Journal of Microbiology, Immunology and Infection (2015) 48, 92–100

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ORIGINAL ARTICLE

Clinical impact of Gram-negative nonfermenters on adults with community-onset bacteremia in the emergency department

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Received 26 April 2013; received in revised form 10 July 2013; accepted 8 August 2013
Available online 21 September 2013

KEYWORDS
Bacteremia;
Emergency department;
Gram-negative nonfermenters

Background: To determine clinical predictors and impact of Gram-negative nonfermenters (GNNFs) infections among adults with community-onset bacteremia in the emergency department (ED).
Methods: Adults with bacteremia visiting the ED from January 2007 to June 2008 were identified retrospectively. Demographic characteristics, underlying illnesses, clinical conditions, bacteremic pathogens, antimicrobial agents, and outcome, were retrieved from chart records.
Results: After the exclusion of 261 patients with contamination of blood cultures and 24 patients referred from other hospitals, 518 adults with community-onset bacteremia were eligible; their mean age was 65.1 years, with slight predominance of female (262 patients, 50.6%). Of a total of 565 bacteremic isolates, *Escherichia coli* (228 isolates, 40.4%) and *Klebsiella pneumoniae* (100, 17.7%) were the major microorganisms. GNNFs caused bacteremia in 31 (6.0%) patients. A higher proportion of inappropriate antibiotic therapy in the ED (87.1% vs. 26.5%, $p < 0.001$) and higher 28-day crude mortality rate (19.4% vs. 8.4%, $p = 0.05$) were observed in bacteremic patients caused by GNNFs than those not caused by GNNFs. In further analysis of Kaplan–Meier survival curve, patients with GNNF bacteremia had a worse outcome than those due to other pathogens ($p = 0.04$). Multivariate analysis revealed that the independent predictors related to GNNF bacteremia included surgery during previous 4 weeks prior to

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http://dx.doi.org/10.1016/j.jmii.2013.08.004

ED arrival [odds ratio (OR), 10.79; 95% confidence interval (CI), 1.84–63.24; $p = 0.01$], residents in long-term healthcare facilities (OR, 4.62; 95% CI, 2.08–10.29; $p < 0.001$), and malignancy (OR, 2.24; 95% CI, 1.10–5.40; $p = 0.02$).
Conclusion: For adults with bacteremia visiting the ED, GNNF is associated with a higher mortality rate and more inappropriate empirical antibiotic therapy in the ED. To allow early administration of empirical antibiotics, several clinical predictors of GNNF infections were identified.

Introduction

Bacteremia is a serious life-threatening condition and is associated with significant healthcare costs and mortality, with a case-fatality rate as high as 30%.[1,2] Bacteremia is also a common and deadly problem in patients visiting emergency departments (EDs).[3] Early administration of appropriate empirical antibiotics has been shown repeatedly to decrease the mortality in patients with community-acquired infections.[1,4,5]

Gram-negative nonfermenters (GNNFs) are classified as aerobic microorganisms that are incapable of utilizing carbohydrates as a source of energy or degrade them via an oxidative rather than fermentative pathway.[6] Of GNNFs, *Pseudomonas aeruginosa* is the most important pathogen and other members include diverse genera, such as *Acinetobacter*, *Alcaligenes*, *Burkholderia*, *Chryseobacterium*, *Flavimonas*, and *Weeksiella*.[7] These organisms are naturally *in vitro* resistant to commonly used antimicrobial agents, such as penicillin, aminopenicillins, and first or second generation cephalosporins, and are increasingly important opportunistic pathogens in immunocompromised hosts.[7,8] These infections have been increasingly reported and result in a high mortality rate among these patients.[9–15]

Focusing on *P. aeruginosa* or *Acinetobacter baumannii* bacteremia, the most prevalent GNNF in USA and Taiwan,[6,9,15] several investigations also demonstrated that the delay in initiation of effective treatment would be associated with adverse outcomes.[16–20] Community-acquired bacteremia caused by these microorganisms had been also reported in recent years.[9,15,19,21,22] It is not surprising that the appropriate antibiotics for community-onset GNNF infections are dissimilar to those for common community-onset pathogens (i.e., *Escherichia coli*, *Klebsiella pneumoniae*, staphylococci, and streptococci). However, no clinical predictors of GNNFs in patients with community-onset bacteremia have been recognized to assist the ED clinicians. This led us to conduct this study to compare the clinical characteristics and outcomes of patients with GNNF bacteremia and those infected by other pathogens and to determine clinical predictors for GNNF infections in bacteremic adults who visited the ED.

Methods

Study design

This retrospective study was conducted at a teaching hospital of approximately 1000 beds in southern Taiwan, and there were approximately 65,000 annual visits to the ED during the study period. The local institutional review board approved this study.

Study setting and protocol

The records of adult patients (age $\geq$ 18 years) who visited the ED between January 2007 and June 2008 with a positive blood culture were included. Patients with contaminated blood cultures or the identification of bacteremia prior to visiting the ED and those transferred from other hospitals were excluded.

The medical records of adults visiting the ED with bacteremia were reviewed. Clinical characteristics, vital signs, Pittsburgh bacteremia severity scores, comorbidities, initial syndrome, and laboratory data, were collected after each patient's visit to the ED. At that time, the duration and type of antimicrobial agent administration in the ED, microbiological results, source of bacteremia, further hospitalization, and length of stay were derived from the chart records. Moreover, recent events during the 4 weeks prior to ED arrival, including hospitalizations, prior antimicrobial use, invasive procedures, and/or surgery performed, were also recorded as a previous report.[23] Multiple bacteremic episodes in a single patient were considered to be distinct episodes, if separated by at least 7 days or if there were different causes for the ED visits.

The primary outcome was the 28-day mortality after ED arrival. If patients were discharged within 28 days after ED arrival and were not followed-up at our hospital, the required information was retrieved by telephone interview. The patients who could not be reached by telephone were excluded.

Microbiologic studies

Nurses collected two sets of blood cultures from different peripheral veins or arteries within 30 minutes. Each set of blood cultures routinely consisted of one bottle for aerobic culture and another for anaerobic culture, with 5–8 mL of blood/bottle. The culture bottles were immediately transported to the clinical microbiology laboratory, loaded into the BACTEC 9240 system (Becton Dickinson and Company, Franklin Lakes, NJ, USA), and incubated for 5 days or until the system indicated bacterial growth. Culture bottles that had bacterial growth were Gram-stained, and the contents of the bottles were subcultured onto plates with blood agar (Trypticase soy agar II 5% sheep blood; Becton Dickinson), Levine eosin–methylene blue agar (Becton Dickinson and Company), chocolate agar, and Centers for Disease Control and Prevention (CDC) anaerobic blood agar (Becton Dickinson and

Company) for further identification. Biochemical tests and automatic identification systems were used for final identification. *In vitro* antimicrobial susceptibility of blood isolates were studied by the Kirby—Bauer method on Mueller—Hinton agar, and was interpreted according to the Clinical Laboratory Standard Institute guidelines.[24]

Definitions

Polymicrobial bacteremia was defined as the isolation of more than one microbial species from each bacteremic episode. A polymicrobial culture with a mixture of GNNF and non-GNNF pathogen was regard as a GNNF episode. Community-onset bacteremia indicates that the place of onset of the bacteremic episode is the community, including long-term healthcare facility (LTHCF)-acquired and community-acquired bacteremia, as previously described.[25] Therefore, patients transferred from the hospital-associated LTHCF or other hospitals were not enrolled in our populations. Appropriate antimicrobial therapy was defined as the use of a drug to which the isolated pathogen was *in vitro* susceptible, and inappropriate antimicrobial therapy as a drug to which the isolated pathogen was *in vitro* nonsusceptible or no administration of any antibiotic in the ED. If, for a patient, there was administration of more than one drug of the same class, we counted the drug used longer as the prescribed antibiotic. The severity of bloodstream infection at the time of onset would be measured by the Pittsburgh bacteremia score, a validated scoring system based on vital signs, mental status, mechanical ventilation, and the presence of cardiac arrest.[26] Malignancy refers to hematological malignancies or solid tumors. The definitions of comorbidities were as previously described.[27] The growth of coagulase-negative staphylococci, *Propionibacterium acnes*, *Micrococcus*, *Bacillus*, or *Peptostreptococcus* in the blood culture bottle, will be regarded as contaminated, according to the previously described criteria.[28] The sources of bacteremia were regarded to be low respiratory tract infections, urinary tract infections, wound infections, skin and soft-tissue infections, intra-abdominal infections, or primary bloodstream infections according to the definitions of the CDC.[29]

Data analysis

Statistical analyses were performed using SPSS for Windows, Version 15.0 (SPSS, Chicago, IL, USA). Continuous variables are expressed as mean ± standard deviations and were compared by the Student *t* test. Categorical variables, expressed as numbers and percentages, are compared by the Chi-square test or Fisher exact test. Kaplan—Meier survival curves was performed for the different duration of survival after the onset of bacteremia between patient due to GNNF and those to non-GNNF. All variables with $p < 0.1$ in the univariate analysis are contributory by means of a Cox regression model with a backward deletion algorithm to develop the risk factors of 28-day mortality and clinical predictors of GNNF infections. A p value < 0.05 is considered statistically significant.

Results

Demographics and clinical characteristics of adults with bacteremia

During the 18-month study period, there were blood culture samples from 19,308 patients. There were 518 (2.6%) eligible adults visiting the ED with clinically significant bacteremia (i.e., true bacteremia), as shown in Fig. 1. Most (403, 77.8%)

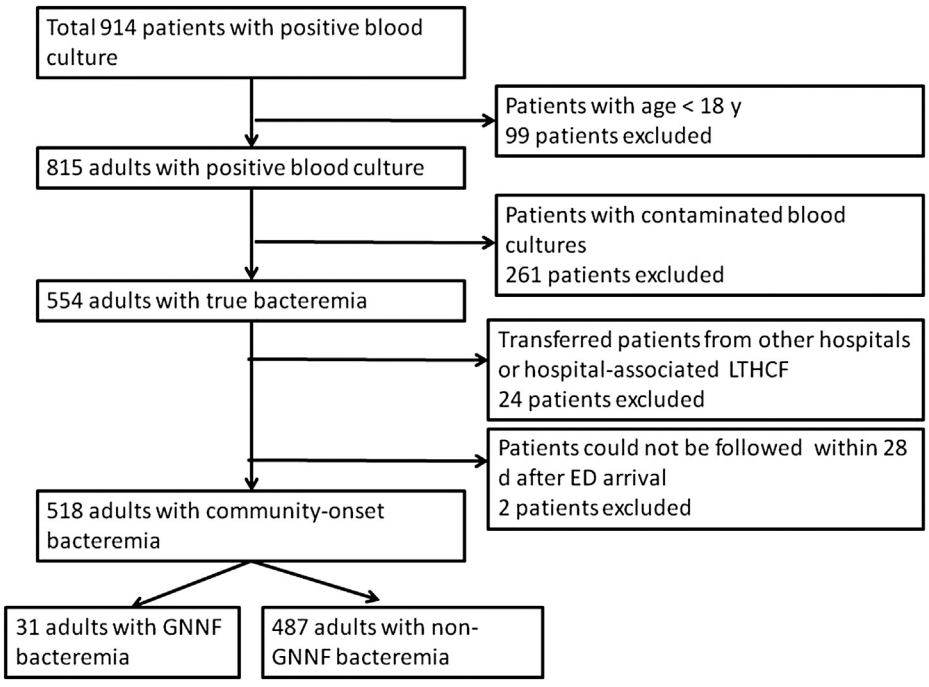

Figure 1. Flowchart of patient enrollment. GNNF = Gram-negative nonfermenters; LTHCF = long-term healthcare facilities.

patients came from the community, 78 (15.1%) from LTHCFs, and 37 (7.1%) were transferred from the EDs of the other hospitals. Their mean age was 65.1 years, and 262 (50.6%) were females. Major comorbidities were cardiovascular diseases (259 patients, 50.6%), diabetes mellitus (190 patients, 36.7%), malignancy (112 patients, 21.6%), chronic renal insufficiency (85 patients, 16.4%), liver cirrhosis (69 patients, 13.3%), old stroke (34 patients, 6.6%), and chronic pulmonary diseases (24 patients, 4.6%), as shown in Table 1.

In our population, 365 patients (70.5%) were subsequently admitted to general wards, and 68 patients (13.1%) to the intensive care units (ICU), whereas 10 patients (1.9%) were transferred to other hospitals. Fourteen patients had recent invasive procedures within 4 weeks prior to ED arrival, and endoscope was the major procedure (9 patients, 1.7%), followed by bronchoscopy (4 patients, 0.8%), and cystoscopy (1 patient, 0.2%), whereas eight patients had recent surgery, mainly abdominal operation (4 patients, 0.8%). Fourteen patients died in the ED and 37 patients died after admission. None died after discharge from the ED or after being transferred to other hospitals. Therefore, the 28-day mortality rate was 9.1% (47 patients) and the crude mortality 9.8% (51 patients).

Clinical predictors of GNNF bacteremia

To determinate clinical predictors of GNNF bacteremia in the ED, the univariate analysis compared the ED variables of patients with GNNF bacteremia and those infected by pathogens other than GNNFs. The concerned variables included patients' characteristics, events prior to the ED, initial presentations, the place of disease onset, comorbidities, and laboratory parameters, as shown in Table 1. Patients with a recent surgical (9.7% vs. 1.0%, $p = 0.009$) or invasive procedure (9.7% vs. 2.3%, $p = 0.04$), recent hospitalization within the past 4 week (35.5% vs. 15.6%, $p = 0.004$), underlying malignancy (41.9% vs. 20.3%, $p = 0.005$), or residents in LTHCF (45.2% vs. 13.1%, $p < 0.001$), were more likely to have GNNFs bacteremia. However, patients with leukocytosis ($>9.0 \times 10^9$ cells/L; 53.5% vs. 65.3%; $p = 0.009$) or hypoalbuminemia (<3.5 g/dL; 40.0% vs. 65.9%, $p = 0.006$) were less likely to have GNNF infections. In a multivariate analysis of these data (Table 1), three factors independently associated with GNNF bacteremia were recent surgery [odds ratio (OR) 10.79; 95% confidence interval (CI), 1.84–63.24; $p = 0.006$], residents in LTHCF (OR, 4.62; 95% CI, 2.08–10.29; $p < 0.001$), and underlying malignancy (OR, 2.24; 95% CI, 1.10–5.40; $p = 0.02$).

Table 1 Clinical characteristics, comorbidities, initial syndrome, and laboratory parameters of adults with or without Gram-negative nonfermenters (GNNF) bacteremia in the emergency department

Clinical variables	GNNF bacteremia, patient number (%)		Total patient number (%), $n = 518$	p[a]
	Yes, $n = 31$	No, $n = 487$		
Old age, ≥ 65 y	16 (51.6)	272 (55.9)	288 (55.6)	0.64
Female	11 (35.5)	251 (51.5)	262 (50.6)	0.08
Recent events within the past 4 weeks				
Hospitalization	11 (35.5)	76 (15.6)	87 (16.8)	0.004
Invasive procedures	3 (9.7)	11 (2.3)	14 (2.7)	0.04
Surgery	3 (9.7)	5 (1.0)	8 (1.5)	0.009
Residents in LTHCF	14 (45.2)	64 (13.1)	78 (15.1)	<0.001
Initial presentation in the ED				
Sepsis	21 (67.7)	311 (63.9)	332 (62.2)	0.66
Febrile neutropenia	2 (6.5)	5 (1.0)	7 (1.4)	0.06
Comorbidities				
Cardiovascular diseases	17 (54.8)	242 (49.7)	259 (50.0)	0.57
Diabetes mellitus	7 (22.6)	183 (37.6)	190 (36.7)	0.09
Malignancy	13 (41.9)	99 (20.3)	112 (21.6)	0.005
Chronic renal insufficiency	5 (16.1)	80 (16.4)	85 (16.4)	>0.99
Liver cirrhosis	1 (3.2)	68 (14.0)	69 (13.3)	0.10
Old stroke	0 (0)	34 (6.9)	34 (6.6)	0.25
Chronic pulmonary diseases	0 (0)	24 (4.9)	24 (4.6)	0.38
Laboratory abnormalities in the ED[b]				
Leukocytes $> 9 \times 10^9$/L	16/30 (53.3)	314/481 (65.3)	330/511 (64.5)	0.009
Platelets $< 100 \times 10^9$/L	3/29 (10.3)	85/476 (17.9)	88/505 (17.4)	0.30
Blood urea nitrogen $>$ 20 mg/dL	17/29 (58.6)	265/474 (55.9)	282/503 (56.1)	0.77
Serum creatinine $>$ 1.5 mg/dL	11/29 (37.9)	143/478 (30.0)	154/507 (30.4)	0.36
C-reactive protein $>$ 100 mg/L	9/29 (31.0)	167/443 (37.7)	176/472 (37.3)	0.47
Glucose $>$ 200 mg/dL	7/25 (28.0)	129/421 (30.6)	136/446 (30.5)	0.78
Serum albumin $<$ 3.5 g/dL	4/10 (40.0)	85/129 (65.9)	89/139 (64.0)	0.006

[a] Comparison of variables between bacteremic adults infected by GNNF and those by other pathogens in univariate analysis.
[b] Not all patients had the indicated laboratory data.
ED = emergency department; LTHCF = long-term healthcare facilities.

Microbiological analysis

Table 2 reveals the total of 565 isolates in 518 patients with true bacteremia, with a predominance of Gram-negative aerobes (406 isolates, 71.9%). The family *Enterobacteriaceae* (364 isolates, 64.4%) played a major role; and *E. coli* (228, 40.4%) and *Klebsiella* species (100, 17.6%) were the major pathogens. The isolates with extended-spectrum β-lactamase producers accounting for 5.2% (12 isolates) and 9.0% (9 isolates) respectively were discovered in *E. coli* and *Klebsiella* species. *Staphylococci* (68 isolates, 12.0%) and *Streptococci* (69, 12.2%) were the major Gram-positive aerobes, and methicillin-resistant *S. aureus* account for 42.6% of *S. aureus*. Only seven anaerobes (*Clostridium* species, 4 isolates; 3 *Bacteroides* species) were discovered in our population. Of note, the distribution of bacteremic isolates in the monomicrobial and polymicrobial episode was similar.

Of 31 GNNF isolates, *P. aeruginosa* (16 isolates, 51.6%) was the most common pathogen, followed by *Acinetobacter* species (6 isolates, 19.4%), *Burkholderia pseudomallei* (3 isolates, 9.7%), *Burkholderia cepacia* (2 isolates, 6.5%) *Chryseobacterium* species (2 isolates, 6.5%), *Flavimonas oryzihabitans* (1 isolates, 3.2%), and *Weeksella virosa* (1 isolates, 3.2%). Notably, of 31 episodes of GNNF bacteremia, 14 (45.2%) were noted in patients from LTHCF and seven (22.5%) were polymicrobial infections. In *in vitro* susceptibility analysis of 31 GNNF bacteremic isolates, > 90% were susceptible to cefepime (96.7%), imipenem (93.5%), ceftazidime (90.3%), or piperacillin/tazobactam (90.3%). Fewer isolates were susceptible to ciprofloxacin (80.6%), amikacin (83.8%), or piperacillin (87.1%).

Clinical outcome and antibiotic therapy of GNNF bacteremia

The association of severity in the ED, subsequent hospitalization, length of hospital stay, source of bacteremia, antibiotic therapy in the ED, and clinical outcome was assessed in the univariate analysis (Table 3). More polymicrobial infections (22.6% vs. 7.8%, $p = 0.01$), vascular catheter-related bloodstream infections (16.1% vs. 8.2%, $p = 0.003$), intensive care unit (ICU) admissions (29.0% vs. 12.1%, $p = 0.01$), and the receipt of inappropriate antimicrobial therapy in the ED

Table 2 The distribution of 565 isolates in 513 patients with community-onset bacteremia

Bacteremic isolates	Number of bacteremic isolates (%)		
	Total, $n = 565$	Monomicrobial, $n = 450$	Polymicrobial, $n = 115$
Gram-negative aerobes	406 (71.9)	325 (72.2)	81 (70.4)
Enterobacteriaceae	364 (64.4)	293 (65.1)	71 (61.7)
Escherichia coli	228 (40.4)	186 (41.3)	42 (36.5)
Klebsiella species	100 (17.7)	78 (17.3)	22 (19.1)
Enterobacter cloacae	14 (2.5)	10 (2.2)	4 (3.5)
Proteus species	12 (2.1)	9 (2.0)	3 (2.6)
Salmonella enteritidis	3 (0.5)	3 (0.6)	0 (0)
Citrobacter species	3 (0.5)	3 (0.6)	0 (0)
Serratia marcescens	2 (0.4)	2 (0.4)	0 (0)
Morganella morganii	2 (0.4)	2 (0.4)	0 (0)
Glucose nonfermenters	31 (5.5)	24 (5.3)	7 (6.1)
Pseudomonas aeruginosa	16 (2.8)	11 (2.4)	5 (4.3)
Acinetobacter species	6 (1.1)	4 (0.8)	2 (1.7)
Burkholderia pseudomallei	3 (0.5)	3 (0.6)	0 (0)
Burkholderia cepacia	2 (0.4)	2 (0.4)	0 (0)
Chryseobacterium species	2 (0.4)	2 (0.4)	0 (0)
Flavimonas oryzihabitans	1 (0.2)	1 (0.2)	0 (0)
Weeksella virosa	1 (0.2)	1 (0.2)	0 (0)
Vibrio vulnificus	4 (0.7)	4 (0.8)	0 (0)
Aeromonas	4 (0.7)	2 (0.4)	2 (1.7)
Haemophilus influenzae	2 (0.4)	1 (0.2)	1 (0.9)
Moraxella catarrhalis	1 (0.2)	1 (0.2)	0 (0)
Gram-positive aerobes	152 (26.9)	120 (26.6)	32 (27.8)
Staphylococci	68 (12.0)	57 (12.6)	11 (9.6)
Methicillin-resistant *S. aureus*	29 (5.1)	25 (5.5)	4 (3.5)
Streptococci	69 (12.2)	52 (11.6)	17 (14.8)
Streptococcus viridans	15 (2.6)	11 (2.4)	4 (3.5)
Streptococcus pneumoniae	10 (1.8)	8 (1.8)	2 (1.7)
Streptococcus bovis	8 (1.4)	6 (1.3)	2 (1.7)
Enterococci	15 (2.6)	11 (2.4)	4 (3.5)
Anaerobes	7 (1.2)	4 (0.8)	3 (2.6)
Bacteroides species	4 (0.7)	2 (0.4)	2 (1.7)
Clostridium species	3 (0.5)	2 (0.4)	1 (0.9)

(87.1% vs. 26.5%, $p < 0.001$) were observed in patients with GNNF bacteremia than those without GNNF bacteremia. Of note, there was a trend in a higher 28-day mortality rate in patients with GNNF infections (19.4% vs. 8.4%, $p = 0.05$), and in the survival analysis, the difference of 28-day survival rate between two groups was significant ($p = 0.04$; Fig. 2).

In further analysis of crude mortality in patients with bacteremia due to species within GNNFs, the highest was *P. aeruginosa* (5/16, 31.3%), followed by *Acinetobacter* species (1/6, 16.7%). No fetal episode was discovered in patients with bacteremia due to *B. pseudomallei*, *B. cepacia, Chryseobacterium* species, *F. oryzihabitans*, and *W. virosa*.

Risk factors of mortality in bacteremic patients

The association of clinical variables, laboratory parameters, the source and severity of bacteremia, appropriate antibiotic treatment, and 28-day mortality rates in bacteremic patients are shown in Table 4. The following were significantly associated with 28-day mortality: old age (≥ 65 years; 70.2% vs. 54.1%; $p = 0.03$); male (70.2% vs. 47.3%; $p = 0.003$); residents in LTHCF (36.2% vs. 12.9%; $p < 0.001$); GNNF (12.8% vs. 5.3%; $p = 0.04$); high Pittsburgh bacteremic score (≥ 4 points; 68.1% vs. 13.6%, $p < 0.001$); admitted to ICU through the ED (25.5% vs. 11.7%, $p = 0.007$); initial presentation with sepsis (83.0% vs. 62.2%, $p = 0.005$) or febrile neutropenia (6.4% vs. 0.8%, $p = 0.01$); comorbidities with malignancy (42.6% vs. 19.5%, $p = 0.001$); high serum creatinine (> 1.5 mg/dL; 52.1% vs. 28.1%, $p = 0.001$); high serum blood urea nitrogen (>20 mg/dL; 81.3% vs. 53.4%; $p < 0.001$); and high C-reactive protein (>100 mg/L; 53.5% vs. 34.9%; $p = 0.02$).

However, in multivariate analyses, only four factors independently associated with 28-day mortality were high Pittsburgh bacteremic score (≥ 4 points; OR, 11.11; 95% CI, 5.38—22.92; $p < 0.001$), underlying malignancy (OR, 4.49; 95% CI, 2.05—9.84; $p < 0.001$), residents in LTHCF (OR,

Table 3 Clinical variables and outcome among adults visiting the emergency department (ED) with or without bacteremia due to Gram-negative nonfermenters. Data are expressed as numbers (percentage), unless indicated specifically

Characters	Gram-negative nonfermenter bacteremia, patient number (%)		*p*
	Yes, *n* = 31	No, *n* = 487	
Polymicrobial bloodstream infections	7 (22.6)	38 (7.8)	0.01
Pittsburgh bacteremia score ≥ 4 points	6 (22.6)	90 (18.5)	0.90
Source of bacteremia			
Urinary tract	7 (22.6)	175 (35.9)	0.13
Lower respiratory tract	6 (19.4)	54 (11.1)	0.15
Biliary tract	5 (16.1)	40 (8.2)	0.17
Vascular catheter	5 (16.1)	13 (2.7)	0.003
Skin and soft-tissue	3 (9.7)	41 (8.4)	0.74
Primary bacteremia	3 (9.7)	82 (16.8)	0.29
Bone and joint	1 (3.2)	6 (1.2)	0.35
Intra-abdomen	0 (0)	22 (4.5)	0.63
Liver abscess	0 (0)	27 (5.5)	0.39
Infective endocarditis	0 (0)	22 (4.5)	0.63
Antibiotic therapy in the ED			
Time to administration (hours), mean ± SD	0.87 ± 2.59	0.94 ± 3.97	0.92
Inappropriate empirical therapy	27 (87.1)	129 (26.5)	<0.001
Type of antibiotics			
Cephalosporins, 1st generation	13 (41.9)	171 (35.1)	0.59
Cephalosporins, 2nd generation	5 (16.1)	56 (11.5)	0.57
Cephalosporins, 3rd generation	4 (12.9)	103 (21.1)	0.21
Cephalosporins, 4th generation	2 (6.5)	16 (3.3)	0.31
Aminopenicillins/β-lactamase inhibitors	2 (6.5)	82 (16.8)	0.10
Ureidopenicillins/β-lactamase inhibitors	2 (6.5)	6 (1.2)	0.08
Ureidopenicillins	2 (6.5)	8 (1.6)	0.12
Fluoroquinolones	1 (3.2)	12 (2.5)	0.57
Glycopeptides	0 (0)	5 (1.0)	>0.99
Penicillin G	0 (0)	2 (0.4)	>0.99
Combination with an aminoglycoside	1 (3.2)	17 (3.5)	>0.99
No antibiotic	0 (0)	26 (5.3)	0.93
Clinical outcome			
Hospitalization through the ED	26 (83.9)	407 (83.6)	>0.99
ICU Admission through the ED	9 (29.0)	59 (12.1)	0.01
28-day crude mortality	6 (19.4)	41 (8.4)	0.05

ICU = intensive care unit; SD = standard deviation.

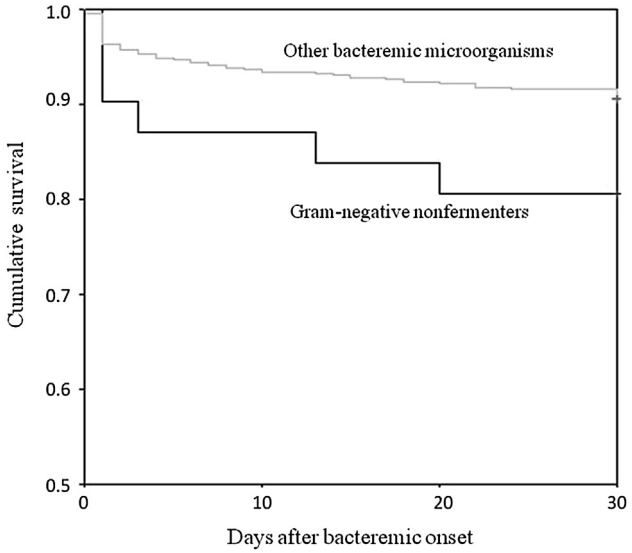

Figure 2. Kaplan–Meier survival curves showing the difference between patients with or without bacteremia due to Gram-negative nonfermenters ($p = 0.04$).

2.61; 95% CI, 1.21–5.61; $p = 0.01$), and bacteremia due to urinary tract infections (OR, 0.16; 95% CI, 0.12–0.49; $p = 0.001$).

Risk factors of mortality in patients with GNNF bacteremia

The association of clinical variables, laboratory parameters, the source and severity of bacteremia, appropriate antibiotic treatment, and 28-day mortality rates in GNNF bacteremic patients were examined by univariate analysis. The following were significantly associated with 28-day mortality: malignancy (6/13, 46.2% vs. 0/18, 0%; $p = 0.002$); high Pittsburgh bacteremic score (≥ 4 points; 4/6, 66.7% vs. 2/25, 8.0%, $p = 0.006$); initial presentation with febrile neutropenia (2/6, 33.3% vs. 0/25, 0%, $p = 0.03$); thrombocytopenia ($<150 \times 10^9$/L; 4/6, 66.7% vs. 3/23, 13.0%, $p = 0.01$); and high serum blood urea nitrogen ($>$ 20 mg/dL; 6/6, 100% vs. 11/25, 44.0%; $p = 0.02$). However, in multivariate analyses, a risk factor independently associated with 28-day mortality was not discovered.

Discussion

In the present study, a high proportion of inappropriate empirical therapy and a worse outcome in patients with bacteremia due to GNNF was discovered in the ED. Therefore, clinical variables noted in the present study, especially the presence of recent surgery (i.e., during 4 weeks prior to ED arrival), would be useful for ED clinicians to identify the population at risk for GNNF bacteremia and choose appropriate antimicrobial agents.

Previous studies have repeatedly demonstrated that the administration of appropriate empirical antibiotics will improve the clinical outcome in patients with community-acquired or nosocomial bloodstream infections.[1,4,5] To our knowledge, there was no clinical study dealing with the association between appropriate antibiotics and the outcome of individuals with GNNF bacteremia in the English literature. However, with regard to *Pseudomonas* and *Acinetobacter* bacteremia, several reports have demonstrated that a delay in the use of effective antimicrobial agents would be associated with a higher mortality.[17,18,20] In the present study, these two pathogens also account for a major proportion of GNNF infections, and the relationship of a high mortality rate and GNNF bacteremia was observed in our population. Thus, it was important to identify clinical predictors of GNNF bacteremia to facilitate early administration of appropriate therapy.

Similar to previous investigation focusing on patients with bacteremia due to individual bacterium within GNNF (especially on *P. aeruginosa*),[8,23] the poor outcome in patients with GNNF bacteremia was discovered in the analysis of Kaplan–Meier curve in the present study. However, no study grouping all GNNFs together was discovered to analyze the mortality in the past. Although, in a multivariate analysis, the GNNF was not an independent risk factor of 28-days mortality, which was similar to a previous opinion that underlying host factors was strongly associated with the outcome for each of these organisms.[8] Our suspicion is that it may be explained by the smaller patient number due to GNNF bacteremia than due to other causative microorganisms (31/518, 6.0% vs. 487/518, 94.0%; $p < 0.001$) in our population.

GNNFs are known to be major causes of healthcare-associated infections, particularly in patients who were hospitalized and critically ill,[8] and *Pseudomonas* and *Acinetobacter* species were the prevalent pathogens among nosocomial GNNF infections in the USA and Taiwan.[6,9,15] However, community-acquired infections due to GNNFs have been increasingly reported in recent years.[9,15,19,21,22] Similar to these reports, 54.8% of GNNF bacteremic episodes were regarded as acquired in the community in our population, because ED clinicians mainly manage patients from the community (440/518, 84.9%) and LTHCFs (78/518, 15.1%). GNNF infections were often prevalent in hospitalized patients; the present study only indicated the population after exclusion of hospitalized patients in other hospitals, to assist the ED clinicians to administer the appropriate antibiotics early.

Of GNNF bacteremia in the ED, there were three (9.7%) episodes of community-acquired *B. pseudomallei* infection. To our knowledge, *B. pseudomallei* infection is often reported from northern Australia and Southeast Asia,[30,31] Until recently Taiwan could be regarded as an endemic area of melioidosis, because there were many indigenous cases from southern Taiwan reported to the CDC, Taiwan, after floods or typhoons.[29] So it is not surprising that these cases of melioidosis can be found in our population. Our clinical data may be the representative overview of community-onset bacteremia in southern Taiwan and helpful for local ED clinicians in the choice of appropriate antimicrobial agents.

In this ED-based study emphasizing clinical predictors of GNNF bacteremia in the ED, the most powerful predictor was recent surgery. It was consistent with a study of *P. aeruginosa* infection.[32] It was not surprising that *P. aeruginosa* was a leading pathogen in our population. In addition to a strong association of GNNF infection and healthcare facilities in a previous demonstration,[7,8] another independent predictor associated with GNNF bacteremia (i.e., malignancy) had been also discovered in previous studies with a majority of nosocomial-acquired *P. aeruginosa*

Table 4 Univariate analysis of risk factors for 28-day mortality in all bacteremic adults visiting the emergency department

Variables	Patient number (%)		*p*
	Nonsurvivor, $n = 47$	Survivor, $n = 471$	
Old age, $\geq$ 65 y	33 (70.2)	255 (54.1)	0.03
Male	33 (70.2)	223 (47.3)	0.003
Residents in LTHCF	17 (36.2)	61 (12.9)	<0.001
Inappropriate antibiotics in the ED	20 (42.6)	136 (28.9)	0.05
Bacteremic isolates			
Polymicrobial	4 (8.5)	41 (8.7)	>0.99
Enterobacteriaceae[a]	26 (55.3)	321 (68.1)	0.07
Gram-positive cocci[a]	18 (38.2)	131 (27.8)	0.13
Gram-negative nonfermenters[a]	6 (12.8)	25 (5.3)	0.04
Severity-of-illness markers in the ED			
Pittsburgh bacteremia score $\geq$ 4 points	32 (68.1)	64 (13.6)	<0.001
Admitted to intensive care units	12 (25.5)	55 (11.7)	0.007
Initial syndrome in the ED			
Sepsis	39 (83.0)	293 (62.2)	0.005
Febrile neutropenia	3 (6.4)	4 (0.8)	0.01
Major comorbidities			
Cardiovascular diseases	26 (55.3)	233 (49.5)	0.44
Malignancy	20 (42.6)	92 (19.5)	0.001
Diabetes mellitus	18 (38.3)	172 (36.5)	0.80
Chronic renal insufficiency	10 (21.3)	75 (15.9)	0.34
Liver cirrhosis	7 (14.9)	62 (13.2)	0.73
Major source of bacteremia			
Low respiratory tract	15 (31.9)	45 (9.6)	<0.001
Primary bacteremia	12 (25.5)	73 (15.5)	0.07
Urinary tract	4 (8.5)	178 (37.8)	0.001
Skin and soft-tissue	4 (8.5)	40 (8.5)	>0.99
Biliary tract infections	2 (4.3)	43 (9.1)	0.41
Laboratory examination in the ED[b]			
Leukocyte $> 9 \times 10^9$/L	25/47 (53.2)	305/464 (65.7)	0.08
Platelet $< 100 \times 10^9$/L	13/47 (27.7)	75/458 (16.4)	0.05
Blood urea nitrogen > 20 mg/dL	39/48 (81.3)	243/455 (53.4)	<0.001
Serum creatinine > 1.5 mg/dL	25/48 (52.1)	129/459 (28.1)	0.001
C-reactive protein > 100 mg/L	23/43 (53.5)	153/439 (34.9)	0.02
Glucose > 200 mg/dL	11/45 (24.4)	125/401 (31.2)	0.35

[a] All included monomicrobial and polymicrobial bacteremic isolates.
[b] Not all patients had the indicated laboratory data.
ED = emergency department; LTHCF = long-term healthcare facilities.

bacteremia.[17,22] Although the investigation discussing the risk factors of *Acinetobacter* species infection was not reported in the English literature, we suspect that these predictors were reasonably demonstrated because the *P. aeruginosa* was a major pathogen in our population.

In general, it was important to identify clinical predictors of GNNF bacteremia to facilitate early administration of appropriate therapy. When ED clinicians face patients with a high risk of GNNF bacteremia, the *in vitro* susceptibility analyses in the current study also offer them to choose ceftazidime, cefepime, imipenem, or piperacillin/tazobactam as empirical therapy. Even for patients with a history of β-lactam allergy, ciprofloxacin with or without gentamicin combination may be an alternative therapy. This susceptibility in the present study was similar to that in a previous investigation focusing on community-acquired *P. aeruginosa* bacteremia,[21] and higher than that in previous reports on hospital-acquired *P. aeruginosa* bacteremia.[16,17]

There are several limitations inherent to the design of this study. First, although we included all patients with bacteremia in the ED for an 18-month period, the study was conducted in the ED of a single tertiary hospital in Taiwan. Our findings may not be generalizable to other populations. Second, the outcome data of two groups must be cautiously interpreted, given the differences in their characteristics. However, the multivariate analyses should minimize this limitation. Third, the data of recent antimicrobial exposure prior to ED visits were unavailable based on the study design, it may be an important risk factor of GNNF infections. Finally, the small size of the GNNF bacteremia group may have limited the detection of other risk factors.

In conclusion focusing on adults with bacteremia in the ED, the impact of GNNF infections on appropriateness of empirical antimicrobial therapy and mortality rate was found in our population. Three clinical predictors of GNNF infections, including recent surgery, residences in LTHCFs,

and the presence of underlying malignancy, were identified. Based on these findings, clinicians are able to identify the patients with GNNF infections at an early stage, allowing timely administration of appropriate drugs, such as cefepime, imipenem, ceftazidime, or piperacillin/tazobactam.

Conflicts of interest

The authors have no conflicts of interest to declare.

Acknowledgments

This study was supported by a grant (NCKUH-10103029) from National Cheng Kung University Hospital.

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