Factors Affecting the Time to First Dose Antibiotic in Sepsis in Acute Emergency

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Abstract

Background: The Surviving Sepsis Campaign recommends the administration of antibiotics within 1 hour of triage time in sepsis patients. The purpose of this study was to determine the factors affecting the time to first dose antibiotics in sepsis patients presenting to the emergency department (ED).

Methods: We conducted a prospective observational study on factors affecting the time to first dose antibiotics in patients with sepsis presenting to the ED over a period of 7 months (July 2019 to January 2020). The purpose of this study was to determine the factors affecting the time to first dose antibiotics in sepsis patients.

Results: During the study period, a total of 410 patients with a mean age of 51.6 years were presented to the ED with sepsis. Majority was triaged to priority 1 (84.8%). The median door to antibiotic time was 50 minutes (IQR, 40–90). Two-thirds (68%) of the patients (279) received antibiotics within 60 minutes. The blood culture positivity rate was 22.9%, and the contamination rate was 6%. The most common factors for the delay were atypical presentation (36.6%) and unknown focus of infection (36.6%). Triage to non-acute areas of the ED (priority 2) was associated with delayed antibiotic administration [odds ratio (OR), 7.3; 95% confidence interval (CI), 4.03–13.36; *p*-value <0.001]. Patients presented with cellulitis and necrotizing soft tissue infection (NSTI) had received antibiotics within an hour compared to other diagnoses (18.3 vs 8.4%; OR, 2.4; 95% CI, 1.2–4.9; *p* = 0.009).

Conclusion: Two-thirds of our patients received their first dose of antibiotics within an hour of presentation to the ED. Triage to lower priorities was an independent risk factor for delay in first-dose antibiotic administration, and patients presented with an obvious focus of infections like cellulitis and NSTI received their first dose of antibiotic much earlier when compared to other diagnoses.

Keywords: Antibiotics, Blood culture, Emergency department, qSOFA, Sepsis.

Indian Journal of Critical Care Medicine (2021): 10.5005/jp-journals-10071-23994

Introduction

Sepsis is defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection. A total sequential organ failure assessment (SOFA) score ≥2 consequent to any infection implies organ dysfunction.[1] The baseline SOFA score can be assumed to be zero in patients not known to have preexisting organ dysfunction. Patients with septic shock can be identified in sepsis patients with persisting hypotension requiring vasopressors to maintain the mean arterial pressure (MAP) ≥65 mm Hg and having a serum lactate level >2 mmol/L despite adequate volume resuscitation.[2] Among prognostic factors for sepsis, delayed administration of the initial dose of antimicrobial agents and its adequacy plays a vital role.[3,4] Early recognition and prompt treatment of sepsis are proven to improve the outcome among morbid patients. Delay to first dose antibiotic is confounded by atypical presentation, unreliable history, and lead time in procuring drugs. Achieving targets of the 1-hour bundle in a busy emergency department (ED) is still a challenge to many of the physicians, raising concern whether all the components of the 1-hour bundle could be completed within the stipulated time. Hence, we decided to determine whether we were able to manage patients as per the Sepsis 3 guidelines with an emphasis on the timing of first dose antibiotics and the factors associated with the delay in first dose antibiotics.

Patients and Method

Design: This was a prospective observational cross-sectional study.

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Setting: The study was conducted in the ED of 2,500 bedded tertiary care hospital in South India over a period of 7 months (July 2019 to January 2020). Our ED is a 49-bed department with about 300 admissions per day, including medical, surgical, and trauma emergencies.

Inclusion Criteria

All adult patients (>18 years) with features suggestive of sepsis and septic shock with qSOFA ≥2 were included.

Exclusion Criteria

Patients who denied consent and had no organ dysfunction (SOFA <2) were excluded.

Variables

Data were recorded on a standard data abstraction sheet by interviewing the patient or their close relatives after getting a written informed consent and also obtained from the hospital electronic database. Details of presenting illness, physical examination, demographic factors associated with presentation, triage priority at presentation, clinical diagnosis, time of blood culture, time of antibiotic administration, blood culture growth, hospital admission, and mortality were analyzed.

Triage priority level was defined by the standard Canadian Triage Association Society guidelines.

Outcome Variable

The primary objective was to assess the factors causing a delay in the administration of first dose antibiotics. The door to antibiotic time, presenting complaints, clinical parameters, lactate level, serum pH, ED outcome (alive/dead/left against medical advice), and hospital outcome (alive/dead) were compared between the patients who received antibiotics within 1 hour and after 1 hour. The factors affecting the outcome among sepsis patients were assessed.

Bias

The data were collected by the primary investigator or coinvestigators, not by the treating physician; also consecutive patients were enrolled in the study.

Study Size

Based on the study done in ED by Peltan et al., physician variation in time to antibiotic administration was 118 ± 25.75 minutes.[5] The sample size calculated using nMaster software version 2.0 with standard deviation (SD) 25.75, precision 2.5%, and confidence level 95% was 410.

Statistical Analysis

The data were entered in Excel sheet and analyzed using Statistical Package for Social Science (SPSS Inc. Released 2018, version 25.0.0.0 Armonk, New York, USA) software. Descriptive statistics were reported using mean (SD) for continuous variables and frequency and percentage for categorical variables. Association between the variables was done using Chi-square or Fisher's exact test for categorical variables, and independent sample *t*-test for continuous variables after checking for normality. Predictors of poor outcome mortality were determined by bivariate followed by multivariate logistic regression analysis, and their 95% confidence intervals were calculated. For all tests, a two-sided *p*-value less than 0.05 was considered statistically significant.

Ethical Considerations

This study was approved by the Institutional Review Board (IRB) prior to the commencement of the study, and approval from the IRB ethical committee was obtained (IRB Min no: 11982 dated April 2, 2019). Patient confidentiality was maintained using unique identifiers and by password-protected data entry software with restricted users.

Results

During the study period, 41,378 patients presented to the ED, of which 2,756 patients with suspected infection were screened using qSOFA. Among them, 524 (1.3%) patients were found to have qSOFA score of ≥2. The final cohort of 410 patients was recruited after applying the exclusion criteria (Flowchart 1).
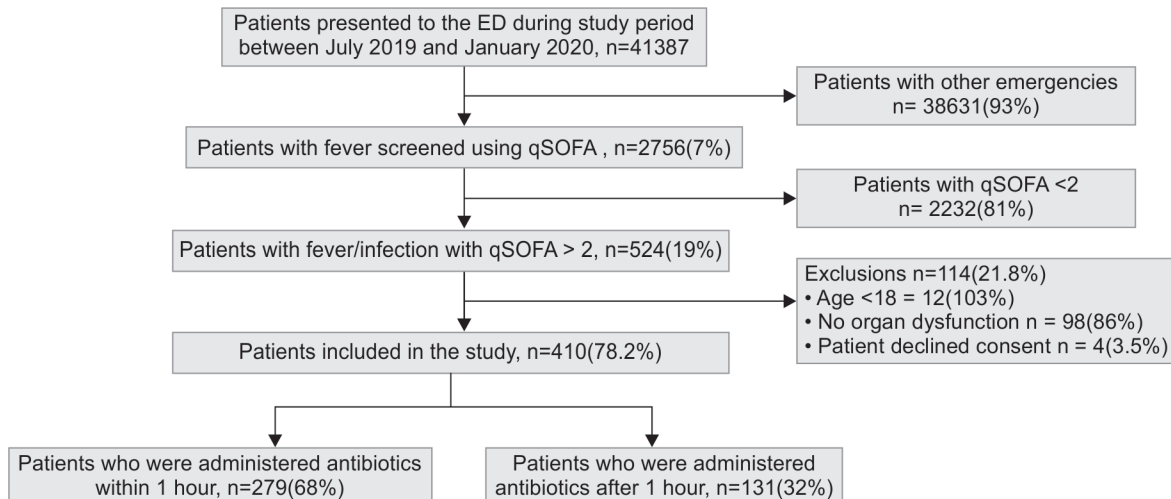
Demographic Profile

Our study cohort had a mean age of 51.56 (SD, 15.5) years with a male predominance (62.9%). Majority (84.8%) were triaged to priority 1, and the most common comorbidities were diabetes mellitus 130 (31.7%) and hypertension 103 (25.1%). The baseline characteristics are shown in Table 1. The median time of door to antibiotic administration was 50 minutes (IQR: 40–90), and 279 (68%) patients were administered the antibiotic within 1 hour.

Presenting Complaints and Clinical Parameters

The most common symptoms reported were breathlessness (55.6%), vomiting/loose stools (25.1%), and altered sensorium (24%). Documented temperature at presentation (93%) was a significant factor for administering antibiotics within 1 hour [95 vs 87%; odds ratio (OR), 0.3; 95% confidence interval (CI): 0.15–0.7; $p = 0.003$]. Among clinical parameters, respiratory rate >30/minute (63.8 vs 44.3%; OR, 0.4; 95% CI: 0.29–0.69; $p <0.001$) and low sensorium GCS ≤8 (12.9 vs 4.6%; OR, 0.3; 95% CI: 0.13–0.79; $p = 0.001$) were statistically significant factors for early administration of antibiotics (Table 2).

Flowchart 1: STROBE diagram


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                Patients presented to the ED during study period
                  between July 2019 and January 2020, n=41387
                                      │
                                      │────────────────────►  Patients with other emergencies
                                      │                              n= 38631(93%)
                                      ▼
                Patients with fever screened using qSOFA , n=2756(7%)
                                      │
                                      │────────────────────►  Patients with qSOFA <2
                                      │                              n= 2232(81%)
                                      ▼
                Patients with fever/infection with qSOFA > 2, n=524(19%)
                                      │
                                      │────────────────────►  Exclusions n=114(21.8%)
                                      │                        • Age <18 = 12(103%)
                                      │                        • No organ dysfunction n = 98(86%)
                                      │                        • Patient declined consent n = 4(3.5%)
                                      ▼
                     Patients included in the study, n=410(78.2%)
                                      │
                         ┌────────────┴────────────┐
                         ▼                          ▼
         Patients who were administered    Patients who were administered
           antibiotics within 1 hour,      antibiotics after 1 hour, n=131(32%)
                 n=279(68%)
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Diagnosis, Blood Culture Profile, and Empirical Antibiotics

We observed that acute undifferentiated febrile illness (AUFI) (28.3%) and lower respiratory tract infection (LRTI) (19.5%) were the most common diagnosis among our study population. Majority of the patients who presented with cellulitis and necrotizing soft tissue infection (NSTI) had received antibiotics within an hour compared to other diagnoses (18.3 vs 8.4%; OR, 2.4; 95% CI: 1.2–4.9; $p = 0.009$) (Table 3). Blood cultures were obtained from all patients prior to antibiotic administration. The culture positivity rate was 22.9% (85 out of 371) with a contamination rate of 6%. The most common bacterial isolate was *Escherichia coli* (*E. coli*) (30.6%) followed by coagulase-negative *Staphylococcus* (CONS) (11.8%) (Table 4).

Table 1: Baseline characteristics of sepsis patients

Characteristics	N = 410 (%)	Antibiotic within 1 hour n = 279 (%)	Antibiotic more than 1 hour n = 131 (%)
Mean age (SD)	51.56 (15.5)	51.94 (16.4)	50.75 (15.4)
Male	258 (62.9)	177 (63.4)	81 (61.8)
Female	152 (37.1)	102 (36.6)	50 (38.2)
Triage priority			
Priority 1	348 (84.9)	261 (93.5)	87 (66.4)
Priority 2	62 (15.1)	18 (6.5)	44 (33.6)
Comorbidities			
Diabetes	130 (31.7)	89 (31.9)	41 (31.3)
Hypertension	103 (25.1)	73 (26.2)	30 (22.9)
Chronic liver disease	34 (8.3)	21 (7.5)	13 (9.9)
Bronchial asthma/COPD	22 (5.4)	16 (5.7)	6 (4.6)
Chronic kidney disease	15 (3.7)	8 (2.9)	7 (5.3)

Table 2: Bivariate analysis comparing antibiotic administration time and clinical parameters

Characteristics	Antibiotic within 1 hour n = 279 (%)	Antibiotic after 1 hour n = 131 (%)	p value	OR (95% CI)
Respiratory rate >30/minute	178 (63.8)	58 (44.3)	<0.001	0.4 (0.29–0.69)
SpO_2 <90	92 (33)	27 (20.6)	0.01	0.5 (0.32–0.86)
GCS ≤8	36 (12.9)	6 (4.6)	0.01	0.3 (0.13–0.79)
qSOFA-3	18 (6.5)	44 (33.6)	<0.001	7.3 (4.03–13.36)
Heart rate >100/minute	221 (79.2)	101 (77.1)	0.627	0.9 (0.54–1.46)
MAP <65 mm Hg	141 (50.3)	62 (47.3)	0.544	0.8 (0.58–1.33)

*SpO_2, oxygen saturation; GCS, Glasgow coma scale; MAP, mean arterial pressure; OR, odds ratio; CI, confidence interval

Table 3: Bivariate analysis comparing antibiotic administration time and diagnosis

Diagnosis	Antibiotic within 1 hour n = 279 (%)	Antibiotic after 1 hour n = 131 (%)	p value	OR (95% CI)
Cellulitis/NSTI	51 (18.3)	11 (8.4)	0.009	2.4 (1.23–4.86)
AUFI	59 (21.1)	29 (22.1)	0.820	0.9 (0.57–1.56)
LRTI	52 (18.6)	28 (21.4)	0.514	0.8 (0.5–1.4)
UTI	30 (10.8)	10 (7.6)	0.321	1.5 (0.69–3.08)
Scrub with eschar	20 (7.2)	8 (6.1)	0.691	1.2 (0.5–2.71)
Spontaneous bacterial peritonitis	15 (5.4)	9 (6.9)	0.548	0.8 (0.33–1.81)
Febrile neutropenia	9 (3.2)	9 (6.9)	0.093	0.5 (0.17–1.17)
Peritonitis	12 (4.3)	6 (4.6)	0.898	0.9 (0.34–2.55)
Meningoencephalitis	7 (2.5)	7 (5.3)	0.141	0.5 (0.16–1.32)
Cholangitis	6 (2.2)	5 (3.8)	0.113	0.4 (0.11–1.27)
Gastroenteritis	5 (1.8)	3 (2.3)	0.734	0.8 (0.18–3.3)
*Others	13 (4.7)	6 (4.6)		

NSTI, necrotizing soft tissue infection; OR, odds ratio; CI, confidence Interval. *Others—Hepatic encephalopathy (6), pancreatitis (5), abscess (5), septic arthritis (2), osteomyelitis (1)

Factors Causing the Delay

Patients triaged to non-acute areas of the ED (priority 2) were independently associated with delayed antibiotic administration (75% vs 29%; OR, 7.3; 95% CI: 4.03–13.36; p-value <0.001). The most common factors for the delay were atypical presentation (36.6%) and patients with the unknown focus of infection (36.6%). Acidotic blood pH and higher blood lactates were significant factors in administering antibiotics within 1 hour (Table 5).

Hospital Outcome

Among the total study population, 211 (51.5%) were discharged in a stable condition, 98 (23.9%) left against medical advice, and the in-hospital mortality rate was 24.6% (101). After excluding patients who left against medical advice, we observed that acidosis, oxygen saturation SOFA score, MAP, platelets, creatinine, bilirubin, and lactate were independent risk factors for mortality in patients with sepsis. Clinical and laboratory predictors of mortality using bivariate and multivariate analyses are shown in Table 6.

DISCUSSION

Our study showed that neither difficulty in securing intravenous access nor the time to obtain blood culture was predictive of antibiotic delay, suggesting that timely antibiotic administration was based on clinical judgment, rather than strict operational factors. Timing of antibiotic administration played no significant role in hospital mortality in our study population.

Peltan et al. study was based on Sepsis 2 guidelines, and their target was to give antibiotics within 3 hours of admission to the ED. The target was achieved in 71% of their study population.[6] Our study was based on Sepsis 3 guidelines, and our target was to give antibiotics within 1 hour of admission. We were able to reach the target in more than two-thirds of our patients.

The importance of timing and appropriateness of the first dose of antibiotics in septic shock have been proven in previous studies.[3,7–9] Puskarich et al. study found no association between in-hospital mortality and the time from ED triage to the administration of antibiotics during the first 6 hours of resuscitation. But they found an increased risk of death if antibiotics were delayed till the recognition of shock.[10] Timing of antibiotic administration played no significant role in hospital mortality in our study population. This can be attributed to seriously ill patients receiving antibiotics early than relatively stable patients.

A study done by Andersson et al. in a Swedish setting found that the most common focus of infection was urinary tract infection (UTI). This was followed by LRTI, skin and soft tissue infection, and AUFI.[11] However, in our tropical location with higher incidence of viral fever and scrub typhus, we observed AUFI was common among our study population.

We were able to obtain blood cultures for all patients prior to the administration of antibiotics. Empirical antimicrobial therapy before blood culture significantly reduces the sensitivity of blood cultures.[12]

Our finding of gram-negative (65%) and gram-positive (35%) isolates was in contrast to the studies reported in other countries by Kumalo et al. where gram-positive bacteria (53.3%) were more than gram-negative bacteria (46.7%).[13] This variation of etiologic agents from country to country might be due to geographical locations, epidemiological variation, or difference in etiologic agents.[14]

Weinstein et al. found that CONS were clinically significant, and they were ranked as the third most common cause of bacteremia because of their high prevalence. In our study, the most common

Table 4: Bacterial isolates and their frequency from blood culture in adults with sepsis

Blood culture baseline characteristics	n = 395	Percentage
No growth	286	286
Blood culture positivity rate	85	85 (22.9%)
Contamination rate	24	6.1%
Bacterial isolates	**n = 85**	**Percentage**
Gram-positive organisms	30	35.3
CONS *10 (11.8%)*		
Streptococcus β hemolyticus 9 (10.6%)		
Enterococcus species 5 (5.9)		
Staphylococcus aureus 4 (4.7)		
Streptococcus pneumoniae 2 (2.4)		
Gram-negative organisms	55	64.7
Escherichia coli 26 (30.6%)		
Klebsiella pneumoniae 8 (9.4%)		
Pseudomonas aeruginosa 7 (8.2%)		
Salmonella species 4 (4.7%)		
Others 10 (11.8%)		

*Others–*Proteus (3), Enterobacter (3), Burkholderia pseudomallei (3), Aeromonas (1)*

Table 5: Factors causing delay in administering first dose antibiotics

Factors causing delay	N = 131 (%)
Atypical presentation/afebrile	48 (36.6)
Unknown focus of infection being evaluated	48 (36.6)
Lead time delay in procuring antibiotics	26 (19.8)
Awaiting randomization for an RCT	6 (4.6)
Patient resuscitation and stabilization	3 (2.3)

Independent t-test to compare means of continuous variables affecting antibiotic administration

Variables	Antibiotic after 60 minutes n = 131 Mean (SD)	Antibiotic within 60 minutes n = 279 Mean (SD)	p value	Mean difference	95% confidence interval
Blood pH	7.35 (0.14)	7.30 (0.19)	0.003	0.05	0.017 to 0.085
Serum lactate	4.29 (4.24)	5.46 (4.9)	0.015	−1.16	−2.09 to −0.23

Table 6: Analysis of factors associated with mortality among sepsis patients

Independent t-test to compare means of continuous variables affecting hospital outcome

Variables	Dead n = 101 Mean (SD)	Alive n = 211 Mean (SD)	p value	Mean difference	95% confidence interval
Time to administer antibiotics	72.02 (61)	78.54 (71)	0.430	−6.52	−22.72 to 9.69
Blood pH	7.25 (0.2)	7.36 (0.1)	<0.001	−0.12	−0.16 to −0.07
Serum lactate	7.63 (5.3)	3.71 (3.8)	<0.001	3.91	2.74 to 5.08
Oxygen saturation	85 (15)	92 (8)	<0.001	−6.95	−10.3 to −3.61
Platelets	133386 (126981)	199727 (134229)	<0.001	−66342	−97753 to −34931
Serum creatinine	2.33 (1.5)	1.89 (1.3)	0.008	0.45	0.12 to 0.78
MAP	57.27 (21.3)	63.41 (17.6)	0.013	−6.14	−10.64 to −1.64
SOFA	9.5 (3.7)	5.9 (3.4)	<0.001	3.57	2.75 to 4.4

Bivariate and multivariate logistic regression analyses of factors associated with mortality

Variable	Dead n = 101	Alive n = 211	Bivariate analysis p value	Bivariate analysis OR (95% CI)	Multivariate analysis p value	Multivariate analysis AOR (95% CI)
Intubation	56 (55.4)	23 (10.9)	<0.001	10.2 (5.67–18.25)	<0.001	5.3 (2.59–10.91)
SOFA score >9	50 (49.5)	32 (15.2)	<0.001	5.5 (3.2–9.4)	0.002	2.9 (1.46–5.81)
Respiratory rate >30/minute	72 (71.3)	104 (49.3)	<0.001	2.6 (1.54–4.25)	0.044	1.9 (1.01–3.65)
Hypoxia (SpO$_2$ <90%)	43 (42.6)	43 (20.4)	<0.001	2.9 (1.73–4.86)	0.262	1.4 (0.76–2.73)
pH <7.35	63 (62.4)	65 (30.8)	<0.001	3.7 (2.26–6.12)	0.143	0.6 (0.34–1.17)
Lactate >2	86 (85.1)	118 (55.9)	<0.001	4.5 (2.45–8.33)	0.150	0.6 (0.29–1.21)
Central line	56 (55.4)	69 (32.7)	<0.001	2.6 (1.57–4.17)	0.511	0.8 (0.34–1.71)
Inotropes	69 (68.3)	102 (48.3)	0.001	2.3 (1.4–3.8)	0.715	0.9 (0.39–1.91)

SD, standard deviation; OR, odds ratio; AOR, adjusted odds ratio; CI, confidence interval

pathogen isolated was *E. coli* followed by CONS.[15] Swedish study by Andersson et al.[11] showed the most common pathogen was *E. coli* followed by Streptococcus pyogenes. In many studies, CONS are considered as a culture contaminant, but now they are considered as potentially important pathogens due to their increasing prevalence among patients with sepsis. We considered only clinically significant CONS and excluded clinically nonsignificant CONS as contaminants when subsequent cultures were negative.

Strength

This was a prospective observational study, minimizing the bias and missing data observed in many retrospective studies. Our study design with consecutive sampling ensured that almost all infected patients admitted to the ED were screened by qSOFA and included in the study.

Scope of Research

Incorporating the assessment of qSOFA score as a triaging parameter/tool will help in initiating resuscitation early in sepsis patients. The experience of the physician and physician variation on antibiotic timing can be studied.

Limitation

This was a single center study, and the representativeness of the study may be limited. However, by only measuring qSOFA on admission, we may have missed some patients who met qSOFA criteria later during their ED stay. Limited data were available on previous hospitalization and antibiotic usage prior to the arrival to our ED.

Conclusion

Two-thirds of the patients received their first dose of antibiotics within an hour of presentation to the ED. Patients who presented with the obvious focus of infection like cellulitis and NSTI received their first dose of antibiotic much earlier than others. Independent triggers for delay were patients being triaged to non-acute areas in ED, atypical presentation, and unknown focus of infection. qSOFA-based initiation of sepsis management will reduce the dependence on laboratory parameters and radiological imaging. Thus, in the ED, a high suspicion and qSOFA-based initiation of sepsis management would help in prompt antibiotic administration and thereby improve patient outcomes.

Research Quality and Ethics Statement

The authors of this manuscript declare that this scientific work complies with reporting quality, formatting, and reproducibility guidelines set forth by the EQUATOR Network. The authors also attest that this clinical investigation was determined to require Institutional Review Board/Ethics Committee review, and the corresponding protocol/approval number is IRB Min no: 11982, dated April 2, 2019. We also certify that we have not plagiarized the contents in this submission and have done a plagiarism check.

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