

Analysis of the Patients with Sepsis Caused by Gram Positive and Gram Negative Bacteria

Gram Pozitif ve Gram Negatif Bakterilerin Yol Açtığı Sepsisli Hastaların Değerlendirilmesi

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ABSTRACT Objective: The objective of this study was to evaluate the epidemiological, clinical, laboratory features and risk factors associated with mortality of the 109 adult cases of sepsis in which gram positive, and gram negative bacteria isolated from blood cultures. **Material and Methods:** One hundred and nine patients with sepsis followed in our hospital between January 2002 and January 2003 were investigated prospectively. **Results:** Gram negative bacteria were isolated from blood cultures in the rate of 58.7%. The most frequent gram negative bacterium was *Escherichia coli*, and gram positive was *Staphylococcus aureus*. Statistically significant difference was not detected between gram positive, and gram negative bacteria sepsis related with development of hypothermia, appropriate antibiotic treatment, septic shock, multiple organ dysfunction syndrome (MODS), disseminated intravascular coagulation (DIC), and mortality rate. The mortality rate was 23%. The risk factors related with mortality were old age, hypothermia, staying in intensive care units, changes in consciousness, septic shock, MODS, DIC, renal failure, acute respiratory distress syndrome (ARDS), inappropriate antibiotherapy, and lack of infectious disease specialist consultation. Inappropriate antibiotic therapy, severe sepsis, and old age were found as independent factors in mortality by logistic regression analysis. **Conclusion:** There was no significant difference between the risk factors of gram positive, and gram negative bacteria sepsis. Prompt diagnosis and appropriate antibiotic treatment was important in decreasing the mortality in both of them.

Key Words: Sepsis; risk factors

ÖZET Amaç: Bu çalışmanın amacı kan kültürlerinde gram pozitif ve gram negatif bakteri üreyen 109 erişkin sepsis olgusunun epidemiyolojik, klinik, laboratuvar özelliklerini ve mortalite ile ilişkili risk faktörlerini değerlendirmektir. **Gereç ve Yöntemler:** Hastanemizde Ocak 2002-Ocak 2003 tarihleri arasında izlenen 109 sepsis hastası prospektif olarak araştırılmıştır. **Bulgular:** Kan kültürlerinin %58.7'sinde gram negatif bakteri izole edildi. En sık gram negatif bakteri *Escherichia coli* ve en sık gram pozitif bakteri *Staphylococcus aureus* idi. Gram pozitif ve gram negatif bakteriler arasında hipotermi, uygun antibiyotik tedavisi, septik şok, multipl organ disfonksiyon sendromu (MODS), yaygın damar içi pıhtılaşması (DIC) ve mortalite oranları ile ilişkili olarak istatistiksel fark saptanmadı. Ölüm oranı % 23 idi. Mortaliteyle ilişkili risk faktörleri; ileri yaş, hipotermi, yoğun bakımda bulunmak, bilinç değişikliği, septik şok, MODS, DIC, böbrek yetmezliği, akut solunum yetmezliği sendromu (ARDS), uygunsuz antibiyotik kullanımı, enfeksiyon hastalıkları uzmanı konsültasyonu olmayıştı. Uygunsuz antibiyotik tedavisi, ağır sepsis ve ileri yaş lojistik regresyon analizinde ölümlle ilişkili bağımsız risk faktörleri olarak bulundu. **Sonuç:** Risk faktörleri yönünden gram pozitif ve gram negatif bakteri sepsisi arasında anlamlı fark yoktu. Her ikisinde de hızlı tanı ve uygun antibiyotik tedavisi mortalite azalmasında önemliydi.

Anahtar Kelimeler: Sepsis; risk faktörleri

Sepsis is seen in an increasing rate and its mortality is still high. Increase of old age in the society, lengthening of the survival of the patients with chronic diseases, broad use of immunosuppressive therapy, increase of invasive procedures in diagnosis and treatment are the causes in increased rate of sepsis incidence.¹ Mortality rate has been reported as between 12% and 80% by different studies and its average rate is about 35%.² Determination of the mortality factors in sepsis is very important.

We investigated the epidemiological, clinical and laboratory features of the 109 adult cases of sepsis in which gram positive and gram negative bacteria isolated from blood cultures and evaluated the risk factors associated with mortality in this study.

MATERIAL AND METHODS

All patients hospitalized in our hospital between January 2002 and January 2003 with sepsis associated with positive blood cultures in which gram positive, and gram negative bacteria isolated were included in this prospective study. The patients were followed until death or discharge from hospital. The study was performed after permission from the Local Committee of Ethics in Science and according to the guidelines of the Helsinki II declaration. The patients with positive blood cultures for *Brucella spp.*, and potentially skin contaminants; and younger than 18 years old were excluded from the study.

Blood was inoculated into BACTEC aerobic bottles. The bottles were incubated in BACTEC 9240 blood culture systems (Becton Dickinson, Sparks, MD, USA) until flagged as positive or seven days. When blood cultures became positive, the broth was gram- stained, and sub cultured onto sheep blood agar, and chocolate agar plates. The organisms were identified using standard conventional methods.³

True bacteremia or contamination: Each positive blood culture was assessed and categorized as true-positives or contaminants after the following

factors were taken into account; the patient's clinical history, physical findings, body temperature at the time of blood culture, leukocyte count, number of positive blood cultures out of the total number performed, results of cultures of specimens from other sites, imaging results, clinical course and response to therapy.^{2,4}

Episode: An episode of bacteremia was defined by first positive blood culture was accepted as a single episode. Any new positive blood culture result that occurred >48 hours after the previous result was accepted as a separate episode if it was clear that the one was not part of the same episode according to the clinical course.⁴

Hospital- acquired sepsis: The patients without clinical symptoms, and signs of sepsis on admission to the hospital; and with positive blood cultures after 72 hours of hospitalization were diagnosed as nosocomial sepsis according to the criteria of Centers for Disease Control and Prevention (CDC).^{4,5}

Community-acquired sepsis: The patients with clinical symptoms, and signs of sepsis on admission to the hospital; and positive blood cultures in 72 hours of hospitalization were diagnosed as community-acquired sepsis according to the criteria of CDC.⁵

Transient bacteremia: The patients with positive blood culture who had not symptoms and signs of local infection and symptoms; and signs of symptoms resolved totally in 24 hours were accepted as transient bacteremia.⁶

Underlying diseases: Underlying diseases were categorized as rapidly fatal (group I), fatal in the end (group II), nonfatal (group III) according to the McCabe and Jackson classification.^{7,8}

Appropriate antimicrobial therapy: The anti-biotherapy was accepted as appropriate if the isolated bacteria was susceptible to at least one antibiotic in vitro, beginning time of the antibiotic therapy was in 24 hours after bacteria isolation; appropriate duration and dose.⁴

Outcome: The patients are classified in two groups as the ones discharged from hospital with

clinical improvement, and the ones with fatal end due to bacteremia or clinical deterioration because of bacteremia.

The classification of the bacteremia was made according to the definitions below:

Patients' clinical status was defined as sepsis, severe sepsis, septic shock and MODS previously described.⁹

Statistical analysis

S0064 MINITAB release 13 program was used in statistical analysis. Data were analyzed by χ^2 , Fisher's exact test, Mann Whitney U test. Independent variables related with mortality with a p value < 0.05 in the univariate analyses were entered into beginning of the stepwise logistic regression models. The odds ratios, 95% confidence intervals (CI), and p values were calculated for each risk factor in the final models. The value of p < 0.05 was accepted as statistically significant.

RESULTS

We identified a total of 109 patients with sepsis who were followed up in our hospital between January 2002, and January 2003. Isolated bacteria from blood cultures were gram negative in 64 (58.7%), and gram positive in 45 (41.3%) patients. *E. coli* and other *Enterobacteriaceae* were the most

frequent isolated gram negative organisms. The other isolated gram negative microorganisms were *Acinetobacter spp.*, *Pseudomonas aeruginosa*. *Staphylococcus aureus* accounted for the most frequent isolated gram positive organism. The other gram positive microorganisms were *Enterococcus spp.*, *Streptococcus spp.*, coagulase negative staphylococcus (CNS). The origin of gram positive bacteremia was vascular catheter in the rate of 31% and the origin of gram negative bacteremia was genitourinary system in the rate of 42%. The hospital acquired bacteremia accounted for higher rate than community acquired bacteremia in both of the gram positive (60%), and gram negative (58%) bacteremia. The development of hypothermia, shock, MODS, DIC, and use of appropriate antibiotic treatment were not statistically different between gram positive, and gram negative bacteremia (p > 0.05). The rate of mortality in gram positive, and gram negative bacteremia was 28.9%, and 20.3% respectively but this difference was not statistically significant (p > 0.05) (Table 1).

When considering total 109 cases with sepsis 68 (62%) of the patients were male; 41 (38%) of them were female. This difference was found statistically significant (p < 0.001). The mean age of the patients was 60.0 ± 18.4 (18-93). Ninety one

TABLE 1: Comparison of the features of the patients with gram positive and gram negative bacteremia.

		Gram (+) Bacteremia		Gram (-) Bacteremia	
		n	%	n	%
The origin of the bacteremia	Respiratory	18	(40)	21	(33)
	Genitourinary	1	(2)	27	(42)*
	Vascular catheter	14	(31)*	1	(2)
The source of the bacteremia	Hospital	27	(60)	37	(58)
	Community	18	(40)	27	(42)
	Hypothermia	5	(11)	2	(3)
	Appropriate antibiotherapy	33	(73)	50	(78)
	Shock	10	(22)	15	(23)
	MODS	5	(11)	6	(9)
	DIC	9	(20)	11	(17)
	Mortality	13	(29)	13	(20)

*p < 0.05

MODS: Multiple Organ Dysfunction Syndrome, DIC: Disseminated Intravascular Coagulation.

(83.5%) of them was older than 40 years old. This finding was statistically significant ($p < 0.001$). Hospital acquired bacteremia accounted for 58.7% of the total cases, and this was found statistically significant ($p < 0.001$). The most frequent origin of infection in community acquired bacteremia, and hospital acquired bacteremia were genitourinary system in the rate of 33.3%, respiratory system in the rate of 45.3% respectively. The most frequent isolated agents from blood cultures in community acquired bacteremia, and hospital acquired bacteremia was *E. coli*, and *S. aureus* respectively. Underlying diseases were in Group I, Group II, and Group III in the rates of 2.8%, 39.4%, and 57.8% respectively. Underlying disease, the source of the bacteremia, and neutropenia were not statistically significant risk factors related with the development of shock, DIC, and MODS ($p > 0.05$). Septic shock was seen mo-

re frequently in the patients with ARDS, MODS, and DIC ($p < 0.05$).

Crude mortality of the patients with bacteremia was detected as 23 %. Evaluation of the risk factors in the mortality is presented in Table 2. Statistically significant risk factors related with mortality were detected as old age, hypothermia, high respiratory rate, high level of blood urea, hospitalization in the intensive care unit, changes in consciousness. Mortality rate in the patients was also high in the patients with shock, MODS, DIC, renal failure, and ARDS ($p < 0.05$). Appropriate antibiotic therapy was given in 83 (76.1%) of all the patients. The appropriate antibiotic therapy was in higher rate (86%) in the patients with community acquired sepsis than the ones with hospital acquired sepsis (68%). This result was found as statistically significant ($p < 0.05$). Septic shock, MODS, and DIC was seen in the pa-

TABLE 2: Risk factors related with mortality due to the bacteremia.

Risk factor		Episode	Mortality		p
		n	n	(%)	
Sex	Male	68	15	(22.1)	Non-significant
	Female	41	11	(26.8)	
Unit	Internal medicine	80	17	(21.3)	Non-significant
	Surgical	21	4	(19)	Non-significant
	Intensive care	8	5	(62.5)	< 0.05
Source of bacteremia	Hospital	64	17	(26)	Non-significant
	Community	45	9	(20)	Non-significant
Type of bacteremia	Gram (+)	45	13	(28.9)	Non-significant
	Gram (-)	64	13	(20.3)	Non-significant
Underlying disease	Group I	3	1	(33.3)	Non-significant
	Group II	43	11	(25.6)	Non-significant
	Group III	63	14	(22.2)	Non-significant
Neutropenia	Present	6	2	(33.3)	Non-significant
Consciousness changes	Present	36	21	(58.3)	< 0.001
Shock	Present	25	15	(60)	< 0.001
MODS	Present	11	9	(81.8)	< 0.001
DIC	Present	20	9	(45)	< 0.05
Renal failure	Present	22	12	(54.5)	< 0.001
Hepatic failure	Present	15	5	(33.3)	Non-significant
ARDS	Present	14	12	(85.7)	< 0.001
Inappropriate antibiotherapy	Present	26	15	(57.7)	< 0.001
Infectious diseases consultation	Present	43	15	(34.9)	< 0.001

ARDS: Acute Respiratory Distress Syndrome, MODS: Multiple Organ Dysfunction Syndrome, DIC: Disseminated Intravascular Coagulation.

tients with inappropriate antibiotic therapy in higher rates ($p < 0.05$), and mortality was also high in these patients ($p < 0.001$). The rate of mortality was high in the patients given inappropriate antibiotic therapy ($p < 0.001$). The rate of appropriate antibiotic treatment was high in the patients who were seen by an infectious diseases specialist ($p < 0.05$). The mortality of the patients were high in patients who were not seen by an infectious diseases specialist, and this was statistically significant ($p < 0.05$). Variables associated with outcome with a p value < 0.05 in the univariate analyses and variables considered clinically significant (age, appropriate antibiotic therapy, severe sepsis, underlying disease, hospitalization in the intensive care unit) were entered into beginning of the stepwise logistic regression models for mortality to identify independent risk factors. Inappropriate antibiotic therapy, severe sepsis, old age was found as independent risk factors in mortality according to the logistic regression analysis (Table 3).

DISCUSSION

Several bacteria are responsible for the etiology of the sepsis. Although the streptococci, and the staphylococci were the most common causes of bacteremia before the antibiotic era gram negative bacteria have been isolated more frequently in sepsis in recent years, and also the rate of gram positive bacteria in the etiology of sepsis has been increased in last decade.¹⁰ As the causative agents in sepsis gram negative bacteria, and gram positive bacteria has been reported in the rates of 20-64%, and 27-74% respectively.¹ We found gram negative bacteria in the rate of 58.7%, and gram positive bacteria in the rate of 41.3% in our study. The most frequently isolated pathogens were *E.*

coli (26.4%), and *S. aureus* (22.9%). In the study of Geerdes et al *E. coli* (26.4%), *S. aureus* (18.9%), and other enteric bacilli (15.2%) were the most frequent agents isolated in the patients with sepsis.¹¹ SENTRY antimicrobial surveillance program organized in 25 university hospitals of Europe in the years of 1997-1998 reported the *S. aureus* (17.6 %), coagulase negative staphylococci (17.1 %), and other enteric bacilli (14.1%) as the most frequent microorganisms after the *E. coli* in sepsis.¹²

Mortality of the sepsis due to gram positive bacteria was reported in higher rate (25.5%) than the gram negative bacteria (18.3%) in a study made in Berlin.¹¹ In another study made about hospital acquired sepsis mortality related with gram negative bacteremia, and gram positive bacteremia was reported as 26.2%, and 11.6% respectively.⁴ Although we found the rate of mortality in sepsis related with gram positive bacteria was found higher than the gram negative bacteria this difference was not detected as statistically significant. Valles et al found that the septic shock development in gram negative bacteremia was more frequent than the gram positive bacteremia but this difference was not found in the studies made by Leibovici et al and Geerdes et al We also found that the complications such as septic shock, MODS and DIC developed in similar rates in sepsis due to gram positive and gram negative bacteria.^{4,11,13}

The mortality rate of total 109 cases with sepsis was found as 23% in our study. We detected old age, hypothermia, high respiratory rate, high level of blood urea, changes in consciousness status, development of shock, MODS, DIC, ARDS, renal failure, inappropriate antibiotic use, absence of infectious diseases consultation as the risk factors related with mortality. Independent risk factors related with mortality were found as old age, severe sepsis, and inappropriate antibiotic use by logistic regression analysis. Sex, underlying disease, neutropenia, leukocyte, thrombocyte count, liver failure was not found statistically significant risk factors in mortality. Old age and metabolic, neoplastic, and immunosuppressive diseases pre-

TABLE 3: Independent risk factors related with mortality.

Risk factors	OR	95% CI	p
Inappropriate antibiotherapy	8.62	2.55-29.1	< 0.05
Severe sepsis	5.97	1.89-18.81	< 0.05
Age	1.04	1.01-1.08	< 0.05

OR: Odd's ratio, CI: Confidence interval.

dispose the infectious diseases. Several studies related with prognosis of bacteremia detected the mortality rate as high in the old age patients.^{2,4,14,15} Some authors did not find such a relation.^{6,16} Mortality was detected in high rate in old patients in our study. Primary, and secondary humoral immunodeficiency, underlying diseases in old age patients are not only predisposing factors in bacteremia but also causes severe outcome and increased mortality.

Microorganisms causing bacteremia differs according to the hospital and community acquired bacteremia. The etiologic agents of hospital acquired sepsis are differs among countries, hospitals, and also units in the same hospital.

Weinstein et al reported the hospital acquired bacteremia in the rate of 50%, and detected *S. aureus*, CNS, enterococcus species, *P. aeruginosa*, and other nonfermentative bacteria as the causative agents in hospital acquired sepsis.¹⁷ The most frequent agents isolated in community acquired bacteremia were *S. aureus*, *S. pneumoniae*, *E. coli* and other enteric bacilli. *E. coli* and *S. aureus* were found as the most frequent agents in community acquired, and hospital acquired bacteremia respectively in our study. The mortality rate is higher in hospital acquired bacteremia than community acquired bacteremia according to the several studies.^{6,17-19} We did not find any difference between them. Higher mortality rate was detected in the patients of intensive care unit than the ones in surgery and internal units, and this difference was statistically significant as in another study.^{16,18,20} A lot of invasive procedures performed, and infections with antibiotic resistant isolates in intensive care unit were suggested factors as the cause of this high mortality rate.

Body temperature elevates in most of the patients with sepsis. Hypothermia has been reported as 2.8-8% in several studies.^{6,17,20} We found this rate as 6.4%, and hypothermia is a predisposing factor in increasing mortality as in other studies.^{6,17,20} While neutropenia is an important factor in increasing mortality in some studies it has been found insignificant in our study.^{4,6,14,17}

Septic shock development is one of the most severe complications in bacteremia. The rate of septic shock has been reported as 10.5% and 20.9% by Leibovici, and Gogos respectively.^{13,15} Uzun et al found this rate as 19.5 % in gram negative bacteremia.⁶ The septic shock was detected in the rate of 22.9% in our patients. Leibovici et al also found that renal failure, ARDS, MODS, DIC, hepatic failure complications were seen more frequently in the patients with septic shock.¹³ We also found same complications excluding hepatic failure in high rate in these patients. Septic shock increases the mortality rate significantly, and has been reported as 56-82%.^{4,13,16,20} We also detected this data in our study. DIC is another severe complication of the bacteremia. Its rate is 5% in hospital acquired bacteremia according to report of Valles et al, and 37% according to the Gogos et al.^{4,15} We detected this rate as 18.3% in total 109 cases with hospital, and community acquired sepsis. Sepsis is seen rarely in healthy people. There is usually a predisposing factor or an underlying disease. Underlying disease has been reported as an important factor in prognosis of bacteremia. Mortality rate was found as significantly high in the patients who were in the groups of diseases that were rapidly fatal, and fatal in the end according to the McCabe and Jackson criteria in several studies performed in 1965-1968, 1983-1986, and 1998 the prognosis.^{17,20,21} Another study from Turkey and we did not find a relationship like those findings.⁶

Besides prompt diagnosis, and treatment of the sepsis, source of the sepsis, probable causative agents, and antibiotic susceptibility of these agents were important factors in the accurate management of the therapy. Appropriate antibiotic therapy accounts for the major role in the successful treatment of the sepsis.^{6,9,17,22,23} The rate of the patients given appropriate antibiotic therapy was significantly high in the ones who were seen by infectious diseases specialist, and diagnosed as community acquired bacteremia. Because the antibiotic resistance rate of the etiologic agents in community acquired bacteremia is lower than hos-

pital acquired bacteremia.²² In hospital acquired bacteremia the probable etiologic agents, and antibiotic resistance pattern is considered better by an infectious diseases specialist. The significantly high rate of mortality, development of shock, MODS, and DIC in the patients of sepsis with inappropriate antibiotic therapy shows that appropriate antibiotic therapy is very important in bacteremic patients.

CONCLUSIONS

Sepsis is a clinical process with high mortality, and morbidity and its mortality decreases with prompt diagnosis, and treatment. Early diagnosis, isolation of the causative agent of the bacteremia, and detection of the antimicrobial susceptibility were the important factors in the management of the therapy, and survival in sepsis.

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