IMPACT OF TIME TO ANTIBIOTICS ON MORTALITY IN SEVERE SEPSIS AND SEPTIC SHOCK

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ABSTRACT

Introduction*: Severe sepsis and septic shock are associated with high mortality. Antibiotherapy must be started as early as possible since it seems to be the most important factor determining survival. In this study, we aimed to evaluate the time intervals between diagnosis and first dose of antibiotherapy and its impact on mortality in severe sepsis and septic shock patients.*

Materials and methods*: Medical records of adult patients (≥18 years old) admitted to medical ICU of a 1200-bed university hospital in Izmir,Turkey with the diagnosis of severe sepsis and septic shock between January 1,2010 and June 30,2014 were evaluated retrospectively. The patients admitted with other diagnosis than severe sepsis and septic shock and patients having an advanced stage of malignancy were excluded.*

Results*: One hundred and ten patients were identified fullfilling the inclusion criteria. 49(44.5%) patients were female and 61(55.5%) were male. Average age of the patients was 74,3±11,6. Average time from diagnosis of sepsis or septic shock to first dose of antibiotherapy was identified to be 6,9±4,7 hours. Patients were classified into two groups according to application of first dose of antibiotherapy (early<3 hours vs late>3 hours). The overall mortality rate was 54.5%. Mortality rates in early group were significantly lower than late group [25%(n=5) vs 61%(n=55),p<0,05]. Chronic renal failure was the only comorbidity significantly affecting mortality (p<0,05). Logistic regression analysis displayed early antibiotherapy (p=0,005), culture positivity (p=0,025) and APACHE II scores (p=0,006) to be important in predicting mortality.*

Conclusions*: Time to antibiotherapy is an extremely important factor predicting mortality in severe sepsis and septic shock. Any delay in diagnosis and intense treatment including appropriate antibiotherapy should be avoided to decrease mortality rates.*

Key words*: sepsis, severe sepsis, septic shock, antibiotherapy, mortality.*
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Introduction

Severe sepsis and septic shock are serious clinical diseases with increasing incidence and mortality affecting millions of patients worldwide. It accounts 2% of all-cause hospitalizations. Annual incidence of sepsis is 50-95/100000 and is increasing 9% each year[(1)]. Sepsis is the main cause of death in non-coronary medical intensive care unit (ICU)s. Mortality rates in sepsis syndromes varies according to the severity of the disease. Cinical studies report the mortality rates in systemic inflammatory response syndrome, sepsis, severe sepsis and septic shock as 6-27%,0-36%,18-52% and 46-82% respectively[(1)]. Despite advances in the field of critical care and new generation antibiotics mortality rates in sepsis syndromes has not declined as much as expected. Epidemiological study by Annane et al reported mortality rates in years 1993 and 2000 as 62% and 56% respectively[(2)].

Sepsis syndromes with accompanying organ dysfunctions display higher mortality rates due to

more immune supressive agent use, more invasive catheterization and intense treatment modalities and multidrug resistant microrganisms[3].

When severe sepsis and septic shock are diagnosed intravenous antibiotherapy should be started in the first hour[4].This strategy may increase treatment success and significantly reduce mortality. The empirical antibiotherapy regimen should include a combination of antibiotics with a wide range spectrum to cover susceptible and possible microorganisms. The severity of the infection, whether community aquired or nosocomial, primary source of infection, known comorbidities and underlying diseases, previous history of antibiotherapy and risk of bacterial colonization with multidrug resistance potency should be considered while choosing empirical antibiotics[4]. Additionally, neutropenic and immunesupressive patients being susceptible to potential wide spectrum pathogens should be kept in mind. Combined antibiotherapy should be preferred in neutropenic patients and Pseudomonas infections[4]. The combination of antibiotherapy should include antifungals in patients with a risk of candidemia. Combination regimens should be applied until culture results are obtained and thereafter should be deescalated according to antibiogram sensitivity results. Antibiotherapy should be daily reevaluated to avoid resistance, toxicity and maintain cost effectivity.

In this study, we aimed to evaluate the time intervals between diagnosis and first dose of antibiotherapy and its impact on mortality in patients admitted to our medical ICU with the diagnosis of severe sepsis and septic shock.

Materials and methods

This study has been conducted as retrospective, observational evaluation of patients' data who were admitted to 12-bed medical ICU of Dokuz Eylul University Hospital, a 1200-bed university hospital in Izmir, Turkey. Every adult patient (≥18 years old) admitted to ICU with the diagnosis of severe sepsis and septic shock between January 1,2010 and June 30,2014 was evaluated. The diagnosis of severe sepsis and septic shock was concluded according to the international guidelines[5]. The patients admitted with other diagnosis than severe sepsis and septic shock and patients having an advanced stage of malignancy were excluded. The age, gender, Acute Physiology and Chronic Health Evaluation (APACHE) II scores, comorbid diseases, time interval to the first dose of antibiotics and culture results were recorded. The study has been approved by the Institutional Ethical Committee.

The data analized for the study were achieved from registration and follow-up forms of ICU and hospital digital registration system. These documents briefly included all laboratory results, vital signs, treatment orders, APACHE II scores and medical records of whole hospitalization period.

Classification variables were expressed as frequency and percentage and continuous variables were expressed as mean ± standard deviation. The differences among cathegorical variables were evaluated by ki-square test and Fisher for sure ki-square test. Mann-Whitney U test was applied for comparison of median values of two groups. Multivariable analysis was evaluated by logistic regression analysis. $p<0.05$ was accepted as statistically significant. All statistical analysis was done by Statistical Packages for the Social Sciences (SPSS) software version 15.0.

Results

One hundred and ten patients were identified fullfilling the inclusion criteria. 49(44.5%) patients were female and 61(55.5%) were male. Average age of the patients was 74,3±11,6. Average APACHE II score was calculated as 19,2±7,4. The overall mortality rate was 54.5% [33(55%) male and 27(45%) female] (Table 1).

The most common source of infection requiring ICU hospitalization was identified as pneumonia. The other less frequent sources were genitourinary system, intraabdominal and central nervous system infections. Microorganisms could only be identified in 30% of culture specimens (blood, urine, secretions etc.) sent to microbiology laboratory before the first dose of empirical antibiotherapy. (Table 1.)

The time from diagnosis of sepsis or septic shock to first dose of antibiotherapy was identified to be 6,9±4,7 hours (Fig.1).

Patients were classified into two groups according to application of first dose of antibiotherapy. According to 2012 Surviving Sepsis Campaign resuscitation bundle recommendations patients who received the first dose of antibiotherapy in first 3 hours were accepted as early group and the ones who received antibiotherapy later were accepted as late group[4].

Age	74,3±11,6
Time to first antibiotherapy(hours)	6,9±4,7
Gender (M/F)	61/49
APACHE II (median±SD)	19,2±7,4
Comorbidities [n(%)]	
· HT	58 (52,7)
· DM	30 (27,3)
· CAD	18 (16,4)
· CHF	34 (30,9)
· COPD	44 (40)
· CVD	16 (14,5)
· CRF	17 (15,5)
Source of infection [n(%)]	
· Pneumonia	91 (82,7)
· Other systems	19 (17,3)
Culture positivity [n(%)]	
· Yes	33 (30)
· No	77 (70)
Mortality [n(%)]	60 (54,5)

Table 1: Characteristics of patients.

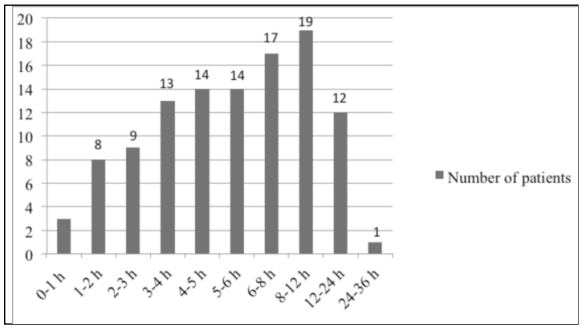

Figure 1: Distribution of patients according to time to antibiotherapy.

According to this resuscitation bundle, 20 and 90 patients were identified in early and late groups respectively. Average age in early and late groups was 76,0±8,6 and 73,9±12,2 respectively. There was no relation between age and timing of antibiotherapy (p>0,05). Average of APACHE II scores displayed no statistical significance in both groups [early group: 18,2±7,5 and late group:19,4±7,4] (p>0,05) (Table 2).

Early group constituted of 10 (50%) female and 10 (50%) male; late group constituted of 39 (44,4%) female and 51 (56,6%) male patients. There was no relation between gender and time to antibiotherapy (p>0,05).Pneumonia was the source of infection in 16 (80%) and 75 (83,3%) patients in early and late groups respectively. The rest of the patients in both groups suffered of infections other than pneumonia. No statistical significance could be detected between source of infection and time to antibiotherapy (p>0,05) (Table 2).

	Early (n=20)	**Late** (n=90)	**p**
Age	76,0±8,6	73,9±12,2	>0,05
Gender (M/F)	10-Oct	51/39	>0,05
APACHE II (median±SD)	18,2±7,5	19,4±7,4	>0,05
Comorbidities [n(%)]			
HT	12 (60)	46 (51,1)	
DM	8 (40)	22 (24,4)	
CAD	4 (20)	14 (15,5)	
CHF	6 (30)	28 (31,1)	>0,05
COPD	11 (55)	33 (36,6)	
CVD	2 (10)	14 (15,5)	
CRF	2 (10)	15 (16,6)	
Source of infection [n(%)]			
Pneumonia	16 (80)	75 (83,3)	>0,05
Other systems	4 (20)	15 (16,7)	
Culture positivity [n(%)]			
Yes	6 (30)	27 (30)	>0,05
ßNo	14 (70)	63 (70)	
Mortality [n(%)]	5 (25)	55 (61,1)	<0,004

Table 2: Characteristics of patients according to timing of antibiotherapy.

M: male, F: female, APACHE: acute physiology and chronic health evaluation, SD: standart deviation, n:number, HT: hypertension, DM: diabetes mellitus, CAD: coronary artery disease, CHF:congestive heart failure, COPD: chronic obstructive pulmonary disease, CVD: cerebrovascular disease, CRF: chronic renal failure.

The most common comorbid disease in both groups were hypertension (HT) and chronic obstructive pulmonary disease (COPD) in decreasing order. The third most common comorbidity was diabetes mellitus (DM) in early group and congestive heart failure (CHF) in late group. Culture positivity of specimens sent before antibiotherapy were similar in both early and late groups [6(30%) and 27(30%) respectively]. Mortality rates in early group were significantly lower than late group [25%(n=5) vs. 61%(n=55), p<0,05] (Table 2).

Among survivors 28(56%) were male and 22(44%) were female. There was no statistical significance regarding gender and mortality (p>0.05). The average ages of the patients who died and survived were 76,0±10,5 and 72,1±12,6 respectively(p>0,05). The average APACHE II

scores of survivors was 17,0±6,4 whereas it was 21,0±7,7 in the ones who died (p<0,005). Chronic renal failure (CRF) was the only comorbidity significantly affecting mortality (p<0,05). Pneumonia was the source of infection in 46(76.6%) patients who died and infection of other organ systems was responsible of the rest 14(23.3%) deaths. There was no statistical significance between the source of infection and mortality (p>0,05). A microrganism responsible of infection could be identified in only 23(38.3%) patients who died. The relation between culture positivity and mortality was statistically significant (p<0,05) (Table 3).

	Non-survivors (n=60)	Survivors (n=50)	P
Age	76,0±10,5	72,1±12,6	>0,05
Gender (M/F)	33/27	28/22	>0,05
APACHE II (median±SD)	21,0±7,7	17,0±6,4	<0,005
Comorbidities [n(%)]			
· HT	30 (50)	28 (56)	>0,05
· DM	17 (28,3)	13 (26)	>0,05
· CAD	8 (13,3)	10 (20)	>0,05
· CHF	20 (33,3)	14 (28)	>0,05
· COPD	19 (31,6)	25 (50)	>0,05
· CVD	10 (16,6)	6 (12)	>0,05
· CRF	13 (21,6)	4 (8)	<0,05
Source of infection [n(%)]			
· Pneumonia	46 (76,7)	45 (90)	>0,05
· Other systems	14 (23,3)	5 (10)	
Culture positivity [n(%)]			
· Yes	23 (38,3)	10 (20)	<0,05
· No	37 (61,7)	40 (80)	
Time to antibiotherapy [n(%)]			
· Early	5(8,3)	15(30)	<0,004
· Late	55(91,7)	35(70)	

Table 3: Characteristics of survivors and non-survivors.
M: male, F:female, APACHE:acute physiology and chronic health evaluation, SD: standart deviation, n:number, HT: hypertension, DM:diabetes mellitus, CAD: coronary artery disease, CHF: congestive heart failure, COPD: chronic obstructive pulmonary disease, CVD: cerebrovascular disease, CRF: chronic renal failure.

Logistic regression analysis displayed early antibiotherapy (p=0,005), culture positivity (p=0,025) and APACHE II scores (p=0,006) to be important in predicting mortality. Early antibiotherapy decreases possibility of mortality 5.6 (1.7-18.4) times compared to late antibiotherapy.

Culture positivity increases possibility of mortality 3 (1.1-7.9) times compared to patients with negative cultures (Table 4).

	OR	%95 CI	p
Early/late antibiotherapy	5,56	1,68-18,35	0,005
Culture positivity/negativity	3,01	1,14-7,92	0,025
APACHE II	1,09	1,02-1,17	0,006

Table 4: Logistic regression analysis.
OR:odds ratio, CI:confidence interval, APACHE:acute physiology and chronic health evaluation

Discussion

Sepsis is the most common cause of death in critical care units generally with a peak at sixth decade[6]. In our study we identified the average age of patients as 74,3 (53-80) which is compatible with literature.

Male gender, ethnicity, accompanying diseases, cancer, immune supression, chronic organ failures, alcoholism and genetic factors are known predisposing factors for sepsis[3,7]. In a multicenter international epidemiological survey Alberti et al reported underlying disease states of septic patients as solid organ cancer 60%, chronic renal failure 46% , COPD 42% and DM 36%[8]. In another French study; chronic alcoholism 26 %, COPD 25%, DM 22% and CHF 18% were identified as most common comorbidities in septic shock patients[9].Most common underlying disease states in our study population were HT(62%), COPD(44%), CHF(34%), DM(30%) and CRF(17%). Immune supression, COPD, CHF, cirrhosis and CRF are known to predict mortality in septic patients[10,11]. In our study among comorbid diseases only CRF was identified to significantly increase mortality.

One of the most important issues in patients diagnosed to have sepsis is to identify the source of infection. In a study by Gao et al conducted in 2005, the source of infection in 87% of severe septic patients was identified and the distribution was as pneumonia 50%, intraabdominal infections 22%, urinary tract infections 6% and other system infections 6%[12]. In a Brasilian study the sources of infection in sepsis were reported as pneumonia 57%, urinary tract infection 21% and intraabdominal infection 11%[13]. In the current study we identified pneumonia 82,7%, urinary tract infections 11,8%, intraabdominal infections 3,6%, central nervous system infections 0,9% and foreign body infections 0,9% as the source of infection causing sepsis.

Our results are compatible with other studies worldwide as pneumonia and urinary tract infections being most common sources.

Despite advances in critical care and microbiology, mortality rates in septic shock are still over 50%[14]. Mortality rates of severe sepsis and septic shock from different regions of the world range between 54-64%[2,9,13,15]. In the last decade there seems to be a decremental trend in mortality which is attributed to early and intense treatment strategies and new generation antibiotics[16]. In our population we detected a mortality rate of 56,4% which is compatible with recent literature findings.

Various studies report that a delay in antibiotherapy increases mortality in sepsis. Every hour delay in appropriate antibiotherapy is shown to increase mortality by 7,6 - 9%[17]. In a retrospective study by Kumar et al it was reported that effective antimicrobial administration within the first hour of documented hypotension in septic shock patients was associated with increased survival[18]. Despite a progressive increase in mortality rate with increasing delays in antibiotherapy,unfortunately there is still serious delay worldwide[18-22].

A recent multicenter retrospective analysis of 17,990 patients with severe sepsis and septic shock reported that a delay in first antibiotic administration was associated with increased in-hospital mortality, with a linear increase in the mortality for each hour delay in antibiotic administration. Moreover, the adjusted hospital mortality odds ratio was observed to increase from 1.00 to 1.52 as time to antibiotic administration increased from 0 to 6 hours and the probability of mortality increased from 24.6% to 33.1%[23]. In our study the average time from diagnosis of severe sepsis and septic shock and first dose of antibiotherapy was 6,9±4,7 hours. In Surviving Sepsis Campaign guidelines it is recommended to start antibiotherapy in an hour after diagnosis. We identified that in our study antibiotherapy was started in only 3 of 110 patients in the first hour of diagnosis. Thus, so few patients did not permit us to conduct a statistical analysis. Therefore, we accepted the patients received antibiotherapy in the first 3 hours as early group since recommended in first 3-hour resuscitation bundle of Surviving Sepsis Campaign guidelines and the ones later as late group[4]. The mortality rate in early group was significantly less than late group (61% vs 25%,$p<0.05$).

Gurnani et al reported a duration of more than 4,5 hours between the diagnosis of septic shock and empirical antibiotherapy, duration of vasopressor infusion, APACHE II score and type of infection (community aquired vs nosocomial) to be risk factors predicting mortality[24]. In a French study evaluating risk factors predicting mortality in 320 septic patients admitted to ICU, requirement of mechanical ventilation, chronic alcoholism, age>65, Simplified Acute Physiology Score (SAPS) II>60, prothrombin ratio<40% and partial oxygen to fractionised inspiratory oxgen (PaO_2/ FiO_2) ratio < 150 were detected as risk factors increasing mortality (9). Multivariable analysis of survivors and non-survivors in our study revealed APACHE II score, early antibiotherapy and culture positivity of specimens as important factors predicting prognosis.

Conclusions

Time to antibiotherapy is an extremely important factor predicting mortality in severe sepsis and septic shock. Therefore, effort should be spent to increase awareness of emergency medicine and intensive care physicians for these clinical entities. A delay in diagnosis and intense treatment including appropriate antibiotherapy should be avoided to decrease mortality rates.

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YS participated in the design of the study, coordination, sequence alignment and drafted the manuscript. BC participated in the design of the study and performed the statistical analysis. YD conceived of the study, and participated in its design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

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