

Epidemiology of Sepsis Syndrome among Intensive Care Unit Patients at a Tertiary University Hospital in Palestine: 2019

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ABSTRACT

Background: Sepsis syndrome is an emerging healthcare problem, especially in critically ill patients, regardless whether it's community- or hospital-acquired sepsis. This study evaluates the characteristics of these patients, in addition to the type, source, and outcome of sepsis and septic shock, in a university tertiary hospital in Palestine. It also studies the most common organisms encountered in these patients.

Materials and methods: This is retrospective observational chart review study of all adult admissions to the intensive care unit over a period of 2 years. The presence of sepsis and septic shock was assessed and documented based on the Third International Consensus Definitions (Sepsis-3). Data regarding demographics, severity, comorbidities, source of infection, microbiology, length of stay, and outcomes (dead/alive at discharge from ICU) were recorded.

Results: A total number of 174 patients were included. The mean age was 57.4 years, with cardiovascular diseases and diabetes being the leading comorbidities encountered in them. Respiratory infections were the most common site of sepsis, found in around 71% of patients, followed by urinary tract infections. More than 70% of cases were due to hospital-acquired infections (HAIs). *Acinetobacter* species were the most common gram-negative organisms encountered, while *Enterococcus* was the most common gram-positive organisms. Around 54% of patients had multidrug-resistant organisms. The average length of stay in the ICU was 8 days. The average mortality rate was 39.7%, which is higher among septic shock patients.

Conclusion: Both sepsis and septic shock carry high morbidity and mortality rates, and they are very frequent among critically ill patients. Special care and developing management bundles are crucial in controlling and preventing this threat.

Keywords: Epidemiology, Intensive care unit, Palestine, Sepsis syndrome.

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INTRODUCTION

Sepsis, in its entire spectrum, remains a major healthcare problem causing morbidity and mortality. It is a common cause of hospital admissions, including intensive care unit (ICU) admissions.¹ Furthermore, the incidence of sepsis syndromes and their consequences are increasing steadily, causing more health and economic burden to countries worldwide.^{2,3} A study performed in the United States showed a rapid increase in the number of cases of sepsis, from 415,280 in 2003 to 711,736 in 2007.⁴

The overall mortality of sepsis syndrome varies, but remains generally high. For example, in a study performed in Spain in 2003, the mortality rate ranged from 12.8% in sepsis up to 45.7% in septic shock.¹ Furthermore, it was found to be up to 58% in a study performed in a Saudi ICU.⁵ Mortality rates were found to be significantly higher with ICU-acquired sepsis, as observed in a study conducted in Italy in 2013.⁶

The type of the sepsis could be community-acquired or hospital-acquired. Tertiary centers usually have a higher incidence of HAIs, as was observed in a study performed in a tertiary hospital ICU in Saudi Arabia, where 60% of cases were hospital-acquired.⁵ Meanwhile, secondary hospitals will first encounter community-acquired infections as noticed in a study performed in Spain, where 71% of cases were community-acquired.¹

The definition of sepsis syndromes has changed over the years. At first, sepsis syndromes included systemic inflammatory response syndrome (SIRS), sepsis, severe sepsis, and septic shock.⁷ Thus, most published research projects regarding sepsis used these definitions for research purposes. However, over the following years and due to the limitations observed in the former definition, a new definition

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was published in 2016 called the Sepsis-3 definition, summarizing the continuum of sepsis syndrome into two entities: sepsis and septic shock, with each having a precise definition.⁸

Surviving Sepsis Campaign guidelines were issued in 2004 as a reference in the management of sepsis syndromes and their

consequences. This was later adopted and supported by most healthcare systems. The last update of this campaign was in 2016, with only a few updates introduced in 2018.⁹

After reviewing the literature, we found that little is published about sepsis and septic shock in the developing world, including Palestine. Also, we found that most of the published researches used the old definition of sepsis, and still not many researchers used the current Sepsis-3 definition, as it has recently been published as a standard definition. Without extensively studying sepsis, we can do nothing to handle it. And so we decided to study the magnitude of this problem in our population and its characteristics. In the context of Palestine as a developing country with limited resources, this will add more value, as prevention of this problem is much more applicable than managing the complications after it has happened. So the objectives of this study are to describe the demographic, clinical, microbiological, and outcome characteristics of patients with sepsis in the ICU and to compare between sepsis and septic shock in relation to background and clinical characteristics. The results of this study are expected to direct healthcare workers in Palestine to the right way to deal with this dangerous threat to this special type of patients, as most of them have multiple comorbidities that complicate the sepsis issue.

MATERIALS AND METHODS

Methods

This is an observational chart review study. All adult patients (age ≥ 18 years) admitted to the ICU at An-Najah National University Hospital (ANUH), a tertiary teaching hospital in Nablus/Palestine, between January 1, 2017, and December 31, 2018, and fulfilling the definition of sepsis or septic shock at admission or during their ICU stay, were included in the study. The ICU at ANUH is a six-bed medical unit with an annual admission rate of around 100 patients, run by a team of critical care specialists assisted by physicians-in-training. Patients who stayed in the ICU for < 24 hours or those who were discharged alive from ICU within 24 hours without developing sepsis or complications were excluded, and no further data were collected from them. Patients who stayed in the ICU after December 31, 2018, were deemed as survivals. Data collection included age, gender, comorbidities, community- or hospital-acquired infection, source of infection, most common organisms, ICU length of stay, and mortality.

Sepsis is defined as confirmed organ dysfunction represented by an increase in the Sequential Organ Failure Assessment (SOFA) score of ≥ 2 points. Septic shock is defined as an acute circulatory failure attributed to sepsis that is not explained by any other causes. Acute circulatory failure is defined as persistent arterial hypotension (SBP < 90 mm Hg, mean arterial pressure (MAP) < 60 mm Hg, or a reduction in systolic blood pressure (SBP) > 40 mm Hg from baseline despite adequate volume resuscitation).⁸ The severity of the acute illness and organ dysfunction at the time of ICU admission was assessed using the SOFA and APACHE II score.

A patient's infection is considered to be community-acquired if the patient had no hospital admissions in the 2 weeks prior to the current admission or if it occurred within 48 hours of admission. Infections manifesting > 48 hours after admission were defined as hospital-acquired infections (HAIs) or if there was a history of hospital admission within the last 2 weeks. Infections that developed while in the critical care unit were defined as infections resulting in sepsis syndromes, which were not present within the first 48 hours of admission to the ICU. The origin of infection was classified according to the mutually exclusive primary infection

source: respiratory, urologic, intra-abdominal, skin and soft tissue, and others.⁵

Comorbidities included in the study were diabetes mellitus (DM), hypertension, cardiovascular disease, neurological disease, chronic kidney disease, chronic liver disease, chronic respiratory disease, hematologic malignancy, other malignancies, and acquired immunodeficiency. The immunosuppression state was defined either by the administration in the 12 months prior to ICU admission of chemotherapy or radiation therapy or the administration of steroid treatment equivalent to 0.2 mg/kg/day prednisolone for at least 3 months or 1 mg/kg/day for a week within the 3 months prior to ICU admission, hematological diseases including chronic neutropenia (≥ 3 months) or ≤ 1000 PN/dL.¹⁰

In addition, we studied the percentage of patients having multidrug resistant (MDR) organisms, because infections with MDR organisms can lead to inappropriate or delayed antimicrobial therapy administration, and so lead to poorer patient outcomes. Multidrug resistant was defined as acquired nonsusceptibility to at least one agent in three or more antimicrobial categories.¹¹

The study was approved by the institutional review board (IRB) at An-Najah National University. The confidentiality of the collected data was assured and was used only for research purposes.

Data Analysis

Data were collected and entered using a Microsoft Excel spreadsheet, then were imported to the Statistical Package for Social Sciences (SPSS), which was used for data analyzes. Descriptive analyzes were performed by reporting the number and percentage for categorical variables, whereas the mean and standard deviation were reported for continuous values. Associations between the groups and categorical variables were performed using the chi-square test, whereas the independent Student's *t*-test and Mann-Whitney test were used to assess the association with continuous variables. A *p* value of < 0.05 was considered to indicate statistical significance.

RESULTS

Table 1 shows the background characteristics and co-morbidities of the all sepsis patients (174 patients) identified during the study period. Their average age was 57.4 ± 18.2 years and 92 patients (52.9%) were male. The most common comorbidities observed among them were cardiovascular disease and DM: 107 and 90 patients, respectively. Sixty patients (34.5%) were found to be immune-compromised and 71 patients (40.8%) had a creatinine level ≥ 1.2 mg/dL at admission. Compared to sepsis patients, creatinine ≥ 1.2 , hematologic malignancy, and metastatic cancer were found to be significantly more highly represented among septic shock patients (*p* value < 0.05). For all patients, the median ICU stay was 8 days (range 1–208); it was significantly higher for septic shock patients (*p* value = 0.011).

Regarding the origin of infection, 124 sepsis patients (71.3%) were found to have the respiratory system as the source of infection, followed by the urinary system (47.7%) and central line-associated bloodstream infection (CLABSI) (25.0%). Seventy-two cases (41.4%) were found to have more than one source of infection. These distributions did not significantly differ between sepsis and septic shock patients (*p* value > 0.05) (Table 2).

Results of the clinical characteristics and outcomes of sepsis patients are presented in Table 3. The average SOFA score was $8.11 (\pm 3.9)$; and it was significantly higher for septic shock patients (9.7 ± 3.4) compared to sepsis patients (5.5 ± 3.2), *p* value < 0.001 .

Table 1: Background characteristics and comorbidities of patients (*n* = 174)

Variable	Total (<i>n</i> = 174)	Sepsis (<i>n</i> = 66)	Septic shock (<i>n</i> = 108)	<i>p</i> value
Age-years (mean ± SD)	57.4 ± 18.2	54.1 (±20.1)	59.3 (±16.8)	0.069
Sex				
Male (%)	92 (52.9)	30 (45.5)	62 (57.4)	
Female (%)	82 (47.1)	36 (54.5)	46 (42.6)	0.125
Comorbidities				
Cardiovascular disease (%)	107 (61.5)	39 (59.1)	68 (63.0)	0.611
HTN (%)	92 (52.9)	35(53.0)	51 (52.8)	0.974
CHF (%)	62 (35.6)	19 (28.8)	43 (39.8)	0.141
IHD (%)	53 (30.5)	19 (28.8)	34 (31.5)	0.708
CVA (%)	25 (14.4)	8 (12.1)	17 (15.7)	0.509
COPD (%)	25 (14.4)	8 (12.1)	17 (15.7)	0.509
Creatinine ≥1.2 (%)	71 (40.8)	19 (28.8)	52 (48.1)	0.012*
Dialysis (%)	29 (16.7)	7 (10.6)	22 (20.4)	0.094
Diabetes (%)	90 (51.7)	32 (48.5)	58 (53.7)	0.504
Hyperlipidemia (%)	84 (48.3)	31 (47.0)	53 (49.1)	0.78
Smoker (%)	69 (39.7)	25 (37.9)	44 (40.7)	0.708
Hematology malignancy (%)	34 (19.5)	13 (19.7)	21 (19.4)	0.97
Solid malignancy (%)	19 (10.9)	3 (4.5)	16 (14.8)	0.035*
Metastatic cancer (%)	19 (10.9)	2 (3.0)	19 (15.7)	0.009*
Immune-compromised (%)	60 (34.5)	25 (37.9)	35 (32.4)	0.461
ICU stay-days (median-range) (%)	8 (1–208)	7 (2–105)	10 (1–208)	0.011#

*Chi-square test; #Mann-Whitney *U* test**Table 2:** Origin of the primary infection of patients (*n* = 174)

Variable	Total (<i>n</i> = 174)	Sepsis (<i>n</i> = 66)	Septic shock (<i>n</i> = 108)	<i>p</i> value*
Sepsis origin				
Respiratory, <i>n</i> (%)	124 (71.3)	43 (65.2)	81 (75.0)	0.164
Urinary, <i>n</i> (%)	83 (47.7)	30 (45.5)	53 (49.1)	0.640
CIABSI, <i>n</i> (%)	44 (25.0)	12 (18.2)	32 (30.2)	0.079
Skin, <i>n</i> (%)	22 (12.6)	6 (27.3)	16 (72.7)	0.270
Wound, <i>n</i> (%)	18 (10.3)	4 (6.2)	14 (13.4)	0.155
Abdomen, <i>n</i> (%)	10 (5.7)	4 (6.1)	6 (5.6)	0.890
CVS, <i>n</i> (%)	5 (2.9)	1 (1.5)	4 (3.9)	0.410
Sepsis origin				
Single origin (%)	102 (58.6)	43 (65.1)	59 (54.6)	0.172
Multiple origins (%)	72 (41.4)	23 (34.9)	49 (45.4)	

*Chi-square test; CVS, cardiovascular system

Table 3: Clinical characteristics and outcomes of patients (*n* = 174)

Variable	Total (<i>n</i> = 174)	Sepsis (<i>n</i> = 66)	Septic shock (<i>n</i> = 108)	<i>p</i> value
SOFA score (mean ± SD)	8.11 (±3.9)	5.5 (±3.2)	9.7 (±3.4)	<0.001
APACHE score (mean ± SD)	20.7 (±9.2)	16.5 (±9.2)	23.3 (±8.3)	<0.001
Types of sepsis				
Community acquired (%)	38 (21.8)	18 (27.3)	20 (18.5)	
Hospital acquired (%)	127 (73.0)	46 (69.7)	81 (75.0)	0.281
ICU acquired (%)	9 (5.2)	2 (3.0)	7 (6.5)	
Referred from				
Inside ANUH (%)	118 (68.2)	47 (71.2)	71 (66.4)	0.505
Outside ANUH (%)	55 (31.6)	19 (28.8)	36 (33.6)	
Outcome				
Alive on discharge (%)	105 (60.3)	56 (84.8)	49 (45.4)	
Dead on discharge (%)	69 (39.7)	10 (15.2)	59 (54.6)	<0.001

Similar results were found concerning APACHE score, which was 23.3 (± 8.3) in septic shock patients, compared to 16.5 (± 9.2) for sepsis patients, p value < 0.001 .

As for the type of sepsis, 127 cases (73.0%) were found to be hospital-acquired sepsis, and only 9 cases (5.2%) were acquired in the ICU. More than two-thirds of sepsis patients were referred to the ICU from inside our hospital (ANUH), and 39.7% of them were dead on discharge. Mortality was significantly higher among septic shock patients, where 54.6% of them were discharged dead compared to 15.2% of sepsis patients, p value < 0.001 .

Of the total 174 patients, 131 of them had at least one organism isolated from respiratory secretions, blood, urine, or other body parts as had been shown in Table 4. Some had organisms isolated from one source, while some had multiple organisms isolated. Overall, the most prevalent gram-negative microorganism was *Acinetobacter*, which was found in 47 patients (33.8%). *Pseudomonas* and *E. coli* were the second most common gram-negative microorganisms: 20.5 and 18.5%, respectively.

On the other hand, *Enterococcus* was the most prevalent gram-positive microorganism; it was positive in 44 (31.7%) patients, where 24 (54.6%) of them were vancomycin-resistant *Enterococcus* (VRE). As for Fungi, *Candida albicans* was positive among 33 (23.7%) sepsis syndrome patients. When these organisms were further classified according to drug resistance, 58 cases (41.7%) were found to have single MDR organisms, and 17 cases (12.2%) had multiple MDR organisms. The distribution of microorganisms was slightly different between sepsis and septic shock patients; however, these differences were not significant (Table 4).

DISCUSSION

Sepsis is considered to be one of the most common global healthcare problems, affecting millions of people worldwide,

causing a huge burden on healthcare systems.⁸ After an extensive literature review, it appears that data regarding the epidemiology of sepsis patients in Palestine are very scarce and limited, which could significantly affect our estimation of this major threat. This study included all patients diagnosed as sepsis syndrome (sepsis or septic shock according to Sepsis III definition) admitted to the ICU over a 2-year period. The mean age of the patients was 57.4 years, and the patient gender was not a significant contributor, which was very similar to what was found in a similar study performed in Saudi Arabia in 2015.⁵ The high prevalence of comorbidities could be explained by the fact that ANUH is a tertiary hospital, and our cohort had a high mean age. Most of our patients were referred from the medical wards. The most prevalent comorbidities were cardiovascular diseases (61.5%), and DM (51.7%), which is in line with other studies in the surrounding countries.^{5,12} Of these comorbidities, only abnormal creatinine, solid malignancy, and metastatic cancer were found to be significantly more highly represented among septic shock patients compared to sepsis, which could help us predict that this cohort will have more severe forms of sepsis syndromes. Contrarily, having a hematologic malignancy was not significantly associated with more severe forms, and this could be explained by the fact that these patients were often younger and had no other comorbidities to complicate sepsis into a more severe form.

Respiratory infections were the most common origin encountered (71.3%), followed by the urinary tract infections (47.7%), which goes in harmony with the results of other similar studies.^{5,6,13–15} This study showed that having single or multiple origin of infection was not associated with having a more severe form of sepsis. This finding is supported by the fact that severity scores of sepsis did not include these variables. The average length of stay was 8 days, which is much lower than other

Table 4: Distribution of microorganisms isolated from culture-positive patients ($n = 139$)

Microorganism	Total ($n = 139$)	Sepsis ($n = 53$)	Septic shock ($n = 86$)	p value
Gram negative				
<i>Acinetobacter</i> (%)	47 (33.8)	(26.4)	33 (38.4)	0.148
<i>Pseudomonas</i> (%)	28 (20.1)	10 (18.9)	18 (20.9)	0.768
<i>Escherichia coli</i> (%)	31 (22.3)	11 (20.7)	20 (23.3)	0.809
<i>Klebsiella</i> (%)	13 (9.4)	4 (7.4)	9 (9.4)	0.566
<i>Enterobacter</i> (%)	3 (2.2)	0	3	–
Others	22	–	–	–
Gram positive				
<i>Enterococcus</i> (%)	44 (31.7)	16 (30.2)	28 (32.6)	0.771
VRE ($n = 44$) (%)	24	7 (13.2)	17 (19.8)	0.320
<i>Staphylococcus</i> (%)	40 (28.4)	16(30.2)	24(27.9)	0.773
<i>Staphylococcus aureus</i>	5	2	3	–
MRSA	1	–	1	–
Others	1	–	–	–
Fungi				
<i>Candida albicans</i> (%)	33 (23.7)	10 (18.9)	23 (36.7)	0.289
<i>Candida non-albican</i> (%)	18 (12.9)	6 (11.3)	12 (14.0)	0.653
<i>Aspergillus</i>	1	1	–	–
Drug resistance ($n = 139$)				
No drug resistance (%)	64 (46.0)	22 (46.8)	42 (45.7)	
Single MDR (%)	58 (41.7)	22 (46.8)	36 (39.1)	0.192
Multiple MDR (%)	17 (12.3)	3 (6.4)	14 (15.2)	

surrounding countries,^{5,12,13} despite that our hospital is the only tertiary center receiving patients from all surrounding districts.

Regarding the type of sepsis syndrome, the study showed that more than 73% of patients had hospital-acquired sepsis, compared to only 21.8% of community-acquired cases, and only 5.2% of ICU-acquired sepsis, and this is similar to what was found in other epidemiological studies carried out within a similar context.^{5,13,16} This could be explained by the tertiary setting of our center, which represents one of the largest oncology, hematology, and renal replacement therapy centers in Palestine. When assessing the severity of sepsis syndrome, we found that patients with septic shock had higher SOFA and APACHE II scores compared to sepsis patients, which could validate the use of these scores in assessing the severity and mortality of our patients.^{13,17}

The mortality rate from sepsis syndrome is known to be very high in different parts of the world. In our study, the average mortality rate in sepsis patients was 39.7%, which is much lower than what was found in other parts of the world. For example, the overall mortality rate of severe sepsis was 58% in a Saudi ICU, 55.8% in Turkish ICUs, 55.7% in Brazilian ICUs, and 64.6% in Indian ICUs.^{5,13,18,19} Patients with septic shock had higher mortality rates than those with only sepsis, concordant with other studies.¹³

Concerning the microorganisms isolated, we found that gram-negative organisms were the leading pathogen in our ICU, similar to what was found in other studies.¹² Surprisingly and in contrary to other literature, *Acinetobacter* was the most common organisms isolated from cultures in our ICU (33.8%), followed by *Enterococcus* (31.7%) and *Staphylococcus* (28.4%). This will help us direct our empirical therapy to the most common organisms found at our ICU. We also found that *Candida albican* was the most frequently isolated fungus (23.7%), rate similar to that which was found in another study in Turkey.¹³ This high rate of fungal infection could be explained by the high use of invasive procedures, parenteral nutrition, the fact that many of our patients were immune-compromised, and other risk factors for *Candida* infections. This study is unique in finding that a high percentage of ICU patients had MDR organisms (41.7% had single MDR, 12.2% had multiple MDR), which again could be explained by the tertiary setting of our center, as its considered a pool for patients coming from a large sector of Palestine. In addition, a large number of our patients were oncology, hematology, and nephrology patients with recurrent visits to the hospital, making them more vulnerable to recurrent sepsis and the need for antimicrobials as mentioned in many studies,²⁰ which could help them develop MDR organisms. This should alert hospital personnel that an antibiogram should be established not only to the ICU but also to the general wards.

Finally, this study has some limitations to declare. First of all, it was conducted in the medical ICU of the only university hospital in Palestine, which is run by ICU specialists and medical residents, and this could limit its generalization to the other hospital ICUs. Second, this study did not include data regarding initial antibiotic treatment used in this cohort, and this is because our country lacks a common antibiogram to be used in these situations. Despite these limitations, our study is considered an important study that provided information about the epidemiology of sepsis syndrome in an ICU in Palestine.

CONCLUSION

Up to our knowledge, this study is considered the first study to be conducted regarding the epidemiology of sepsis syndromes

in a critical care setting in Palestine. It discloses the background characteristics, type and source, common organisms, and outcome of sepsis patients. This will appropriately direct us to the best way to deal with this dangerous threat to patients admitted to the ICU, and help us to construct further studies regarding risk factors, and proper therapies for this problem in the near future. Finally, this study provided an alert on how important it is to develop a special antibiogram for Palestine, as we found that the organisms isolated from cultures were significantly different from what was found in other parts of the world.

CONTRIBUTORS

All authors contributed to the design of the study, acquisition, analysis, and interpretation of the data. All authors have seen and approved the final version of the abstract for publication.

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