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RESEARCH ARTICLE

Impact of Empirical Antibiotics Therapy on the Clinical Outcomes of Adult Patients Admitted to the Intensive Care Units with Sepsis in Sudan

Tasabeeh Hamad[1], Galal Abdalla[2], Bushra Salman[1], Bashir A. Yousef[3]

[1]Pharmacy Department, Sultan Qaboos Comprehensive Cancer Care and Research Center, Muscat, Oman.
[2]Department of Internal Medicine, Queen Elizabeth The Queen mother Hospital, Kent, United Kingdom.
[3]Department of Pharmacology, Faculty of Pharmacy, University of Khartoum, Khartoum, Sudan.

*t.hamad@cccrc.gov.om

ABSTRACT

Introduction: Sepsis is defined as a life-threatening organ dysfunction caused by a dysregulated host response to an infection. Early recognition and administration of appropriate empirical antibiotic therapy are associated with lower mortality rate and shorter length of stay. This study aims to identify the risk factors for developing sepsis, the common sites of infection, the isolated microorganisms, and to evaluate the impact of appropriate empiric antibiotic on the mortality rate and length of stay the in two tertiary care hospitals in Sudan.

Methodology: A prospective hospital-based study was done on 30 patients who were admitted to the intensive care unit (ICU) during a four-month study period. Data were retrieved from patients' records. Data were analyzed using SPSS Version 20.

Results: Out of the 30 study patients, 43% were females. The median age of the group was 68 years and 57% of the patients were above 65 years. The most common risk factor for developing sepsis was diabetes mellitus (23.33%), followed by malignancy (16.67%). The most common site of infection was the chest (33.33%). In total, 19 different regimens of empirical antibiotics were prescribed, where 43.4% were appropriate and 56.6% were inappropriate. Among the studied population, 18 patients died and the overall mortality was 60%. The study found that in patients who received appropriate empiric antibiotics, mortality significantly decreased ($p = 0.006$). Patients who received appropriate treatment were also found to have a numerically 4-days shorter length of ICU stay but this did not reach statistical significance due to small sample size.

Conclusions: The study concluded that diabetes mellitus is the most common risk factor for developing sepsis, followed by malignancy. Gram-negative organisms are the most common isolated microorganisms. Respiratory infection is the most common source of infections. The prescribed empirical antibiotics were mostly inappropriate. Moreover, patients with appropriate empirical antibiotics had shorter ICU stays and increased survival when compared with those who had inappropriate treatment.

Keywords: Sepsis; ICU; Antibiotics.

Introduction and Literature Review

Sepsis frequently manifests across various infectious diseases and receives insufficient attention in developing regions, where its impact can be most devastating.

DEFINITION

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to an infection. The definition of sepsis was updated in 2016 following the publication of the Third International Consensus Definitions for Sepsis and Septic Shock[1].

Septic shock has been defined as a subset of sepsis in which profound circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone[1]. Sepsis is estimated to affect 31.5 million people worldwide every year, with an estimated 5.3 million deaths annually[2], and the incidence of sepsis is likely to rise. In England, data from the Hospital Episode Statistics (HES) released by the Health and Social Care Information Centre (HSCIC) in 2015 demonstrated that there were nearly 123,000 cases of sepsis with 36,800 associated deaths recorded in 2013/14[3], up from around 25,100 in 2010[4].

Most epidemiological studies revealed that sepsis is more common in men than in women. Patients older than 65 years of age are particularly susceptible, with one study finding almost two-thirds of cases to be in people over 65[5]. Gram-positive and Gram-negative bacteria are identified as the causative organism in approximately 90% of cases, with fungal infection increasing in frequency[6].

RISK FACTORS FOR DEVELOPING SEPSIS

The risk factors are categorized into two groups:

Strong risk factors include the following: underlying malignancy; age above 65; compromised immunity, which may arise from treatment (e.g., chemotherapy, corticosteroid, or other immunosuppressants), underlying disease (e.g., diabetes and sickle cell), or surgery; hemodialysis; alcoholism; diabetes mellitus; recent surgery or other invasive procedure; indwelling line or catheter. Conversely, the weak ones are as follows: lung disease and male sex may be at greater risk.

Diagnostic Criteria

There is ongoing debate about the most appropriate criteria for diagnosing sepsis in clinical practice, with several different approaches suggested. These include the use of the systemic inflammatory response syndrome (SIRS) criteria in the presence of infection, the Sequential (or sepsis-related) Organ Failure Assessment (SOFA) score recommended by the Sepsis-3 international consensus group, and the use of a risk stratification system as recommended by guideline groups in the US and UK[7].

In practice, sepsis is usually diagnosed by the clinical identification of an infection in a patient who meets the clinical criteria for SIRS. SIRS is defined by the presence of two or more of the following clinical signs and laboratory investigations, according to the international consensus definition published in 1991. Hyperglycemia and acutely altered mental status are not part of the original criteria for SIRS but have since been included by the Surviving Sepsis Campaign in their screening tool[8].

Surviving Sepsis Campaign: Evaluation for severe sepsis screening tool

- Temperature> 38.3°C (101°F) or <36.0°C (96.8°F)
- Tachycardia> 90 bpm
- Tachypnea> 20 breaths/minute or PaCO2 <4.3 kPa (32 mmHg)
- Leukocytosis (WBC count> 12x10^9/L [12,000/microliter])
- Leukopenia (WBC count <4x10^9/L [4000/microliter])
- Normal WBC counts with> 10% immature forms
- Hyperglycemia (blood glucose> 7.7 mmol/L [>140 mg/dL]) in the absence of diabetes mellitus
- Acutely altered mental status

Treatment Approach

Early diagnosis and treatment of sepsis is key to improving outcomes. Treatment guidelines have been produced by the Surviving Sepsis Campaign and remain the most widely accepted standards[9]. They include the following:

- Blood cultures should be obtained prior to administration of antibiotics.
- Broad-spectrum antibiotics that target the suspected pathogen(s) are to be administered.
- Then, 30 mL/kg crystalloid for hypotension or lactate ≥4 mmol/L (≥36 mg/dL) is to be administered.
- Serial measurement of blood lactate should be done.
- Vasopressors should be used to maintain a mean arterial pressure (MAP) ≥65 mmHg in patients' refractory to fluid therapy.

In patients with initial lactate ≥4 mmol/L (≥36 mg/dL) or who are persistently hypotensive (i.e., MAP <65 mmHg), volume status and perfusion should be assessed using either a repeat focused examination (including vital signs and cardiopulmonary, capillary refill, pulse, and skin findings) or two of the following methods:

- Measurement of central venous pressure (CVP)
- Measurement of central venous oxygen saturation (ScvO2)
- Bedside cardiovascular ultrasound
- Dynamic assessment of fluid responsiveness with passive leg raises or fluid challenge

Antibiotics Therapy for Sepsis

Broad-spectrum intravenous antibiotics should be administered before identifying a pathogen. They are recommended within the first hour of diagnosing sepsis, preferably after cultures have been taken[9]. Knowledge of locally prevalent pathogens and their antibiotic resistance pattern are important when deciding empirical therapy. Once cultures and sensitivity results are available, antibiotics can be tailored to the known pathogen. Antibiotics should be given according to the infection site. If there is no clinical evidence to suggest the infection site, empirical broad-spectrum antibiotics should still be given[9].

MacArthur et al.[10] conducted a randomized controlled sepsis (MONARCS) trial, which enrolled patients with suspected sepsis. They sought to determine whether adequate antibiotic therapy was associated with a lower mortality rate. The study enrolled 2634 patients, 91% of whom received adequate antibiotic therapy. The mortality rate among patients given adequate antibiotic treatment was 33% vs. 43% among patients given

inadequate treatment ($p < .001$). They concluded that adequate antibiotic therapy significantly decreased the crude mortality rate among patients suspected of sepsis.

Garnacho-Montero et al.[11] conducted a prospective cohort study at the intensive care unit (ICU) of a tertiary hospital. In total, 406 patients were included. Microbiological documentation of sepsis was obtained in 67% of the patients. At ICU admission, sepsis was present in 105 patients (25.9%), severe sepsis in 116 (28.6%), and septic shock in 185 (45.6%). Empirical antibiotic therapy was initiated in all patients. Empirical treatments were considered adequate in 83% of the sample and 17% not adequate. Inappropriate empirical antimicrobial therapy was associated with a significant increase in the risk of death over the whole population (RR, 1.41; 95% CI, 1.11–1.80) and with respect to the patients with ad- equate therapy (RR, 1.55; 95% CI, 1.20–2.02). Moreover, 58 patients (14.3%) died within the first three days (early mortality), the 28-day mortality rate was 44.8% (182 patients), the 60-day mortality rate was 47.8% (194 patients), and 196 patients (48.3%) died during the hospital stay. Hospital length of stay was greater in surviving patients with inadequate empirical antibiotic therapy (55.9 [68.6] days) than that in surviving patients with adequate empirical antibiotic therapy (40.8 [33.8] days). However, this difference did not reach statistical significance.

The retrospective study was conducted on 5,571 patients with septic shock in three countries. Therapy with appropriate antimicrobial agents was initiated in 80.1% of cases. Overall, the survival rate was 43.7%. There were marked differences in the distribution of comorbidities, clinical infections, and pathogens in patients who received appropriate and inappropriate initial antimicrobial therapy ($p < 0.0001$ for each). The survival rates after appropriate and inappropriate initial therapy were 52.0% and 10.3%, respectively. Similar differences in survival were seen in all major epidemiologic, clinical, and organism subgroups. The decrease in survival with inappropriate initial therapy ranged from 2.3-fold for pneumococcal infection to 17.6-fold for primary bacteremia. After adjustment for acute physiology and chronic health evaluation II score, comorbidities, hospital site, and other potential risk factors, the inappropriateness of initial antimicrobial therapy remained most highly associated with the risk of death[12].

Guo et al.[12] performed a systematic literature search in PubMed, EMBASE, Web of Science, and CENTRAL in The Cochrane Library. The relative risk (RR) with 95% confidence interval (CI) was used to evaluate the impact of de-escalation therapy on clinical outcomes. Nine individual studies (1873 patients) were included. Mortality trended lower in the de-escalation group compared with the continuation of the broad-spectrum antibiotics group. However, the results were not statistically significant (RR = 0.74; 95% CI, 0.54–1.03). They found that antibiotic de-escalation therapy has no detrimental impact on mortality in patients with severe sepsis and/or septic shock, compared to the continuation of broad-spectrum antibiotics. Since de-escalation offers the opportunity to limit the overuse of broad-spectrum antibiotics, it should be considered an option in clinical practice.

Rationale

Sepsis is associated with an in-hospital mortality rate of 30%–40%.[1] Despite advances in medical practice, the mortality rate of sepsis has not declined in the last decades, and this condition is associated with high costs[13]. Severe sepsis is a common, expensive, and frequently fatal condition, with as many deaths annually as those from acute myocardial infarction.

Sepsis is estimated to affect 31.5 million people worldwide every year, with an estimated 5.3 million deaths annually[1]. This equates to approximately 20,000 deaths per day and makes sepsis the second leading cause of death after vascular disease[1].

Early empirical antibiotic treatment is standard practice for patients suspected of having sepsis. Despite the fact that adequate antibiotic therapy has been shown to reduce mortality rates, this issue has not been thoroughly researched. The association of early empirical antibiotic treatment with mortality in sepsis patients must, by necessity, be studied in an observational setting.

GENERAL OBJECTIVE

This study aims to evaluate the impact of prescribed empirical antibiotics on the clinical outcomes of adult patients diagnosed with sepsis in the intensive care unit.

SPECIFIC OBJECTIVES

The specific objectives for this study are as follows: to identify risk factors for developing sepsis and the common sites of infection; to identify the isolated microorganisms and their susceptibility patterns; to evaluate the appropriateness of prescribed empirical antibiotics according to Sanford guidelines; to determine the impact of appropriate empirical antibiotics on the length of stay and mortality rate; to measure the overall mortality rate due to sepsis.

Methodology

This was a prospective hospital-based study of patients diagnosed with sepsis and admitted to the ICU of Fedail Hospital and Alribat Hospital. Both hospitals are general tertiary care hospitals in Sudan with a bed capacity of more than 150. The study included all adult patients (> 18 years) diagnosed with sepsis or septic shock at the time of presentation to the ICU from April to August 2018. Pediatric patients were excluded from the studied population. Data were collected using a manual pre-structured pretested check list filled from patient's records. Data collected included demographics, risk factors, suspected source of sepsis, cultures sent and microbiology results, medications used, and outcome data.

STUDY OUTCOMES

Sepsis was diagnosed according to the 2016 consensus definitions for sepsis and septic shock[1]. The mortality rate is the measure of the frequency of occurrence of death in a defined population during a specified interval, which was measured from the first admission day till the last follow-up date. The length of stay covered the period from ICU admission to discharge from the ICU either to home or the medical ward. The appropriateness of prescribed empirical antibiotics was determined according to Sanford guidelines[14]. Overall appropriate antibiotic therapy was documented if the patient received appropriate antibiotic indication, dosage and route of administration. All patients were followed up until hospital discharge or death.

STATISTICAL ANALYSIS

Descriptive statistical analysis was performed. Continuous variables were described using means or medians with standard deviations (SD) or interquartile ranges (IQR), as appropriate. For categorical variables, frequencies and percentages were reported. Chi-square and Fisher's exact test were used to identify the association between categorical variables. Data were analyzed using SPSS version 20.

Ethical approval was obtained from the ethics committee of the pharmacy faculty. Written informed consent and co-patient consent were obtained by the hospital administration.

Results

In total, 30 patients who met the inclusion criteria were included in the study: 12 males and 18 females. The median age of the study cohort was 61 years (IQR: 41–75). Sepsis was the primary diagnosis in 12 (40%) of the cohort and 13 (43%) were diagnosed with septic shock. The diagnosis was not confirmed in five patients. All demographic data and baseline laboratory tests are shown in Table 1.

Culture samples (blood, urine, sputum, swap, and catheter tip) were collected from 93% of the patients, and bacterial growth was observed in 77% of them.

Table 1. Demographic data and clinical characteristics:

N = 30	Age (median, 61; IQR 41–75)	
	Frequency	Percentage
Gender		
Female	12	40
Male	18	60
Diagnosis		
Sepsis	12	40
Septic shock	13	43.33
Not confirmed	5	16.67
Risk factors		
Diabetes mellitus	7	23.33
Cancer	5	16.67
Recent hospitalization	3	10.00
Congestive heart failure	3	10.00
Others	18	40.00
Site of infection		
Chest	10	33.33
Urine	9	30.00
Chest + Urine	4	13.33
Abdomen	2	6.67
Skin	2	6.67
Line	1	3.33

N = 30	Age (median, 61; IQR 41–75)	
	Frequency	Percentage
Others	2	6.67
Fate of patient		
Discharge	12	40.00
Death	18	60.00
Baseline blood count	Mean (Range)	Reference
White blood cell count	20.29	
Hemoglobin	11.18	
Platelet	193.82	
C-reactive protein	153	

In total, 62% of the patients were infected by a single organism, 26% by two microorganisms, 8% by three microorganisms, and 4% by six microorganisms. The identification of microbial isolates in the affected patients is demonstrated in Table 2.

Table 2. Isolated Microorganisms:

Microorganism	Frequency	Percentage %
Escherichia coli	6	15.38%
Candida albicans	6	15.38%
Klebsiella pneumonia	5	12.82%
Pseudomonas aeruginosa	5	12.82%
Methicillin-resistant *Staphylococcus aureus* (MRSA)	3	7.69%
Coagulase-negative staphylococcus	3	7.69%
Acinetobacter	2	5.13%
Gram-negative *bacilli*	1	2.56%
Gram-positive *cocci*	1	2.56%
Proteus mirabilis	2	5.13%
Enterococcus faecalis	2	5.13%
Citrobacter	2	5.13%
Streptococcus	1	2.56%

All the patients were managed with intravenous (IV) antibiotics. According to the Sanford guidelines, 17 patients (56.67%) received inappropriate empirical treatment and 13 patients (43.3%) received appropriate empirical treatment. Considering the fate of the studied population after a median follow-up period of 14 days, 18 patients died during admission and 12 patients were discharged from the hospital, which equates to a mortality

rate of 60% to Table 3. The average length of stay was 14 days (SD 14.3112).

Table 3. Fate of patient according to the appropriateness of empirical antibiotics.

Fate of patient	Appropriate	Inappropriate	Unkown
Discharged	9	3	
Passed	3	14	1
Total	12	17	1

ASSOCIATION OF CLINICAL OUTCOMES WITH PATIENT DEMOGRAPHICS AND OTHER CLINICAL PARAMETERS:

Male sex represents 60% of the studied population, with a numerically higher mortality rate of 61.11%. However, this did not reach statistical significance (p-value = 0.728)

Patients who were diagnosed with septic shock had significantly higher mortality rates compared to those who were diagnosed with sepsis (p = 0.003). The chest was the most common site of infection, followed by urine; patients with urinary tract infections had the highest mortality rate (p = 0.054).

The length of stay did not significantly decrease in patients who received appropriate treatment (p=0.391); however, patients who had appropriate empirical antibiotics stayed an average of 12 days in the hospital compared with 16 days if the antibiotics were not appropriate.

Patients who received appropriate empirical antibiotics had a significantly lower mortality rate (p = 0.006). Patients who died during admission had a shorter length of stay, with an average of 11 days, and patients who were discharged had an average length of stay of 16 days. However, this difference was not statistically significant (p = 0.137).

Discussion

Sepsis is a major health problem that has received a considerable attention over the last decades with increase in awareness of it is presentation and need for early recognition and evidence-based management. This study evaluated a group of critically ill septic patients who were admitted to the intensive care unit due to sepsis. The results highlight the high overall mortality rate in these patients. The findings of the study suggest an association with the appropriateness of the empirical antibiotic choice. This adds to the body of evidence that adherence to internationally accepted guidelines and care bundles, even in low-resource and middle-income countries, has been shown to reduce the odds of hospital mortality[15].

Understanding the population demographics and risk factors can further support early detection and diagnosis, optimized treatment approaches as well as targeted prevention strategies. Our study has highlighted a

number of risk factors associated with the development of sepsis and negative overall outcomes. Demographic features showed that around 60% of the patients were above 65 years old. Aging is a well-known risk factor for sepsis due to pre-existing co morbidities, compromised immune function, sarcopenia, malnutrition, and polypharmacy[16]. This finding is similar to the result of Martin et al.[13] who performed a longitudinal observational study using national hospital discharge data from 1979 to 2000 across the USA. Elderly patients (≥ 65 years) accounted for 12% of the US population and 64.9% of sepsis cases.

Also, demographics about sex have shown that 60% of the population were male. The literature examining the relationship between sepsis and gender is inconclusive and the reasons underlying the higher rate of sepsis in men remain unclear[17]. The former study by Martin et al.[13] found that sepsis was more common among men than women. Other studies have found that men are more commonly affected by endocarditis and bacteremia and tend to develop sepsis more frequently from respiratory infections (36% vs. 29% for women, $p < 0.01$). On the other hand, women tend to develop sepsis more frequently from genitourinary infections (35% vs. 27% for men, $p < 0.01$)[17]. This also aligns with our findings, where the most common site of infection was the respiratory tract followed by genitourinary system. Other studies also observed a similar pattern of target sites including respiratory and genitourinary systems as well as intrabdominal infection and indwelling catheter[18]. The range of involved pathogens further complicates the scenario, with bacteria been one of the most common pathogens that cause sepsis, but there are significant differences in pathogenic mechanisms between gram negative bacteria and gram positive bacteria[17]. For example, Staphylococcus aureus and Pseudomonas aeruginosa were more prevalent in respiratory infections, and Escherichia coli are usually the culprits in urinary tract infections[19]. Among our population, bacterial growth was observed in 77% of patients, where around 60% of these were gram negative bacteria, more than 25% were gram positive bacteria, and and 15% were fungi. The most frequent single microorganism was Eshcersia coli. These findings are comparable in certain aspects with Garnacho-Montero et al.[11] who found that Gram-negative sepsis was the most frequent affecting 31%, followed by Gram-positive sepsis in 18%, polymicrobial sepsis in 13%, and fungal sepsis in less than 3%. However, in our study, fungal sepsis rate was significantly higher. It is known that the sub-Saharan Africa is the world's region with the greatest burden of fungal skin disease[18] and this might have impacted the findings, especially due to the small sample size of the study. Moreover, agriculture is still the backbone of economic growth of many developing countries and the risk of getting infected by pathogenic soil-related fungi in higher[20].

Considering co-morbidities, diabetes mellitus remains one of the major risk factors and the most common predictor of sepsis in our study (23%). Diabetic patients are at a higher risk of developing wounds and sores that do not heal well. Moreover, diabetes impairs the host's immune response, worsening the severity of the infection. Similarly, malignancy accounted for a significant proportion of sepsis cases (16.67%). Danai et al.[21] reported that patients

with a history of cancer are at increased risk for acquiring and subsequently dying from sepsis, compared to the general population.

It is also critical to highlight the association of treatment appropriateness with sepsis outcomes. In our study only 43% received appropriate antibiotics according to the standard practice guidelines, compared to 57% who received inappropriate management. A similar pattern, albeit to a lesser extent, was also found by Fraser et al.[3] who reported that inappropriate initial antibiotic treatment was prescribed in 36% of patients. This might be due to the lack of hospital guidelines, with limited access to international guidelines. Furthermore, there was a tendency to prescribe one-size-fits-all regimen rather than a personalized case-by case, site and disease specific approach. In patients who received appropriate treatment, the mortality rate was found to be 46%, compared to an alarming rate of 76% in patients who did not receive appropriate treatment with a statistically significant difference ($p = 0.006$). This result is consistent with that of Kollef et al.[22] who performed a prospective cohort study to evaluate the relationship between inadequate antimicrobial treatment of infections and hospital mortality for patients requiring ICU admission. This study demonstrated that the hospital mortality rate of infected patients receiving inadequate antimicrobial treatment (n=169) was 52%. This was statistically significantly greater than the hospital mortality rate of the remaining patients in the cohort (n = 1,831) who received appropriate management (12%) (RR 4.26; 95% CI, 3.52–5.15; $p < 0.001$).

The difference in other outcomes, such as the length of stay, did not reach statistical significance between the two groups (appropriate vs. inappropriate antibiotic treatment), probably due to small sample size ($p=0.3912$). However, numerically a difference was seen, as patients who had appropriate empirical antibiotics stayed on average of 12 days in the hospital compared with 16 days if the antibiotics were not appropriate. Likewise, Khan et al.[23] demonstrated that there was a significant 4-days difference in the ICU length of stay between pneumonia patients receiving appropriate antibiotics compared to those who received inappropriate antibiotics, but they had a slightly larger sample size of 44.

There are a number of limitations in this study. Mainly, the small sample size of 30 patients limits the generalizability of the result as well as the ability to detect statistically significant associations between variables. Additionally, factors such as resistant patterns were not captured in this study. However, the study presents solid data as all patients were followed during ICU admission enabling the evaluation of empirical antibiotics therapy, addressing the isolated microorganism and their susceptibility pattern, identifying higher risk group for developing sepsis in association with co-morbidities, and the most common sites of infection in this underrepresented population. Since there are no published Sudanese guidelines regarding the choice of empirical antibiotics in patients diagnosed with sepsis, the study was one the first studies in the region to highlight the critical need of maximizing efforts to publish such guidelines.

Conclusion and recommendations

The study reflected a high mortality rate of patients admitted to the ICU with sepsis in

Sudan, which might be largely related to the high percentage of inappropriate antibiotic treatment. It is important to pursue further studies with a larger group of patients. Moreover, future research should focus on identifying common pathogenic organisms and their susceptibility patterns addressing the critical need of clinical guidelines to improve patient outcomes.

Conflict of Interest:

None

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