoxiclav	65	110
Co-amoxiclav	325	650
Co-amoxiclav	180	305
Co-amoxiclav	225	450
Co-amoxiclav	120	225
Co-amoxiclav	150	295
Co-amoxiclav	325	595
Cefotaxime	400	595
Cefazolin	400	600
Meropenem	80	104
Piperacillin/tazobactam	550	740
Vancomycin	28	44

Table 10: Doses higher than calculated SAMF Doses in 2017

Antibiotic	Dose prescribed mg/kg/dose	SAMF(2016) calculated dose mg/kg/dose
Cefotaxime	140	105
Cefotaxime	275	205
Cefotaxime	120	89
Cefotaxime	190	143
Ceftriaxone	1800	1380
Vancomycin	186	80
Vancomycin	115	84
Vancomycin	28	44
Meropenem	205	192

4.8 Duration of antibiotics

The longest antibiotic duration in 2016 was erythromycin (12.5 days) and cefotaxime (8.33 days) in 2017. Vancomycin had the shortest duration (0.25 days) in 2016 whereas in 2017 there were four antibiotics with shortest duration (ampicillin, cefotaxime, co-amoxiclav, meropenem and vancomycin), all with 0.33 days duration (Table 11). Medical records of patients did not have information on why certain antibiotics have one day or less than one day duration. Rationale for 1 day duration could not be retrospectively determined.

In both periods, most antibiotics duration was five days or less. Four antibiotics had a duration of between 5 days and 10 days in 2016 and in 2017 there were 5 antibiotics with the same duration. There was only one antibiotic in 2016 with a duration of more than 10 days and none in 2017 (Figure 4)

Table 11: Average duration of prescribed antibiotic in 2016 and 2017

Prescribed Antibiotic	2016	2017
	Average days on antibiotics (min-max)	**Average days on antibiotics (min-max)**
Ampicillin	1.60 (0.333-3.500) n= 16	2.25(0.333-4.5) n= 17
Amikacin	2.63 (1.000-5.000) n= 8	2.00(1.000-4.000) n= 4
Cefotaxime	3.75 (1.000-10.333) n= 4	2.14(0.333-8.333) n= 7
Ceftriaxone	2.83 (0.667-5.000) n= 2	2.50(2.000-3.000) n= 3
Cefazolin	1.33 (1.000-2.000) n= 3	1.25(1.000-1.333) n= 4
Co-amoxiclav	2.00 (1.000-4.000) n= 6	2.80(0.333-7.330) n= 13
Co-trimoxazole	5.56 (3.000-7.000) n= 3	-
Colistin	--	3.78(1.000-5.333) n= 3
Cloxicillin	1.25 (0.500-2.000) n= 2	1.00(1.000-1.000) n= 1
Chloramphenicol	-	-
Doxycycline	-	3.00(3.000-3.000) n= 1
Ertapenem	2.50 (2.500-2.500) n= 1	-
Erythromycin	4.19 (0.500-12.500)	-
Gentamicin	2.20 (1.000-4.000) n=10	2.73(1.000-5.000) n= 11
Imipenem/cilastin	3.69 (0.333-9.000) n= 18	-
Meropenem	4.67 (2.000-7.333) n= 2	3.41(0.333-8.667) n= 25
Piperacillin/tazobactam	2.33 (0.667-4.000) n= 6	2.40(1.000-4.000) n= 5
Rifampicin	-	8.00(8.000-8.000) n= 1
Vancomycin	3.26 (0.250-10.000) n= 19	2.06(0.333-4.667) n= 23

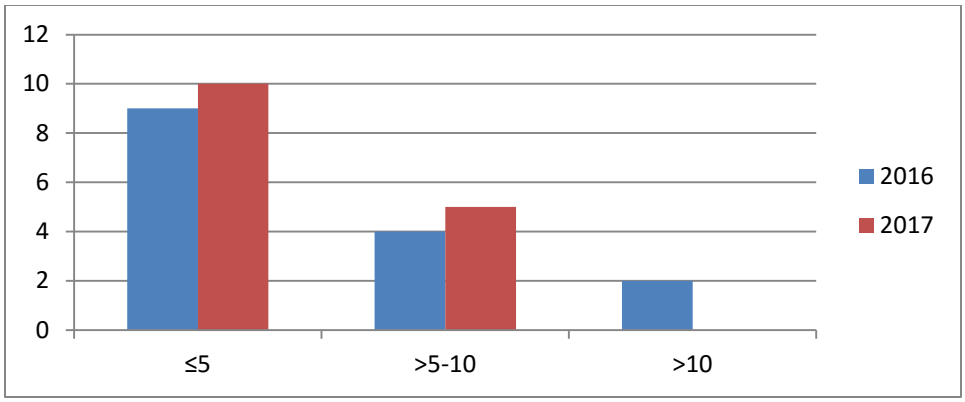


Figure 4: Duration of antibiotics prescribed (days)

4.9 Missed doses

There were the same number of missed doses in 2016 (n=10) compared to 2017 (n=10). It is not possible to confirm retrospectively if these doses were given but not recorded, whether additional instructions were given to nurses to delay the dose or if the antibiotic was out of stock.

Table 12: Average number of doses missed

	2016	**2017**
Antibiotic	**Average number of doses missed**	**Average number doses missed**
Ampicillin	0.82	0.58
Cefotaxime	1.00	0.14
Ceftriaxone	-	0.67
Cefazolin	-	0.75
Co-amoxiclav	1.12	0.36
Co-trimoxazole	0.67	-
Colistin	-	1.00
Doxycycline	-	0.00
Erythromycin	1.50	-
Gentamicin	0.10	0.09
Imipenem/cilastin	0.89	-
Meropenem	1.00	1.08
Piperacillin/tazobactam	0.33	0.78
Vancomycin	0.90	1.25

4.10 Hang time

Time that the dose was prescribed and administered was documented in 80 doses during 2016 and 78 doses during 2017 from which hang time was calculated. Doses where prescriptions were written after antibiotics were administered and those where prescriptions were written but antibiotics were given the following day were excluded from these calculations. The exclusion of doses that were given the following day was to eliminate instance were verbal order was given to

the nurses to delay initiating therapy until the following day in cases where patients were transferred to ICU from the general ward already on antibiotics. In 2017, there were 46.2% (n=36) doses with hang time less than 60 minutes and 32.5% (n=26) in 2016 study. A similar pattern was observed for doses with hang times greater than 180 minutes, which occurred in only 17.9 % of doses in the 2017 study period compared to 32.5% in the 2016 study period. Hang times between 61-180 min show a similar pattern between the two study periods (Table 13). There was no significant difference between the hang times for 2016 compared to 2017 (Chi^2 5.186. p=0.0747).

Table 13: Doses hang time

Hang time	**2016 (n=80)**	**2017 (n=78)**
≤60 Min	26 (32.5%)	36 (46.2%)
61-180 Min	28 (35%)	28 (35.9%)
≥180 min	26 (32.5%)	14 (17.9%)

4.11 Blood cultures ordered

Blood cultures (blood) were ordered in 73% (n=29) of patients in 2016 and 75% (n=41) in 2017 Total number of cultures taken in 2016 was 53 as compared to 62 cultures in 2017. There were 19% (n=10) positive cultures in 2016 as compared to 5% (n=3) in 2017 (Table 13). There was no significant difference in the blood culture profile between 2016 and 2017 ($Chi^2$5.469, p=0.0649).

Table 14: Culture specimen results

	2016		2017	
Prescribed Antibiotic	**Growth status**	**Sensitivity**	**Growth status**	**Sensitivity**
Ampicillin	No growth	N/A	No growth	N/A
Amikacin	Positive	Cloxicillin	No growth	N/A
Cefotaxime	No growth	N/A	No growth	N/A
Ceftriaxone	No growth	N/A	No growth	N/A
Cefazolin	Positive	Meropenem	Positive	Penicillin/Ampicillin Cloxicillin
Co-amoxiclav	Positive	Vancomycin	No growth	N/A
Co-trimoxazole	Not done	N/A	N/A	N/A
Colistin	N/A	N/A	No growth	N/A
Cloxicillin	Positive	Cloxicillin	Not done	N/A
Chloramphenicol	N/A	N/A	N/A	N/A
Doxycycline	N/A	N/A	Not done	N/A
Ertapenem	No growth	N/A	N/A	N/A
Erythromycin	No growth	N/A	N/A	N/A
Gentamicin	No growth	N/A	Positive	Colistin
Imipenem/cilastin	Positive	Imipenem	N/A	N/A
Meropenem	No growth	N/A	Positive	Fluconazole
Piperacillin/tazobactam	Positive	Cloxicillin	No growth	N/A
Rifampicin	N/A	N/A	Not done	N/A
Vancomycin	Positive	Ceftazidime	No growth	N/A

4.12 Infection markers (CRP)

It was observed that CRP was routinely used in this unit. CRP samples were taken from 85% (n=34) of patients in 2016 and 82% (n=45) of patients in 2017.

4.13 Summary of diagnosis

Diagnosis classifications were similar between the two study periods (Appendix 4). This is consistent with the number and class of antibiotics used during the two study periods. In both study periods, the highest number of diagnosis classifications related to surgical procedures,

followed by medical and lastly with infections being the least classified diagnosis (Table 14). The diagnosis recorded was that which appeared on the ICU chart. This normally reflected the initial diagnosis when the patient was admitted into the hospital or ICU. It may not correlate with the reason for antibiotics been prescribed. There was no significant difference in the diagnosis profile between the two years (Chi^2 0.1416, p=0.9317).

Table 15: Summary of diagnosis

Diagnosis	**2016**	**2017**
Infections	8	8
Medical	14	11
Surgery	21	18

4.14 **Conclusion**

This chapter provided the results of the study. Similar antibiotics were used in the two time periods. Duration of use of antibiotics was short, and the majority of doses were comparable to calculated values. Blood cultures and CRPs were ordered routinely. Hang times seemed to improve from 2016 to 2017 with more patients receiving their antibiotics within an hour after prescription.

The next chapter discusses the results and relates the study findings to available literature.

Chapter 5

DISCUSSION

5.1 Introduction

This chapter discusses results of the study and focuses on antibiotics prescribed including dosing and duration, hang time measurements as well as, culture specimen and CRPs.

5.2 Antibiotics prescribed

Antibiotics are frequently prescribed in paediatric ICUs. There are limited studies which have reviewed and documented antibiotic utilization in paediatric ICU at public hospitals in South Africa.

This study was a retrospective review of 40 patient files in 2016 and 55 patients in 2017. Majority of the patients in both years were neonates.

The most frequently prescribed antibiotics were vancomycin, imipenem, ampicillin, gentamycin amikacin and co-amoxiclav in 2016 whereas in 2017, the most prescribed antibiotics were meropenem, vancomycin, co-amoxiclav, ampicillin, gentamycin and cefotaxime. In addition, this study showed that colistin, was only used twice during the study period.

Frequently patients were prescribed two concurrent antibiotics, 47.5% in 2016 and 40% in 2017. The most frequently used antibiotics in concurrent therapies were imipenem and vancomycin; ampicillin and gentamycin as well as meropenem and vancomycin.

Imipenem was the most frequently used carbapenem in 2016, with meropenem used less frequently, however in 2017, only meropenem was used. Hornik *et al* (2013) observed small but statistically significance difference in the proportion of infants diagnosed with seizure when treated with meropenem (5.4%) and 7.6% when treated with imipenem. This provides a possible reason for the use of meropenem rather than imipenem. Other reasons could be that selected antibiotics are not available on tender and possible stock shortages.

Mabila *et al* (2016) showed that ampicillin, gentamycin, co-amoxiclav, amoxicillin and co-trimoxazole were commonly prescribed antibiotics even though their study was based in a general ward in South Africa in a public hospital.

Their study also showed that the use of colistin was very limited, which is consistent with our study. This observation is not surprising due to significant side effects concerns with colistin (Halaby *et al,* 2013) and the emergence of colistin-resistant strains among the Gram- negative bacteria (Mammina *et al,* 2012). Furthermore, Brink (2016) also discussed concerns related to the use of colistin as results of the latest discovery of two plasmid-mediated genes, (mcr-1 and mcr-2) which give resistance to colistin.

The study results support the ICU algorithm as shown in Figure 3. In both the study periods, the highest percentage of prescriptions were in instances where a patient was prescribed two antibiotics during their ICU stay, 47.7% (n=19) in 2016 and 40.0% (n=22) in 2017.

There is also an agreement between this study results and the unit's antibiotic treatment guidelines in terms of concurrent use of antibiotics. From our study, it was noted that in 2016, imipenem and vancomycin were concurrently used 11 times and ampicillin and gentamycin were concurrently used nine times. In 2017, meropenem and vancomycin were concurrently used 19 times and ampicillin and gentamycin were concurrently used 11 times. The selected concurrent antibiotic therapy covered both the Gram-positive and Gram-negative organisms. However, it was also noted that it was difficult to assess the appropriateness of concurrent use of antibiotics retrospectively as consultation with the prescribing doctor could have explained any differences.
The unit's decision for the choice of empiric therapy was based on the surveillance of antimicrobial sensitivity patterns in culture isolates done at the unit. A retrospective review of all bacterial isolates in blood cultures obtained for a period of a year observed that Coagulase-negative staphylococci (CoNS) was the most common isolate overall (19.1%), followed by *Klebsiella pneumoniae* extended spectrum beta-lactamase (12.1%) and *Acinetobacter baumanii* (10.9%). They also noted that Gram-positive infections predominated in early onset sepsis (EOS) with *Streptococcus agalactiae* being the most common isolate. Both Gram-positive and Gram-negative infections were noted as being prevalent in late onset sepsis (LOS), with CoNS the most frequent isolate (Ballot *et al,* 2012).

They confirmed that the above bacteria profile identified during their study informed the current empiric treatment guideline for the unit. Based on the bacteria profile, penicillin/ampicillin plus an aminoglycoside (gentamycin/amikacin) were confirmed as suitable empiric antibiotic therapy for EOS. The selected combination of antibiotic therapy widens the antimicrobial cover and provides double coverage. They indicated that vancomycin would provide cover for CoNS whereas in critically ill neonates, meropenem plus either gentamycin or ciprofloxacin would be the therapy of choice. Alternatively, they indicated that the combination of ceftazidime and amikacin would provide cover for the majority of the Enterobacteriaceae and non-fermenters.

The results from the neonatal unit study done by Ballot *et al (*2012) are supported by many studies done in neonatal units (Tzialla *et al,* 2015); Sivanandan *et al,* 2011). It was emphasized that an empiric antimicrobial treatment for LOS should generally cover both Gram-positive and Gram- negative microorganisms. They suggested a combination of ampicillin and aminoglycosides (gentamycin) or ampicillin and cefotaxime for LOS. In addition, Cantey *et al* (2016) also observed in their study that ampicillin and gentamycin were used for empirical therapy for EOS sepsis whereas for LOS, gentamycin and oxacillin were used.

The results in Chapter 4 must be taken in the context of the high percentage of neonates in the ICU. Neonates are immune compromised individuals who are prone to infection (Ballot *et al,* 2012). They further indicated that sepsis is a common infection in neonates and that neonatal sepsis has a high morbidity and mortality and is not easy to diagnose on presentation. Clinical diagnosis on presentation is complex as there are nonspecific signs and symptoms which require the start of empirical antibiotic therapy until suspected sepsis is ruled out (Eman *et al*, 2015).

Sepsis is a big cause of morbidity and mortality among neonates, with 8.5% incidence of sepsis and 20.8% mortality due to sepsis (Motara *et al,* 2005). In their study EOS was an unusual isolate and LOS was more common with CoNS the most common microorganism in LOS. The epidemiology of neonatal sepsis and the antibiotic resistance patterns from their study were used as a guideline for the management of neonatal sepsis at Charlotte Maxeke Johannesburg Academic Hospital. EOS was predominately caused by Gram-negative organisms and therefore the recommended empiric therapy choice for EOS was aminoglycosides (gentamicin) plus

penicillin (ampicillin). Regarding LOS, the recommended empiric antibiotic therapy was vancomycin and carbapenems.

The majority (> 95%) of microorganisms causing EOS were susceptible to the two most commonly used antibiotic therapies (penicillin and gentamycin or amoxicillin and cefotaxime).It was further noted that CoNS constituted 54% of LOS cases. Furthermore, most of LOS isolates were susceptible to the two most frequently used empiric antibiotic combinations such as flucloxacillin and gentamycin or amoxicillin and cefotaxime as supported by Russell *et al* (2010).

5.3 Duration of antibiotics

This study showed that in both periods, the duration of most antibiotics was five days or less. There were only two antibiotics in 2016 with duration of more than 10 days and none in 2017. The longest antibiotic duration in 2016 was erythromycin (12.5 days) and cefotaxime (8.33 days) in 2017.

Shorter durations of antibiotic therapy were also observed in Fisher *et al,* (2009). Their study, evaluating antibiotics prescribing practices for pediatric patients (ages 0-13 years) admitted to referral hospital in Botswana looked at total duration of antibiotic use. Their study found out that 15 of 31 patients with lower respiratory tract infection had median duration of antibiotic use of 9.5 days (IQR=5-10 days) with 60% of these patients having a duration of greater than 7 days. They also found out that for most patients with suspected bacterial pneumonia, the duration of antibiotic use was longer than the WHO recommendation; however the median total duration of 9.5 days was less than the often recommended 10 day course in developed countries. Their results illustrated that the overuse of antibiotics was not a result of incorrect initiation of antibiotic but the failure to stop antibiotic use once there was no longer a concern for infections. They further discussed concerns related to the ultimate duration of prescribed antibiotic, firstly the fact that the duration of antibiotic use for those with and without an infectious diagnosis was similar and secondly that the likelihood that some of the infectious diagnosis were viral in etiology, making prolonged courses of antibiotic therapy unnecessary.

Sivanandan *et al (*2011) indicated that there is limited number of well-designed clinical studies assessing the suitable duration of empiric antibiotic treatment in negative blood culture sepsis. They further pointed out that there is a variation between centers related to the suitable duration of empiric antibiotic for suspected EOS in the case of negative blood cultures. The advantages of optimal duration of empiric antimicrobial therapy which includes decreasing the emergence of antimicrobial resistance, prevention of undesirable alterations in the gastrointestinal flora and minimization of avoidable expenses for infants were pointed out in this study. In their conclusion, they indicated that the standard practice duration of empiric treatment in neonate should be 48-72 hours pending cultures for suspect sepsis and 10-14 days for blood culture positive sepsis without meningitis.

5.4 Antibiotics dosing

Results from this study showed that majority of antibiotics doses given were in compliant with doses specified in South Africa Medicines Formulary (SAMF) paediatric dosage guidelines (Appendices 8 - 9). Only the doses where a 10% variation in dose was calculated were reported as either below or above SAMF recommended doses. There is a paucity of data which confirms the acceptable variation. However, the calculated doses did not take into account the severity of the infections. The guidelines used in the unit are based on gestational age and birth weight.

Usage of antibiotics in critically ill neonates and pediatric patients is not well understood, with evidence suggesting that current dosing is frequently inadequate (Dorofaeff *et al,* 2016). A European-wide point prevalence study involving 89 neonatal ICUs from 21 countries found that 75% of vancomycin doses were below the recommended dosage. Furthermore, recommended neonates and pediatric antibiotic dosing regimens are often extrapolated from healthy adult data using basic empiric scaling factors such as body weight or body surface area. In their conclusion, they stated that infections in critical ill neonate and pediatric patients is a challenging health issue and current antibiotic regimens for critically ill neonates and pediatrics are suboptimal due to poor understanding of altered pharmacokinetic properties (Dorofaeff *et al,* 2016).

Similarly, despite the widespread use of antibiotics in premature (< 37 weeks gestation) infants, dosing regimens are often extrapolated from data in adult or older children, increasing the risk of

drug side effects and lack of clinical effectiveness (Pineda and Watt, 2015). Dosing regimens may be incorrect as they do not account for infants' developmental changes in renal function, metabolic capacity, body composition and surface area, gastrointestinal absorption and immune competence. They also showed that ampicillin and gentamycin are the most commonly prescribed antibiotics in neonatal ICU which is consistent with the finding in this study.
Halczli and Adam (2013) further mentioned that medication under dosing could contribute to poor treatment outcome, polypharmacy and significant cost to health care system as results of potential longer hospital stay.

5.5 The importance of measuring hang time

This study results showed that in 2017, there were a higher number of doses (46.2%) with hang time less than 60 minutes. International standards require that doses should be administered within one hour of the prescription being written. It is important to ensure that antibiotics are administered timeously to ensure proper management of patients with infections (Messina *et al,* 2015). They further pointed out that in relation to the management of patients with severe sepsis and septic shock, mortality increases by 7.6 % for every hour of delay in giving antibiotic treatment to patients. In addition, they indicated that numerous studies have supported the fact that administering antibiotic timeously greatly assist in the improvement of patient outcomes. Ferrer *et al* (2014) in their study of septic patients have shown that patient outcomes were negatively impacted irrespective of disease severity or hospital setting when antibiotic treatment was late.

In their study, Messina *et al* (2015) assessed hang time compliance following implementation of an antimicrobial stewardship program across 33 hospitals in South Africa. Their study assessed 32,985 patients who were administered intravenous antibiotic on day 1 for compliance with hang time. They observed that 64% patients were administered antibiotics within one hour of written prescription and therefore were considered to be hang time compliant. Furthermore, they discuss process barriers contributing to hang-time non-compliance. Examples of those barriers include: difficulties in getting buy-in from nursing staff to administer a new first dose of antibiotics within an hour of the prescription due to of routine standard medicines dosing schedules as well

as delayed dispensing process from the pharmacy in case the "stat" dose was not requested by the nursing staff. They concluded that ensuring timeous administration of antibiotics therapy should be the taken as the first target for "easy win" as low- hanging-fruit component of antimicrobial stewardship programme.

5.6 Culture ordering practices

Culture samples were ordered routinely in most patients and were consistent with the unit's ICU admission process and are supported by Mabila *et al* (2016). Their study discussed the importance of ordering culture samples for accurate diagnosis of infection. They further noted that accurate diagnosis will guide the prescriber in decision making related to appropriate choice between empiric, prophylactic and specific therapy. In their study, most indications for antibiotic prescriptions were empiric with a few cases where treatment was specific and prophylactic. Their observations are consistent with observations in this study, which also showed that blood cultures were ordered in 73% of patients in 2016 and 75% of patients in 2017.This study also concluded that most indications for antibiotic prescriptions were presumed empiric in both study periods

5.7 The value of infection markers (CRP)

As per the ICU unit admission process flow, CRP samples were taken for any admission where there is a suspicion of nosocomial infection. The importance of taking CRP measurement as part of diagnosis confirmation and decision making in terms of duration of antibiotics therapy is supported by various studies.

CRP is a good selective marker of bacterial sepsis in the newborn (Bomela *at el,* 2000 and Sivanandan *et al,* 2011). They further pointed out that it has been successfully used historically as a marker of infection and is most reliable and effective as a marker between 24 and 48 hours after presentation with suspected infection in neonates. In addition, instead of doing one CRP measurement, it is recommended to perform several serial CRP assessments in order to have sufficient results to guide decision making in terms of de-escalation of antibiotic therapy. Serial CRP assessments provides for the assessment of duration of antibiotic therapy resulting in

possible reduction in antibiotic therapy duration. Several studies, Ehl *et al (1997*) and Benitz *et al* (1998) assessed the role of CRP measurement as a means to monitor duration of antibiotic treatment and confirmed that CRP values that remain negative for more than 24 hours after initiation of antibiotic treatment in neonates with suspected sepsis had a negative predictive value of 99% and 98.7 % respectively. Those studies showed that clinical application of negative CRP allowed the duration of antibiotics treatment to be reduced. Both studies confirmed that the use of CRP guided therapy seems to be safe and useful approach in a developing country.

C- reactive protein is useful marker for diagnosed neonatal bacterial infections however it is not beneficial for early diagnosis because the levels are elevated in only 35 to 65 % of neonates at the start of illness. Numerous studies have appraised the role of serial CRP measurement as a guide to the duration of antimicrobial treatment. Philip and Mills (2000) recommended that normalization of CRP levels could be taken as criteria to discontinue antibiotic treatment as well reducing hospital stay. CRP level of less than 10 mg/L measured 24 hours after antibiotic initiation correctly confirmed 120 of 121 infants as not needing antibiotics therapy continuation (Ehl *et al, 1997*).

5.8 Conclusion

This chapter reviewed the study results to available literature. There is a porosity of information relating the antibiotic utilization in the public sector to which our results could be compared.
The next chapter will discuss study limitation, recommendations and conclusion.

Chapter 6

STUDY LIMITATIONS, RECOMMENDATIONS AND CONCLUSION

6.1 Introduction

This chapter discusses limitations of our study, provides recommendations for study site and for future research. It also includes the conclusion of the study as well as confirming conflict of interest and funding received.

6.2 Study Limitations

This study was retrospective in design hence it was impossible to confirm information found missing with the clinicians or nurses working in the ICU. Missing files and incomplete information could not be traced.

Clinicians did not indicate whether the antibiotics were prescribed for empiric, definite or prophylactic purpose. This is an important antibiotic stewardship principle (Boyles TH *et al*, 2013).

The diagnosis recorded on the ICU related to the diagnosis upon admission and did not always correlate to the diagnosis of infection.

The study period was short and did not take seasonal variation of antibiotic use into account.

6.3 Recommendations for the site and future research

Electronic dispensing systems can be used to record dispensed medication which can assist in determining utilization. The implementation of a computerised system, incorporating the microbiology and a decision system assisted in reducing the unnecessary use of broad-spectrum antibiotics (Thursky *et al,* 2006)

Currently the pharmacists at this site are not present in the ward and could be useful intervention for future studies. A close collaboration between, nurses, clinicians and pharmacist has been suggested as an approach towards optimizing antibiotic use (Brink *et al,* 2016).

An antibiotic stewardship prescription chart was implemented in the middle of 2017 across the hospital and a future study could investigate the impact this has had on utilization.

Studies such as these provide pertinent information and should be conducted on a regular basis especially in the paediatric population where there is a porosity of information. Ongoing operational research relating to antibiotic usage is important to inform practices within the unit.

6.4 Conclusion:

This study reviewed antibiotics prescribed in 95 patients over two periods. A high percentage of patients, 47.7% in 2016 and 40% in 2017 were prescribed two antibiotics during their ICU stay. Prescription of antibiotics was mostly given empirically for the ICU patients. Ampicillin plus gentamycin, imipenem plus vancomycin and meropenem plus vancomycin were the most empiric concurrent used antibiotic therapy. This concurrent used therapy was appropriate as it covered both the Gram-positive and Gram-negative organisms. Co-amoxiclav was used prophylactically in the unit. Cultures and CRP samples were routinely taken upon initiation of antibiotics therapy and the results were used to guide further treatment decisions. Duration of most antibiotic therapy was five days or less. There was no significant difference between the diagnosed conditions between the two study periods. The prescribing of antibiotics was mostly aligned to the unit's policies and guidelines; however there is a need for ongoing surveillance and establishment of hospital specific antimicrobial stewardship program which could further improve the rational use of antibiotics.

6.5 Conflict of Interest: I declare that there was no conflict of interest in conducting this study.

6.6 Funding: funding for the research was provided by the researcher, there was no external funding.

REFERENCES

Alanis AJ (2005). Resistance to antibiotics: are we in the post-antibiotic era? Archives of Medical Research, 36(6): 697-705.

Ballot, D.E, Nana, T, Sriruttan, C et al. (2012) Bacterial bloodstream infections in neonates in a developing country. ISRN pediatrics,

Barlam T F, Cosgrove S E, Abbo L M *et al.* (2016). Implementing an antibiotic stewardship program: guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. Clinical Infectious Diseases, 62(10), pp.e51-e77.

Benitz W Han M Y, Madan A. *et al.* (1998). Serial serum C-reactive protein levels in the diagnosis of neonatal infection. Pediatrics, 102(4): e41-e41.

Bomela H N, Ballot D E, Cory B J *et al*. (2000). Use of C-reactive protein to guide duration of empiric antibiotic therapy in suspected early neonatal sepsis. The Pediatric infectious disease journal, 19(6):531-535.

Boyles TH, Naicker V, Rawoot N *et al*. (2017). Sustained reduction in antibiotic consumption in a South African public sector hospital: Four year outcomes from the Groote Schuur hospital antibiotic stewardship programme. South African Medical Journal, 107(2): 115-118.

Boyle TH, Whitelaw A, Bamford C *et al*. (2013). Antibiotic stewardship ward round and a dedicated prescription chart reduce antibiotic consumption and pharmacy costs without affecting inpatient mortality or re-admission rates. PLoS One 8.12 e79747.

Brink A, (2005). Antimicrobial resistance in nosocomial infections. Southern African Journal of Epidemiology and Infection, 20(2): 42-45.

Brink, A.J., van den Bergh, D., Mendelson, M. *et al*. (2016). Passing the baton to pharmacists and nurses: New models of antibiotic stewardship for South Africa? South African Medical Journal, 106(10): 947-948.

Brinkman, I., Verstappen, G., Veeger, N., *et al*. (2015). Evaluation of a vancomycin dosing protocol for ICU patients. Neth J Med, 73(4): 195-8.

Brink AJ, Messina AP, Feldman C *at el*. (2016) Antimicrobial stewardship across 47 South African hospitals: an implementation study. The Lancet Infectious Diseases, 16(9): 1017-1025.

Cantey, J.B. and Patel, S.J (2014). Antimicrobial stewardship in the NICU. Infectious Disease Clinics, 28(2): 247-261.

Cantey, J.B., Wozniak, P.S., Pruszynski, J.E. *et al* (2016). Reducing unnecessary antibiotic use in the neonatal intensive care unit (SCOUT): a prospective interrupted time-series study. The Lancet Infectious Diseases, 16(10): 1178-1184.

Chunnilall D, Peer AK, Naidoo I *et al*. (2015). An evaluation of antibiotic prescribing patterns in adult intensive care units in a private hospital in Kwazulu- Natal. South African Journal of infectious diseases, 30(1): 17-22

da Silva Araujo, A.R., Albernaz, D.D.A.D., Marqueset A.F *et al*. (2017). Role of antimicrobial stewardship programme in children: a systematic review. The Journal of hospital infection, 99(2): 117-123

Dorofaeff T, Bandini RM, Lipman J *et al*. (2016). Uncertainty in Antibiotic Dosing in Critically Ill Neonate and Paediatric Patients: Can Microsampling Provide the Answers? Clinical Therapeutics, 38(9): 1961-1975.

Ehl S, Gering B, Bartmann P *et al*. (1997). C-reactive protein is a useful marker for guiding duration of antibiotic therapy in suspected neonatal bacterial infection. Pediatrics, 99(2): 216-221.

Fanos V, Cuzzolin L, Atzei A *et al.* (2007). Antibiotics and antifungals in neonatal intensive care units: a review. Journal of Chemotherapy, 19(1): 5-20.

Fisher BT, Meaney PA, Shah SS *et al*. (2009). Antibiotic use in pediatric patients admitted to a referral hospital in Botswana. The American Journal of Tropical Medicine and Hygiene, 81(1): 129-131.

Fjalstad, J.W., Esaiassen, E., Juvet, L. K *et al.* (2017). Antibiotic therapy in neonates and impact on gut microbiota and antibiotic resistance development: a systematic review. Journal of Antimicrobial Chemotherapy, 73(3): 569-580

Goff DA, Kullar R, Goldstein EJC *et al*. (2017). A global call from five countries to collaborate in antibiotic stewardship: united we succeed, divided we might fail. The Lancet Infectious Diseases, 17(2): e56-e63.

Halaby T, Al Naiemi N, Kluytmans J, *et al.* (2013). Emergence of colistin resistance in Enterobacteriaceae after the introduction of selective digestive tract decontamination in an intensive care unit. Antimicrobial Agents and Chemotherapy, 57(7): 3224-3229.

Halczli A and Woolley AB (2013). Medication under dosing and under prescribing: Issues that may contribute to polypharmacy, poor outcomes. Formulary, 48(6): 194-197.

Howard P, Pulcini C, Hara G *et al*. (2014). An international cross-sectional survey of antimicrobial stewardship programme in hospital. Journal of Antimicrobial Chemotherapy, 70(4): 1245-1255.

Hornik, C.P., Herring, A.H., Benjamin Jr, D.K *et al.* (2013). Adverse events associated with meropenem versus imipenem/cilastatin therapy in a large retrospective cohort of hospitalized infants. *The Pediatric infectious disease journal*, *32*(7): 748.

Isaacs D (2006). Unnatural selection: reducing antibiotic resistance in neonatal units. Archives of Disease in Childhood-Fetal and Neonatal Edition, 91(1): F72-F74.

Jaswal RS, Kaushal RK, Goel A *et al*. (2003). Role of C-reactive protein in deciding duration of antibiotic therapy in neonatal septicemia. Indian Pediatrics, 40(9): 880-883.

Lee KR, Bagga B and Arnold S (2016). The reduction of broad–spectrum antimicrobial use in a tertiary children's hospital post antimicrobial stewardship programme guideline implementation. Paediatric Critical Care Medicine, 17(3): 187-193.

Leroux S, Zhao W, Betremieux P *et al.* (2015). Therapeutic guidelines for prescribing antibiotics in neonates should be evidence-based: a French national survey. Archives of Disease in Childhood, pp.archdischild-2014.

Luyt CE, Bréchot N, Trouillet JL *et al*. (2014). Antibiotic stewardship in the intensive care unit. Critical Care, 18(5): 480.

Mabila N, Schellack N and Gous A.G.S. (2016). Antibiotic prescribing pattern among health care professionals at Van Velden memorial hospital in Tzaneen, Limpopo province, South Africa. African Journal for Physical Activity and Health Sciences, 22(1.1): 79-97.

Magsarili HK, Girotto JE, Bennett NJ *et al*. (2015). Making a case for paediatric antimicrobial Stewardship program. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy, 35(11): 1026-1036.

Mammina C, Bonura C, Di Bernardo F *et al* (2012). Ongoing spread of colistin-resistant Klebsiella pneumoniae in different wards of an acute general hospital, Italy, June to December 2011. Eurosurveillance, 17(33): 20248.

Medernach, R.L. and Logan, L.K., 2018. The Growing Threat of Antibiotic Resistance in Children. Infectious Disease Clinics, *32*(1): 1-17

Mendelson M. (2015). Role of antibiotic stewardship in extending the age of modern medicines. South African Medical Journal, 105(5): 414-419.

Messina AP, van den Berg D and Goff DA (2015). Antimicrobial stewardship with pharmacist intervention improves timelines of antimicrobials across thirty three hospitals in South Africa. Infectious Diseases and Therapy, 4(1): 5-14.

Mok, K., Christian, M.D., Nelson S *et al.* (2014). Time to administration of antibiotics among in patients with severe sepsis or septic shock. The Canadian journal of hospital pharmacy, 67(3): 213.

Motara F, Ballot DE, Perovic O *et al*. (2005) Epidemiology of neonatal sepsis at Johannesburg Hospital. Southern African Journal of Epidemiology and Infection, 20(3): 90-93.

Pacevski G, Ahel V, Valahovic-Palcevski V *et al*. (2004). Antibiotic use profile at paediatric clinics in two transitional countries. Pharmacoepidemiology and Drug Safety, 13(3): 181-185.

Paruk F, Richards G, Scribante J *et al*. (2012). Antibiotic prescription practices and their relationship to outcome in South Africa intensive care units: Findings of the prevalence of infection in South African intensive care units (PISA) study. South African Medical Journal, 102(7): 613-616.

Patel SJ and Saiman L. (2012) Principles and strategies of antimicrobial stewardship in Neonatal Intensive care unit. Seminars in perinatology 36 (6): 431-436.

Philip, A.G. and Mills, P.C., 2000. Use of C-reactive protein in minimizing antibiotic exposure: Experience with infants initially admitted to a well-baby nursery. Pediatrics, 106(1): e4-e4.

Pineda LC and Watt KM (2015). New antibiotic dosing in infants. Clinics in Perinatology, 42(1): 167-176.

Rogawaski ET, Platts-Mills J, Seidman JC *et al*. (2017). Use of antibiotics in children younger than two years in eight countries: a prospective cohort study. Bulletin of the World Health Organization, 95(1): 49

Russell AB, Sharland M, Heath PT (2012). Improving antibiotic prescribing in neonatal units: time to act. Archives of Disease in Childhood - Fetal and Neonatal Edition 97: F141-F146.

Shankar RP, Partha P, Shenoy NK *et al.* (2003). Prescribing patterns of antibiotics and sensitivity patterns of common microorganisms in the Internal Medicine ward of a teaching hospital in Western Nepal: a prospective study. Annals of Clinical Microbiology and Antimicrobials, 2(1): 7.

Shehab El-Din, Eman M. Rabie *et al*. (2015). Epidemiology of Neonatal Sepsis and Implicated Pathogens: A Study from Egypt. Bio Med Research International.

Shipp KD, Chiang T, Karasick S, *et al*. (2016). Antibiotic stewardship challenges in a referral neonatal intensive care unit. American Journal of Perinatology, 33(5): 518-524.

Sivanandan S, Soraisham AS, and Swarnam K, (2011). Choice and Duration of Antimicrobial Therapy for Neonatal Sepsis and Meningitis. International Journal of Pediatrics.

Sprenger M and Fukuda K (2016). New mechanisms, new worries. Science, 351(6279): 1263-1264.

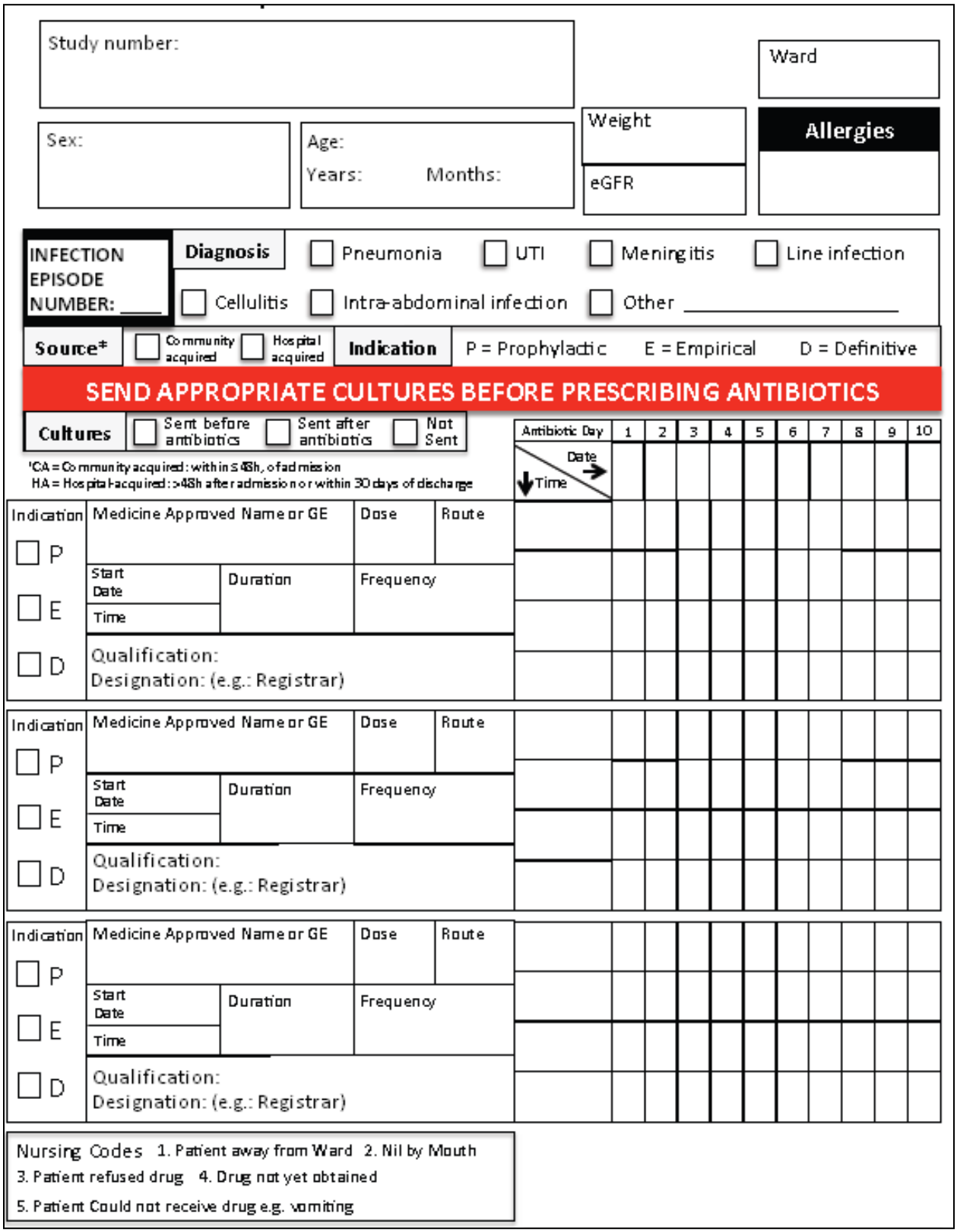
Spyridis N, Syridou G, Goossens H *et al*. (2016). Variation in paediatric hospital antibiotic guidelines in Europe. Archives of Disease in Childhood, 101(1): 72-76.

Tzialla C, Borghesi A, Serra G *et al*. (2015). Antimicrobial Therapy in Neonatal Intensive Care Unit. Italian Journal of Pediatrics 41(1): 27

Thursky, K.A., Buising, K.L., Bak, N*et al.* (2006). Reduction of broad-spectrum antibiotic use with computerized decision support in an intensive care unit. International Journal for Quality in Health Care, 18(3): 224-231.

Vindenes T, Beaulac KR and Doron S. (2016). The legislative momentum of antimicrobial stewardship: An International Perspective. Current Treatment Options in Infectious Diseases, 8(2): 72-83.

Appendix 1: Modified version of the South African Antibiotic Prescription Chart



Study number:

Ward

Sex:

Age:
Years: Months:

Weight

eGFR

Allergies

INFECTION EPISODE NUMBER: ____

Diagnosis ☐ Pneumonia ☐ UTI ☐ Meningitis ☐ Line infection
☐ Cellulitis ☐ Intra-abdominal infection ☐ Other _____

Source* ☐ Community acquired ☐ Hospital acquired

Indication P = Prophylactic E = Empirical D = Definitive

SEND APPROPRIATE CULTURES BEFORE PRESCRIBING ANTIBIOTICS

Cultures ☐ Sent before antibiotics ☐ Sent after antibiotics ☐ Not Sent

*CA = Community acquired: within ≤48h of admission
HA = Hospital-acquired: >48h after admission or within 30 days of discharge

Antibiotic Day	1	2	3	4	5	6	7	8	9	10
Date → / Time ↓										

Indication ☐ P ☐ E ☐ D
Medicine Approved Name or GE | Dose | Route
Start Date / Time | Duration | Frequency
Qualification:
Designation: (e.g.: Registrar)

Indication ☐ P ☐ E ☐ D
Medicine Approved Name or GE | Dose | Route
Start Date / Time | Duration | Frequency
Qualification:
Designation: (e.g.: Registrar)

Indication ☐ P ☐ E ☐ D
Medicine Approved Name or GE | Dose | Route
Start Date / Time | Duration | Frequency
Qualification:
Designation: (e.g.: Registrar)

Nursing Codes 1. Patient away from Ward 2. Nil by Mouth
3. Patient refused drug 4. Drug not yet obtained
5. Patient Could not receive drug e.g. vomiting

Appendix 2: Hang time

Prescribed Antibiotic	2016 Hang time(minutes) Avg (Min-Max)	2017 Hang time(minutes) Avg (Min-Max)
Ampicillin	99 (25-200)	205(30-510)
Amikacin	166 (30-560)	65(10-120)
Cefotaxime	155 (0-325)	167(60-465)
Ceftriaxone	70 (0-140)	26(24-30)
Cefazolin	157 (15-300)	190(0-315)
Co-amoxiclav	124 (60-263)	81(0-333)
Co-trimoxazole	146 (80-240)	N/A
Colistin	N/A	236(236-236)
Cloxicillin	126 (15-236)	120(120-120)
Chloramphenicol	N/A	N/A
Doxycycline	N/A	0
Ertapenem	270 (270-270)	N/A
Erythromycin	178 (25-420)	N/A
Gentamicin	85 (25-200)	160(35-285)
Imipenem/cilastin	153 (0-600)	N/A
Meropenem	235 (140-330)	113(15-420)
Piperacillin/tazobactam	138 (50-330)	46(0-120)
Rifampicin	N/A	0
Vancomycin	141 (30-375)	70(15-150)

Appendix 3: Diagnosed Conditions

Diagnosed conditions 2016	**Diagnosed conditions 2017**
Meconium Aspiration (Medical)	Head injury, extradural hemorrhage(Surgery)
Post Adnectomy & Tonsillectomy (Surgery)	ILEO- colic intussusception(Surgery))
Respiratory distress syndrome (Medical)	AKI (Medical)
Pneumonia (Infection)	Intussusception, post exploratory laparotomy and hemicolectomy (Surgery)
SIMD (Medical)	Spontaneous bacterial peritonitis (Infection)
Respiratory distress syndrome (Medical)	Bowel obstruction of distal ileum day1 post laparotomy (Surgery)
Bronchospasm (Medical)	Laparotomy, jejunal atresia, sepsis (Infection)
Perforated necrotizing enterocolitis (infection)	Pneumoperitoneum Medical)
Congenital heart block (Medical)	TBM stage 3, milirary TB, septic shock (Infection)
Correction of sclerosis and vertebrae column resection (Surgery)	Tonsillectomy (Surgery)
Insertion of VP shunt (surgery)	Nephrectomy/Laparotomy (Surgery)
Cyanotic heart disease (Medical)	Hepatoblastoma (Medical)
Post repair cleft palate (Surgery)	Cyanotic heart disease, critical pulmonary sepsis (Infection)
Post EVD and myelomeningocele repair (Surgery)	Post-surgery posterior fossa mass resection (Surgery)
Incision and drainage RT-Tibig (Surgery)	Previous tracheoesophageal repair, duodenal stenosis cardiac arrest, tracheostomy (Surgery)
Exploratory Laparotomy for bowel obstruction (Surgery)	Previous tof repair, rigid oesophagoscopy for coin removal (Surgery)
LBW Gastroschisis (Surgery)	Traumatic brain injury, subarachnoid hemorrhage, left parietal subdural skull fracture (Surgery)
MSL Grade III (medical)	T18- Known to RMHC, community acquired pneumonia (Infection)
Pulmonary Hemorrhage (Medical)	Ex prem, prev nec- bowel obstruction adhesions (Surgery)
VP Shunt (Surgery)	Pyoderma gangrenous stridor, necrotic ulcers (Medical)
RDS (Medical)	Tonsillectomy (Surgery)
PCP (infection)	Nephrectomy/Laparotomy (Surgery)
Hereditary multiple Osteochondromas (Medical)	Hepatoblastoma-post (Medical)
Coarctution of aorta (Surgery)	Cyanotic Heart disease- critical pulmonary stenosis (Medical)
Respiratory distress Preterm (Medical)	Post-surgery posterior fossa mass resection (Surgery)
Crainostomy PVA MVA (Surgery)	Pneumothorax (Infection)

Diagnosed conditions 2016	Diagnosed conditions 2017
Incision and Drainage RT-Tibig (Surgery)	Previous tracheoesophageal repairs/Duodenal stenosis (Surgery)
Hemicolectomy ileostomy (Surgery)	Twin/hmd-svt-ippv- method for ventilation
GNB sepsis (Infection)	RVD exposed/gastroschisis (Surgery)
Bronchopneumonia (Infection)	Meconium Aspiration syndrome(medical)
Severe respiratory distress, metabolic acidosis, rash(medical)	Hmd-svt-ncpap/preterm method for ventilation
Jugular artery repair(surgery)	Malrotation volvulus(surgery)
Perforated NEC(surgery)	Spinalbifida, Meningitis(Infection)
Respiratory distress syndrome(Medical)	Ulcer left foot (Medical)
Gastrossclosis(surgery)	Hydrocephaly(medical)
Exploratory Laparotomy(surgery)	Pneumonia(infection)
Nosocomial infection/Pneumonia(infection)	Anemia/seizures(medical)
Sepsis(infection)	Rectal Perforation(Surgery)
Bilateral inguinale hernia repair(surgery)	Malrotation(Surgery)
Debridement of right hand(surgery)	
Post exploratory Laparotomy(surgery)	
Severe respiratory acidosis, NEC, Sepsis(infection)	
Post cricoid split(surgery)	
Meningococcal hydrocephalous(infection)	

Appendix 4: Protocol approval

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

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

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

18 July 2017
Person No: 336759
PAG

Mr NS Sinyela
3962 Natrium Street
Clayville Ext 34
Olifantsfontein
1666
South Africa

Dear Mr Sinyela

Master of Science in Medicine: Approval of Title

We have pleasure in advising that your proposal entitled *The usage of antibiotics in paediatric patients while admitted to the intensive care unit at a public tertiary hospital* has been approved. Please note that any amendments to this title have to be endorsed by the Faculty's higher degrees committee and formally approved.

Yours sincerely

Mrs Sandra Benn
Faculty Registrar
Faculty of Health Sciences

Appendix 5: Ethical clearance letter

R14/48 Mr Nkhumiseni Sinyela

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M1703110

NAME: (Principal Investigator)	Mr Nkhumiseni Sinyela
DEPARTMENT:	Pharmacy and Pharmacology Charlotte Maxeke Johannesburg Academic Hospital
PROJECT TITLE:	The Usage of Antibiotics in Paediatrics Patients While Admitted to the Intensive Care Unit at a Public Tertiary Hospital
DATE CONSIDERED:	Adhoc
DECISION:	Approved unconditionally
CONDITIONS:	Sub-Study (M141141)
SUPERVISOR:	Mrs Deanne Johnston
APPROVED BY:	Professor P. Cleaton-Jones, Chairperson, HREC (Medical)

DATE OF APPROVAL: 03/05/2017

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary 3rd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand. I/We fully understand the the conditions under which I am/we are authorised to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated from the research protocol as approved, I/we undertake to resubmit to the Committee. **I agree to submit a yearly progress report.** The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially review in March and will therefore be due in the month of March each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature

Date 10/5/17

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix 6: Hospital approval letter



GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL

Enquiries:
Mr. J. Maepa
Office of the Clinical Director
Tell: (011) 488-3365
Email:Johannes.maepa@gauteng.gov.za
16 November 2015

Dear Ms D Johnston and Ms Y van Deventer

STUDY TITLE: Situational analysis of antibiotic stewardship in Gauteng Public Hospitals.

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

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

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

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

Supported/~~not supported~~

Dr. M.E Mofokeng
Clinical Director
DATE:

Approved/~~not approved~~

CEO

Ms. G. Bogoshi
Chief Executive Officer
DATE: 19/11/2015

Appendix 7: 2016 Doses given versus calculated SAMF doses

Patient Numbers		Antibiotic 1			Antibiotic 2			Antibiotic 3			Antibiotic 4			Antibiotic 5
	Antibiotic	**Dose Given**	**SAMF(2016) Dose**	**Antibiotic**	**Dose Given**	**SAMF (2016)Dose**	**Antibiotic**	**Dose Given**	**SAMF (2016)Dose**	**antibiotic**	**Dose Given**	**SAMF (2016)Dose**	**Antibiotic**	**Dose Given**
2016/1	Tazocin	2.6	2.71	Amikacin	400	406	Cloxicillin	1	1.4					
2016/2	Augmentin	250	380											
2016/3	Ampicillin	150	153	Gentamycin	15	18								
2016/4	Ampicillin	55	55	Gentamycin	5	6.5								
2016/5	Ampicillin	200	235	Gentamycin	20	38								
2016/6	Ertapenem	280	285	Vancomycin	200	285	Amikacin	280	342					
2016/7	Ampicillin	230	220	Gentamycin	22	26	Bactrim	40	44					
2016/8	Kefzol	120	184	Cefotaxime	190	184	Imipenem	75	92	Vancomycin	55	55		
2016/9	Amikacin	375	375	Tazocin	1	2.5								
2016/10	Imipenem	37	37	Vancomycin	22	22								
2016/11	Ampicillin	280	280	Gentamycin	30	33	Erythromycin	55	56					
2016/12	Vancomycin	30	42	Imipenem	70	71								
2016/13	Vancomycin	18	24	Imipenem	40	41	Amikacin	24	24					
2016/14	Tazocin	250	340	Amikacin	50	51	Erythromycin	35	34					
2016/15	Cloxicillin	210	215	Cefotaxime	250	215								
2016/16	Vancomycin	10	16	Imipenem	25	27								
2016/17	Imipenem	38	48	Vancomycin	20	28								
2016/18	Ampicillin	220	220	Gentamycin	20	26	Bactrim	38	44	Tazocin	400	440	Amikacin	60
2016/19	Imipenem	40	40	Vancomycin	16	24								
2016/20	Augmentin	100	170	Vancomycin	34	51								
2016/21	Augmentin	300	500											
2016/22	Imipenem	29	30	Vancomycin	16	18								
2016/23	Kefzol	700	1250	Amikacin	375	375	Tazocin	1	2.5					
2016/24	Augmentin	100	170	Cefotaxime	85	85								

Patient Numbers		Antibiotic 1			Antibiotic 2			Antibiotic 3			Antibiotic 4			Antibiotic 5
	Antibiotic	**Dose Given**	**SAMF(2016) Dose**	**Antibiotic**	**Dose Given**	**SAMF (2016)Dose**	**Antibiotic**	**Dose Given**	**SAMF (2016)Dose**	**antibiotic**	**Dose Given**	**SAMF (2016)Dose**	**Antibiotic**	**Dose Given**
2016/25	Imipenem	60	57	Vancomycin	25	34	Meropenem	60	46					
2016/26	Cefotaxime	270	200	Bactrim	60	54	Ampicillin	200	200					
2016/27	Imipenem	30	26	Meropenem	40	42								
2016/28	Imipenem	45	46	Vancomycin	17	28								
2016/29	Ampicillin	70	72	Gentamycin	7	9								
2016/30	Ampicillin	180	180	Gentamycin	18	21								
2016/31	Ampicillin	90	87	Gentamycin	9	10	Imipenem	50	43					
2016/32	Imipenem	36	29	Vancomycin	12	18								
2016/33	Imipenem	30	29	Vancomycin	12	17								
2016/34	Kefzol	100	120											
2016/35	Ampicillin	72	72	Gentamycin	7	7	Imipenem	35	36					
2016/36	Augmentin	60	110	Imipenem	44	55	Vancomycin	22	33					
2016/37	Augmentin	360	600											
2016/38	Gentamycin	5	6	Imipenem	20	26	Vancomycin	15	15					
2016/39	Ceftriaxone	140	141	erythromycin	28	28	Tazocin	280	283	Amikacin	42	42		
2016/40	Rocephin	N/A												

Appendix 8: 2017 Doses given versus calculated SAMF doses

Patient Numbers		Antibiotic 1			Antibiotic 2			Antibiotic 3			Antibiotic 4			Anti
	Antibiotic	**Dose Given**	**SAMF(2016) Dose**	**Antibiotic**	**Dose Given**	**SAMF (2016)Dose**	**Antibiotic**	**Dose Given**	**SAMF (2016)Dose**	**antibiotic**	**Dose Given**	**SAMF(2016) Dose**	**Antibiotic**	**Dose**
2017/1	Vancomycin	15	16	Meropenem	45	45								
2017/2	n/a			n/a			n/a							
2017/3	Meropenem	70	71	Vancomycin	26	27	Cefotaxine	120	89	Colistin	80000	75000		
2017/4	Meropenem	240	240	Vancomycin	186	80								
2017/5	Meropenem	65	63	Vancomycin	24	23								
2017/6	Ampicillin	160	161	Gentamycin	16	19	Meropenem	65	64	Vancomycin	48	48		
2017/7	Ampicillin	56	56	Gentamycin	5.6	6.7	Meropenem	42	45	Vancomycin	15	17		
2017/8	Ampicillin	190	185	Gentamycin	19	22								
2017/9	Augmentin	43	43	Meropenem	120	114	Vancomycin	40	43	Cefotaxime	190	143		
2017/10	Augmentin	120	132											
2017/11	Ampicillin	55	55	Gentamycin	5.5	6.6								
2017/12	Cefotaxime	400	595	Cloxacillin	600	595	Augmentin	325	595					
2017/13	Ampicillin	100	100	Gentamycin	10	12								
2017/14	Meropenem	48	48	Vancomycin	18	18	Colistin	48000	75000					
2017/15	Cefazolin	360	165/550											
2017/16	Meropenem	45	45	Vancomycin	17	17	Colistin	45200	45200					
2017/17	Augmentin	360	580	Meropenem	465	464	Vancomycin	175	174					
2017/18	Meropenem	56	56	Vancomycin	14	21								
2017/19	Meropenem	125	132	Vancomycin	50	50								
2017/20	Meropenem	36	37	Vancomycin	14	14								
2017/21	Cefazolin	200	210											
2017/22	Cefotaxime	140	105											
2017/23	Ampicillin	125	128	Gentamycin	12.5	15								
2017/24	Ceftriaxone	375	375											

Patient Numbers		Antibiotic 1			Antibiotic 2			Antibiotic 3			Antibiotic 4			Anti
	Antibiotic	**Dose Given**	**SAMF(2016) Dose**	**Antibiotic**	**Dose Given**	**SAMF (2016)Dose**	**Antibiotic**	**Dose Given**	**SAMF (2016)Dose**	**antibiotic**	**Dose Given**	**SAMF(2016) Dose**	**Antibiotic**	**Dose**
2017/25	Augmentin	250	450											
2017/26	Meropenem	43	43	Vancomycin	16	16								
2017/27	Cefazolin	400	600	Meropenem	480	480	Vancomycin	180	180					
2017/28	Ampicillin	100	98	Gentamycin	9.5	12								
2017/29	Cefazolin	1g	1.9											
2017/30	Cefotaxime	275	205	Meropenem	160	164	Vancomycin	60	61					
2017/31	Meropenem	80	104											
2017/32	Augmentin	145	240	Meropenem	205	192	Vancomycin	77	72					
2017/33	Augmentin	120	185											
2017/34	Ceftriaxone	1800	1350	Doxycycline	100	90	Rifampicin	360	360					
2017/35	Ampicillin	47	48	Gentamycin	4.7	5.7								
2017/36	Augmentin	180	280	Vancomycin	115	84	Amikacin	85	84					
2017/37	Meropenem	55	54	Vancomycin	21	21	Cefotaxime	88	69	Chloramphenicol	Not clear	55	Colistin	5280
2017/38	Ampicillin	130	133	Gentamycin	13	16								
2017/39	Augmentin	65	110											
2017/40	Augmentin	325	650											
2017/41	Tazocin	2	2.6	Amikacin	400	390								
2017/42	Ampicillin	150	152	Gentamycin	15	18								
2017/43	Meropenem	138	138	Vancomycin	52	52								
2017/44	Augmentin	180	305											
2017/45	Augmentin	225	450	Tazocin	900	900	Amikacin	135	135					
2017/46	Cefotaxime	200	175	Vancomycin	53	53								
2017/47	Meropenem	32	32	Vancomycin	12	12								
2017/48	Ampicillin	150	153	Gentamycin	15	19								
2017/49	Tazocin	550	740	Meropenem	140	148								

Patient Numbers		Antibiotic 1			Antibiotic 2			Antibiotic 3			Antibiotic 4			Anti
	Antibiotic	**Dose Given**	**SAMF(2016) Dose**	**Antibiotic**	**Dose Given**	**SAMF (2016)Dose**	**Antibiotic**	**Dose Given**	**SAMF (2016)Dose**	**antibiotic**	**Dose Given**	**SAMF(2016) Dose**	**Antibiotic**	**Dose**
2017/50	Augmentin	120	225											
2017/51	Meropenem	40	45	Vancomycin	17	17								
2017/52	Ceftriaxone	2	3.2											
2017/53	Meropenem	450	440	Vancomycin	170	165	Amikacin	165	165					
2017/54	Ampicillin	100	109	Tazocin	100	109	Meropenem	40	44					
2017/55	Tazocin	280	289	Amikacin	20	43	Vancomycin	28	44					
2017/56	Augmentin	150	295	Meropenem	120	118	Vancomycin	90	89					
2017/57	Meropenem	124	124	Vancomycin	47	47								