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Original Article

Clinical Characteristics and Risk Factors for Fatality in Patients with Bloodstream Infections Caused by Glucose Non-fermenting Gram-negative Bacilli

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BACKGROUND/PURPOSE: Glucose non-fermenting Gram-negative bacilli (GNF-GNB) bloodstream infections (BSIs) are often hospital-acquired and are important causes of morbidity and mortality. Our objectives were to evaluate the epidemiology and clinical characteristics of GNF-GNB BSIs, and to identify risk factors for fatality.

METHODS: We retrospectively reviewed cases of GNF-GNB BSIs in adult patient (≥18 years of age) hospitalized between January and December 2005.

RESULTS: A total 221 GNF-GNB bacteremic episodes (200 hospital-acquired and 21 community-acquired) in 215 patients (123 men and 92 women; mean age, 63.38±16.10 years) were included in our study. Of these, 52.5% were elderly (age>65). Malignancy (43.0%), diabetes mellitus (22.6%) and steroid use (22.6%) were the major underlying diseases/conditions. Central venous catheter (CVC) placement had been carried out in 57.5% of patients. The 28-day mortality was significantly higher in those patients with: liver cirrhosis, steroid use, pneumonia as the primary source of infection, intensive care unit-acquired infections, septic shock, and a high Pitt bacteremia score (≥4 points). Liver cirrhosis [odds ratio (OR)=6.4; 95% confidence interval (CI)=1.7–23.9; $p<0.01$)], hematologic malignancy (OR=3.9; 95% CI=1.1–14.1; $p=0.04$), pneumonia (OR=4.0; 95% CI=1.4 – 11.0; $p<0.01$), septic shock (OR=13.0; 95% CI=4.6–36.6; $p<0.01$), and intensive care unit-acquired infections (OR=2.9; 95% CI=1.1–8.0; $p=0.04$) were all independent risk factors for fatality.

CONCLUSION: Our data suggested that CVC placement and steroid use predispose to GNF-GNB bacteremia. Early removal of CVC and avoidance of steroids may minimize the chances of acquiring this infection, which is of particular importance for patients at high risk of mortality once they are infected with GNF-GNB.

KEYWORDS: bloodstream infection, clinical characteristics, fatality, glucose non-fermenting bacilli, risk factors

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Introduction

Bloodstream infections (BSIs) caused by Gram-negative bacilli (GNB) are reported to constitute approximately 50% of nosocomial BSIs.[1] These GNB comprise members of the Enterobacteriaceae family and glucose non-fermenting Gram-negative bacilli (GNF-GNB). GNF-GNB may include *Pseudomonas aeruginosa* and other *Pseudomonas* species, *Acinetobacter* spp., *Stenotrophomonas maltophilia*, *Alcaligenes* spp., *Flavimonas oryzihabitans*, and *Sphingobacterium* spp. etc.[2–4] It is notable that *P. aeruginosa* is one of the most prevalent pathogens in nosocomial BSIs.[2,3] These pathogenic GNF-GNB are characterized by their resistance to multiple antibiotics and often contaminate the hospital environment, medical equipment and the skin of healthcare workers. They often cause infections in seriously ill hospitalized patients, resulting in a high mortality rate among these patients.[5,6] To better understand the risk factors for acquisition of GNF-GNB bacteremia and the outcomes for the affected patients, this study was designed to investigate the epidemiology and clinical characteristics of GNF-GNB BSIs, and to identify risk factor(s) for fatality in infected patients.

Methods

We performed a retrospective study in adult patients (≥ 18 years of age) admitted to Chang Gung Memorial Hospital Kaohsiung (CGMH-KS) between January and December 2005. CGMH-KS is a 2,500-bed primary care and tertiary referral center in Southern Taiwan. The patients with GNF-GNB BSIs included in the study were chosen from the computerized database of the hospital's clinical microbiology laboratory. A repeated GNF-GNB bacteremia that occurred more than 2 weeks apart from the previous one was regarded as a new GNF-GNB bacteremia. The medical charts of patients were reviewed and demographic, clinical and laboratory information were collected.

The bacteremia was defined as hospital-acquired if it occurred 72 hours or more after admission, and/or if the affected patient had been hospitalized in the 2 weeks before the current admission. Intensive care unit (ICU)-acquired bacteremia was defined as occurring 72 hours or more after admission to the ICU. Any case in which additional microbes other than GNF-GNB were isolated from blood cultures was regarded as a polymicrobial bacteremia. The source of the BSI in each patient was determined on a clinical basis. Sources of BSI such as lung, urinary tract, biliary tract and intra-abdominal were defined as previously described.[7] A case was regarded as a primary bacteremia when no overt infection focus other than the bloodstream was identified. Catheter-related bacteremia was defined as isolation of the same organism from blood cultures and from semiquantitative cultures of a catheter segment (> 15 CFU/tip culture), accompanied by the clinical syndrome of bloodstream infection in the absence any other apparent source.[8] Renal failure was defined as a serum creatinine level > 2.0 mg/dL, or levels similar to those of a patient receiving regular hemodialysis. Diabetes mellitus was defined by one of the following criteria: (1) random plasma glucose level > 200 mg/dL; (2) plasma glucose of 126 mg/dL, or greater after overnight fast on recovery from sepsis; and (3) being previously diagnosed as a diabetic and taking oral anti-diabetic agents, or receiving insulin injections. Hematological malignancy was defined as lymphoma, acute or chronic leukemia, or multiple myeloma diagnosed by a hematologist. The Pitt bacteremia score was used to assess the illness severity of patients,[9,10] and was calculated according to the following criteria: (1) oral temperature: 2 points for a temperature of ≤ 35°C or ≥ 40°C, 1 point for a temperature 35.1–36.0°C or 39.0–39.9°C; (2) hypotension: 2 points for an acute hypotensive event with decreases in systolic (> 30 mmHg) and diastolic (> 20 mmHg) blood pressure, the use of intravenous vasopressor agents, or systolic blood pressure < 90 mmHg; (3) receipt of mechanical ventilation: 2 points; (4) cardiac arrest: 4 points; and (5) mental status: alert, 0 points; disoriented, 1 point; stuporous, 2 points; and comatose, 4 points. Critical illness was defined as a Pitt bacteremia score of ≥ 4 points.[9] Antibiotic therapy, started on an empirical basis upon suspicion of sepsis, was considered appropriate if the pathogen grown from blood cultures was susceptible *in vitro* to the prescribed antimicrobial agent(s), and was started within 48 hours after the blood was sampled for culture. Antibiotic therapy was regarded as effective if treatment with the appropriate antimicrobial(s) was carried out for at least 1 week. Steroid use was defined as use of prednisolone (≥ 10 mg/day), or other equivalent steroid, for at least 2 weeks before the development of

bacteremia. The endpoint for the assessment of fatality was death within 28 days of developing a GNF-GNB bacteremia. A fatality was considered to be directly related GNF-GNB-bacteremia if the case involved a patient who died of unrelenting sepsis within 28 days after his or her blood had been sampled for culture, and GNF-GNB was isolated from that culture.

The protocols for sampling blood for culture in patients suspected of having bacteremia and the general handling of blood specimens within CGMH-KS follows: Briefly, at least two blood samples were drawn (approximately 8 mL) into a Plus Aerobic/F bottle and a Standard Anaerobic/F bottle (as monitored by the BACTEC 9240 instrument; Becton-Dickinson Microbiology System, Becton Dickinson, MD, USA). The bottles were then incubated at 35°C. Cultures were regarded as negative if no bacterial growth had occurred within 7 days. GNF-GNB was identified using standard methods[11] and was verified using the automated ID 32GN System (BioMérieux, Vitek, Hazelwood, MO, USA). Antimicrobial susceptibility testing was performed on a clinical service basis using the disk diffusion method, and using interpretative criteria for non-fermentative Gram-negative rods.[12]

Patients were divided into non-fatal and fatal groups. The Student's *t* test or the Mann-Whitney *U* test was used for comparison of continuous variables, and the χ^2 test or Fisher's exact test was used for comparison of dichotomous variables when analyzing the differences between variables in patients with hospital-acquired and community-acquired GNF-GNB bacteremia, as well as the differences between variables in patients in the non-fatal and fatal groups. Differences between the non-fatal and fatal groups with a p value < 0.1 were entered into a logistic regression model to determine the independent factor(s) for fatality. A p value of < 0.05 was considered to be statistically significant. All statistical analyses were performed using the SPSS version 13.0 (SPSS Inc., Chicago, IL, USA).

Results

A total 221 GNF-GNB bacteremic episodes (200 hospital-acquired and 21 community-acquired) in 215 patients (123 men and 92 women; mean age, 63.38 ± 16.10 years) were included in the study. As shown in the Figure,

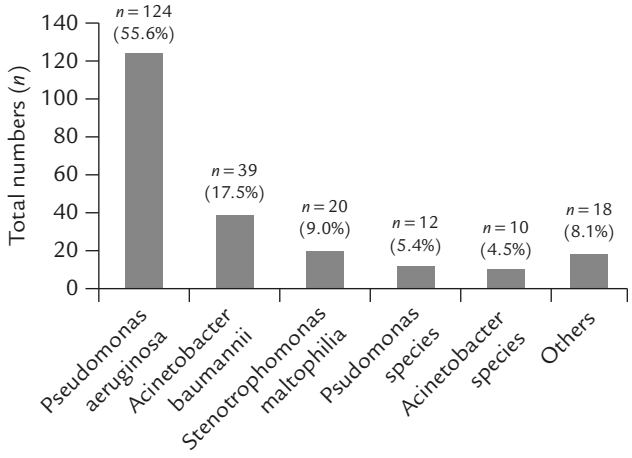

Figure. Glucose non-fermenting Gram-negative bacilli found in 221 bacteremic episodes. Others included *Schewanella* species ($n = 3$), *Sphingobacterium* species ($n = 1$), *Brevudimonas* species ($n = 1$), *Chryseomonas* species ($n = 2$) and unidentified species ($n = 11$).

the three most commonly isolated GNF-GNB organisms were *P. aeruginosa* (124 episodes; 55.6%), *A. baumannii* (39 episodes; 17.5%), and *S. maltophilia* (20 episodes, 9.0%). Of the 221 cases of GNF-GNB bacteremia, 62 were polymicrobial, the concurrent pathogens being Enterobacteriaceae ($n = 40$), staphylococci ($n = 17$), enterococci ($n = 8$), streptococci ($n = 5$) and anaerobes ($n = 4$). Of the 40 cases of co-infection with Enterobacteriaceae, *Escherichia coli* ($n = 14$) and *Klebsiella pneumoniae* ($n = 7$) were the most common.

The demographic and clinical characteristics of the patients infected with GNF-GNB bacteremic are summarized in Table 1. The three most common underlying diseases/conditions were solid tumors (71/221; 32.1%), diabetes mellitus (50/221; 22.6%), and steroid use (50/221; 22.6%). Of the 200 hospital-acquired GNF-GNB bacteremic episodes, 85 (42.5%) occurred in ICU (ICU-acquired). Regarding the use of invasive procedures; 127/221 (57.5%) episodes had a central venous catheter (CVC) placement when bacteremia developed. The three most frequently encountered infection sources among the 221 GNF-GNB bacteremic episodes were lung ($n = 49$; 22.2%), urinary tract ($n = 33$; 14.9%) and biliary tract ($n = 25$; 11.3%). Of the 221 GNF-GNB infections included in the study, there were 79 (35.7%) episodes in which the affected patients were found to be critically ill (Pitt bacteremia score ≥ 4), and there were 56 (25.3%) episodes of septic shock.

Eighty patients died, giving an overall mortality rate of 36.2%. Fifty-seven (25.8%) of the fatalities were directly

Table 1. Demographic and clinical characteristics of 221 episodes of glucose non-fermenting Gram-negative bacillus bacteremia[a]

Variable	Total (n=221)	Hospital-acquired (n=200)	Community-acquired (n=21)
Age (yr)			
18–45	31 (14.0)	29 (14.5)	2 (9.5)
46–55	33 (14.9)	29 (14.5)	4 (19.0)
56–65	41 (18.6)	38 (19.0)	3 (14.3)
>65	116 (52.5)	104 (52.0)	12 (57.1)
Underlying disease/condition			
Diabetes mellitus	50 (22.6)	46 (23.0)	4 (19.0)
Liver cirrhosis	21 (9.5)	20 (10.0)	1 (4.8)
Renal failure	32 (14.5)	30 (15.0)	2 (9.5)
Solid tumor	71 (32.1)	64 (32.0)	7 (33.3)
Hematologic malignancy	24 (10.9)	23 (11.5)	1 (4.8)
Neutropenia	16 (7.2)	14 (7.0)	2 (9.5)
Steroid use	50 (22.6)	50 (25.0)	0 (0)
Organ transplant	3 (1.4)	3 (1.5)	0 (0)
CVC placement	127 (57.5)	127 (63.5)	0 (0)
Infection source			
Pneumonia	49 (22.2)	45 (22.5)	4 (19.0)
Urinary tract infection	33 (14.9)	27 (13.5)	6 (28.6)
CVC-related infection	22 (10.0)	22 (11.0)	0 (0)
Biliary tract infection	25 (11.3)	23 (11.5)	2 (9.5)
Intra-abdominal infection	14 (6.3)	11 (5.5)	3 (14.3)
Surgical site infection	8 (3.6)	7 (3.5)	1 (4.8)
CNS infection	1 (0.5)	1 (0.5)	0 (0)
Primary bacteremia	62 (28.1)	58 (29.0)	4 (19.0)

[a]Data presented as *n* (%) and one patient might have more than one underlying disease/condition. CNS=Central nervous system; CVC=central venous catheter.

related to GNF-GNB bacteremia. Twenty-three deaths were not considered to be directly related to GNF-GNB bacteremia, but to other events such as massive active gastrointestinal bleeding, hemoptysis, progressive intracranial hemorrhage or the development of sepsis caused by other pathogens after effective therapy for GNF-GNB bacteremia initially yielded an apparent clinical improvement. Comparisons between the 114 patients who survived and the 57 patients who died from GNF-GNB bacteremia are summarized in Table 2. Patients in the fatal group had a significantly higher proportion of liver cirrhosis (17.5% *vs.* 5.7%; p=0.01), steroid use (38.6% *vs.* 17.0%; p<0.02), GNF-GNB bacteremia secondary to pneumonia (38.6% *vs.* 12.1%; p<0.01), ICU-acquired GNF-GNB bacteremia (50.9% *vs.* 31.9%; p=0.02), septic shock (59.6% *vs.* 9.9%; p<0.01) and a Pitt bacteremia score ≥4 points (49.1% *vs.* 22.7%; p<0.01) compared with those in the non-fatal group. In contrast, patients in the non-fatal group had a significantly higher incidence of GNF-GNB bacteremia secondary to urinary tract infections (19.9% *vs.* 5.3%; p<0.01) compared with those in the fatal group. Notably, no significant differences were found in the number of polymicrobial bacteremia cases, or the administration of inappropriate empirical antibiotic therapy, between the non-fatal and fatal groups. Also, there was no significant differences in the causative agent; *P. aeruginosa*, *A. baumannii*, or *S. maltophilia*. Logistic regression showed that liver cirrhosis (OR=6.4; 95% CI=1.7–23.9; p<0.01), hematologic malignancy (OR=3.9; 95% CI=1.1–14.1; p=0.04), pneumonia as the primary source of infection (OR=4.0; 95% CI=1.4–11.0; p<0.01), septic shock (OR=13.0; 95% CI=4.6–36.6; p<0.01) and ICU-acquired infection (OR=2.9; 95% CI=1.1–8.0; p=0.04)

Table 2. Demographic and clinical information of patients involving 198 glucose non-fermenting Gram-negative bacillus bacteremic episodes[a]

Variable	Non-fatal (n=141)	Fatal (n=57)	p
Age (yr)	63.2±16.8	62.7±15.6	0.84
Sex, male	72 (51.1)	39 (68.4)	0.03
Underlying disease/condition			
Diabetes mellitus	34 (24.1)	11 (19.3)	0.58
Liver cirrhosis	8 (5.7)	10 (17.5)	0.01
Renal failure	20 (14.2)	10 (17.5)	0.66
Solid tumor	37 (24.2)	23 (40.4)	0.06
Hematologic malignancy	13 (9.2)	10 (17.5)	0.14
Neutropenia	9 (6.4)	6 (10.5)	0.38
Steroids use	24 (17.0)	22 (38.6)	<0.02
Organ transplant	1 (0.7)	1 (1.8)	0.45
Infection source			
Pneumonia	17 (12.1)	22 (38.6)	<0.01
Urinary tract infection	28 (19.9)	3 (5.3)	<0.01
CVC-related infection	18 (12.8)	3 (5.3)	0.14
Biliary tract infection	20 (14.2)	4 (7.0)	0.23
Intra-abdominal infection	7 (5.0)	6 (10.5)	0.20
Surgical site infection	7 (5.0)	1 (1.8)	0.44
CNS infection	1 (0.7)	0 (0)	1.00
Primary bacteremia	38 (27.0)	17 (29.8)	0.73
Nosocomial bacteremia	123/200 (61.5)	55/200 (27.5)	0.07
Shock when bacteremia	14 (9.9)	34 (59.6)	<0.01
Pitt bacteremia score	2.0±2.5	4.7±3.1	<0.01
Pitt bacteremia score ≥4	32 (22.7)	28 (49.1)	<0.01
ICU-acquired infection	45 (31.9)	29 (50.9)	0.02
Inappropriate empirical antimicrobial therapy	96 (68.1)	34 (59.6)	0.32
Polymicrobial infection	40 (28.4)	16 (28.1)	1.00
Pseudomonas aeruginosa	76/115 (66.1)	39/115 (33.9)	0.08
Acinetobacter baumannii	24/35 (68.6)	11/35 (31.4)	0.69
Stenotrophomonas maltophilia	11/16 (68.7)	5/16 (31.3)	0.82

[a]Data presented as mean±standard deviation, n (%) or number of positive cases/total cases examined (%). CNS=Central nervous system; CVC=central venous catheter; ICU=intensive care unit.

were all independent risk factors for fatality in patients with GNF-GNB bacteremia.

Discussion

The incidence of GNF-GNB bacteremia in general and that caused by different GNF-GNB species in particular, varies from one hospital to another.[1,13–15] Consistent with a previous report,[13] *P. aeruginosa* was the most commonly encountered cause of BSI in CGMH-KS.

Our data show that GNF-GNB BSI may develop in patients of all ages, with a higher incidence in elderly patients (age>65 years) (Table 1). In agreement with previous reports,[16–18] the most frequently seen underlying diseases/conditions in patients with GNF-GNB BSI were solid tumors and steroid use. Although CVC-related

GNF-GNB BSI is not uncommon,[19,20] the incidence of CVC-related GNF-GNB BSI in this study was remarkably low compared with other reports.[21] CVC-related GNF-GNB BSI may, therefore, have been under diagnosed at our institute, and further study is needed to clarify this; indeed, if this was the case, upon encountering a patient with BSIs due to GNF-GNB and skin flora alike (e.g. coagulase-negative staphylococci), a careful evaluation is needed to determine whether or not that indwelling CVC should be removed.

Similar to other reports,[2,22] *P. aeruginosa* was the most common GNF-GNB pathogen causing BSIs and was often nosocomially-acquired. A high mortality rate (>33.9%) in patients with *P. aeruginosa* BSIs has been previously reported.[22] In general, the use of antimicrobial regimens lacking activity against the pathogenic microbes in critically ill patients is associated with greater hospital mortality.[23–25] It has also been reported that inappropriate empirical antimicrobial therapy for BSIs specifically caused by *P. aeruginosa* leads to a significantly higher mortality rate and is an independent predictor of hospital mortality.[26] However, this was not the case for empirical antimicrobial therapy for BSIs caused by GNF-GNB other than *P. aeruginosa*.[21] Multi-drug resistance is not uncommon among GNF-GNB, and may result from either intrinsic resistance and/or rapidly acquired resistance after antimicrobial exposure.[5,6] Consequently, it is not unusual for patients with GNF-GNB BSI to be given inappropriate antibiotic(s) prescribed on an empirical basis before the pathogen is identified by culture tests.[27] Therefore, it is very important to carefully tailor antibiotic therapy for GNF-GNB BSI based on susceptibility testing, and to identify the particular risk factors for fatality in this patient population.

Being a retrospective study, some limitations must to be addressed. First, the collection of specimens for culture was not based on a standardized protocol, resulting in some missing data (e.g. some CVC tips were not sent for culture), which may bias our assessment of the risk factors for acquisition of GNF-GNB bacteremia. Second, the patients with GNF-GNB BSIs were not subject to standardized treatments, which may have affected the final outcome.

Independent risk factors for fatality in GNF-GNB bacteremia found in this series included liver cirrhosis, hematologic malignancy, pneumonia, septic shock and ICU-acquired infections. They were reflective of the underlying immunocompromise, and/or clinical severity of the affected patients,[21] leading to substantial mortality. Because CVC placement and steroid use were found to predispose to GNF-GNB bacteremia, early removal of CVC and avoidance of steroid use may minimize acquisition of this infection, which is of particular importance in those patients at high risk for mortality once infected with GNF-GNB.

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