Risk Factors for Mortality in Patients with Nosocomial Gram-Negative Bacteremia

Nozokomiyal Gram-Negatif Bakteriyemili Hastalarda Mortalite ile İlişkili Risk Faktörleri

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Geliş Tarihi/*Received:* 16.11.2011
Kabul Tarihi/*Accepted:* 02.04.2012

This research was presented as an abstract in 19th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID), Helsinki, Finland 16-19 May 2009.

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doi: 10.5336/medsci.2011-27342

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ABSTRACT Objective: Nosocomial bloodstream infections are serious health problems in hospitals all over the world. They are associated with a high rate of morbidity and mortality, prolonged hospital stay and higher costs. The aim of this study was to evaluate the clinical outcomes of the patients with gram-negative bacteremia and to identify the risk factors for mortality. **Material and Methods:** A prospective observational study was performed in the 1196-bed Ankara Numune Education and Research Hospital. The patients with nosocomial gram-negative bacteremia were included in the study from July 2006 to June 2008. Bacteremia was considered to be nosocomial when it was diagnosed at least 48 h after hospital admission. Gram-negative bacteremia was defined as the presence of gram-negative bacteria in the blood, documented by at least 1 positive hemoculture. In patients who had more than one episode of gram-negative bacteremia, only the first episode was considered. Antibiotic therapy was considered to be appropriate if the drugs used had in vitro activity against the isolated strain. **Results:** Among the 253 cases (mean age: 54.5± 20 years old, male/female: 159/94) of Gram-negative bacteremia included in the study, the most frequently detected microorganisms were *Escherichia coli* (n=96, 37.9%), *Acinetobacter* spp. (n=54, 21.33%), *Pseudomonas aeruginosa* (n=41, 16.2%), *Klebsiella* spp. (n=39, 15.4%), *Enterobacter* spp. (n=9, 3.5%) and *Stenotrophomonas maltophilia* (n=6, 2.3%). The mean duration of hospital stay until Gram-negative bacteremia was 19 ±17 (range 3-82) days. Mortality rates at 14 days and at 30 days after the bacteremia were, respectively, 28.5% and 38.4%. We found that Acute Physiology and Chronic Health Evaluation (APACHE) II score over 20, inappropriate antibiotic treatment, receiving total parenteral nutrition, unconsciousness and thrombocytopenia were significant independent risk factors for mortality at day 30 after the Gram-negative bacteremia. **Conclusion:** Awareness of mortality risk factors is important for the prognosis. Appropriate antibiotic treatment could decrease deaths associated with Gram-negative bacteremia.

Key Words: Gram-negative bacteria; bacteremia; mortality; risk factors

ÖZET Amaç: Nozokomiyal kan dolaşımı enfeksiyonları tüm dünyada hastanelerdeki en önemli sağlık problemlerinden birisidir. Bu enfeksiyonlar morbidite ve mortalite oranlarının artmasına, hastanede kalış süresinin uzamasına ve tedavi maliyetlerinin artmasına neden olmaktadır. Biz bu çalışmada Gram-negatif bakteriyemili hastaların klinik sonuçlarının değerlendirilmesini ve mortalite ile ilişkili risk faktörlerinin belirlenmesini amaçladık. **Gereç ve Yöntemler:** Bu çalışma prospektif bir gözlem çalışması olarak 1196 yataklı Ankara Numune Eğitim Araştırma Hastanesinde yapıldı. Haziran 2006-Temmuz 2008 tarihleri arasındaki Gram-negatif bakteriyemili hastalar çalışmaya dahil edildi. Hastaların hastaneye kabulünden en az 48 saat sonra alınan kan kültürlerinde üreme olanlar nozokomiyal bakteriyemi olarak kabul edildi. En az bir kan kültüründe Gram-negatif bakteri üremesi Gram-negatif bakteriyemi olarak tanımlandı. Birden fazla bakteriyemi epizodu gelişen hastalarda sadece ilk epizod değerlendirmeye alınmıştır. İzole edilen suşa karşı in vitro aktivitesi olan antibiyotik kullanımı uygun antibiyotik kullanımı olarak değerlendirildi. **Bulgular:** Toplam 253 Gram-negatif bakteriyemi gelişen hasta (ortalama yaş: 54.5±20 yıl, erkek/kadın: 159/94) çalışmaya dahil edildi. En sık izole edilen mikroorganizmalar *Escherichia coli* (n=96, %37,9), *Acinetobacter* spp. (n=54, %21,33), *Pseudomonas aeruginosa* (n=41, %16,2), *Klebsiella* spp. (n=39, %15,4), *Enterobacter* spp. (n=9, %3.5) ve *Stenotrophomonas maltophilia* (n=6, %2,3) idi. Hastaların Gram-negatif bakteriyemi tespit edilene kadarki ortalama hastanede kalış süresi 19±17 (dağılım 3-82) gün olarak saptandı. Bakteriyemi sonrası 14. ve 30. günlerdeki mortalite oranları sırası ile %28,5 ve %38,4 olarak tespit edildi. Uygunsuz antibiyotik kullanımı, Akut Fizyoloji ve Kronik Sağlık Değerlendirmesi (APACHE) II skorunun 20'nin üzerinde olması, total parenteral nutrüsyon alımı, bilinç kaybı olması ve trombositopeni, Gram-negatif bakteriyemi sonrası 30. gün için mortalite ilişkili bağımsız risk faktörleri olarak bulundu. **Sonuç:** Hastalık prognozu için mortalite ilişkili risk faktörlerinin farkında olmak oldukça önemlidir. Uygun antibiyotik kullanımı Gram-negatif bakteriyemiye bağlı ölümleri azaltmada etkili olabilir.

Anahtar Kelimeler: Gram-negatif bakteri; bakteriyemi; ölüm oranı; risk faktörleri

Turkiye Klinikleri J Med Sci 2012;32(6):1641-7

Nosocomial bloodstream infections (BSI) are serious health problem in hospitals all over the world, associated with high rate of morbidity and mortality, prolonged hospital stay and higher costs.[1,2] Gram-negative bacteria are responsible for a considerable percentage of all bloodstream infections in approximately 50% of nosocomial BSIs.[3] The most common Gram-negative bacteria isolated in nosocomial BSIs are *Pseudomonas aeruginosa*, *Acinetobacter* species, *Klebsiella pneumoniae*, and *Enterobacter* species.[4,5]

Gram-negative bacteremia is a serious infection related with significant morbidity and mortality.[6] Mortality is usually associated with shock, multi-organ failure, severity of underlying disease, and appropriateness of antibiotic therapy.[7-9]

This study was planned to evaluate the clinical outcomes of the patients with Gram-negative bacteremia and to identify the risk factors for mortality.

MATERIAL AND METHODS

A prospective observational study design was employed with the main outcome measures 14- and 30-days in-hospital mortality. This study was conducted at a 1,196 bed teaching hospital, Ankara Numune Education and Research Hospital, in Turkey. The hospital contains all major departments except pediatric department, including medical and surgical sub-specialties, medical and surgical Intensive Care Units (ICUs). During a 2-year period (1 July 2006 to 30 June 2008), all hospitalized patients with a positive blood culture for Gram-negative bacteria were included if they were ≥16 years old, the blood culture met the Centers for Disease Control and Prevention criteria for infection and infection occurred ≥48 hours after hospital admission. Gram-negative bacteremia was defined as at least 1 positive hemoculture for Gram-negative bacteria. In patients who had more than one episode of Gram-negative bacteremia, only the first episode was considered. Patients with polymicrobial bacteremia were excluded. Primary bacteremia was defined as a confirmed BSI without any recognizable primary site of infection. The diagnosis of bacteremia was based on the criteria of the Centers for Disease Control and Prevention.[10,11]

E.coli and *Klebsiella* spp. strains were defined as multi-drug resistant (MDR) if resistance was observed to at least 3 out of 5 classes of antimicrobial agents, ie, ampicillin-sulbactam, piperacillin tazobactam, cephalosporins, quinolones, aminoglycosides.

In *Pseudomonas* spp. ve *Acinetobacter* spp. strains, imipenem resistance were explored.

If a patient received at least one antimicrobial agent at the day of blood culture collection to which the causative microorganisms were susceptible, empirical antimicrobial therapy was considered to have been appropriate. Inappropriate empirical antibiotic treatment was switched to an appropriate regimen according to antimicrobial susceptibility result. If a patient did not receive any antimicrobial agent overall to which the causative microorganisms were susceptible, antimicrobial therapy was considered to have been inappropriate.

Blood culture positivity was established with BacT/Alert (BioMerieux, Dunham, NC) automated blood culture system. Identification and antimicrobial susceptibility of the Gram-negative bacteria were performed by VITEK 2 automated system (BioMerieux, France). GN panel was used for the identification, and GN 528 panel was used for the detection of antimicrobial susceptibility.

The following data were obtained for each patient from the medical records and a computer database: Demographics, primary diagnosis, surgery, hospitalization period before Gram-negative bacteremia, source of bacteremia, length of hospital stay, presence of any coexisting diseases (malignancy, diabetes mellitus, chronic renal failure, immunosuppression, etc.), severity of illness [as calculated by the Acute Physiology And Chronic Health Evaluation (APACHE) II score], presence of a central venous, catheter, urinary catheter, or mechanical ventilation, hematological and biochemical test results, appropriateness of antibiotic treatment, culture and antimicrobial susceptibility test results.

Potential risk factors for all-cause 14- and 30-day mortality among all patients were assessed. A p-value of <0.05 was considered statistically significant. The Chi-square test or Fisher's exact test was used, when appropriate to compare proportions. Continuous variables were compared using an independent-groups Student's t test. Survival curves with a 95% confidence interval were computed using the Kaplan-Meier method. Cox regression was used to model 30-day in hospital mortality. The starting time point was the Gram-negative bacteria positive blood culture collection and the ending time point was either death or 30th day. For multivariate analysis, only variables with a p value <0.05 were entered into a Cox proportional hazards model and selected using a backward stepwise selection procedure. Hazard ratios (HR) and 95% confidence intervals (95% CI) were computed from estimated parameters of the final regression model. Software package Stata 11.0 (College station, Texas, USA) was used for the analysis.

The study protocol was approved by the Local Ethics Committee of Ankara Numune Education and Research Hospital.

RESULTS

Among the 253 cases (mean age: 54.5±20 years, male/female: 159/94) of Gram-negative bacteremia included in the study, the most frequently detected microorganisms were *E. coli* (n=96, 37.9%), *Acinetobacter* spp. (n=54, 21.33%), *P. aeruginosa* (n=41, 16.2%), *Klebsiella* spp. (n=39, 15.4%), *Enterobacter* spp. (n=9, 3.5%) and *S. maltophilia* (n=6, 2.3%) (Table 1). The mean duration of hospital stay until Gram-negative bacteremia was 19±17 (range 3-82) days. Mortality rates at 14 days and at 30 days after the bacteremia were, respectively, 28.5% and 38.4%.

Univariate analysis revealed that the risk factors for mortality at day 14 included: Older age, higher APACHE II scores, intensive care unit stay, mechanical ventilation support, existence of arterial line and central venous catheter, urinary catheter, receiving total parenteral nutrition (TPN), hypotension, hypothermia, unconsciousness, elevated levels of urea (Table 1).

At day 30, mortality-related risk factors in univariate analysis were as follows: Older age, higher APACHE II scores, intensive care unit stay, unconsciousness, elevated levels of urea, mechanical ventilation support, thrombocytopenia, receiving TPN, hypotension, existence of arterial line, central venous catheter and urinary catheter (Table 1). Independent risk factors for mortality were having an APACHE II score over 20, inappropriate antibiotic treatment, receiving TPN, unconsciousness and thrombocytopenia at day 30 in Cox proportional hazards model (Table 2, Figure 1).

In patients with MDR *E.coli* and *Klebsiella* spp. Bacteremia, 22 out of 64 (34.4%) patients; and in patients with antibiotic susceptible bacteremia, 18 out of 71 (25.4%) had a fatal outcome (p=0.252) at day 30.

Thirty out of 54 (55.6%) patients with imipenem-resistant *Acinetobacter* spp. and *Pseudomonas* spp. bacteremia and 17 out of 54 patients with imipenem-susceptible bacteremia died within 30 days (p=0.174).

Empirical antibiotics were given to 240 patients and the remaining 13 patients were not started empirical antibiotic treatment at the day of blood culture collection. In 144 of 240 (60.0%) patients, empirical antibiotic treatment was appropriate and 112 out of 144 (77.8%) patients survived whereas 60 out of 96 (62.5%) patients with inappropriate empirical therapy survived at day 14 (p=0.010). In 76 patients antibiotic treatment was switched to an appropriate regimen within 4.19 days. Antibiotic treatment was inappropriate in 33 (13%) patients overall. Mortality rate was 72.7% (24/33) in patients receiving inappropriate antibiotic treatment and 22.3% (49/220) in patients receiving appropriate antibiotic treatment at day 14 (p<0.001) and 78.8% (26/33) and 32.3% (71/220) respectively at day 30 (p<0.001).

DISCUSSION

This study was undertaken to evaluate the risk factors for mortality in patients with Gram-negative bacteremia. In this study, the most frequently detected microorganisms were *E.coli*,

TABLE 1: Risk factors associated with 14 and 30-day mortality in Gram-negative bacteremia based on the univariate analysis.

Risk factors	14-day after bacteremia			30-day after bacteremia		
	Survivors	Fatal cases	p	Survivors	Fatal cases	p
Mean age	52.1±20.5	60.3±17.7	0.003	51.8±19.7	58.8±19.9	0.007
Age >65 years	67 (37.22)	36 (49.32)	0.076	55 (35.26)	48 (49.48)	0.025
Male sex	112 (62.22)	47 (64.38)	0.747	97 (62.18)	62 (63.92)	0.781
Admission diagnosis						
Infection	18 (10)	8 (10.96)	0.820	16 (10.26)	10 (10.31)	0.989
Leukemia	37 (20.56)	14 (19.18)	0.804	34 (21.79)	17 (17.53)	0.410
Solid tumor	42 (23.33)	19 (26.03)	0.649	39 (25)	22 (22.68)	0.674
Burn	11 (6.11)	6 (8.22)	0.544	9 (5.77)	8 (8.25)	0.444
Neurological disorders	28 (15.56)	12 (16.44)	0.861	24 (15.38)	16 (16.49)	0.813
Trauma	17 (9.44)	8 (10.96)	0.714	10 (6.41)	15 (15.46)	0.019
Other	27 (15)	6 (8.22)	0.146	24 (15.38)	9 (9.28)	0.160
APACHE II score (mean)	17.2±5.6	21.4± 4.9	<0.001	15.4±4.8	21.5±4.9	<0.001
ICU stay	63 (35)	48 (65.75)	<0.001	45 (28.85)	66 (68.04)	<0.001
Comorbidity	77 (42.78)	29 (39.73)	0.656	68 (43.59)	38 (39.18)	0.489
Diabetes mellitus	12 (6.67)	5 (6.85)	0.958	10 (6.40)	7 (7.22)	0.803
COPD	12 (6.67)	9 (12.33)	0.139	9 (5.77)	12 (12.37)	0.064
Chronic renal failure	10 (5.56)	1 (1.37)	0.185	10 (6.40)	1 (1.03)	0.055
Immunsupression	39 (21.67)	17 (23.29)	0.778	35 (22.44)	21 (21.65)	0.884
Surgical operation	32 (17.78)	9 (12.33)	0.287	26 (16.67)	15 (15.46)	0.801
Primary Bacteremia	135 (75)	61 (83.56)	0.140	116(74.36)	80 (82.47)	0.133
Secondary Bacteremia	45 (25)	12 (16.44)		40 (25.64)	17 (17.53)	
Isolated bacteria						
E.coli	72 (40)	24 (32.88)	0.290	66 (42.39)	30 (30.93)	0.070
Klebsiella spp.	32 (17.78)	7 (9.59)	0.102	29 (18.59)	10 (10.31)	0.076
Pseudomonas spp.	24 (13.33)	17 (23.29)	0.052	20 (12.82)	21 (21.65)	0.064
Acinetobacter spp.	38 (21.11)	16 (21.92)	0.887	28 (17.95)	26 (26.80)	0.095
Enterobacter spp.	6 (3.33)	3 (4.11)	0.720	5 (3.21)	4 (4.12)	0.736
S.maltophilia	5 (2.78)	1 (1.37)	0.676	5 (3.21)	1 (1.03)	0.411
Other	3 (1.67)	5 (6.84)	0.047	3 (1.92)	5 (5.15)	0.266
Mechanical ventilation	51 (28.33)	43(58.90)	<0.001	36(23.08)	58 (59.79)	<0.001
Total parenteral nutrition	66 (36.67)	53(72.60)	<0.001	46(29.49)	70 (72.16)	<0.001
Enteral nutrition	19 (10.56)	6 (8.22)	0.573	17 (10.90)	8 (8.25)	0.492
Nasogastric tube	15 (8.33)	6 (8.22)	0.976	12 (7.69)	9 (9.28)	0.657
Central venous catheter	103 (57.22)	60(82.19)	<0.001	82 (52.56)	81 (83.51)	<0.001
Arterial line	31 (17.22)	25(34.25)	0.003	24 (15.38)	32 (32.99)	0.001
Urinary catheter	116 (64.44)	66(90.41)	<0.001	94 (60.26)	88 (90.72)	<0.001
Tracheostomy	24 (13.33)	9(12.33)	0.830	17 (10.90)	16 (16.49)	0.199
Surgical drain	23 (12.78)	12(16.44)	0.445	17 (10.90)	18 (13.83)	0.086
Appropriate empirical treatment	112 (65.12)	32 (47.06)	0.010	96 (63.58)	48 (53.97)	0.141
Fever >38,0 C	164 (91.11)	66 (90.41)	0.861	145(92.95)	85 (87.63)	0.152
Hypothermia <36,0 C	0 (0.00)	3 (4.11)	0.023	0 (0.00)	3 (3.09)	0.055
Unconsciousness	47 (26.11)	52 (71.23)	<0.001	31 (19.87)	68 (70.10)	<0.001
Hypotension	14 (7.78)	12 (16.44)	0.040	10 (6.41)	16 (16.49)	0.010
Leucocytosis	81 (45)	36 (49.32)	0.533	74 (47.44)	43 (44.43)	0.630
Leucopenia	34 (18.89)	18 (24.66)	0.304	30 (19.23)	22 (22.68)	0.509
Serum urea >50 mg/dL	66 (36.67)	39 (53.42)	0.014	52 (33.33)	53 (54.64)	0.001
Creatinine >1.2 mg/dL	46 (25.56)	22 (30.56)	0.419	38 (24.36)	30 (31.25)	0.231
Anemia	163 (90.56)	67 (91.78)	0.759	141(90.38)	89 (91.75)	0.713
Thrombocytopenia	76 (42.22)	40 (54.79)	0.069	61 (39.10)	55 (56.70)	0.006

Data are no. (%) of patients or mean value±standart deviation (SD).

APACHE: Acute physiology and chronic health evaluation; ICU: Intensive care unit; COPD: Chronic obstructive pulmonary disease.

TABLE 2: Estimated standard error, p value, and hazard ratio as a function of the risks of the variables according to the Cox proportional hazards model.

Risk factors	p	Hazard Ratio	95% Confidence interval
APACHE II score >20	<0.001	1.6	1.3-2.1
Total parenteral nutrition	0.001	2.6	1.4-4.1
Unconsciousness	0.006	2.2	1.2-3.9
Thrombocytopenia	<0.001	2.1	1.4- 3.2
Inappropriate antibiotic treatment	<0.001	4.5	2.8-7.3

APACHE: Acute physiology and chronic health evaluation.

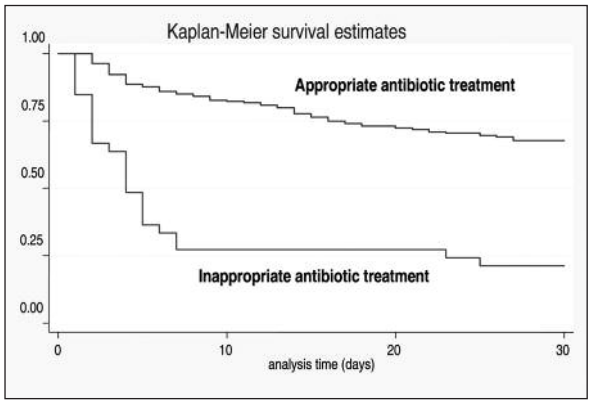

FIGURE 1: Kaplan-Meier survival estimates by suitability of the treatment. The inappropriate treatment group has the lower probability of survival compared to the appropriate therapy group.

Acinetobacter spp., *P. aeruginosa*, *Klebsiella* spp., *Enterobacter* spp. and *S. maltophilia* in rank order. We found that APACHE II score over 20, inappropriate antibiotic treatment, receiving TPN, unconsciousness and thrombocytopenia were significant independent risk factors for mortality at day 30 after the Gram-negative bacteremia. Inadequately treated patients had mortality rates significantly higher than adequately treated patients. The 30th day mortality rate was 38.4%, with rates of 32.3% and 78.8% for patients that received appropriate and inappropriate antimicrobial therapy, respectively. Furthermore, in 144 (60.0%) patients empirical antibiotic treatment was appropriate and 112 out of 144 (77.8%) patients survived whereas 60 out of 96 (62.5%) patients with inappropriate empirical therapy survived at day 14.

Bacteremia continues to be a major cause of morbidity and mortality in hospitals. Gram-negative bacilli are responsible for a considerable percentage of all nosocomial bacteremia.[12] The crude mortality associated with bloodstream infection approximates 35%, ranging from 12% to 80% and the attributable mortality due to nosocomial bloodstream infection averaged 26%.[13] In this study, we found an in-hospital crude mortality rate of 41.9%, 28.5% at 14th day and 38.4% at 30th day in Gram negative bacteremia.

The outcomes of bloodstream infections depend on underlying conditions, the severity of illness and the suitability of antibiotics.[14] ICU patients represented 34% of all hospital Gram-negative bacteremias.[15] In this study, 43.8% of the patients were followed up at ICUs. Gram-negative bacteremia in the setting of critical illness, as determined by admission to ICU, has been associated with higher mortality rates and prolonged ICU stay.[16,17]

The mortality rate in a study of Gram-negative sepsis in five ICUs in Taipei was 36.1%, with 77.4% of all deaths directly related to the bloodstream infection.[18] Sligl et al. reported mortality rate for patients with nosocomial Gram-negative bacteremia as 53.3% in the ICU.[5] In this study, 30 day mortality rate in the ICUs was 59.5% whereas 21.8% in wards.

High APACHE II score have been reported as an independent risk factor in patients with bacteremia in several studies.[19-21] In this study high APACHE II score also was an independent risk factor for mortality.

It was reported that critically ill patients with primary bacteremia present significant mortality strongly associated with age.[22] In this study, 49.5% of the fatal cases and 35.3% of the survivors were over the age of 65 years.

There are several studies indicating that antibiotic resistant Gram-negative bacteremia were resulted in prolonged hospitalization and increased mortality.[7,23-26] However, there are studies showing no significant impact of antibiotic resistance on mortality.[27,28] Blot et al. reported the mortality rates antibiotic susceptible bacteremia and those with

antibiotic resistant bacteremia were, respectively, 41.8% and 45.0%.[19] In this study, MDR in *E. coli* and *Klebsiella* spp. and imipenem resistance in *Acinetobacter* spp. and *Pseudomonas* spp. strains were not associated with increased risk of mortality. There were not any pan-resistant strains of Gram-negative bacteria in this study, therefore the patients had at least one antibiotic option for treatment.

Appropriate antimicrobial therapy has been shown to reduce mortality among patients with Gram-negative bacteremia and, when initiated early, to have a favorable effect on outcome in critically ill patients with bacteremia or other serious infections.[14,29] Patients who received appropriate antimicrobial therapy throughout the course of infection had the lowest mortality.[30] Blood culture is the gold standard for the detection of bloodstream microbial pathogens. However, lack of rapidity is a major problem, identification of pathogen causing bacteremia requires 12 to 48 hours or more in the bacterial or fungal infection.[31] In addition, time loss caused by delay in reporting system further increases the amount of time spent in initiating appropriate treatment. In this study, antibiotic treatment was inappropriate in 33 (13%) patients due to negative characteristics of blood culture system described above. Mortality rate was 72.7% in patients receiving inappropriate antibiotic treatment and 22.3% in patients receiving appropriate antibiotic treatment at day 14 and 78.8% (26/33) and 32.3% (71/220) respectively at day 30. The use of molecular diagnostic methods that allow a faster identification of microorganisms in blood can be effective in preventing such losses.[32,33]

Inappropriate initial antimicrobial therapy, defined as an antimicrobial regimen that lacks in vitro activity against the isolated organism responsible for the infection, can lead to treatment failures and adverse patient outcomes.[34] Kumar et al. examined outcomes in 2,500 subjects with septic shock and concluded that each 1-hour delay in the administration of appropriate antibiotics was associated with a 10% increase in the probability of death.[35] Peralta et al. reported that adequacy of empirical antibiotic treatment is an independent risk factor for mortality in patients with *E. coli* bacteremia.[36] In this study, empirical antibiotics were given to 240 patients at the day of blood culture collection, and in 144 (60.0%) patients empirical antibiotic treatment was appropriate and 112 out of 144 (77.8%) patients survived whereas 60 out of 96 (62.5%) patients with inappropriate empirical therapy survived at day 14.

To conclude, awareness of mortality risk factors is important for the prognosis. Appropriate antibiotic treatment could decrease deaths associated with Gram-negative bacteremia.

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