A RETROSPECTIVE EVALUATION OF ANTIMICROBIAL MANAGEMENT AMONG PATIENTS WITH SEPSIS IN INTENSIVE CARE UNIT (ICU) AT GABORONE PRIVATE HOSPITAL IN BOTSWANA

A MINI THESIS SUBMITTED IN PARTIAL FULFILMENT OF THE REQUIREMENTS

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CHARLES WAITSE JOLOMBA

218219966

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MAIN SUPERVISOR: PROF LAUREN JONKMAN (UNIVERSITY OF NAMIBIA)

CO-SUPERVISOR: PROF DAVE HACHEY (IDAHO STATE UNIVERSITY)

ABSTRACT

Sepsis, a life-threatening response to infection, demands swift and precise antimicrobial intervention. Even though antimicrobial guidelines crafted in high-income countries are employed in low-income settings, these regions encounter unique challenges, including differences in pathogen ecology, high HIV co-infection rates, prevalent comorbidities, and frequent antimicrobial shortages. Such challenges can lead to deviations from standard guidelines, impacting sepsis management and potentially influencing mortality rates. This research adopted a quantitative cross-sectional approach aimed to scrutinize the appropriateness of antimicrobial treatment for sepsis and to determine the susceptibility patterns of prevalent pathogens among sepsis patients in an ICU at a private hospital in Gaborone. A time period prior to COVID-19 was selected to avoid the effects of the pandemic on prescribing. This study used a total population sample of 132, where all patients meeting the inclusion criteria in the selected data range were included. Results show central nervous system infections are the most prevalent infectious source, constituting 20.5% of cases. Notably, even though a substantial proportion of empirical antibiotic treatments are confined to standard guidelines, utilization of local guidelines was associated with an increased odds of death, which requires further study and evaluation. (OR 3.68, CI 1.28-10.6, p=0.012), The study underscores the importance of regularly updating guidelines to reflect current practices, ensuring optimized sepsis management.

Keywords: Sepsis, Antimicrobial Stewardship, Antibiotic resistance, Low- and Middle-Income Countries, Empirical Antibiotics, Botswana, ICU, Patient Outcomes.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS/ACRONYMS

CKD	Chronic Kidney Disease
HIC	High Income Countries
HIV	Human Immunodeficiency Virus
ICU	Intensive Care Unit
LMIC	Low to Middle Income countries
qSOFA	Quick Sequential Organ Failure Assessment
SD	Standard Deviation
SIRS	Systemic Inflammatory Response Syndrome
SSA	Sub-Sahara Africa
SSC	Surviving sepsis Campaign
MSSA	Methicillin Sensitive Staphylococcus Aureus
AMR	Antimicrobial Resistance
MDR	Multi-Drug Resistant
CRP	C-Reactive Protein
PCT	Procalcitonin
APACHE II	Acute Physiology and Chronic Health Evaluation

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Finally, and most importantly, I want to thank all the participants in the sepsis study for their contributions to science and the betterment of care for future patients in the hospital and Botswana.

DEDICATION

This work is dedicated to my father John Jolomba and my Children, Elang Atang and Gia

Thank you for all your support and motivation throughout my life. This work would not be possible without your love, and inspiration to do more in life.

DECLARATIONS

I, Charles Jolomba, hereby declare that this study is my own work and is a true reflection of my research, and that this work, or any part thereof has not been submitted for a degree at any other institution.

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Charles Jolomba		October 2024
Name of Student	Signature	Date

1. INTRODUCTION

Sepsis is a life-threatening medical condition resulting from an abnormal host response to infection. Sepsis is a life-threatening condition caused by the body's excessive response to infection, leading to organ dysfunction (1). Naturally, sepsis is a highly intricate illness, and its progression can vary significantly among individuals. Diagnosing sepsis often depends on the clinician's overall clinical judgment, as definitive microbiological proof of an underlying infection is frequently absent. Management of sepsis includes the processes of resuscitation, organ support and eliminating the primary infection. Antimicrobials are the cornerstone for the management of sepsis. Most antimicrobial guidelines for the management of sepsis are formulated in high income countries (HICs). However, in Sub-Saharan Africa (SSA), the high prevalence of HIV co-infection along with different ecologies of pathogenic organisms makes the application of those guidelines unclear (1-2). Botswana, an upper middle-income country in southern Africa has a high incidence of patients with comorbidities and frequent shortages of antimicrobials leading to the need to deviate from sepsis guidelines, which may impact sepsis management, and consequently, affect mortality. Comprehensive epidemiological information regarding the antimicrobial treatment of sepsis in Low-Middle Income Countries (LMICs) is currently lacking.

1.1 Background to the study

Sepsis is the most primary reason for both admission to and mortality in the intensive care unit (ICU) (4). Globally, approximately 19 million cases of sepsis and 5 million deaths related to sepsis are reported each year (5). While in LMICs sepsis significantly contributes to maternal and neonatal morbidity and mortality, the true incidence is not

well known or documented (6). In HICs, approximately 6–30 percent of all patients admitted to ICUs develop sepsis with resulting morbidity and mortality (21 and 28 percent, respectively) (7). Nations in SSA have a disproportionately high sepsis mortality rate compared to HICs due to factors such as limited access to resources, delay in administration of antibiotics and lack of uniformity in antibiotic administration (3). Inappropriate or suboptimal use of antibiotics can lead to multidrug-resistance and mortality, particularly in ICU patients with sepsis and septic shock(8).

1.2 Problem statement

In LMICs in SSA, mortality rates from sepsis are higher than in HICs and may be related to inappropriate antibiotic management. In Botswana, there is a lack of documented data regarding both the mortality rate linked to sepsis and the proper use of antibiotics in sepsis management; as a result, their values are unknown. The purpose of this study is to fill the knowledge gaps regarding antibiotic use in sepsis management in Botswana using primary evidence.

1.3 Objectives

Aim

To evaluate the adequacy of antimicrobial therapy for sepsis at a private hospital in Gaborone.

Specific objectives

1. To identify common sites of infection and common pathogens isolated among patients with sepsis admitted to the ICU at a private hospital in Gaborone.

2. To assess the susceptibility pattern of organisms isolated in patient with sepsis admitted to the ICU at a private hospital in Gaborone.
3. To assess the appropriateness of antimicrobial therapy among sepsis patients admitted to the ICU at a private hospital in Gaborone.
4. To document the outcome of the management of patients with sepsis admitted to the ICU in a private hospital in Gaborone.

1.4 Significance of the study

As sepsis recommendations for antibiotic use are generally informed by research in HICs, there is a need for data to inform practice in LMICs. By focusing this research on sepsis in Botswana, the Ministry of Health in Botswana, the World Health Organization, Private and Public Hospitals and Clinics within and beyond Botswana will benefit from new sepsis management information. The results may inform clinicians and policymakers to aid in the development of clinical pathways and treatment algorithms, ultimately leading to more appropriate use of antibiotics, a decrease in multidrug resistance and ICU mortality. This research may contribute evidence-based information to the improvement of sepsis management in LMICs such as Botswana, South Africa, and Namibia, and stimulate additional prospective studies on sepsis in these nations.

1.5 Limitation of the study

The study is limited to a single institution, and its findings may not be representative of other institutions. Incomplete patient medical information may hinder data collection and undermine the study's credibility. The management of sepsis at Gaborone Private Hospital may not be representative of practices at other facilities in

Botswana and in the surrounding region. Even though the study is examining the appropriateness of antibiotic selection for sepsis management, antibiotics alone cannot be used to determine the effect of antibiotics on sepsis mortality.

1.6 Delimitation

The study is limited to the antimicrobial management of patients with sepsis in the ICU at Gaborone Private Hospital. This hospital was selected as it is the primary workplace of the primary investigator. As such key information about antibiotic use and outcomes in this ICU can be used to improve care in this area. Only the medical records of patients diagnosed with sepsis were evaluated. Complete patient files were utilized to ensure the validity of the research. Only patients admitted for longer than three days will be enrolled in the study. As this study was developed prior to the COVID pandemic, the decision was to focus on sepsis management prior to the pandemic. The ICU at Gaborone Private Hospital was restricted during the pandemic to only COVID patients, therefore the dates included for the chart review were from the period immediately before the outbreak of cases in Botswana.

2. LITERATURE REVIEW

This section presents a literature review of the study. In reviewing the literature, theories, models and frameworks are discussed by various authors. The idea is to evaluate areas of common discussions and existing gaps in the overall discussions.

2.1 Theoretical concepts

The last three decades have made substantial efforts in categorizing, diagnosing, and systematically treating sepsis. During this time, the definition and diagnostic criteria

for sepsis have been revised, eliminating the concept of severe sepsis and instead categorizing the condition into sepsis and septic shock (9). Sepsis is a life-threatening condition resulting from a dysregulated response to systemic infection, necessitating the presence of signs of systemic inflammatory response syndrome (SIRS) along with a potential infection source (10). Septic shock, a subset of sepsis, is characterized by severe circulatory, cellular, and metabolic abnormalities, substantially increasing the risk of mortality (11). The screening for sepsis utilizes the quick sepsis-related organ failure assessment (qSOFA) score, which is based on three variables: respiratory rate, mental status, and diastolic pressure (9 , 12). However, SIRS criteria are still utilized to determine sepsis in sub-Saharan countries (3).

The underlying cause of sepsis is infection. Next patients develop bacteraemia where the infection spreads to the bloodstream. Then patients with sepsis develop signs of an abnormal inflammatory response. Septic shock is characterized by the combination of sepsis, the requirement for vasopressors to sustain mean arterial pressure, and an elevated lactate level despite adequate fluid resuscitation (13). Since the underlying pathology is the infection, antimicrobial therapy is a key component of treatment (14). A conceptual framework of sepsis is provided in figure 1.

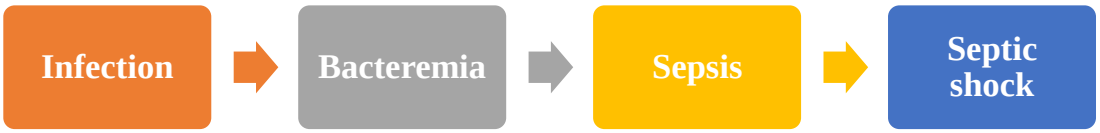

Figure 1: Conceptual framework of infection to septic shock.

2.2 Burden of sepsis in LMICs

In 2017, the United Nations World Health Assembly acknowledged sepsis as a global health priority and passed a resolution to enhance its prevention, diagnosis, and

management on a global scale (15). That said, there are no effective strategies for alleviating the impact of sepsis in Low-Middle Income Countries (LMICs), possibly due to the fact that current scientific evidence and guidelines for sepsis management predominantly come from High-Income Countries (HICs) (16). Furthermore, in Sub-Saharan African (SSA) nations, the additional challenge of HIV and tuberculosis infections imposes a substantial burden on the healthcare system and could complicate the management of sepsis. Sepsis has been implicated in 25% of deaths related to HIV/AIDS diagnoses (9).

The majority of the global sepsis burden takes place in LMICs (5). However, the burden is not well understood given the lack of laboratory infrastructure that has excluded an assessment of pathogens leading to sepsis. The lack of antibiotic and microbiological stewardship complicates the management of sepsis in lower-resourced LMICs (17). Currently, there have been no clinical trials conducted to evaluate the appropriateness of specific antibiotic treatments, despite numerous studies indicating the detrimental effects of even slight delays in administering antibiotics (11). The early identification and proper management of sepsis are similar to stroke, acute myocardial infarction and polytrauma management. Meaning that early management in the first hours soon after sepsis develops can improve the outcome (18).

2.3 Surviving Sepsis Campaign

Compelling literature demonstrates the association between adherence to clinical care bundles and survival of patients dealing with sepsis (19). The management of sepsis is supported by SSC measures which have been acknowledged across the globe. For example, in the United States, these SSC measures have been adopted by the National Quality Forum.

Table 1 Surviving Sepsis Campaign Bundles of Care

Bundle element	**Level of evidence**
Measure lactate level. Remeasure if initial lactate is >2 mmol/L	Weak recommendation, low quality of evidence
Obtain blood cultures prior to administration of antibiotics	Best practice statement
Administer broad-spectrum antibiotics	Strong recommendation, moderate quality of evidence
Begin rapid administration of 30ml/kg crystalloid for hypotension or lactate ≥ 4mmol/L	Strong recommendation, low quality of evidence
Apply vasopressors if patient is hypotensive during or after fluid resuscitation to maintain mean arterial pressure (MAP) ≥65 mmHg	Strong recommendation, moderate quality of evidence

Adopted from: Levy et al. (2018)

Paramount in sepsis patient management is to consider the condition a medical emergency. Prompt identification and addressing of sepsis within the initial hours of development is key in ensuring fluid resuscitation, controlling the source of infection, ordering further tests in the laboratory, and ensuring precise hemodynamic status measurements (18). Patients with sepsis need thorough evaluation and continuous reassessment of treatment responses. The elements outlined in table 1 above requires implementation within the first hour. Broad-based literature has demonstrated the

association between the implementation of these bundle elements as part of quality improvement initiatives with improved outcomes. For example, a study conducted in three hospitals under the Los Angeles County Department of Health Services showed a reduced overall mortality rate among individuals who received care adherent to the bundle, as opposed to those who did not (17.9% vs. 20.4%; p=0.035) (20).

2.4 Most common pathogens isolated among sepsis patients within ICUs

Sepsis and septic shock can be a result of an infection occurring anywhere in the body, such as the lung, skin, urinary tract and bloodstream infection. Pathogens responsible for sepsis follow the most common pathogens for each infection source. While the majority of sepsis cases arise from bacterial infections, individuals with comorbid conditions and immunosuppression may exhibit viruses and fungi as causative agents (6). most prevalent bacteria identified in bloodstream isolates include *Staphylococcus aureus, Escherichia coli, Klebsiella spp, Pseudomonas aeruginosa*, enterococci, streptococci, and coagulase-negative staphylococci. (6). Ullan et al. (2016) recognised the role that viral and fungal infections contribute to sepsis mortality (6). That said, gram-negative infections still cause the overwhelming majority of sepsis cases, and *Streptococcus pneumonia* and *Staphylococcus aureus* are the leading gram-positive organisms contributing to sepsis infections (7).

In adult sepsis, the predominant causative pathogens were identified as *E. coli, K. pneumoniae* and methicillin sensitive S. aureus (MSSA) (21). Despite previous studies often designating *E. coli* as the most common pathogen in severe infectious diseases, *K. pneumoniae*, and MSSA are common in adult sepsis. Moreover, various studies have consistently shown that *Staphylococcus aureus* is a predominant isolated microorganism among gram-positive pathogens (22). While bacterial infections are

the predominant type of infection in adults and children with sepsis, it is noteworthy that parasitic infections, including *Entamoeba histolytica, Giardia lamblia*, and intestinal worms, emerge as the third most prevalent cause of sepsis in both age groups in LMICs. This pattern is rarely reported in sub-Saharan Africa, representing a significant contrast with the epidemiology observed in HICs (1). In LMICs, gram-negative microorganisms are the primary culprits for both early- and late-onset sepsis, with these microbes exhibiting elevated rates of antimicrobial resistance (AMR)(23).

2.5 Appropriateness of antimicrobial therapy among sepsis patients admitted into ICU

The Surviving Sepsis Campaign (SSC) published the first international sepsis management guidelines in 2004 (24). The SCC is a collaboration between the Society of Critical Care Medicine in the United States and the European Society of Intensive Care Medicine with aim of reducing sepsis mortality globally. These standards, updated frequently, became the basic standard to be observed by HICs, with most critical care settings considered high-resource settings(25). However, challenges have been observed in implementing the guidelines in LMICs (26).The guidelines recognize some of these challenges and give suggestions for implementation in low-resource settings.

The divergence from established guidelines in prescribing has been deemed "inappropriate" in specific situations, and there is clear evidence of inappropriate prescribing occurring in (LMICs) (23). In low- and middle-income countries (LMICs), recommended antibiotics for bacterial sepsis include intravenous ceftriaxone (1 g daily) or ampicillin (2 g every four hours) along with gentamicin (1.5 mg/kg every eight hours). While these combinations provide comprehensive coverage for

susceptible gram-positive and gram-negative pathogens, they may not be sufficient for addressing other prevalent conditions in sub-Saharan Africa, particularly the high incidence of concurrent HIV infection (3). Hospitalized patients with sepsis admitted in the ICU requires early empirical antimicrobial treatment for a positive outcome (27). The mortality rate can be affected by the timing of initial antibiotic therapy. Dewi et al. (2018) found that increase in mortality and morbidity in sepsis patients is attributed to delays in prescriptions of appropriate antibiotics (25).The retrospective analysis of surgically treated peritonitis cases revealed that the mortality rate was not influenced by the use of inadequate empirical antibiotic therapy. Nevertheless, there was a noticeable rise in morbidity (28). Genga and Russell (2017) recognize that there was an association between early initiation of adequate antibiotic treatments in bacteremia patients with reduction in mortality rate (4). In clinical trials of sepsis, a high frequency of inappropriate empirical therapy was independently associated with high mortality(29). But, others have found that appropriate antibiotic use was not associated with clinical outcomes amongst those with severe infections (30).

In low-income countries the optimal treatment of sepsis is unknown (31). Moreover, in LMICs, antimicrobial resistance is prevalent, making commonly accessible antimicrobials ineffectual (32). Nevertheless, due to the extensive prevalence of multi-drug resistant (MDR) pathogens, the empiric regimens frequently utilized are often inappropriate (33). The Botswana National Guideline incorporates Cefotaxime for effective gram-negative coverage. Cefotaxime is notably beneficial for treating non-typhoidal salmonella, a frequent cause of bacteraemia in Africa, especially among HIV-infected individuals but rare in Botswana (34).

2.6 In-hospital mortality rate among patients with sepsis admitted into the ICU

Dewi et al. (2018) reports that roughly 6-30% of patients admitted to ICU develop sepsis in HICs. There is a disproportionally higher mortality in LMICs than in HICs due to co-infection and ecology of pathogens and resource limitations (3). Furthermore, sepsis and septic shock were the primary causes of morbidity and mortality in ICU representing 21% and 28% respectively in Jakarta, Indonesia (25).

High sepsis and septic shock mortality rates of 64.4% and 82.1%, respectively, were reported in two Rwandan intensive care units (31). In contrast, extensive observational studies in major referral centres in Kenya and Uganda showed sepsis mortality rates ranging from 20.4% to 24.2%, while a rural Ugandan hospital study revealed a notably lower rate of 3.9%(31). A study discovered that ICU sepsis in sub-Saharan Africa had a prevalence of 31% and a mortality rate of 46%. It further indicated that significant regional disparities in sepsis burden were due to factors such as the aging population, differing comorbidities, the burden of infectious diseases and the resources available for sepsis treatment in ICUs (43).

2.7 Studies

The empirical studies are based on other studies in HICs and LMICs.

Busci & Kadri (2020), undertook research on sepsis management in the United States. Based on primary evidence, sepsis mortality has seen improvement due to advancements in early recognition and standardized management, with a focus on promptly administering appropriate antimicrobials. Despite these improvements, guidelines for the duration of antimicrobial treatment in sepsis remain limited. Reduced antibiotic exposure is linked to lower instances of developing de novo resistance, *Clostridioides difficile-associated* disease, antibiotic-related toxicities, and decreased healthcare costs. In sepsis management, there is a need for data comparing

the safety and effectiveness of shorter treatment durations. A narrative review of evidence has been conducted to guide antibiotic duration in sepsis.

Primary evidence was found to be significantly limited by non-inferiority trial designs and many trails excluded critically ill patients. Reducing the duration of antimicrobial treatment in sepsis encounters challenges like inadequate source control, managing multidrug-resistant organisms, and potential pharmacokinetic issues resulting in insufficient antimicrobial levels. Targeting patients with clinical sepsis indicators is essential to develop strategies for safely decreasing antimicrobial exposure in this high-risk group while preserving clinical effectiveness.

In Australia, each year, 5,000 out of 18,000 adults treated for sepsis in intensive care units do not survive. Survivors commonly endure long-term physical, cognitive, and psychological dysfunction, a condition that is often overlooked and left untreated (29). Currently, there are no specific pharmacological treatments for sepsis, emphasizing the critical role of early recognition, resuscitation, and timely administration of appropriate antibiotics to alleviate the consequences of the disease. The fact that the majority of sepsis cases, roughly 70-80%, arise in the community underscores the importance of improving recognition and early management in emergency departments and primary care settings. Case fatality rates for sepsis are on the decline in numerous countries, and this reduction is credited to national or regional screening and quality improvement programs that prioritize early identification and immediate treatment. The strategies for treating established sepsis have been influenced by high-quality, multicentre investigator-initiated randomized trials, with substantial data contributions coming from trials funded by the National Health and Medical Research Council in Australia. While early recognition and enhanced management of the acute episode are crucial for reducing death and disability from sepsis. However, the study

emphasizes that achieving a significant reduction in the burden of sepsis-related disease necessitates comprehensive actions across the entire healthcare system.

In Indonesia, Pradipta et al. (2013) explored the proper choice of empirical antibiotics considering the local antibiotic resistance profile and observed that employing suitable antibiotics can decrease mortality rates and promote the judicious use of antibiotics (35). The study aimed to analyse antibiotic usage patterns and sensitivity profiles, supporting the rational use of antibiotics in sepsis patients. Conducted at an Indonesian hospital from January to December 2011, the retrospective observational study included 76 adult sepsis patients, with data obtained from the hospital's medical record department. The study employed descriptive analysis for data processing and interpretation. Lung infection was identified as the most common source of infection. Among the 66.3% of culture-positive clinical specimens, *Klebsiella pneumoniae*, *Escherichia coli, and Staphylococcus hominis* were the most frequently detected microbes. Notably, the six most commonly used antibiotics (levofloxacin, ceftazidime, ciprofloxacin, cefotaxime, ceftriaxone, and erythromycin) exhibited an average resistance rate surpassing 50%. The study underscores the necessity for a policy promoting rational antibiotic use, given the extensive utilization of antibiotics with heightened resistance levels. The use of local microbial patterns, based on site infection and antibiotic sensitivity data, is deemed crucial for optimizing the appropriateness of empirical antibiotic therapy for patients with sepsis.

Kwizera *et al*. (1) undertook research in Rwanda, a middle-income country in east-central Africa (1). They aimed to identify the epidemiology and outcome of 1 412 adults and children with and without sepsis in a rural sub-Sahara African setting who were admitted for an acute infection. This non-interventional study looked at demographic, clinical, and laboratory data, as well as danger signs, to identify sepsis

(defined as a quick Sequential Organ Failure Assessment score count ≥ 2) upon admission. Sepsis was observed in 69 adults (14.1%) and 248 children (26.9%). Those with sepsis showed differences in various demographic and clinical aspects compared to those without sepsis. Malaria was the predominant infection type in both adults (66.7%) and children (63.7%) with sepsis, followed by suspected bacterial and parasitic infections. Adults with sepsis had higher rates of respiratory failure, in-hospital mortality, lower discharge rates, and increased median costs of care compared to those without sepsis. In children, sepsis was associated with a lower discharge rate. Malaria and respiratory tract infections accounted for the highest absolute numbers of fatalities. The authors concluded that, alongside suspected bacterial, viral, and fungal infections, malaria and other parasitic infections play common and significant roles in causing sepsis among adults and children admitted to a rural hospital in sub-Saharan Africa. The mortality rate associated with sepsis is notably high, particularly among adults.

In Malawi, a low-income African country, Prin *et al.* (17) undertook research based on scarce data describing the aetiology and clinical sequelae of sepsis (17). The study aimed to profile the prevalence and aetiology of sepsis among critically ill patients in a referral hospital in Malawi. Conducted as an observational prospective cohort study, it focused on adults admitted to the intensive care unit or high-dependency unit with sepsis from January 29, 2018, to March 15, 2018. Sepsis was defined using three criteria: a quick sequential organ failure assessment (qSOFA) score of 2, clinical suspicion of systemic infection, and qSOFA score of 2 plus suspected systemic infection. The analysis included clinical characteristics, blood and urine cultures, and antimicrobial sensitivities for positive cultures from 76 out of 103 admitted patients during the study period. The cohort included 39% males, with a median age of 30

(interquartile range: 23–40) years. Sepsis was identified in 24%, 66%, and 16% of patients based on the three definitions, respectively. Out of four positive blood cultures (5%), two were from patients meeting all three sepsis definitions, and two were from those with clinically suspected infection only. All blood bacterial isolates were multidrug-resistant. Among five patients with urinary tract infection, three had sepsis caused by multidrug-resistant bacteria. Hospital mortality ranged from 42% to 75% for patients with sepsis based on the three definitions, compared to 12% to 26% for no sepsis patients.

In conclusion, the mortality linked to sepsis at this hospital was elevated. Bacteremia was seldom identified, but the isolated pathogens exhibited resistance to multiple drugs.

In Uganda, research by Rudd *et al.* (20) was based on scarce information on sepsis in low-resource settings, especially beyond urban referral centres. The study, conducted in May 2013, was a prospective observational single-canter cohort study aimed at evaluating the presentation, management, and outcomes of both adult and pediatric patients admitted with sepsis to a community hospital in rural Uganda. The research method entailed systematically screening all patients admitted to medical wards who met sepsis criteria. Eligible patients underwent assessments within 24 hours of presentation and again within 24-48 hours after admission, with continuous follow-up until hospital discharge. Alongside chart reviews, the study incorporated evaluations of mental status, peripheral capillary oxygen saturation, and point-of-care venous whole blood lactate and glucose. The analysis concentrated on 51 patients (20 adults and 31 children) out of the 56 eligible individuals, revealing a median age of 8 years (IQR 2–23 years). Sepsis accounted for 25% of all adult and paediatric medical ward admissions. The HIV prevalence among adults was 30%. Upon enrolment, over half

of the patients had elevated point-of-care whole blood lactate levels, while few experienced hypoglycaemia or altered mental status, and a third were hypoxic. More than 80% of patients received at least one antibiotic, all severely hypoxic patients received supplemental oxygen, and half of those with elevated lactate underwent fluid resuscitation. Malaria and pneumonia emerged as the primary causes of sepsis. The in-hospital mortality rate was 3.9%.

2.7 Conclusion

Sepsis mortality is high in low-income countries due to resource constraints and high HIV/TB rates. Guidelines from affluent nations may not address unique challenges in sub-Saharan Africa. Inadequate studies in developing countries create a research gap, impacting sepsis management. Theoretical concepts and empirical evidence from diverse developed and developing contribute to understanding sepsis management.

3. RESEARCH METHODS

3.1 Research design

This study employed a retrospective quantitative research approach, with a cross-sectional descriptive design. Data was extracted from the medical records of patients admitted to the ICU with sepsis between 1 March 2019 and 28 February 2020.

Definitions: Appropriate antibiotic management was defined as an antibiotic prescription that satisfied the following: appropriate drug selection (empirical broad spectrum appropriate for the suspected source), appropriate dosage of the drug based on patient factors, sufficient duration as per local guidelines, de-escalation as per sensitivity results, and compliant to administration time (i.e. within 1 hour of diagnosis) as per SCC guideline.

A) Population

Patients admitted at Gaborone Private Hospital ICU between 1st March 2019 to 29th February 2020 who met the criteria for sepsis (i.e. two or more SIRS criteria plus a suspected or confirmed infection). All records during this time that met inclusion criteria were included in the analysis.

***Inclusion criteria*:** Age 18 years and above with sepsis diagnosis

Exclusion criteria: Incomplete file, less than 2 days in ICU, and no antibiotics prescribed.

b) Study setting

The study was conducted at Gaborone Private Hospital ICU, in which patients charts of patients with sepsis would be evaluated. This ICU provides services primarily to adult patients.

3.2 Sample

Open Epi was employed to determine the required sample size, considering a 12% prevalence of sepsis in ICU in developed nations, a 95% confidence interval, P>0.005, and a 5% margin of error, resulting in a sample size of 214. Due to the limited number of medical records meeting the inclusion criteria within the specified data range, this study utilized the entire population sample.

3.3 Research instruments

A data collection tool was developed to collect the key information required. A copy of the tool is provided in Annex 1. The tool was transferred into google forms to assist in data collection and data management. The online version was used in a pilot study to collect the variables of interest for this research and showed to be valid and

reliable in collecting necessary data to answer the research objective. Data to be collected included demographics, antibiotic/s prescribed, dose and duration, time of first administration, co-morbidity, suspected source of infection, organism/s isolated and outcome of therapy.

3.4 Data collection procedure

After ethical approval from the University of Namibia and from the Hospital, data collection began. The ICU has a ward admission book where patient's information and file numbers of every patient who were admitted are documented. This book was used to identify patient's files that were admitted in ICU in the identified period of interest. The documented patient file numbers were used to request specific patient files from filing room. For each file, the investigator identified whether the patient had a diagnosis of sepsis and included only those files in the data collection. For each eligible file, an online form was completed collecting all of the relevant and documented demographic and clinical information.

3.5 Data analysis

After the data was fully collected in the online form, an excel spreadsheet was downloaded from google with the data set. The data was then checked for accuracy and completeness. Each of the variables were summarised using descriptive statistics such as frequency and percentage of events, mean and standard deviation for continuous variables, and proportion of organisms isolated from patients with sepsis. This was conducted using excel. Variables used in the analysis included socio-demographic variables (age, gender, co-morbidities), clinical variables (source of infection, organism isolated and sensitivity results, and mortality), and antibiotic

quality measures (bloods drawn prior to antibiotic, appropriate empiric antibiotics selected based on international and local guidelines, antibiotics administered within one hour of diagnosis, and antibiotics de-escalated after culture results). To identify the relationship between mortality and demographic or quality metrics, chi-square tests were used. Odds ratio for death with 95% confidence intervals was calculated using MedCalc. A p-value of <0.05 was set as statistical significance.

3.6 Reliability and validity

The research tool was reviewed for face-validity by the research team to ensure that it included the key measures to be analysed. Piloting the tool ensured content and face validity of the questionnaire. Benchmarking with similar studies data collection tool also improved the face and content validity of the questionnaire, as a data collection tool.

4 RESEARCH ETHICS

Ethical approval was obtained from the University of Namibia School of Pharmacy Decentralized Ethics Committee and the local Hospital prior to the commencement of the study. The key ethical principles of autonomy, beneficence/non-maleficence, and justice were adhered to. As this was a retrospective chart review, patient consent was not necessary. Only information required for data analysis was collected to reduce risks to patients. Information collected was relevant to the research based on the scope of the study in that no information beyond the agreed information shall be collected, and no name or any data that will identify patients or expose the participants or organisation in the research. All patient information has been kept confidential and protected. The information collected has been captured and stored in a code-locked

laptop only accessed by the researcher. The information shall be kept until the academic results are published and will only be disposed after graduation and publication. The disposal of information will be done through burning of all primary and secondary data collected to avoid any traces. Files and folders where information has been kept will be deleted permanently from the computer. Emphasis is made on research outcomes to not cause any harm, whether physical or emotional to patients or institutions. The research will adhere to the non-maleficence principle, there will be no medical intervention or presentation that will affect the organisation as no hospital name will be used. Quality metrics will be presented to the hospital to develop a plan to improve patient care and outcomes at the hospital.

5. RESULTS

A total of 132 patients with sepsis met the study criteria and were included. The mean age was 42 years ± 12.7. The majority were female (n=78, 59%). Hypertension was the most common underlying comorbidity (n=36, 35.6%) followed by HIV (n=37, 28%), diabetes (n=36, 27%), and cancer (n=36, 27%). Surprisingly, 21.2% of patients present with no co-morbidities. The characteristics of subjects at enrolment are given in Table 2.

Table 2: Characteristics of sepsis patients admitted to the intensive care unit of Gaborone Private Hospital

Characteristics	n=132	%
Gender		
Male	54	40.9
Female	78	59.1
Age, years (mean, SD)	42 ±12.7	
<65 years	122	92
≥65 years	10	8
Type of admission		
Direct admission	50	37.9
Transfer	82	62.1
Comorbidities		
Hypertension	47	35.6
Diabetes	36	27.3
HIV	37	28
Cancer	36	27.2
Respiratory disorder (includes tuberculosis)	24	18.2
Chronic kidney disease (CKD)	15	11.4
Others	16	12.1
None	25	18.9

In this sample, central nervous system infections (meningitis) were the most prevalent, constituting 20.5% of cases, followed by blood infections at 15.2%, and respiratory infections at 11.4%. Sepsis secondary to the bone (osteomyelitis), of the cardiovascular system (infective endocarditis), and surgical site infections were less common, each accounting for 2.3% or less. Notably, 18.2% of cases had an unknown source of infection.

Figure 2 highlights the suspected sources of infection across the sample. The majority of sources of infection in the sample were meningitis, though a large percentage were from an unknown source.

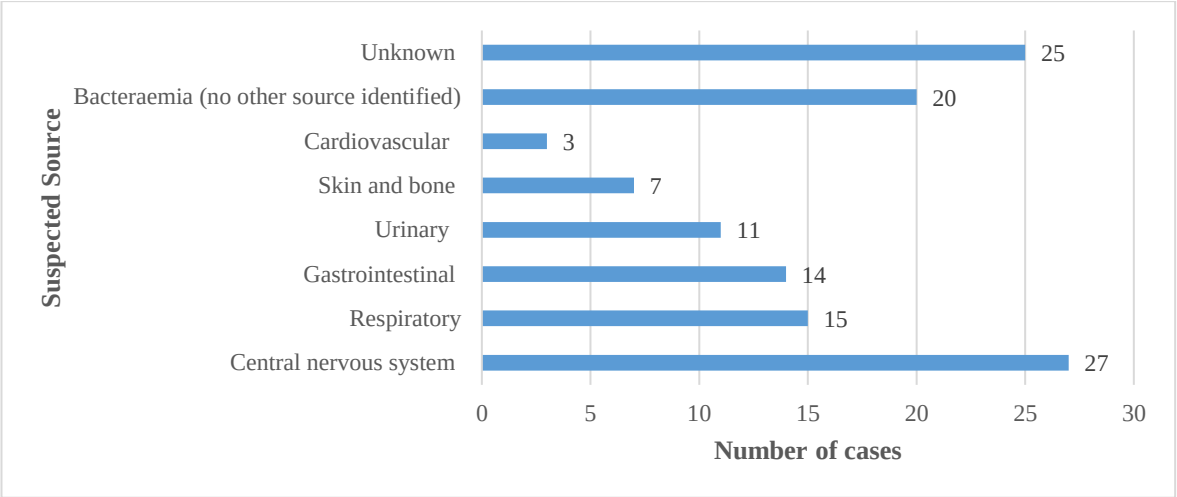

Figure 2: Suspected source of infection for patients with sepsis

Table 3 below shows clinical makers and patient outcomes. About 65.2% had blood collected prior to initiating antibiotics with one organism isolated per individual about 38.6%. The median duration of treatment was 9 days with in-hospital mortality reaching 25%. Many patients (n=75) were prescribed more than one antibiotic to treat their infection.

Table 3:Patient outcomes and clinical markers

Clinical criteria	n=132	%
Blood collection prior to initiation of empirical (yes)	86	65.2
Duration of antibiotic treatment, days (median, IQR)	9 (8-13)	
≤8 days	34	25.8
9 days	34	25.8
≥ 10 days	64	48.5
Biomarker obtained		
Procalcitonin (PCT)	28	21.2
C-reactive protein (CRP)	82	62.1
None	22	16.7
Number of organisms isolated		
None	43	32.6
One	51	38.6
More than one	38	28.8
Number of antibiotics per patient		
One	57	43.2
Two	69	52.3
Three	6	4.5
Outcome		
Deceased		25
Discharged, alive		37
Transferred, alive		38

Gram negative *Escherichia coli* was the most isolated identified organism followed by *Staphylococcus aureus* at 26.7%, however, 31.7% of isolates had culture negative results. Overall gram-positive organisms were isolated more commonly at about 85 of cases than gram-negative organisms 56 cases.

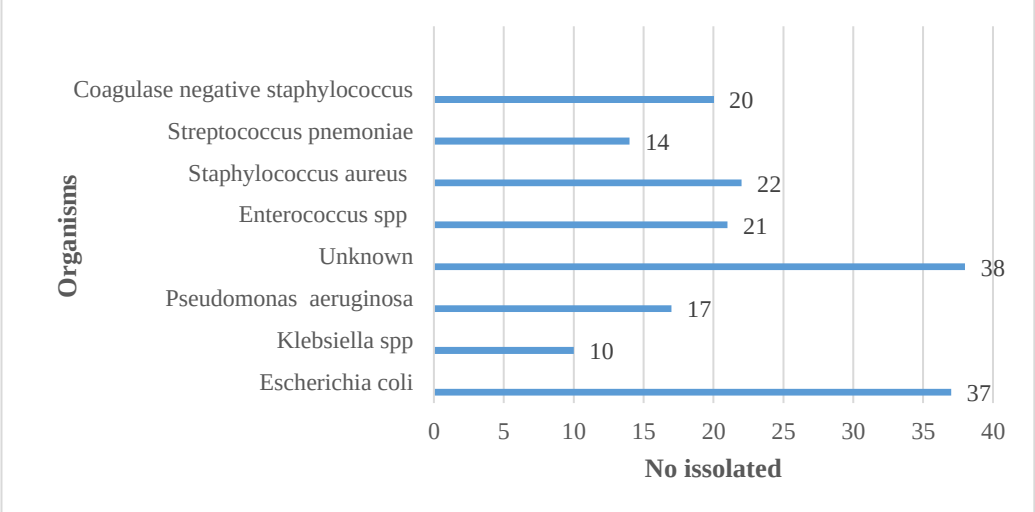

Figure 3:Percentage of isolated organisms

The antibiogram data highlights that meropenem and piperacillin-tazobactam are highly effective among the organisms cultured, showing 100% success against *Staphylococcus aureus* and *Klebsiella* spp in this sample. Conversely, amoxicillin-clavulanic acid exhibited lower efficacy, with susceptibility rates below 75% for all tested organisms. Meropenem was the most frequently prescribed empirical broad-spectrum antibiotic (n=50, 41%), followed by piperacillin-tazobactam and ceftriaxone.

Table 4:Resistance pattern of pathogen isolated from patients with sepsis

	Number Susceptible / total tested (susceptible %)						
	Escherichia coli	*Klebsiella spp*	*Pseudomonas aeruginosa*	*Streptococcus Pneumoniae*	*Staphylococcus Aureus*	*Enterococcus*	*Coagulase Negative Staphylococcus*
Co-trimoxazole	0/2 **(0%)**	1/3 **(33%)**	1/2 **(50%)**	3/6 **(50%)**	6/8 **(75%)**	0/4 **(0%)**	3/3 **(100%)**
Meropenem	8/9 **(88%)**	8/8 **(100%)**	7/9 **(78%)**	4/5 **(80%)**	6/8 **(75%)**	8/9 **(88%)**	7/7 **(100%)**
Imipenem	8/9 **(88%)**	6/7 **(85%)**	4/5 **(80%)**		7/7 **(100%)**	8/9 **(88%)**	7/7 **(100%)**
Ertapenem	6/9 **(67%)**		3/6 **(50%)**	4/5 **(80%)**	3/6 **(50%)**	6/7 **(85%)**	2/2 **(100%)**
Vancomycin	5/6 **(83%)**	4/5 **(80%)**	5/7 **(71%)**	3/3 **(100%)**	4/5 **(80%)**	4/6 **(50%)**	6/6 **(100%)**
Ceftriaxone	3/6 **(50%)**	5/7 **(71%)**	0/7 **(0%)**	0/5 **(0%)**	0/8 **(0%)**	4/9 **(44%)**	1/3 **(33%)**
Cefuroxime	3/4 **(75%)**	2/3 **(67%)**	1/5 **(20%)**	0/5 **(0%)**	3/6 **(50%)**	2/8 **(25%)**	
A**moxicillin/clavulanic acid**	4/7 **(57%)**	4/6 **(67%)**	0/5 **(0%)**	1/5 **(20%)**	4/7 **(58%)**	0/10 **(0%)**	4/7 **(57%)**
Amikacin	5/7 **(71%)**	3/6 **(50%)**		2/3 **(67%)**	3/4 **(75%)**	6/7 **(86%)**	5/7 **(71%)**
Ciprofloxacin	8/9 **(88%)**	2/3 **(67%)**	3/6 **(50%)**	3/3 **(100%)**	4/6 **(67%)**	5/6 **(83%)**	3/6 **(50%)**
Gentamycin	3/4 **(75%)**	3/5 **(60%)**		0/4 **(0%)**	3/3 **(100%)**	6/8 **(75%)**	
Cefepime	3/4 **(75%)**	3/4 **(75%)**		0/2 **(0%)**	2/3 **(67%)**	6/8 **(75%)**	3/3 **(100%)**
Piperacillin/tazobactam	6/7 **(85%)**	8/9 **(88%)**	6/7 **(85%)**	4/5 **(80%)**	3/5 **(60%)**	5/7 **(71%)**	7/7 **(100%)**

Table 5 shows the odds based on the demographic variable of the sample. The table below shows the non-significant odds of death of individuals above 65 as high at 1.26 and 1.94 for males, p= 0.0717 and 0.098 respectively. It further shows the non-significate of odd of death due to comorbidity as 1,04 and hypertension at 1.83, p= 0.926 and 0.132 correspondingly.

Table 5:Odds of death according to demographic variables

	Survival		**Death**			
Demographics	*Yes (n, %)*	*No (n, %)*	*Yes (n, %)*	*No (n, %)*	Odds of death	*p*-value
Gender, male	36 (66.7)	62 (79.5)	18 (33.3)	16 (20.5)	1.94 (0.88-4.26)	0.098
Age, ≥65 years	7 (70)	91 (74.6)	3 (30)	31 (25.4)	1.26 (0.31-5.17)	0.717
Hypertension	32 (66.7)	66 (78.6)	16 (33.3)	18 (21.4)	1.83 (0.82-4.06)	0.132
Diabetes	31 (79.5)	67 (72)	8 (20.5)	26 (28)	0.67 (0.27-1.64)	0.372
HIV	28 (73.7)	70 (74.5)	10 (26.3)	24 (25.5)	1.04 (0.44-2.45)	0.926
Cancer	26 (66.7)	72 (77.4)	13 (33.3)	21 (22.6)	1.71 (0.75-3.91)	0.197
CKD	9 (60)	89 (76.1)	6 (40)	28 (23.9)	2.12 (0.69-6.48)	0.180
Respiratory disorder*	11 (64.7)	87 (75.7)	6 (35.3)	28 (24.3)	1.69 (0.57-5.00)	0.335

*includes COPD, asthma, and tuberculosis

Table 6 shows the odds of death based on key antibiotic quality metrics. Two of the metrics showed a statistically significant relationship and had an increased odd of death. If antibiotics were de-escalated after culture results were reported, the odds of death were reduced by 60% (OR 0.42 (0.19-0.93). If antibiotics were prescribed according to local guidelines, the odds of death were higher (OR 3.68 (1.28-10.60). None of the other criteria showed a statistically significant increased odds of death.

Table 6: Odds of death based on key antibiotic quality metrics

	Survival		Death			
Quality metrics	*Yes (n, %)*	*No (n, %)*	*Yes (n, %)*	*No (n, %)*	Odds of death	*p*-value
Bloods drawn prior to antibiotics	62 (72.1)	36 (78.3)	24 (27.9)	10 (21.7)	1.39 (0.60-3.24)	0.440
Appropriate empiric antibiotics selected	46 (68.7)	52 (80)	21 (31.3)	13 (20)	1.82 (0.82-4.05)	0.136
Antibiotics administered within 1 hour of diagnosis	74 (71.8)	24 (82.3)	29 (28.2)	5 (17.2)	1.88 (0.66-5.40)	0.235
Antibiotics de-escalated after culture results	64 (81)	34 (64.1)	15 (19)	19 (25.8)	0.42 (0.19-0.93)	**0.030**
All 4 Surviving Sepsis antibiotic recommendations met	13 (61.9)	85 (76.6)	8 (38.1)	26 (23.4)	2.01 (0.75-5.38)	0.159
Appropriate antibiotics based on local guidelines	33 (71.7)	56 (90.3)	13 (28.3)	6 (9.7)	3.68 (1.28-10.60)	**0.012**
Empiric antibiotics covered pathogen isolated	30 (81.1)	26 (76.5)	7 (18.9)	8 (23.5)	0.58 (0.19-1.80)	0.635

6. DISCUSSION

This study has highlighted that gram-negative *Escherichia coli* is the most common pathogen shown to be responsible for causing sepsis from patients admitted in GPH ICU, followed by gram positive *Staphylococcus aureus* hence the distribution of isolated organisms in sepsis cases is comparable to global reports, with gram-negative E. coli being the predominant organism associated with sepsis. This suggests that the causes of sepsis in low- and middle-income countries (LMIC) like Botswana, despite high rates of HIV and TB, may share similarities with international prevalence patterns. For example, a study in Japan showed the majority of isolated organisms were *Escherichia coli* (21.5%) and *Klebsiella pneumoniae* (9%) (22). *Streptococcus pneumoniae* and *Staphylococcus aureus* have been identified as the leading gram-positive organisms contributing to sepsis infections, while gram-negative infections still cause the overwhelming majority of sepsis cases (29). This current study shows a higher total number of gram positive organisms isolated, though many were coagulase

negative staphylococcus which could suggest increased contamination during sample collection. The study reveals that despite the presence of two highly virulent organisms, a significant portion of 38 blood samples exhibited negative results, indicating unknown organisms. This discrepancy is attributed to challenges such as limited laboratory resources and inadequate equipment commonly experienced in low- and middle-income countries (LMICs). Furthermore, the high incidence of negative culture results could also be influenced by the prior administration of antibiotics to patients before their admission to the intensive care unit (ICU) as one-third of patients had antibiotics administered before blood cultures. Furthermore, none of the samples were tested for non-bacterial pathogens such as fungi and parasites which have been found in other settings (6). This is particularly important as about 73 % of the sample were patients with cancer, HIV, and TB which increase the likelihood of non-bacterial pathogens (6).

The research findings indicate that males had approximately 1.94 times higher odds of death compared to females, as evidenced by an odds ratio (OR) of 1.94 with a p-value of 0.098. However, the p-value suggests that this difference is not statistically significant which may be related to sample size. Other demographic criteria similarly had no statistically significant relationship with mortality, although some conditions such as CKD showed a clearer trend towards higher odds of death (OR 2.12). Overall, the lack of statistical significance suggests that, in this study, the mentioned chronic conditions did not have a clear and significant impact on the odds of death. Further work with a larger sample may be required to elucidate the true relationship between demographics and mortality in this setting.

The finding that adherence to local guidelines significantly increased the odds of death (OR 3.68, CI 1.28-10.6, p=0.012) is unexpected and warrants careful consideration of

other confounding variables such as patient-specific conditions or variations in disease severity. One important missing variable is the APACHE II score. The Acute Physiology and Chronic Health Evaluation (APACHE) II score is a system used in intensive care units (ICUs) to predict disease severity, hospital mortality risk, evaluate ICU treatment effectiveness, and compare patient outcomes across various ICUs (36). Calculating an APACHE II score requires various data points: the patient's age, medical history (including any chronic health conditions), and acute physiology measurements. These measurements include temperature, mean arterial pressure (MAP), heart rate, respiratory rate, oxygenation (PaO2 and FiO2), arterial pH or serum bicarbonate (HCO3-), serum sodium and potassium levels, serum creatinine level, hematocrit, white blood cell count (WBC), and Glasgow Coma Scale (GCS) score which were unfortunately not included in the data collection tool.. This omission might explain the observed results. Increased severity of illness would be expected to lead to increased and earlier administration of both antimicrobials and IV fluids but may still be associated with an increased risk of in-hospital death. Nevertheless, this contradicts other recent studies that indicate optimal benefits from adequate antibiotic treatment are achieved in patients with higher severity-of-illness scores (16). Previous research in sub-Saharan Africa regarding sepsis indicated a rise in inpatient mortality as the proportion of HIV-infected individuals increased. Additionally, the inability to walk unassisted was identified as a factor associated with an elevated risk of death in some sepsis studies (27 , 28). The omission of the APACHE II variable in this study is a noteworthy limitation that could impact the outcome of the current study. In South Africa, a study found that the Surviving Sepsis Campaign guidelines are often ignored. Nonetheless, one hospital reduced sepsis mortality from 29% to 21% by implementing

nurse-led screening and detection, followed by protocol-driven interventions led by nurse practitioners (12).

Another explanation for the higher mortality among patients receiving antibiotics based on local guidelines may relate to the limitations of the local guidelines. The local guideline, established in 1986 and last reviewed in 2012 (39) may have shortcomings impacting patient care, including worsened outcomes. The extended period since its last review raises concerns about the guideline's relevance and alignment with the current antibiogram of the specific patient population, despite appropriate drug dosing. Consequently, there's a suggestion that the guideline might be suboptimal for addressing contemporary challenges in patient management and may not fully align with the evolving patterns of antibiotic resistance in the local context. Martinez and colleagues encourage continuous updates to empirical antibiotic guidelines to facilitate appropriate prescribing (26). They suggest that guidelines should be “based on current practice guidelines and incorporate local and national ecology/resistance patterns” (16). In resource-poor countries, the development or updating of medical guidelines lacks adequate documentation.

Nonetheless, reliable guidelines necessitate comprehensive documentation and must remain relevant, incorporating the latest medical practices (26). The current study result, however is in contrast with the view that, sepsis protocols developed in HICs should not simply be exported unchanged to SSA (40). Fewer than 20% of patients in this analysis met the key surviving sepsis antibiotic quality measures (blood drawn before first antibiotic dose, de-escalation of broad spectrum uses of biomarkers and antibiotic administered with one hour), leaving significant opportunities for improvement of sepsis management. The overall mortality rate in this study was 25%. The median duration of therapy in this study was 9 days with a significate mortality

rate observed, however, SSC guidelines make a general recommendation of 7 to 10 days is likely sufficient (41). Guidance on duration is surprisingly limited and not adhered to because is also influences clinical presentation of the patient, source of infection and type of pathogen isolated need to be assessed. Few studies significantly opt toward change toward shorter durations of antibiotic therapy as the outcome of 4 days shows similar out as more than 8 days (41). Determining the appropriate duration of antibiotic treatment should be tailored to each individual, taking into account various factors specific to the patient (16).

A hospital antibiogram is a valuable tool for guiding initial antibiotic choices before specific susceptibility results are accessible, aiding in effective empirical treatment decisions (6). However, developing an appropriate and accurate antibiogram is challenging. It requires sufficient numbers of isolates of each pathogen to make meaningful recommendations which requires clinicians to obtain bacterial samples frequently at baseline and not only after initial treatment has failed (42). Therefore, strong collaborations between pharmacists, physicians, and microbiologists are essential in crafting hospital antibiograms. The antibiogram analysis in this study highlights concerning results concerning the effectiveness of Ceftriaxone and cefuroxime, often prescribed for meningitis and pneumonia. It demonstrates their limited effectiveness against various organisms like *Streptococcus pneumoniae,* underscoring the necessity for prudent antimicrobial usage to combat resistance. Additionally, Meropenem was frequently used empirically without narrowing the spectrum following blood test results, indicating inappropriate antibiotic use contributing to anti-microbial resistance development. Antimicrobial resistance is a growing global threat, especially in developing countries, where the irrational use and overuse of antimicrobials have made common treatments ineffective (43).

The study suggests that selecting appropriate empiric antibiotics, as per guidelines, might be associated with worse survival outcomes, but the study did not have enough statistical power to confirm this. This surprising finding underscores the importance of considering guideline-based antibiotic selection in sepsis management and the need for updated guidelines that respond to antibiotic availability and local resistance rates.

Limitations

This study has several limitations. This study cannot make firm recommendations about antibiotic resistance in this sample as the total number of isolates for each organism was under 30 (41). A shortage of testing media in the laboratory constrained the study's capacity to comprehensively assess susceptibility patterns, thus narrowing its scope and recommendations. Furthermore, it is important to note that this study was observational, gathering data retrospectively from patient medical records. The analysis did not control for all potential confounding factors, including clinical severity. A large number of patients in the sample were transferred out of the hospital so their final clinical outcome is unknown. For the analysis, if the patient was alive at their discharge from the ICU (including those transferred), they were included in the survival group. There are a variety of reasons that patients were transferred. Many were transferred from the private ICU to a state hospital as their medical aid services were insufficient to cover the cost of continued admission. Others who initially presented at state hospital but because of bed availability were transferred to this private hospital were then transferred back when the state hospital had space available in their ICU. As a result, the findings may not fully capture the odds of appropriate antimicrobial therapy on critically ill sepsis patients in the ICU setting in Botswana. The entire population was included but had a smaller sample size than required,

consequently, it achieved 10% precision in measuring the rate of inappropriate antibiotic use instead of the intended 5% precision. The study recommends further investigations with larger datasets to enhance the comprehensiveness and reliability of the findings.

7. CONCLUSION

The observed increased odds of mortality that was associated with adherence to local sepsis guidelines may possibly be due to unmeasured factors like APACHE II or to the inappropriateness of local guidelines. Furthermore, it underscores the importance of regularly updating guidelines to reflect current practices. Researchers and clinicians should interpret findings cautiously, recognizing the potential impact of excluded variables. Urgently recommended are follow-up studies incorporating the patient condition assessment score (APACHE II) to improve sepsis management in low- and middle-income countries (LMICs). The inappropriate empirical use of meropenem contributes to resistance, similar to how ceftriaxone and cefuroxime have shown significant ineffectiveness against a broad spectrum of organisms.

8. RECOMMENDATION

The main recommendation to come from this current study is the need for improved sepsis algorithms at this hospital to improve compliance with quality measures for sepsis management. It is advisable to establish and regularly update recommended empirical antibiotic regimens at the local level informed by local data. This practice aims to facilitate the prescription of empiric antimicrobials in accordance with current guidelines, taking into consideration local and national ecology, as well as resistance patterns. Additionally, clinical pharmacists must be involved in the design and update of local guidelines and enforce their utilisation at an institutional level.

There are opportunities for further research stemming from this study. For example, researchers should consider a broader scale, including government institutions, and incorporating patient APACHE II measures to ensure more reliable and valid outcomes. Moreover, researches are needed to further verify research findings of the current research. Looking beyond antibiotic prescribing to evaluate fluid management and cardiovascular and respiratory support systems should be another next step. More scholarly research on sepsis is needed due to the limited data on its epidemiology and management in low-resource settings, such as sub-Saharan countries, which affects the quality of existing data sources. Additionally, it is necessary to evaluate sepsis management following the COVID-19 pandemic to ensure good outcomes for patients.

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10. APPENDICES

Appendix 1

UNAM
UNIVERSITY OF NAMIBIA

ETHICAL CLEARANCE CERTIFICATE

Ethical Clearance Reference Number: SOP004 **Date: 14 June 2023**

This Ethical Clearance Certificate is issued by the University of Namibia Ethics Committee (REC) in accordance with the University of Namibia's Research Ethics Policy and Guidelines. Ethical approval is given in respect of undertakings contained in the Research Project outlined below. This Certificate is issued on the recommendations of the ethical evaluation done by the ethics committee.

Title of Project: A Retrospective Evaluation of Antimicrobial Management Among Patients with Sepsis in Intensive Care Unit (ICU) in a Private Hospital in Gaborone, Botswana.

Principal researchers: Charles Waitse Jolomba

Staff Number/ Student number: 218219966

Remarks: Approved

Centre for Research Services

Take note of the following:

1. Any significant changes in the conditions or undertakings outlined in the approved Proposal must be communicated to the ethics committee. An application to make amendments may be necessary.
2. Any breaches of ethical undertakings or practices that have an impact on ethical conduct of the research must be reported to the ethics committee.
3. The Principal Researcher must report issues of ethical compliance to the ethics committee (through the Chairperson) at the end of the Project or as may be requested by the ethics committee.
4. The ethics committee retains the right to:

i) Withdraw or amend this Ethical Clearance if any unethical practices (as outlined in the Research Ethics Policy) have been detected or suspected,

ii) Request for an ethical compliance report at any point during the course of the research.

The ethics committee wishes you the best in your research.

(Chairperson Decentralized Ethics Committee)

Prof. Davis Mumbengegwi (Head, Multidisciplinary Research)

Appendix 2

Life Healthcare Head Office
Oxford Manor, 21 Chaplin Road, Illovo 2196
Private Bag X13, Northlands 2116, South Africa
Telephone: +27 11 219 9000
Telefax: +27 11 219 9001
www.lifehealthcare.co.za

National Health Research Ethics Committee registration: **REC 251015-048**

REF: LHCHREC-PR-29082023/11

Date: 26 September 2023

Dear Mr Jolomba

RE: PERMISSION TO CONDUCT AT LIFE GABARONE HOSPITAL

Title of study: A retrospective evaluation of antimicrobial management among patients with sepsis in intensive care unit (ICU) at Gaborone Private Hospital in Botswana

The Life Healthcare Human Research Ethics Committee (LHC HREC) hereby grant permission for you to conduct your above-titled research study at the abovementioned hospitals under the following conditions:

1. Permission is granted for a period of 12 months from the date of this letter.
2. No direct reference may be made to Life Healthcare, its subsidiaries or any of its facilities or institutions in the research report or any publications thereafter. The Company and its facilities, patients and staff must be de-identified in the study, and remain so for any other studies which may utilise this information. Any abstracts submitted or presentations given which will utilise the results of any research done in a Life Healthcare facility, must comply with the same conditions.
3. If patient or institutional confidentiality is breached, Life Healthcare is entitled to withdraw this permission immediately. The Company reserves the right to take legal action against you, should Life Healthcare feel that this is warranted.
4. An electronic copy of the research report or compiled results, in the case of a clinical trial, must be submitted to Life Healthcare HREC on completion of the project or trial. This copy of the research report, and any publications which may develop from it will be placed on the Company's Gateway research page for reference purposes. The researcher is required to make these documents available in PDF format.
5. Research being done for educational purposes must be completed within the time allotted by the higher education institution. If the research is being done in an individual capacity by an employee of the life Group, the research must be conducted within one year of permission being given by the LHC HREC, OR must be completed in the proposed time period specified in the approved proposal. Permission may be withdrawn if the research extends beyond the approved time period.
6. Six to 12 months after receiving permission/ethics clearance from Life Healthcare HREC to conduct a research study at Life Healthcare facilities, it is mandatory for the researchers to report on the progress of their study by completing a monitoring and evaluation form which is accessible on the research website at https://www.lifehealthcare.co.za/careers/life-college-of-learning/research-and-human-research-ethics-committee/. The completed form must be returned to Research@lifehealthcare.co.za.
7. Life Healthcare will not take responsibility for any unforeseen circumstances within its institutions which may materially change the context and potential outcomes of a student's research. Should this occur, the student will be required to approach their Higher Learning institution for guidance around alternatives.
8. Life Healthcare will not be liable for any costs incurred during or related to this study.

9. In cases where a researcher is found to be guilty of misconduct, or in contravention of any national or international legislation or Life Healthcare policies or guidelines, permission to continue with the research will be withdrawn immediately pending investigation. In the case of student research, the higher education institution under which the researcher is registered will be notified. In the case of a clinical trial, The South African Health Products Regulatory Authority (SAHPRA) will be notified, as well as the trial sponsor and any other necessary parties.

Yours sincerely,

Dr Sharon Vasuthevan
Chairperson
Life Healthcare HREC

Prof Esmeralda Ricks
Research Specialist

On behalf of Life Healthcare HREC