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Research Article

Impact of Inappropriate Empirical Antibiotics Therapy on Clinical Outcomes in Adult Patients with Sepsis and Septic Shock at Wad Medani Teaching Hospital, Sudan

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Abstract

Background: Inappropriate empirical antimicrobial therapy for sepsis or septic shock patients is independently linked to higher mortality rates. This study aims to evaluate the impact of inappropriate empirical antibiotic therapy on mortality and length of Intensive Care Unit (ICU) stay in adult patients with sepsis and septic shock.

Methods: A cross-sectional, retrospective study was conducted in the ICU of Wad Medani Teaching Hospital, Sudan, from January 1st, 2018 to May 31st, 2020.

Results: Out of the 101 patients analyzed, 95 (94.06%) received more than one antibiotic (2.772 ± 1), and 78 (77.2%) received inappropriate empirical antibiotics. In total, 17 antimicrobial drugs were used, of which metronidazole was used the most used in 70 patients (69.3%). Aspiration pneumonia was identified as the predominant source of infection in 33 (32.7%) patients. The ICU mortality rate was 77 patients (76.2%), which is significantly associated with inappropriate antibiotics used (*P*-value: 0.00), with a relative risk of 3.12 (CI 95% 1.66–5.84). Additionally, there was a significant difference in survival depending on the appropriate use of antimicrobials (*P*-value: 0.00) and Sequential Organ Failure Assessment (SOFA) score (*P*-value: 0.00).

Conclusion: Inappropriate empirical antibiotic use in sepsis or septic shock patients was associated with a higher risk of patient death and more extended hospital stays. This study revealed a significant percentage of inappropriate antibiotic use. These results highlight the significance of creating evidence-based empirical antibiotic protocols for treating sepsis and septic shock and educating healthcare staff on the urgent treatment of these patients and the application of sepsis bundles.

Keywords: sepsis, septic shock, antibiotics, inappropriate, Sudan

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1. Introduction

Sepsis is a medical emergency that impacts millions of individuals and is a leading cause of death globally [1]. Sepsis is defined as a "life threatening organ dysfunction caused by a dysregulated host response to infection". In contrast, septic shock is defined as "a subset of sepsis in which particularly profound circulatory, cellular and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone" [2]. When treating sepsis and septic shock, the "Surviving Sepsis Campaign" (SSC) guidelines emphasize early identification; early source control; and timely, appropriate antibiotics use [1].

Sepsis and septic shock have a direct impact on death rates. Therefore, one or more antibiotics with fighting properties against all suspected bacteria should be administered within the first hour of diagnosis [2–4]. The three fundamentals of effective antibiotic therapy are the appropriate initial empiric antimicrobial therapy, prompt delivery without delays, and urgently reaching therapeutic concentration. These three concepts will limit microbial load, lowering the likelihood of irreversible shock and the rates of death [5]. Inappropriate empirical antibiotic therapy for sepsis or septic shock patients is independently linked to higher mortality rates [6].

Many studies worldwide evaluating antibiotics used in sepsis and septic shock patients have shown that empirical antibiotics are a good predictor of improving survival and shortening length of stay (LoS) in the Critical Care Unit [7–10]. A retrospective cohort study conducted in Croatia revealed that appropriate empirical antibiotics for septic patients decrease mortality by 3.9% [11]. Furthermore, a systematic review and meta-analysis study showed that inappropriate empirical antibiotic use in bacteremia patients was associated with an unfavorable mortality rate [12].

In sub-Saharan Africa, while the quality of care for sepsis or septic shock patients has increased over time, mortality rates have not significantly improved. They correlate directly with inappropriate fluid and antibiotic use (RR = 1.55, 95% CI 1.10–2.00) [13]. In Sudan, a study conducted in Khartoum to assess the impact of the correct use of empirical antibiotics on the outcomes of sepsis and septic shock patients in the Intensive Care Unit (ICU) revealed that appropriate antibiotics use was correlated to a decrease in ICU-LOS ($P = 0.001$) and reported a mortality rate of 67.9%, which correlated to septic shock ($P = 0.001$) [14]. A prospective cohort study conducted in two tertiary hospital ICUs in Khartoum evaluated the impact of inappropriate empirical antibiotics in adult sepsis patients and reported that 43.4% of antibiotic therapy was appropriate, significantly decreasing the mortality rate and ICU-LoS [15].

The Wad Medani Teaching Hospital has a 298-bed capacity. It is the main hospital of the capital city of Gezira state, Wad Medani, Sudan, and has 13 beds that serve as a medical and surgical ICU. In Wad Medani, there are no published data on the impact of the inappropriate use of empirical antibiotics on mortality and ICU-LoS for sepsis or septic shock patients. Therefore, this study aimed to evaluate the effect of inappropriate empirical antibiotic therapy on mortality and length of ICU stay in adult patients with sepsis and septic shock.

2. Materials and Methods

2.1. Study setting

The study was conducted at the ICU of the Wad Medani Teaching Hospital, Gezira State, Sudan.

2.2. Study design

A cross-sectional, retrospective design was used.

2.3. Data collection

Data were collected from the patient's medical records, drug charts, and laboratory and microbiology test results.

2.4. Inclusion criteria

Adult patients diagnosed with sepsis or septic shock based on the Third International Consensus Criteria for Sepsis and Septic Shock (Sepsis-3) [2], who received antibiotic therapy and were hospitalized in the ICU from January 1st, 2018 to May 31st, 2020 were enrolled.

2.5. Exclusion criteria

Patients with incomplete medical records.

2.6. Outcomes measure

Appropriate antibiotic coverage was defined as an empiric regimen that covers all suspected microorganisms depending on the site of infection. In contrast, inappropriate antimicrobial coverage was described as an empirical antibiotic treatment that lacks the specific anti-infective agent that targets a particular class of microorganisms most likely responsible for the infectious process [4].

Wad Medani Teaching Hospital lacks local empirical antimicrobial guidelines. Therefore, empirical antibiotic therapy was evaluated for its appropriateness according to the source of infection using updated international guidelines for community-acquired pneumonia [16], aspiration pneumonia [4], urinary tract infections [17], cellulitis, necrotizing/surgical site infection [18], infections associated with burns [19, 20], intra-abdominal infection [21], diabetic septic foot [22], hospital-acquired pneumonia [23], infective endocarditis [24], tuberculosis [25], and unknown [1], as summarized in Table **1**.

2.7. Variable definition

The mean Sequential Organ Failure Assessment (SOFA) score measures the degree of organ dysfunction that quantifies abnormalities based on laboratory results, clinical findings, or therapeutic interventions. A higher SOFA score is linked to a higher risk of death [2].

The Acute Physiology and Chronic Health Evaluation (APACHE) score is a scale used to measure the severity of disease in critically ill patients in the ICU [26].

2.8. Statistical analysis

The Statistical Package for the Social Sciences (SPSS), version 25.0, was used for data analyses. Quantitative data were presented using the mean, standard deviation (SD), median, and range. Qualitative data were presented as frequencies (percentages). After checking the applicability conditions, the chi-square and Fisher's exact tests were used for categorical data when comparing the study groups. An independent *t*-test was run for continuous data that followed a normal distribution when comparing the study groups while a *P*-value of <0.05 was considered significant. The relative risk (RR) and 95% confidence intervals (CI) were calculated to quantify inappropriate empirical antibiotic therapy's effect on mortality. The survival differences based on inappropriate empirical antibiotic therapy and SOFA score were assessed using the Kaplan-Meier method. The log-rank test was used to compare results, with statistical significance defined as a *P*-value of 0.05.

3. Results

During the study period, 850 patients were admitted to the ICU of Wad Medani Teaching Hospital. Of those, 158 (18.6%) were found to have sepsis or septic shock. The study excluded 57 (36.1%) patients due to insufficient data. The baseline characteristics of the patients included are summarized in Table **2**.

Overall, 101 patients underwent analysis; 95 (94.1%) received more than one antibiotic (mean 2.772 $\pm$ 1 SD; median, 3; range, 1–5). Most patients (78; 77.2%) received inappropriate empirical antibiotics, while only 23 (22.8%) received appropriate empirical antibiotics. Additionally, in 42 (41.6%) patients, the antimicrobial regimen was escalated, in 12 (11.9%) de-escalated, and in 47 (46.5%) patients, no change was made. The blood culture was done in only 2 (2%) patients, and no other culture types were performed. One of these two patients received an inappropriate empirical antibiotic.

The mean LoS was 6.17 $\pm$ 5.02 days, with a median of 5 and a range of 1–35 days. There was a statistically significant difference (*P*-value = 0.014) between sepsis (7.68 $\pm$ 6.4) and septic shock (5 $\pm$ 3.22).

The SOFA score was 9.27 $\pm$ 3.65, which was higher in septic shock patients (11.07 $\pm$ 3.15) than in sepsis patients (6.93 $\pm$ 2.85), with a statistically significant difference (*P*-value = 0.000). The mean APACHE score was 22.85 $\pm$ 7.57, which was more significant in septic shock patients (25.72 $\pm$ 6.96) than in sepsis patients (19.14 $\pm$ 6.71), with a statistically significant difference (*P*-value = 0.000).

A total of 17 antimicrobial drugs were used, among which metronidazole was the most commonly prescribed drug, prescribed to 70 patients (69.3%). It was followed by meropenem, which was prescribed to 54 patients (53.5%), and the remaining antibiotics (Figure **1**).

The most common infections were aspiration pneumonia in 33 patients (32.7%), followed by community-acquired pneumonia in 15 patients (14.9%), intra-abdominal infection in 9 patients (8.9%), urinary tract infections in 8 patients (7.1%), cellulitis in 7 patients (6.9%), necrotizing in 7 patients (6.9%), bacterial meningitis in 6 patients (5.9%), diabetic septic foot in 6 patients (5.9%), unknown in 4 patients (4%), surgical site infection in 2 patients (2%), and one patient (0.9%) each for burn, endocarditis, tuberculosis, and hospital-acquired pneumonia.

The majority of patients (80; 79.21%) had comorbidities, most commonly cardiovascular diseases (48; 43.2%) followed by diabetes mellitus (34; 30.6%) and chronic kidney disease (10; 9%).

The mortality rate in the ICU for the patients under investigation was 76.2% (77/101). Most of the deaths occurred in septic shock patients (49/57; 86%; *P*-value: 0.024). Only 13.9% (14/101) of enrolled patients were discharged and 9.9% (10/101) were referred to other departments or a different hospital. Mechanically ventilated patients also showed a higher mortality rate at 82.8% (24/29) compared to non-ventilated patients at 73.6% (53/72).

Aspiration pneumonia was the infection most strongly associated with a fatal outcome, constituting 37.7% (29/77) of total deaths, followed by community-acquired pneumonia which was associated with 13% (10/77) of the fatalities.

Table 1: Suggested antibiotic treatment for sepsis/septic shock based on the origin of the infection.

Community acquired pneumonia (16):
– Ampicillin/sulbactam + either a respiratory fluoroquinolone or a macrolide
– Ceftriaxone + either a respiratory fluoroquinolone or a macrolide
– Ceftaroline + either a respiratory fluoroquinolone or a macrolide
Aspiration pneumonia (4):
– CAP regimen + clindamycin IV or change ceftriaxone to piperacillin/tazobactam
Urinary tract infection (17):
– Fluoroquinolone or aminoglycoside or ceftriaxone (consider a β-lactam with antipseudomonal)
Cellulitis (18):
– Penicillin G or first-generation cephalosporin (cefazolin, cephalexin) (+/– vancomycin if suspected MRSA)
– Ceftriaxone or clindamycin (+/– vancomycin if suspected MRSA)
Necrotizing/Surgical site infection (18):
– Vancomycin or linezolid + piperacillin/tazobactam
– Carbapenem or ceftriaxone + metronidazole (+/– clindamycin or High-dose IV penicillin plus clindamycin)
Burn (19)(20):
– Piperacillin/tazobactam or carbapenem (+/– vancomycin +/– an aminoglycoside)
Intra-abdominal infection (21):
– Broad-spectrum carbapenem (+/– fluconazole/vancomycin)
– Cefepime/ceftazidime + metronidazole (+/– fluconazole/vancomycin)
– Piperacillin/tazobactam (+/– fluconazole/vancomycin)
Diabetic septic foot (22):
– Ceftazidime/cefepime + metronidazole + vancomycin or linezolid
– Meropenem + vancomycin or linezolid.
Endocarditis (24):
– PCN G + gentamicin/ceftriaxone or vancomycin (only if unable to tolerate PCN or ceftriaxone)
Tuberculosis (25):
– Isoniazid + rifampin + pyrazinamide + ethambutol
Hospital-acquired pneumonia (23):
– Antipseudomonal β-lactam +/– vancomycin or linezolid
– Aminoglycoside, fluoroquinolone (ciprofloxacin, levofloxacin) +/– vancomycin or linezolid
Unknown (1):
– Antipseudomonal β-lactam or carbapenem + an aminoglycoside or antipseudomonal fluoroquinolone + vancomycin

A statistically significant association was found between the appropriate selection of empirical antibiotics and patients' death (*P*-value = 0.00), as most deaths (70/77; 90.9%) occurred after inappropriate antimicrobial drugs use with an RR of 3.12 (CI 95% 1.66–5.84) compared to appropriate empirical antimicrobial medications used. Moreover, a statistically significant association was found between the SOFA score and patients' outcome (*P*-value = 0.001) in which a score of more than eight accounts for a majority (63.6%; 46/77) of deaths.

The Kaplan-Meier curve (log-rank) showed a significant variation in time to discharge from the ICU based on the appropriate use of empirical antimicrobial drugs (*P*-value = 0.00), in which

Table 2: Baseline characteristic of study participants.

Characteristics	*N* (%)
Age (yrs)	
18–39	15 (14.9)
40–59	24 (23.8)
≥60	**62 (61.4)**
Sex	
Female	57 (56.4)
Male	44 (43.6)
Diagnosis	
Sepsis	44 (43.6)
Septic shock	57 (56.4)
Type of admission	
Medicine	79 (78.2)
Surgery	22 (21.8)
Length of stay (days)	
≥7	32 (31.7)
<7	69 (68.3)
Mean ± (SD)	6.17 (5.022)
Ventilation use	
Yes	29 (28.7)
No	72 (71.3)
Number of comorbidities	
≥2	27 (26.7)
1	53 (52.5)
None	21 (20.8)
Mean ± (SD)	1.1 (0.77)
Culture	
Yes	2 (2)
No	99 (98)
Escalation/de-escalation	
Escalated	42 (41.6)
De-escalated	12 (11.9)
None	47 (46.5)

SD, standard deviation

patients who received appropriate empirical antibiotics stayed 35 days compared to 21 days for inappropriate empirical antibiotics and SOFA score (P-value = 0.00). The ICU discharge time was >35 days for the SOFA score ≤8 compared to <20 days for the SOFA score >8 as depicted in Figures **2**A and **2**B.

4. Discussion

The primary outcome of this retrospective analysis was the significant correlation between the inappropriate selection of empirical antibiotics and patient death. The other independent risk factor for death is a high SOFA score. These essential facts

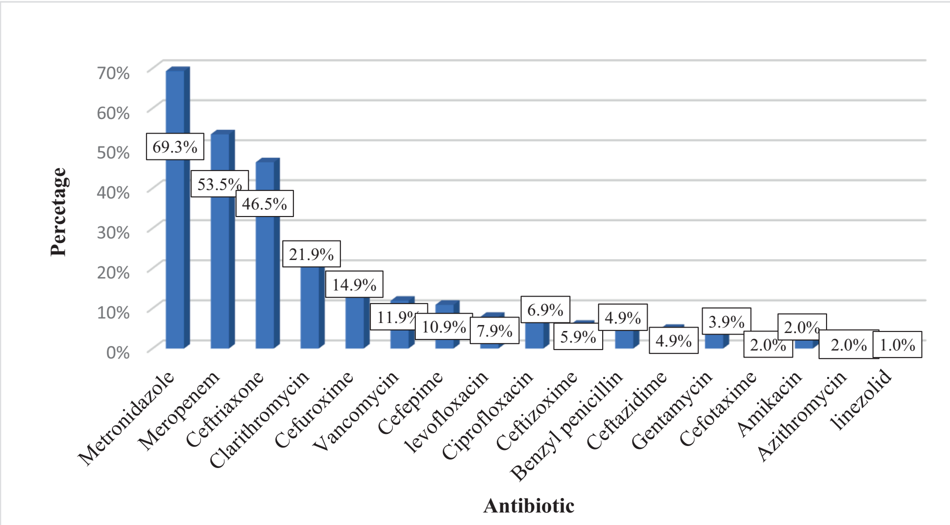
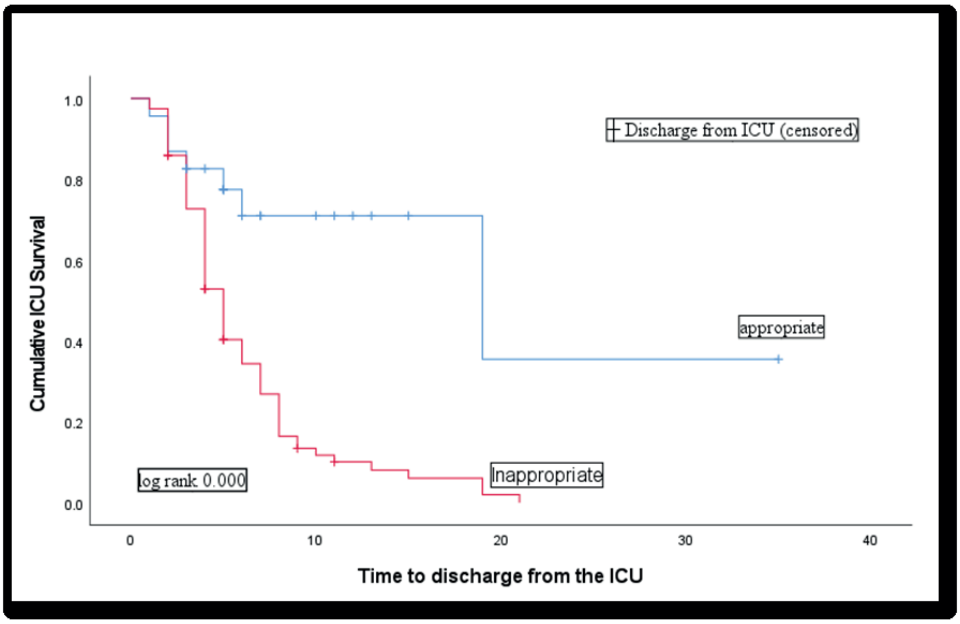


Figure 1: Percentage of antimicrobial drugs used in sepsis/septic shock patients.

were demonstrated by the Kaplan-Meier curve (log-rank), in which the maximum ICU-discharge time in patients who received appropriate empirical antibiotics was 35 days compared to 21 days for inappropriate empirical antibiotics used, and >35 days with SOFA score ≤8 compared to <20 days with SOFA score >8. These findings are in agreement with the prospective study in the medical ICU in Zagreb, Croatia which showed that independent risk factors for ICU mortality were higher SOFA scores at admission (OR 2.37, 95% CI 1.59–3.52), and inappropriate antimicrobial treatment (OR 9.99, 95% CI 2.57–38.87) in addition to reduced mobility level and failure recognize sepsis at its early stage in the emergency department [27]. In another study, appropriate initial empirical antibiotic therapy was the only independent predictor of outcome (*P*-value = 0.023) [3]. These demonstrate how optimal empirical antimicrobial drug selection contributes to effective management and serves as a quantifiable safety scale that reduces mortality [3]. In addition, several reports have shown that the optimal management of life-threatening infections in critically ill individuals largely depends on the appropriate use of antimicrobial agents. Inappropriate antimicrobial use is linked to a five-fold decrease in patient survival [28, 29].

Inappropriate empirical antibiotic use may worsen patient outcomes and increase bacterial resistance. In this study, 22.8% of the studied patients were prescribed appropriate empirical antibiotic agents. This figure is lower than the result of a retrospective study conducted in the surgical ICU at the Methodist Hospital, Texas [4] and another multicenter retrospective study carried out in Saudi Arabia, the United States, and Canada which revealed that appropriate empirical antibiotics were prescribed in 81% of all cases [4, 29]. This discrepancy may be because our study setting lacked a local empirical antimicrobial policy whereas other settings might have one. Furthermore, the health systems in these locations are far more advanced than those in Wad Medani, Sudan.

The current study reported a high mortality rate among studied patients, especially when compared to a prospective observational study conducted in Zagreb, Croatia which showed a total mortality rate of 37.9% among the studied cases and 63.4% among septic shock patients [27].



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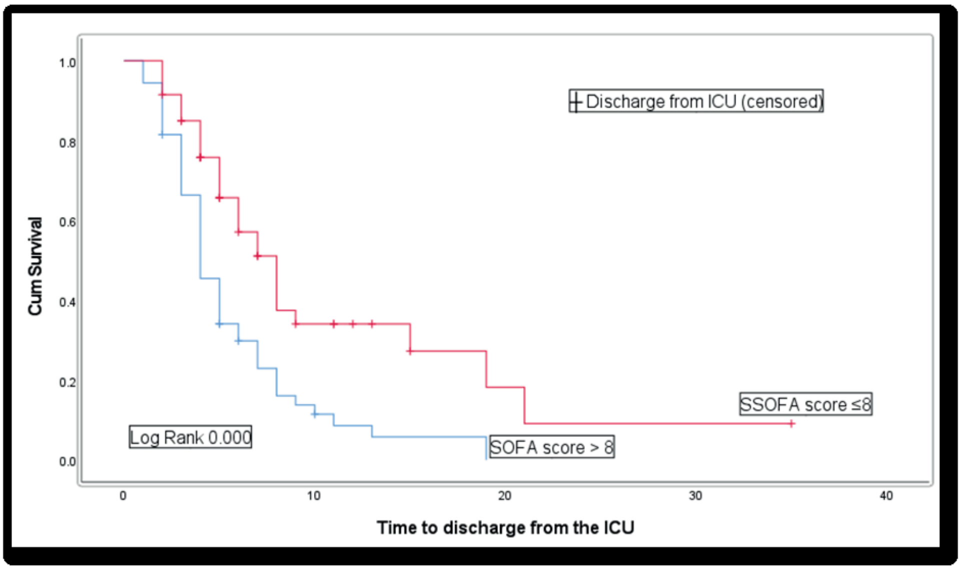

B

Figure 2: (A) Survival of sepsis/septic shock patients in the intensive care unit determined by the appropriateness of antimicrobial treatment. (B) Survival of sepsis/septic shock patients in the intensive care unit determined by the SOFA score.

In contrast, similar percentages of total mortality among studied patients and septic shock patients were found in a cross-sectional study carried out in Khartoum, Sudan [14]. On the other hand, our study showed a high mortality rate among studied patients who received inappropriate antibiotics which is much higher than that reported by a prospective observational study conducted in Marseilles, France (39%) and a retrospective study conducted in China University Hospital (36.8%) [30, 31]. A high mortality rate in this study might be linked to numerous factors such as a high percentage of inappropriate empirical antibiotics therapy and high percentages of aspiration pneumonia that statistically correlated with mortality rate, drawing attention to the role and quality of nursing care in our study setting.

One-third of studied patients were mechanically ventilated with a relatively high mortality rate of 82.75% compared to non-ventilated patients, representing 31.1% of all deaths. This finding is considered low compared to a cross-sectional study conducted in Singapore, which found >85% of deaths occurred in ventilated patients [32]. Sakr *et al.* reported that mechanical ventilation has been identified as a factor that increases the risk of in-hospital death [33]. This variation might be related to differences in study populations in relation to patient's age and comorbidities.

The majority of our patients were older than 60 years and had a higher rate of mortality. This finding is similar to that in a cross-sectional study done in Indonesia which reported a 75% mortality rate (*P*-value 0.579) among patients above 60 years [34].

Most of the studied patients had comorbidities, among which cardiovascular diseases were the most frequent and accounted for about half of the mortality, followed by diabetes accounting for about one-third of total death. In contrast, a cross-sectional study conducted in Indonesia reported that malignancy was the most common comorbidity at 100% (60) with a mortality rate of 68.3% (41), followed by respiratory insufficiency at 85% (51) with a mortality rate of 70.6% (36) [34].

Management of infection associated with sepsis and septic shock is significantly impacted by controlling the source of the infection [28]. Respiratory tract infections including pneumonia, CAP, and HAP are the most common sources, accounting for about half of the infections. These findings are similar to those found in a cross-sectional study conducted in Khartoum, Sudan, which revealed that respiratory tract infections were the most common source of infection (34%) [14]. However, they differ from two studies, one of which was a prospective study conducted in Zagreb and the second a retrospective study in Texas, which found genitourinary tract (56.9%) and IAI (56%) to be the most common sources of infections [4, 24].

Aspiration pneumonia was one of the leading causes of mortality. Most cases of aspiration pneumonia were developed during the hospitalization period which highlights the importance of studying this problem and discussing it with a multidisciplinary team in the hospital to identify the causes and recommend solutions.

Correct antibiotic selection based on culture data highlights a crucial point in sepsis treatment and septic shock [35]. In this study, culture was done for only two patients, which might be related to the lack of resources and facilities. Furthermore, Sudan lacks national empirical antibiotic recommendations [14], and the studied hospital also lacks local empirical therapeutic protocol. Furthermore, the selection of empiric therapy was not guided by antibiotic susceptibility modalities which emphasize the importance of culture sensitivity test.

Antibiotic escalation was found in nearly half of the patients, which highlights the need for increased awareness regarding the importance of escalation/de-escalation of antibiotics to minimize the likelihood of developing antimicrobial resistance and enhance patient outcomes. This high percentage of antibiotic escalation might be due to the lack of response from inappropriate empirical antibiotic therapy. Therefore, a local antibiotic protocol should be developed for safe and effective antibiotic use.

Metronidazole was found to be the most commonly used drug followed by meropenem, which differs from an observational prospective study conducted in Japan in which carbapenem was most frequently used (55%), followed by Tazobactam/Piperacillin (21%) and Vancomycin (18%) [36]. The high frequency of metronidazole used in this study might be related to the combination of meropenem and metronidazole, accounting for more than half of the administered metronidazole. Meropenem and metronidazole combination was the common practice in our study setting, although there is no scientific evidence to support this combination because meropenem is one of the carbapenem antibiotic classes that covered anaerobic bacteria. To change this practice, an education session about antibiotic classes, spectrum, and coverage should be implemented among healthcare practitioners for the safe and effective use of antibiotics. In addition, local antimicrobial protocol should be developed and implemented.

5. Conclusion

Using appropriate empirical antibiotics in the management of sepsis or septic shock would enhance the patient's outcomes. The currently used antibiotics provide inappropriate and inaccurate antimicrobial coverage. These results highlight the significance of creating evidence-based empirical antibiotic protocols for treating sepsis and septic shock to minimize harm to patients and improve patient safety, particularly in developing countries where rapid diagnostic tests to detect microorganisms are scarce. In addition, microbiology culture and drug susceptibility tests should be available and routinely used in the management of sepsis or septic shock patients. Furthermore, pre- and post-interventional studies on the importance and application of the 1- and 3-hr bundles of sepsis should be conducted to improve clinical practice and patient outcomes. Finally, this study highlighted the importance of the presence and implementation of local and/or national guidelines for antimicrobial prescribing in Sudan.

6. Strengths and Limitations

The strength of this study includes the fact that we evaluated all admitted patients for more than two years. However, this study was conducted in one center which limits the results' generalizability, with a retrospective study design that restricts the ability to recognize a patient who is highly prone to having multiple drug resistance and evaluate the impact of first-hour antibiotics used in sepsis and septic shock patients on patients' mortality. Additionally, due to the lack of local empirical antibiotic protocol, the only way to evaluate the appropriateness of empirical antibiotic therapy was international guidelines as well as the seldom use of culture and drug susceptibility tests. Furthermore, about one-third of the total septic and septic shock patients were not included in the study analysis due to their incomplete data.

Declarations

Acknowledgments

None.

Ethical Considerations

Ethical approval was obtained from the Ministry of Health, Gezira State, N: 44/T/Kh/1, (13/3/2022), and informed consent was not required by the Ethical Committee, Ministry of Health, Gezira State.

Competing Interests

None declared.

Availability of Data and Material

The corresponding author can provide access to the datasets used and/or analyzed in the current study upon request.

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Abbreviations and Symbols

SSC: Surviving Sepsis Campaign

LoS: Length of stay

ICU: Intensive care unit

Sepsis-3: Third International Consensus Criteria for Sepsis and Septic Shock

SOFA: Sequential Organ Failure Assessment

APACHE: Acute Physiology and Chronic Health Evaluation

SPSS: Statistical Package for the Social Sciences

SD: Standard deviation

RR: Relative risk

CI: Confidence interval

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