European Review for Medical and Pharmacological Sciences 2013; 17: 951-957

Risk factors for mortality in patients with nosocomial Gram-negative rod bacteremia

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Abstract. – BACKGROUND: The percentage of hospital-acquired bloodstream infections associated with Gram-negative bacilles has decreased during last decade but it is still a major cause of morbidity and mortality.

OBJECTIVES: The aim of this study was to determine the outcome of Gram-negative rod (GNR) bacteremia, which is an important clinical problem with high mortality rates, and the risk factors for GNR related mortality in our Clinic.

MATERIALS AND METHODS: During the study period, 520 episodes of bacteremia were detected in 411 patients. Only patients with GNR bacteremia in blood cultures were included in the study (n = 197). Among 197 patients fulfilling study criteria, GNR were grown in 239 samples.

RESULTS: *Escherichia coli* (n = 97, 40.5%), *Klebsiella pneumoniae* (n = 54, 22.5%), *Pseudomonas aeruginosa* (n= 24, 10%), *Acinetobacter baumannii* (n = 24, 10%) were the most commonly isolated bacteria. The most frequently identified infection sources of bacteremia were pneumonia (n = 35, 17.7%), catheter-related infections (n = 24, 12.2%), urinary tract infections (n = 20, 10%). In multivariate analysis, it was found that the GNR bacteremia mortality risk increased in patients treated in intensive care units (ICU) (OR: 0.2, p = 0.03) and patients with ventilatory support (OR: 20.8, p = 0.05).

CONCLUSIONS: In clinical practice of the hospital settings, efforts should concentrate on preventive measures for nosocomial infections since pneumonia, catheter-related infections, and urinary infections appear to be the most frequent causes of secondary bacteremia.

Key Words:
Nosocomial infections, Gram-negative bacteremia, GNR sepsis, Risk factors, Mortality.

Introduction

Numerous factors continuously contribute to an increase in the prevalence of Gram-negative rod (GNR) infections. Underlying diseases, advanced age, increasing prevalence and severity of concomitant diseases, malignancy, administration of aggressive chemotherapies in organ transplantation, and intensive antibiotic use have often been implicated[1,2]. The role of modern intensive care units (ICUs) and the increasing number of patients colonized with GNR sepsis prevalence should not be overlooked. Invasive techniques, particularly indwelling catheters, endotracheal intubation, and mechanical ventilation (MV), are significant risk factors for nosocomial infections and bacteremia associated with GNRs[3,4]. The aim of this study was to determine the outcome of GNR bacteremia, which is an important clinical problem with high mortality rates, and the risk factors for GNR related mortality in our Clinic.

Materials and Methods

In this study, clinical characteristics, laboratory findings, and risk factors for mortality were prospectively evaluated in patients who were hospitalized in Istanbul University Istanbul Faculty of Medicine Clinics and ICUs for at least 48 hours between June 2005 and June 2006 and in whom GNRs were isolated from blood cultures. A total of 520 cultures positive for bacteremia were detected in 411 patients during this time; 239 of these bacteremia attacks were associated with GNRs. A total of 197 patients fulfilling the study criteria were included and were followed up during the study period and until 30 days after discharge. Bedside assessment was performed as soon as a positive blood culture detected. Patient information was obtained from the patient and/or the physician, and laboratory results were obtained from the patient file.

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Demographic information, previous hospitalizations (including the clinic and duration of stay), previous and ongoing (within the last month) antibiotic therapy (dose and duration of treatment) and medications other than antibiotics, underlying diseases and risk factors (malignancy, diabetes mellitus, renal failure, cardiac failure, past myocardial infarction (MI), liver failure, trauma, parenteral nutrition, age ≥ 65 years, cardiac arrest during hospitalization, neutropenia, surgery within the last month, chemotherapy, radiotherapy, and glucocorticoid use) and all invasive procedures were recorded and the patients were followed-up until 30 days after discharge in relation to prognosis. Exclusion criteria were age < 16 years, Gram-positive bacteremia**,** fungemia, and growth in blood culture within the first 48 hours of hospitalization.

Microbiological Data

Bacterial growth in blood cultures obtained during febrile episodes in patients who were hospitalized > 48 hours (or < 48 hours after transfer from another hospital), or demonstrating clinical signs of systemic infection were considered to represent nosocomial bacteremia (NB) and were included in the study. During each febrile episode, blood samples obtained at different times from the peripheral vein of the patient, including one sample from the central venous catheter (CVC) if present, and were inoculated in 2 or 3 blood culture media. Blood samples were inoculated into BacT/AlerT "Automated System" (BioMerieux, Durham, NC, USA) blood culture bottles. Growth in at least two bottles was considered significant. Growth of more than one GNR in the blood culture was classified as polymicrobic bacteremia. Results of other cultures (catheter, urine, sputum, tracheal aspirate, pus) obtained simultaneously from the patient were followed up as well. API 20E and API 20NE (BioMerieux, Hazelwood, MO, USA) tests were used for the identification of bacteria. Antibiotic sensitivity tests of the strains were performed by disc diffusion method using standard antibiotic discs and Mueller-Hinton agar as defined in Clinical and Laboratory Standards Institute (CLSI) Document M2-A8[5]. Bacterial sensitivity and resistance were determined according to NCCLS/CLSI criteria[6].

Statistical Evaluation

Statistical Package for Social Sciences (SPSS 12.0, Chicago, IL, USA) was used for statistical evaluation. Parameters considered to be risk factors (previous antibiotic use, the clinic in which patient stayed or was staying during the last week, underlying diseases, the history of chemotherapy or surgery, invasive procedures) were evaluated by χ^2 test. $p < 0.05$ was considered statitically significant. The Student *t* test was used for the comparison of continuous variables and χ^2 or Fisher's exact test was used for the comparison of categorical variables.

Results

A total of 41 835 patients were hospitalized in Istanbul Medical Faculty Hospital during the study period (total number of beds 1 641), and 36 460 of these patients were adolescent/adult patients (total number of beds 1 412). Of these 36.460 patients, 8.893 (24.4%) were treated in Internal Medicine Units, 24 948 (68.4%) in surgical Units and 2,619 (7.2%) in ICUs. Mean duration of hospitalization was 43.1 ± 34.9 (range 3-327) days. During the study period, 520 episodes of bacteremia were detected in 411 patients. GNR bacteremia prevalence was 57.1 cases in 10,000 admissions. NB infection rate in a one-year period was 1.2%. Blood cultures were obtained from 2 698 patients, and 15 648 blood culture bottles were used. Of these attacks, 258 (49.6%) were due to Gram-positive cocci (GPC), 239 (45.9%) to GNRs, and 23 (4.4%) to fungi. Only patients with GNR bacteremia were included in the study (n= 197).

Among 197 patients fulfilling study criteria, GNR were grown in 239 samples. Of these, 107 (54.3%) were male and 90 (45.7%) were female. Of these patients, one attack was detected in 160 (81%), two in 33 (16.7%), and 3 attacks in 4 (2%). Multiple microorganisms were grown in one patient (who was in two-attack bacteremia group). *Escherichia coli* (n= 97, 40.5%), *Klebsiella pneumoniae* (n= 54, 22.5%), *Pseudomonas aeruginosa* (n= 24, 10%), and *Acinetobacter baumannii* (n= 24, 10%) were the most commonly isolated bacteria. *E. coli* (n= 97), *K. pneumoniae* (n= 54), and *K. oxytoca* (n= 12) were further evaluated for Extended-Spectrum Beta-Lactamase (ESBL) positivity; ESBL-positivity rate was 32.9% (32/97) for *E. coli*, 53.7% (29/54) for *K. pneumoniae*, and for *K. oxytoca* 41.6% (5/12).

A total of 92 episodes of bacteremia (38.5%) were detected in 73 patients treated in the ICU, and 147 episodes of bacteremia were detected in 124 patients treated in non-ICU units. Of 147 episodes of bacteremia were detected in non-ICU clinics, 76 (31.8%) were in Surgery Units, and 71 (29.7%) were in Internal Medicine Units. GNR

bacteremia was most frequent in general ICU (n = 70, 29.2%), and General Surgery Unit (GS) (n = 45, 18.8%).

According to causative agent of bacteremia and Units where they were detected, *E. coli* bacteremia was most frequent in GS clinics (n= 29, 29.9%), Hematology clinic (n= 16, 16.5%), and Gastroenterohepatology clinic (n= 12, 12.3%); *K. pneumoniae* bacteremia was most frequent in General ICU (n= 17, 31.5%), GS clinics (n= 10, 18.5%) and Hematology clinic (n= 8, 14.8%); *P.aeruginosa* (n= 14, 58.3%) and *A. baumannii* (n= 16, 66.6%) bacteremia were most frequent in general ICU.

The source of bacteremia could not be found in 88 out of 197 patients (44.6%). The most frequently identified infection sources of bacteremia were pneumonia (n= 35, 17.7%), catheter-related infections (n= 24, 12.2%), and urinary tract infections (n= 20, 10%) (Table I). The distribution of bacteremia sources in patients treated in ICU and non-ICU units and patients having a surgical intervention or not was compared. While pneumonia was the most frequent source of bacteremia in patients treated in ICU and patients not having a surgical intervention, intraabdominal infections were most frequent in patients treated in non-ICU clinics and patients having a surgical intervention (Table I).

Among the 197 patients included in the study, there were 82 fatal cases. While the crude mortality rate for patients with GNR bacteremia at one year was 1.96 in 1000, 28-day crude mortality rate was 1.29/1000. The fatality rate was 41.6 in 100. The mean duration of fatal cases was 31.2 ± 37.9 days. Underlying diseases and laboratory values of patients developing GNR bacteremia were evaluated by univariate analysis to investigate whether or not they presented any risk for mortality; increased mortality was associated with being treated in ICU (p = 0.009), presence of diabetes mellitus (p = 0.003), antibiotic use within 1 month prior to bacteremia (p < 0.02), MV application (p = 0.000), CVC use (p = 0.000), intraabdominal surgical intervention (p = 0.01), and growth of nonfermentative Gram-negative rods (NFGNR) in blood culture (p = 0.04) (Table II). While being treated in ICU increased the mortality risk (72.6% vs. 23.4%), no risk was found in patients hospitalized in Surgical Units and Internal Medicine Units in regard to mortality rates (46.9% vs. 30.7%; p = 0.09) (Table II).

Compared to use of other antibiotic groups, use of beta-lactam antibiotics prior to bacteremia led to a significantly increased mortality risk (p =0.01). Also, mortality risk was found to be higher in patients using combined antibiotics prior to bacteremia compared to those using one antibiotic (p = 0.003) (Table II).

Hospitalization duration (p < 0.005), low hemoglobin level ([9.4 ± 1.9] vs. [8.6±1.8]) (p < 0.014), elevated CRP level ([129.08 ± 66.2] vs. [167.3 ± 81.3]) (p < 0.007), elevated BUN level ([26.3 ± 20.8] vs. [40.4 ± 29.3] (p < 0.001), increased serum creatinine level ([1.4 ± 1.7] vs. [2.1 ± 2.1]) (p = 0.02), and age > 65 years (p ≤ 0.001) were found to be risk factors for mortality.

In multivariate analysis, it was found that the GNR bacteremia mortality risk increased in patients treated in ICU (OR: 0.2, p = 0.03) and patients with ventilatory support (OR: 20.8, p = 0.05). Increase in number of episodes of bacteremia did not increase the mortality risk (p > 0.5).

The time interval between hospitalization of the patients and growth in blood culture was investigated. The mean duration of blood culture growth was 26.1 ± 34.9 (4-212) days. Mean time of

Table I. Type of infections leading to nosocomial GNR bacteremia: n (%).

	Patients in ICU	Patients in non-ICU	Patients with surgical intervention	Patients without surgical intervention	Total
Pneumonia	21 (10.6)	14 (7.1)	9 (4.6)	26 (13.1)	35 (17.7)
Catheter-related infection	14 (7.1)	10 (5)	7 (3.5)	17 (8.6)	24 (12.2)
Urinary infection	7 (3.5)	13 (6.6)	2 (1)	18 (9.l)	20 (10)
Intraabdominal infection	4 (2)	15 (7.6)	19 (9.6)	–	19 (9.6)
Surgical site infection (deep incisional)	3 (1.5)	7 (3.5)	10 (5)	–	10 (5)
Burn infection	–	1 (0.5)	1 (0.5)	–	1 (0.5)
Unidentified	24 (12.2)	64 (32.5)	67 (34)	21 (10.6)	88 (44.6)
Total	73 (37)	124 (62.9)	115 (58.4)	82 (41.6)	197

Table II. Clinical characteristics and risk factors for mortality in patients with nosocomial GNR bacteremia.

	Surviving cases	Fatal cases	*p* value*
Sex: male/female	61/54	46/36	0.9
Clinic: ICU/non-ICU (+)/(-)	20/95	53/29	< 0.001
Clinic: Surgery Clinics (+)/(-)	70/45	45/37	0.09
Age: < 65 years/> 65 years	85/30	46/36	< 0.05
Underlying diseases			
Chronic renal failure (+)/(-)	105/10	76/6	0.6
Liver failure (+)/(-)	96/19	74/8	0.2
Trauma (+)/(-)	110/5	80/2	0.2
Febrile neutropenia (+)/(-)	95/20	67/15	0.8
Heart failure (+)/(-)	108/7	76/6	0.5
Hematological malignancy (+)/(-)	91/24	63/19	0.6
Solid malignant tumors (+)/(-)	90/25	61/21	0.4
Transplantation (+)/(-)	110/5	81/1	0.4
BMT (+)/(-)	112/3	81/1	0.7
Surgical intervention (+)/(-)	70/45	45/37	0.6
Diabetes mellitus (+)/(-)	7/108	17/65	0.003
Chronic lung disease (+)/(-)	110/5	78/4	0.4
Inflammatory bowel disease (+)/(-)	113/2	78/4	0.3
Prior use of antibiotics (+)/(-)	83/32	70/12	0.02
Prior use of beta-lactam antibiotics (+)/(-)	78/37	38/44	0.01
Prior use of combined antibiotics (+)/(-)	37/78	44/38	0.003
Respiratory support (+)/(-)	41/74	63/19	0.000
Central venous catheter use (+)/(-)	52/63	64/18	< 0.001
Drain use (+)/(-)	83/32	60/22	0.9
Intraabdominal surgery (+)/(-)	35/80	38/44	0.01
NFGNR growth (+)/(-)	11/104	22/60	0.004
ESBL-positivity (+)/(-)	46/69	20/62	0.6

$p < 0.05$ was considered statistically significant.

growth was 21.2 ± 37.3 (5-212) days for GNRs, and 26.6 ± 34 (4-171) days for NFGNRs. While the mean time for nosocomial bacteremia (NB) development after hospitalization in ICU patients was 17.1 ± 19.4 (4-130) days, it was 29.6 ± 38.9 (4-212) days in patients treated in non-ICU clinics. There was a statistically significant difference between NB development ($p = 0.02$). The detection time for *E. coli, P. aeruginosa* and *Enterobacter* spp. bacteremia in ICU patients was shorter than that of patients treated in non-ICU clinics, while the detection time for *K. oxytoca* bacteremia in non-ICU settings was shorter. When detection time for GNR bacteremia was compared between patients treated in Surgical and Non-Surgical Units, the detection time for *P. aeruginosa* bacteremia was found to be shorter in patients treated in Surgical Clinics than those treated in Non-Surgical Clinics, (14.3 ± 10.2 days vs. 212 days). No cases of *A. baumannii, K. oxytoca, Enterobacter* spp., *and S. marcescens* related bacteremia were detected in Non-Surgical Clinics. There was a significant difference between the duration of hospitalization of patients with GNR bacteremia treated in ICU and non-ICU settings (22.4 ± 15.1 days vs. 51.4 ± 56.8 days) ($p \leq 0.001$).

Discussion

Bacteremia is the most important cause for morbidity and mortality. Bacteremia has been reported to be the tenth most frequent cause of death in the United States. Although the real incidence of NB is unknown, it has been proposed that nearly 250,000 patients have an episode of bacteremia per year in the United States[7-9]. The incidence of NB within each hospital appears to have a heterogeneous character. The NB attack rate per 1000 patient admissions has been reported to vary between 1.3 and 18.4, based on patient type, hospital size, location of the clinics, and length of stay in hospital[10-12].

A total of 520 episodes of bacteremia were detected in 411 patients in our study. GNR bacteremia frequency was found to be 54 per 10,000

admissions, and the one-year NB infection rate was 1.1%. Reports on NB incidence demonstrate significant variations among hospitals and clinics, depending on factors such as underlying diseases and length of stay.

GNRs were the most frequent agents isolated in NBs between 1960s and 1970s. In the SCOPE (Surveillance and Control of Pathogens of Epidemiological Importance)[9] study, 65% of monomicrobial infection attacks were found to be due to GPC and 25% due to GNRs. In NNIS (National Nosocomial Infections Surveillance) system data[13] collected between 1990 and 1999, coagulase-negative staphylococci (CNS), *Staphylococcus aureus, Enterococcus* spp. were found to be the most frequent causative agents. In their study conducted between 1996 and 2003, Wu et al[14] have found that GNRs were the causative agents of infection in 51%, GPC in 37%, and fungi in 10%, while Sulgajic et al[15] have reported that bacteremia was caused by GNRs in 51% and by GPC in 44.9%.

In our Hospital, yearly percentage rate for GPC bacteremia was 49.6%, and the rate for GNR bacteremia was 45.9%. This finding was not in parallel with the reported increase in GPC bacteremia incidence in recent years. The close GNR and GPC bacteremia rates in our study might be explained by the higher frequency of GNR bacteremia noted in patients treated ICUs, GS and hematology clinics.

E. coli, K. pneumoniae, P. aeruginosa, and *A. baumannii* were the most frequently isolated bacteria in our investigation. *E. coli* was the most frequently isolated agent in GS, Emergency Surgery, Urology, Internal Medicine, and Hematology services. GNR bacteremia in ICUs constituted 39.3% of all GNR bacteremia. *K. pneumoniae* (n = 20, 8.3%), *P. aeruginosa* (n = 20, 8.3%), and *A. baumannii* (n= 19, 7.9%) were the most frequently isolated agents in ICUs. *K. pneumoniae* and CNS were reported as the most frequent agents in ICU in the study by Sulgajic et al[15]. *E. coli, K. pneumoniae*, and *P. aeruginosa* were found to be the most frequent agents in Hematology Clinic (Table I).

When we evaluated infection focus as a source of bacteremia, a focus could not be found in approximately half (44.6%) of the patients. Secondary bacteremia, pneumonia (17.7%), catheter-related infections (12.2%), and urinary tract infections (10%) were the most common foci of infection. Among secondary bacteremias, pneumonia was the most frequent source of bacteremia in patients treated in ICU and those who did not have surgical intervention, while intraabdominal infections were found to be the most frequent source of bacteremia in patients treated in non-ICU clinics and those who had surgical intervention. In the study by Sulgajic et al, the most frequent type of bacteremia was primary bacteremia, and among secondary bacteremia, pneumonia was the most frequent source of bacteremia in the ICU, and surgical site infections were the most frequent in non-ICU settings[15]. In the SCOPE study, primary bacteremia was present in 53% of the patients and secondary bacteremia in 47%. Sources of bacteremia were intravenous catheters in 24%, urinary tract in 6.5%, and respiratory tract in 6%[9].

Mortality rates are high in GNR bacteremia. Crude mortality rate of the hospitals has been reported to be 12%, and may reach 80% in ICUs[11,16,17]. Total length of stay of patients with bacteremia in ICU was 4.5-32 days, and bacteremia was increased duration of hospitalization by 7.5-25 days[11,18,19].

In a Swiss study conducted in a University hospital, GNR bacteremia was reported to have a 7-fold increase mortality rate[20]. In addition, mortality rates have been found to be high in cases of GNC bacteremia in patients admitted to ICU, and length of stay in ICU was long in these cases[20,21]. Fatality rates have also been reported to be higher in GNR bacteremia compared to GPC bacteremia[22]. In our study, 82 fatal cases were noted among 197 patients included in the study. Crude mortality rate in patients with GNR bacteremia was 1.96 in 1000 at one year and 1.29 in 1000 at 28 days. Fatality rate was 41.6 in 100. Our crude mortality rates both at one year and at 28 days were lower than those reported by previous studies.

The mean duration of fatal cases was 31.2 ± 37.9 days in our study. GNR bacteremia mortality rate in ICU was 53.3% in the study by Sligl et al[23], and the crude mortality rate was 27% in SCOPE study [9]. Risk factors for mortality have been investigated in patients with *Enterobacter* spp. bacteremia (n = 183) by Kang et al[24], and the crude mortality rate was 37% in neutropenic patients and 31% in non-neutropenic patients. Robenshtok et al[25] compared risk factors and outcome of *A. baumannii* and *K. pneumoniae* bacteremia. The mortality rate at 30 days was found to be significantly higher in *A. baumannii* bacteremia compared to *K. pneumoniae* bacteremia (61.6% vs. 38.9%, p = 0.001). Sulgajic et al[15] compared NB in patients treated in ICU and non-ICU settings, and the crude mortality rate at 28 days in ICU was 69%.

Compared to other clinics, ICUs pose significant risk for the development of nosocomial infection. While NB frequency in ICUs have been reported between 1% and 6.5%, it has been found to be 0.65% in non-ICU clinics[18,26,27]. In recent epidemiological studies, 34% of GNR bacteremia in all hospitals occurred in ICUs [28]. The number of patients treated in ICUs during a one-year period was 2,619 in our study, representing 7.2% of all hospitalized patients. NB developed in 73 of these patients. The number of patients treated in non-ICU settings was 33 841, and NB developed in 124 of these patients. Frequency results of bacteria isolated from samples of patients treated in ICUs revealed that GNR and GPC were observed in equal proportions (47.3%) in general ICU, while GNRs were detected in 58% of the cases in Emergency Surgery Intensive Care Unit (ESICU).

In our study, the time interval between hospitalization and detection of growth in blood culture showed a statistically significant difference between the mean time until development of NB in patients treated in ICU and non-ICU settings (p = 0.02). The mean time until development of *Escherichia coli, Pseudomonas aeruginosa*, and *Enterobacter* spp. bacteremia in ICU patients was shorter than in patients treated in non-ICU clinics, while the mean time until development of *K. oxytoca* bacteremia was shorter in non-ICU clinics. The shorter time duration until NB development in ICUs can be explained by several factors, such as exposure of ICU patients to high-risk procedures, past or current use of extended spectrum and/or combined antibiotic treatment, severity of underlying diseases, and frequent use of medical instruments, all of which may facilitate development of NB. In general, mean times until blood culture positivity were closer in the isolated GNRs.

A significant difference was found between the hospitalization duration of patients with GNC bacteremia treated in ICU and non-ICU clinics and patients who had surgical intervention and those who have not ($p < 0.001$). This was explained by the higher mortality rates in ICUs. Similarly, a significant difference was also found between the duration of hospitalization in patients who did and did not have surgical intervention ($p = 0.04$).

While being treated in ICU increased the mortality risk (72.6% vs. 23.4%), no statistically significant difference was found between mortality rates of patients treated in Surgical Units and Internal Medicine Units (46.9% vs. 30.7%; p =0.09). The use of beta-lactam antibiotics prior to bacteremia led to a statistically significant increase in mortality risk compared to use of other antibiotic groups ($p = 0.01$). Also, mortality risk was found to be higher in patients using combined antibiotics prior to bacteremia than those using only one antibiotic ($p = 0.003$). In our study, ESBL producing GNRs *(E. coli, K. pneumoniae, K. oxytoca)* were not found to be risk factors for mortality ($p > 0.5$). Although some studies have reported that ESBL-positive *K. pneumoniae* bacteremia did not increase mortality compared to ESBL-negative *K. pneumoniae* bacteremia, controversial studies have also been reported[29,30]. When evaluated with multivariate analysis, the mortality risk was found to be increased by NFGNC bacteremia (OR: 2.5, p = 0.04) in ICU patients (OR: 0.2, $p = 0.03$) and in patients receiving ventilatory support (OR: 20.8, p = 0.05). Numerous studies have been and are still being conducted in order to determine independent risk factors, which contribute to mortality in patients with NB.

Conclusions

NB prevalence, pathogenetic agents, and the frequency of these agents in different hospital settings should be monitored closely to provide guidance for empirical antibiotic treatment. Furthermore, efforts should concentrate on preventive measures for nosocomial infections since pneumonia, catheter-related infections, and urinary infections appear to be the most frequent causes of secondary bacteremia.

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