RESEARCH ARTICLE

Community-acquired sepsis in the medical intensive care unit: An experience from a lower-middle-income country

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Abstract

Objective: To determine microbiological pathogens and in-hospital mortality in patients admitted with community-acquired sepsis to the intensive care unit in a tertiary-care setting in a low- and middle-income country.

Methods: The retrospective, observational study was conducted at the medical intensive care unit of a large tertiary care hospital in Karachi, and comprised data from January 1 to December 31, 2019 of patients with community-acquired sepsis who were assessed using the Sepsis-3 criteria. Data was compared between survivors and non-survivors, and independent factors associated with in-hospital mortality were identified. Data was analysed using SPSS 23.

Results: Of the 135 patients with mean age 49.8±18.0 years, 91(67.4%) were males and 44(32.6%) were females. The most common primary site of infection was the respiratory tract 63(46.7%). Multi-drug-resistant organisms were isolated in 39 (28.9%) patients. In-hospital mortality was noted in 52(38.5%) cases, while there were 83(61.5%) survivors. Serum levels of lactate and bicarbonate as well as urine output, fungal pathogens, septic shock and sequential organ failure assessment score were significantly associated with mortality ($p<0.05$).

Conclusions: Clinical and microbiological spectrum of community-acquired sepsis in a low- and middle-income country was found to be different from other regions of the world. Clinicians should keep these differences in mind while managing these critically ill patients.

Keywords: Sepsis, Septic shock, Critical care, Drug resistance, Fungi. (JPMA 74: 1942; 2024)

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Introduction

Sepsis is a global public health concern that affects millions of people, leading the World Health Assembly to pass a resolution in 2017 to improve the prevention, diagnosis and management of sepsis.[1] The genitourinary and respiratory tracts are the most common sites of infection among patients with sepsis.[2] Age-adjusted mortality is the highest in patients with pulmonary sepsis.[3] Seasonal variations have also been observed with higher rates of sepsis seen in the winter.[4]

In-hospital mortality from severe sepsis was 26% in a meta-analysis of seven studies from high-income countries (HICs).[5] The highest in-hospital mortality of 39% was observed among patients with septic shock.[6] Mortality rates have been shown to be much higher in developing countries.[7]

It is important to distinguish between hospital-acquired (HA) and community-acquired (CA) sepsis as mortality rates are lower in patients with CA sepsis compared to those with HA or healthcare-associated sepsis.[8] Guidelines for antimicrobial therapy also differ in patients with CA infections compared to those with HA infections[9,10] Organ dysfunction and infection with gram-positive organisms have been shown to be more common among patients with CA severe sepsis, while CA septic shock was more common with abdominal, bloodstream and respiratory infections.[11]

A better understanding of the local clinical and microbiological characteristics of CA sepsis in developing countries, also known as low- and middle-income countries (LMICs), may provide better guidance for initial management and empiric antimicrobial therapy to physicians in such regions. The current study was planned to determine microbiological pathogens and in-hospital mortality in patients admitted with CA sepsis to the medical intensive care unit (MICU) of a large tertiary care hospital in an LMIC setting.

Materials and Methods

The retrospective, observational study was conducted at the MICU of a large tertiary care hospital, The Aga Khan University Hospital enjoying Joint Commission International (JCI) accreditation located in Karachi, and comprised data from January 1 to December 31, 2019. After approval from the institutional ethics review committee (ERC) of the Aga Khan University Hospital, Karachi along with waiver related to informed consent, data was retrieved from medical record files and electronic health records without any interaction with the patients. A list of patients

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admitted to the MICU was obtained for the period from the admissions department, and discharge summaries were screened for the diagnosis of infection, sepsis or septic shock. Files and electronic records were then reviewed to identify those patients with sepsis or septic shock of CA origin.

Those included were patients with sepsis and septic shock identified using the Sepsis-3 criteria defining sepsis as life-threatening organ dysfunction caused by a dysregulated response to infection wherein organ dysfunction was identified by an acute change in the Sequential Organ Failure Assessment (SOFA) score of ≥2 points.[12] Patients with septic shock were identified by the presence of sepsis with persistent hypotension requiring vasopressors to maintain a mean arterial pressure (MAP) ≥65 mmHg and having serum lactate levels >2mmol/L despite adequate volume resuscitation.[12] Patients with a history of hospitalisation within the preceding 90 days of admission, transfer from a nursing care facility, transfer after admission at an outside hospital and those on haemodialysis due to end stage renal disease (ESRD) were excluded.

Data was collected using a proforma. Demographic variables, including age, gender and comorbidities, were noted. Laboratory parameters on admission included haemoglobin (Hb) (mg/dL), haematocrit (Hct) (%), platelet count (PLT) ($\times 10^9$/L), total leucocyte count (TLC) (cells$\times 10^9$/L), blood urea nitrogen (BUN) (mg/dL), total bilirubin (T-Bil) (mg/dL), alaninine aminotransferase (ALT) (IU/L), lactate (mmol/L), potential of hydrogen (pH), serum sodium (Na) (mmol/L), serum bicarbonate (HCO_3^-) (mmol/L), prothrombin time (PT) (seconds), international normalised ratio (INR) and activated partial thromboplastin time (APTT) (seconds). Clinical parameters included site of infection, need of invasive mechanical ventilation (MV), echocardiography findings, SOFA score on admission, presence of septic shock, volume of urine output in the first 24 hours of admission (mL), volume of intravenous (IV) fluids administered in the first 48 hours of admission (mL), need of haemodialysis or continuous renal replacement therapy (CRRT) during admission, length of hospital stay (LOS), and outcome represented by discharge, in-hospital mortality, or transfer to an outside facility/leaving against medical advice (LAMA). The primary outcome of the study was in-hospital mortality. Association of the outcome was also explored based on the weather season at the time of admission to MICU. Pakistan has four seasons, consisting of winter from December to February, spring from March through May, summer from June to September, and the retreating monsoons from October to November.[13]

Data was analysed using SPSS 23. Frequencies and percentages were used to express qualitative variables, while quantitative variables with normal and non-normal distributions were expressed as mean±standard deviation (SD) and median with interquartile range (IQR), respectively. Chi-square test ws used to determine the relationship between categorical variables. The relationship between numerical variables was determined using the independent sample t-test. Univariate logistic regression was used to identify factors associated with escalation to a higher level of care. Variables with $p<0.25$ were included in the multivariable model. Multivariable logistic regression was performed using a backward stepwise selection procedure to identify independent factors associated with in-hospital mortality. $P<0.05$ was considered statistically significant.

Results

Of the 570 patients admitted to the MICU, 135(23.7%) with CA sepsis were included. The mean age of the study population was 49.8±18.0 years. There were 91(67.4%) males, 44(32.6%) females and 59(43.7%) patients had no comorbid condition. The most common comorbidity was hypertension (HTN) 52(38.5%), followed by diabetes mellitus (DM) 39(28.9%), ischaemic heart disease (IHD) / congestive heart failure (CHF) 26(19.3%), and chronic pulmonary disease 16(11.9%). There were 34(25.2%) patients with sepsis, while 101(74.8%) had septic shock.

MICU admissions for CA sepsis were most common during the winter 45(33.3%) and summer 42(31.1%) seasons, while during the spring and retreating monsoon seasons, 27(20.0%) and 21(15.6%) patients were admitted, respectively.

The most common primary site of infection was the respiratory tract 63(46.7%), followed by the central nervous system (CNS) 18(13.3%), primary bloodstream 16(11.9%), abdomen 15(10.4%), and soft tissue/skin 13(9.6%). Of the 13 patients in whom soft tissue/skin was the primary site of infection, 6(46.2%) had DM. The respiratory tract was the predominant primary site of infection during the winter 32(71.1%) and spring 13(50%) seasons. During the summer season, the most common primary site of infection was also the respiratory tract 12(28.6%), followed by CNS 9(21.4%), abdomen 7(16.7%) and primary bloodstream 6(14.3%). Primary bloodstream 7(35.0%) was the most common primary site of infection during the retreating monsoon season. Among the patients in whom respiratory tract was the primary site of infection during the winter season, a history of chronic pulmonary disease or IHD/CHF was present in 15(46.9%). Of the 20 patients admitted during the retreating monsoon season, 6(30%) had dengue fever.

Blood cultures were sent to the laboratory in all 135(100%)

cases, urine in 122(90.4%) patients, and respiratory samples in 117(86.7%). Blood, urine, and sputum/tracheal culture positivity rates were 20(14.8%), 17(14.1%), and 28(23.7%), respectively. Microorganisms were identified from clinical specimens in 76(56.3%) patients. Distribution of the microorganisms isolated with respect to the sites of isolates were noted in detail (Table 1). Multi-drug-resistant organisms (MDROs), either alone or as part of polymicrobial growth, were isolated in 39(28.9%) patients. Nasal swab for swine flu (H1N1) polymerase chain reaction (PCR) was positive in 9(6.7%) patients, while serology for dengue virus was positive in 7(5.2%), and 1(0.7%) patient tested positive for Crimean-Congo Haemorrhagic Fever (CCHF). A fungal pathogen, either alone or as polymicrobial growth, was isolated in 15(11.1%) patients, while it was the sole pathogen in 12(8.9%).

Invasive MV was required in 133(98.5%) patients. Median SOFA score was 8 (IQR: 6-11). The median serum lactate level on admission was 3.4mmol/L (IQR: 1.9-6.5mmol/L), while the mean serum HCO_3^- level on admission was 20.1±7.7mmol/L. The most common vasopressor/inotrope used among patients with septic shock as the sole agent was norepinephrine 55(54.5%). The support of multiple vasopressors/inotropes was required in 44(43.6%) patients. Haemodialysis or CRRT was required in 32(23.7%) patients. Median urine output in the first 24 hours of admission was 1,385ml (IQR: 624-2210ml), while median volume of IV fluids given in the first 48 hours of admission was 6,379ml (IQR: 4,659-9,549ml). Echocardiography findings were available for 95(70.4%) patients among whom 44(46.3%) had evidence of segmental wall motion abnormalities, while an ejection fraction (EF) of <55% was present in 35(36.8%). Prior history of myocardial infarction (MI) or coronary artery disease (CAD) was not present in 28(63.6%) of the patients with segmental wall motion abnormalities on echocardiogram.

Table-1: Distribution of microorganisms identified and site of isolation [n(%)].

Microorganisms	Blood (n=135)	Urine (n=122)	Respiratory (n=117)	Other (n=27)
Gram Positive Bacteria				
Staphylococcus aureus	4 (3.0)	-	2 (1.7)	2 (7.4)
Beta haemolytic streptococci	3 (2.2)	-	-	1 (3.7)
Streptococcus pneumonia	1 (0.7)	-	1 (0.9)	3 (11.1)
Enterococcus	-	1 (0.8)	-	-
Gram-Negative Bacteria				
Escherichia coli	2 (1.5)	11 (9.0)	2 (1.7)	1 (3.7)
Klebsiella pneumonia	-	2 (1.6)	2 (1.7)	
Pseudomonas aeuruginosa	-	-	-	1 (3.7)
Acinetobacter species	1 (0.7)	-	4 (3.3)	-
Raoutella terrigena	-	1 (0.8)	-	-
Salmonella typhi	2 (1.5)	-	-	-
Enterobacter cloacae	-	-	-	1 (3.7)
Stenotrophomonas maltophillia	-	-	1 (0.9)	-
Polymicrobial	2 (1.5)	2 (1.6)	10 (8.5)	3 (11.1)
Fungal				
Candida species	5 (3.7)	2 (1.6)	1 (0.9)	1 (3.7)
Aspergillus species	-	-	8 (6.8)	-
Mycobacteria				
Mycobacterium tuberculosis	-	-	3 (2.6)	-
Parasite				
Naegleria fowleri	-	-	-	1 (3.7)

Median LOS was 8 days (IQR: 5-13 days). The number of patients who expired during the hospital stay was 52(38.5%), while 74(54.8%) were discharged home, and 9(6.7%) were transferred to an outside facility or were LAMA cases. Among patients with septic shock, 49(48.5%) expired during the hospital stay, while in-hospital mortality for patients with sepsis was 3(8.8%) (p<0.001). In-hospital mortality across the weather was highest during the summer season 45.2% (19/42), while it was 37.8% (17/45), 33.3% (9/27), and 33.3% (7/21) during the winter, spring and retreating monsoon seasons, respectively (p=0.716). The primary sites of infection with the highest in-hospital mortality were bloodstream 11(68.8%), abdomen 7(46.7%) and soft tissue/skin 6(46.1%).

Patients who expired during the hospital stay had higher median serum lactate levels on admission 4.8 mmol/L (IQR: 2.59.1mmol/L) compared to those who survived 2.8mmol/L (IQR: 1.6-6.1mmol/L) (p=0.012). These patients also had had lower mean serum HCO_3^- levels 18.3±7.2mmol/L compared to those who expired 21.3±7.8mmol/L (p=0.028). The median urine output in the first 24 hours of admission was lower 808mL (IQR: 200-1,965mL) in patients who expired during the hospital stay compared to those who survived 1,590mL (IQR: 790-2,410mL) (p=0.008). In the 15(11.1%) patients in whom a fungal pathogen was isolated, either alone or as polymicrobial growth, 12(80%) expired during the hospital stay (p=0.001) (Table 2). On multivariable regression analysis, the SOFA score was a significant predictor of in-hospital mortality (odds ratio: 1.227 [95% confidence interval: 1.098-1.372] (p<0.001).

Discussion

The current study described the clinical and microbiological spectrum of patients with CA sepsis admitted to MICU. The respiratory tract was the most common site of infection, while admissions were most common during the winter season. MDROs were isolated in just under a third of patients. Almost half of patients with septic shock expired during the hospital stay. Also, almost half of the patients in whom the respiratory tract was the primary site of infection during the winter season had a history of chronic pulmonary disease or IHD/CHF. This group of patients is known to be at high risk of respiratory infections during the colder seasons.[14,15] As the respiratory

Table-1: Comparison of patients who expired during the hospital stay versus those who survived.

Variable	Total (n=135)	In-Hospital Mortality: Yes (n=52)	In-Hospital Mortality: No (n=83)	*p*-value
Mean Age (years)	49.8±18.0	49.9±18.7	49.8±17.6	0.957
Gender				0.691
Male	91 (67.4)	34 (65.4)	57 (68.7)	
Female	44 (32.6)	18 (34.6)	26 (31.3)	
Co-morbidities				
Diabetes Mellitus	39 (28.9)	14 (26.9)	25 (30.1)	0.690
Hypertension	52 (38.5)	19 (36.5)	33 (39.8)	0.708
Ischaemic Heart Disease/Congestive Heart Failure	26 (19.3)	12 (23.1)	14 (16.9)	0.373
Chronic Pulmonary Disease	16 (11.9)	5 (9.6)	11 (13.3)	0.525
Laboratory Parameters (on admission)				
Haemoglobin (mg/dl)	11.3±3.1	11.3±2.9	11.3±3.2	0.930
Haematocrit (%)	35.7±9.3	35.3±8.6	36.0±9.8	0.654
Platelet Count ($\times 10^9$/L)	235 [139–334]	236 [112–306]	235 [151–353]	0.584
Total Leucocyte Count				
(cells $\times 10^9$/L)	13.7 [9.3–19.7]	11.9 [9.0–17.5]	15.7 [9.6–20.7]	0.713
Blood Urea Nitrogen (mg/dL)	27 [17–46]	26 [15-45]	27 [17-46]	0.447
Creatinine (mg/dL)	1.7 [1.1–3.1]	1.7 [1.1–2.9]	1.7 [1.1–3.3]	0.165
Total Bilirubin (mg/dL)	0.7 [0.4–1.3]	0.9 [0.5-1.8]	0.6 [0.3-1.1]	0.466
Alanine Aminotransferase (IU/L)	51 [25– 88]	61 [27-213]	39 [25-139]	0.061
Lactate (mmol/L)	3.4 [1.9–6.5]	4.8 [2.5–9.1]	2.8 [1.6–6.1]	0.012
pH	7.27±0.15	7.27±0.17	7.28±0.18	0.683
Serum Bicarbonate (mmol/L)	20.1±7.7	18.3±7.2	21.3±7.8	0.028
Serum Sodium (mmol/L)	134.3±6.5	133.4±7.9	134.9±5.4	0.228
Prothrombin Time (sec)	12.3 [11.0–14.9]	13.2 [11.3–16.2]	11.9 [10.8–14.0]	0.192
INR	1.2 [1.0–1.4]	1.3 [1.1–1.7]	1.1 [1.0–1.3]	0.171
Activated Partial Thromboplastin Time (sec)	33.3 [26.1–48.1]	36.6 [27.6–49.8]	30.8 [25.3–46.0]	0.467
Clinical Parameters				
Met criteria for septic shock	101 (74.8)	49 (94.2)	52 (62.7)	<0.001
SOFA score	8 [6-11]	11 [7-13]	7 [5-10]	<0.001
Volume of urine output in first 24 hours of admission (mL)	1385 [624 – 2210]	808 [200 – 1965]	1590 [790 – 2410]	0.008
Volume of I/V fluids administered in the first 48 hours of admission (mL)	6379 [4659 – 9549]	7106 [5094 – 10530]	5938 [4174 – 8284]	0.115
Required haemodialysis/Continuous Renal Replacement Therapy	32 (23.7)	15 (28.8)	17 (20.5)	0.266

pH: Potential of hydrogen, I/V: Intravenous, INR: International normalised ratio, SOFA: Sequential Organ Failure Assessment.

tract was the primary site of infection in more than two-thirds of admissions during the winter season, awareness regarding influenza and pneumococcal vaccination may greatly reduce this burden.[16]

During the retreating monsoon season, dengue fever accounted for around one-third of admissions to the MICU. In a prospective Indian study conducted among patients admitted to the ICU with dengue, the dengue shock syndrome was present in around one-fifth of patients, while over one-third of patients expired.[17] Community engagement during this season to facilitate preventive measures may help reduce this burden.[18]

MDROs were isolated in 28.9% patients presenting from the community with sepsis in the current study. This was higher than the 17% observed by Capsoni et al.[19] However, the study was not limited to the ICU, and the patients were less acutely ill as only 25.4%[19] had septic shock compared to 74.8% in the current study. Also, almost all the patients (98.5%) in the current study required invasive MV compared to only 2.9% in the other study.[19] In a study of 17,430 patients with culture-positive CA sepsis admitted to 136 hospitals in the United States, Rhee et al. observed that the prevalence of resistant organisms was higher in patients who required ICU admission (50.1% versus 44.4%; $p<0.001$), MV (28.3% vs 19.2%; $p<0.001$), and those who had septic shock (28.7% versus 24.2%; $p<0.001$).[20] These findings are important as antimicrobial resistance is a major public health threat[21] necessitating judicious use of antimicrobial therapy to those who really need it.

Fungi, as the sole pathogen, were isolated in 8.9% of patients in the current study. This was much higher than the frequency of fungal pathogens observed in prior studies from Spain (0.6%)[22] and South Korea (0.7%)[11] among patients with CA sepsis. While initiating empirical antibiotic therapy, the possibility of fungal pathogens is rarely considered, especially in patients presenting from the community. Considering the high mortality rate in patients with isolation of a fungal pathogen in the current study, it is important for physicians in the region to consider the possibility of fungal pathogens while selecting empiric antimicrobial therapy. Further studies should aim at identifying frequency and risk factors for fungal infection in patients presenting from the community with sepsis in the region.

The current study observed a significant difference in in-hospital mortality in patients admitted to the MICU with CA sepsis and septic shock. Patients who were not in shock had better outcomes compared to those who met the criteria for septic shock. This variation was also observed

by Rhee et al.[20] Future studies should focus on patients with CA septic shock to identify risk factors for in-hospital mortality in this group.

Median SOFA score and serum lactate levels on admission were significantly higher in patients who expired during the hospital stay versus those who survived in the current study, and both these elements have been shown to be useful predictors of mortality.[23] Additionally, patients who expired during the hospital stay had significantly lower serum HCO_3^- levels on admission and urine output in the initial 24 hours of admission, hence, these markers may also help to identify patients with a worse prognosis. Point-of-care-lactate testing has been shown to be cost-effective,[24] but may not be available in many hospitals in LMICs. In these settings, serum HCO_3^- levels and urine output may help in guiding the prognosis.

Though not statistically significant, in-hospital mortality was higher among patients in whom choice of initial antimicrobial therapy in the emergency department was inadequate compared to those with adequate antimicrobial coverage. The greatest benefit in mortality has been observed in patients who not only receive appropriate antimicrobial therapy, but also within one hour of recognition.[25] Timing of antimicrobial therapy administration was not assessed in the present study.

To the best of our knowledge, the current study is the first on CA sepsis in patients admitted to the MICU done in South Asia. Another major strength of the study is the use of Sepsis-3 criteria[12] to define patients with sepsis in view of the challenges associated with using the International Classification of Diseases (ICD) 9/10 codes.[26]

However, the current study has its limitations, like a relatively small sample size and a single-centre design. Furthermore, a large number of patients with sepsis and septic shock were managed in high dependency units (HDUs), with MICU mainly reserved for those at high risk of or requiring invasive MV. This is due to a high demand for MICU beds and resource limitations.

Larger studies from LMICs are needed to further explore the burden of MDROs, especially bacteria and non-bacterial pathogens such as fungi, in patients with CA sepsis and septic shock both within and outside the ICU.

Conclusion

Clinical spectrum, microbiological pathogens, and outcomes of CA sepsis in Pakistan was found to be different from other regions of the world. Physicians in the region should keep these differences in mind while managing these critically ill patients.

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Author Contribution:

HJ: Proposal writing, data collection, literature review, preparation of original draft.
SAA: Methodology and preparation of original draft.
SA: Formal analysis.
IK: Concept, revision and editing.
All authors agreed to be accountable for all aspects of the work.