Journal of Microbiology, Immunology and Infection (2018) 51, 621–628

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.e-jmii.com

Original Article

Risk factors and outcomes for the acquisition of carbapenem-resistant Gram-negative bacillus bacteremia: A retrospective propensity-matched case control study

Shih-Wen Ting [a], Chen-Hsiang Lee [a,b], Jien-Wei Liu [a,b,*]

[a] *Division of Infectious Diseases, Department of Internal Medicine, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan*
[b] *Chang Gung University College of Medicine, Kaohsiung, Taiwan*

Received 22 April 2016; received in revised form 31 August 2016; accepted 31 August 2016
Available online 23 June 2017

KEYWORDS
Risk factors;
Outcomes;
Carbapenem-resistant;
Gram-negative bacillus;
Bacteremia;
Propensity-matched

Abstract *Background/purpose:* A substantial number of carbapenem-resistant Gram-negative bacilli (CR GNB) have been identified among the etiologic multidrug-resistant GNB in healthcare-associated infections. For achieving a better therapeutic outcome by minimizing inappropriate empirical antibiotic treatment before blood culture and susceptibility testing results are available, it is very important to identify patients who are at risk for the development of CR GNB bacteremia.
Methods: Retrospective analysis of propensity-score matched (PSM) adult patients with CR GNB bacteremia (PSM-group 1 [n = 95]) and those with non-CR GNB bacteremia (PSM-group 2 [n = 190]).
Results: PSM-group 1 was found to a significantly longer length of hospital stay (27 vs. 18 days; $p < 0.001$) after emerging GNB bacteremia and a higher 30-day all-cause mortality rate (27.4% vs. 5.8%; $p < 0.001$), when compared with PSM-2 group. Independent risk factors for the acquisition of CR GNB bacteremia were previous exposure to an antipseudomonal penicillin (odds ratio [OR] = 3.58; 95% confidence interval [CI] = 1.30–9.90), an antipseudomonal cephalosporin (OR = 3.49; 95% CI = 1.09–11.24), and a carbapenem (OR = 3.60; 95% CI = 1.37–9.47), and longer length of hospital stay before the development of GNB bacteremia (OR = 1.03; 95% CI = 1.01–1.05).
Conclusion: Risk factors for acquisition of CR GNB bacteremia identified in this study each may serve as a reminder alerting clinicians to hospitalized patients at risk for CR GNB bacteremia

* Corresponding author. Division of Infectious Diseases, Department of Internal Medicine, Kaohsiung Chang Gung Memorial Hospital, 123 Ta Pei Road, Niao Sung District, Kaohsiung 833, Taiwan.
E-mail address: jwliu@cgmh.org.tw (J.-W. Liu).

http://dx.doi.org/10.1016/j.jmii.2016.08.022

requiring appropriate antibiotic coverage, and in these circumstances, combined antibiotics may be used until antimicrobial de-escalation/adjustment is clearly indicated by the subsequently identified pathogenic GNB and its susceptibility profile.

Introduction

An increasing trend in healthcare-associated infections (HAI) due to Gram-negative bacilli (GNB) has been widely reported,[1,2] and the culprit pathogens, including both Enterobacteriaceae members and non-glucose-fermenting bacilli, were often of multidrug-resistant (MDR) strains.[3] As infections caused by MDR GNB often involved immunocompromised and/or critically ill patients with multiple comorbidities,[4–6] the importance of timely starting appropriate antibiotic therapy therefore cannot be overemphasized.[7,8] When being alerted to the growth of a GNB by a clinical microbiology laboratory before the pathogen is identified and the susceptibility results are available, clinicians are often face the issue of how to make an appropriate antibiotic choice on empirical basis.[9] Resistance of GNBs in HAI involves a great variety of mechanisms[10]; as a results, some of these GNBs are resistant to the 3rd/4th generation cephalosporins, mandating a carbapenem for treatment,[11] while others are carbapenem-resistant (CR).[12] An inappropriate empirical choice of antibiotic for patients suffering HAI due to GNB potentially leads to a dismal outcome.[5] To minimize a mis-choice of antibiotic(s) in these circumstances, we conducted a study at a medical center in southern Taiwan to identify risk factor(s) for acquisition of CR GNB among patients suffering HAI with bloodstream infection (BSI), and analyzed clinical outcomes of these patients.

Methods

Study design and data collection

This is a retrospective study with inclusion of adult patients (aged $\geq$ 18 years) suffering GNB bacteremia admitted to Kaohsiung Chang Gung Memorial Hospital (KSCGMH) between January 2013 and December 2014. KSCGMH is a 2700-bed primary care and tertiary referral center in southern Taiwan.

Patients with GNB BSIs included in this study were retrieved from the computerized database of the hospital's clinical microbiology laboratory. In case more than one episode of GNB bacteremia occurred in the same patient, only the first episode was counted. All GNBs isolated from bloodstream were regarded as clinically meaningful pathogens. Polymicrobial bacteremias were excluded from this study. Electronic medical records (EMR) of GNB bacteremic patients were reviewed for retrieval of demographic, clinical and laboratory information for analysis. This study was approved by the Institutional Review Board of Chang Gung Memorial Hospital with a waiver of patient consent (Document No. 201600173B0).

Selection of case and control patients

The included patients were divided into two groups: patients with CR GNB bacteremia (group 1) and patients with non-CR GNB bacteremia (group 2). These two groups were compared with each other aiming at identifying risk factor(s) for acquisition of CR GNB bacteremia. Because the study was non-randomized, we used the propensity score matching (PSM) to minimize the expected significant bias between the two groups.[13,14]

Clinical practice at KSCGMH

In general, upon encountering clinically suspicious septic patients, 2 specimens of blood were drawn for culture before starting an empirical antibiotic therapy. The sampled blood was separately inoculated into a Plus Aerobic/F bottle and a Standard Anaerobic/F bottle, which were then incubated in BACTEC 9240 instrument (Becton—Dickinson Microbiology System, Becton Dickinson, MD, USA) at 35 °C under monitor for 7 days before being discarded if they were negative for bacterial growth. Were any signal suggestive of a bacterial growth elicited, Gram-staining of the smear of blood drawn from the incubated blood specimen would be carried out immediately. A preliminary blood culture report based on the finding(s) from the Gram-staining would then be electronically issued, and clinician(s) caring for the patient in question would be notified of the preliminary blood culture report by texting. Adjustment of the antibiotic(s) being used might therefore be made. The final (formal) blood culture report with the identified pathogen(s) and susceptibility testing results would be subsequently issued at the 7th day. Bacteria isolated from blood culture were identified using matrix-assisted laser desorption ionization-time of flight (MALDI-TOF) mass spectrometry (MALDI Biotyper; Bruker Daltonics, Billerica, MA); susceptibility tests were performed mainly using automated antibiotic susceptibility testing (Phoenix, BD, Sparks, MD) instruments,[15] and if necessary, supplemented with disk diffusion methods for testing ertapenem, flomoxef and cefoperazone/sulbactam. Interpretive breakpoints for MIC of the tested antibiotics were those recommended by CLSI.[16] A GNB was regarded as a CR strain when tested against it, the MIC of ertapenem was >1 μg/ml and/or the MIC of doripenem, imipenem or meropenem >2 μg/ml.[16] Intermediate results in susceptibility testing were classified as resistance.

Definitions

End-stage renal disease (ESRD) was defined as a profound renal dysfunction that clinically requires either regular dialysis or renal transplantation. Diabetes mellitus was diagnosed in an included patient when at least one of the following criteria was met: (1) random plasma glucose level $>$ 200 mg/dL, (2) plasma glucose $\geqq$ 126 mg/dL after overnight fast at the recovery from sepsis, and (3) receiving oral hypoglycemic agents or insulin therapy for a previously diagnosed diabetes mellitus. Malignancy referred to either a solid tumor or hematologic neoplasm such as lymphoma, leukemia, and multiple myeloma, which was diagnosed by an oncologist/hematologist. Neutropenia was defined as an absolute peripheral neutrophil count $<$500 cells/mm^3. The severities of comorbidities were measured using the Charlson comorbidity indices.[17]

Previously used immuno-suppressants and antibiotics ($\geqq$48 h), steroid ($\geqq$2 weeks), and invasive treatment procedures referred to those that were given within 30 days before the emergence of the GNB bacteremia. Steroid was considered a meaningful immunosuppressant only when therapy with prednisolone $\geq$10 mg/day or with other equivalent steroid per day.

After sampling blood for culture, an immediate empirical antibiotic therapy was started for each of the included patients. It was regarded as an appropriate antibiotic therapy (AAT) if the prescribed antibiotic(s) to which the subsequently grown GNB from blood was susceptible *in vitro*; otherwise, it was referred to an inappropriate antibiotic therapy (IAT). Mortality referred to the all-cause death, and mortality rates were assessed at the 14th and 30th day after the development of the GNB bacteremia.

Statistical analysis

Logistic regression was used to generate a model to calculate propensity scores which were the probability of assignment conditional on observed baseline characteristics of both groups. To do so, variables composed of baseline characteristics such as age, sex, and Charlson comorbidity index[17] were included in a logistic regression model to identify independent factor(s) for risk of the acquisition of CR GNB bacteremia.[14,18] Patients in group 1 and patients in group 2 were matched at a ratio of 1:2 by the nearest neighbor matching method without replacement.

The impact of timely starting appropriate antibiotic treatment for CR GNB bacteremias was assessed by comparing the 30-day mortality rates between patients receiving AAT and those receiving IAT within the propensity-matched CR GNB bacteremic group. In univariate analysis, the *t* test or Mann–Whitney *U* test was used for comparisons of continuous variables, whereas the χ^2 test or Fisher's exact test was used for comparisons of dichotomous variables, when appropriate. A p value $<$0.05 was considered statistically significant for all comparisons. Statistical analyses were performed using the SPSS version 22.0 software (SPS Inc., Chicago, IL).

Results

A total of 2102 GNB (95 CR GNB and 2007 non-CR GNB) bacteremias each were found in one adult patient during the study period, and all of them were subjected to PSM. Eventually, 285 patients were included in a propensity-score matched cohort, and were separated into the following groups for further analysis: patients with CR GNB bacteremia (PSM-group 1) and patients with non-CR GNB bacteremia (PSM-group 2) (Fig. 1).

Distribution of GNB in the propensity score-matched cohort

Among a total of 285 GNB isolates, 174 (61.1%) were of Enterobacteriaceae, 85 (29.8%) were glucose non-fermenting (GNF) GNBs, and 21 (7.4%) were of Vibrionaceae. *Escherichia coli* (n = 105) and *Klebsiella* spp. (n = 39) were the leading Enterobacteriaceae members, while *Pseudomonas* spp. (n = 25) and *Acinetobacter* spp. (n = 20) were the most commonly encountered GNF GNB; *Aeromonas* spp. (n = 20) were the predominant Vibrionaceae members. Bacterial species and the number of CR GNB and non-CR GNB are detailed in Fig. 2. The leading CR GNBs, in decreasing order, were *Aeromonas* sp. (n = 17), *Acinetobacter* sp. (n = 15), *Stenotrophomonas maltophilia* (n = 15), *Chryseobacterium* spp. (n = 14), and *Pseudomonas* spp. (n = 13) (Table 1).

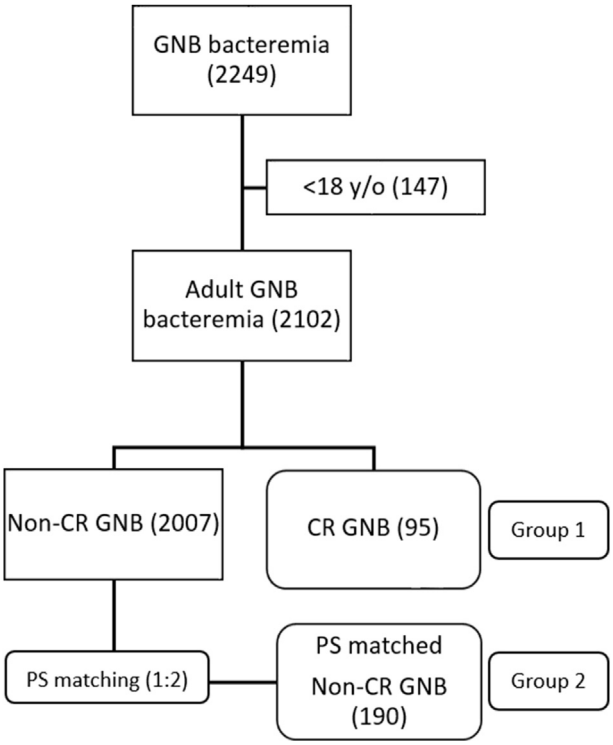

Figure 1. Flow chart of including patients with non-carbapenem-resistant (non-CR) and carbapenem-resistant (CR) Gram-negative bacillus (GNB) bacteremia found between January 2013 and December 2014 for propensity score (PS) matching and analysis. These bacteremias were each found in one patient.

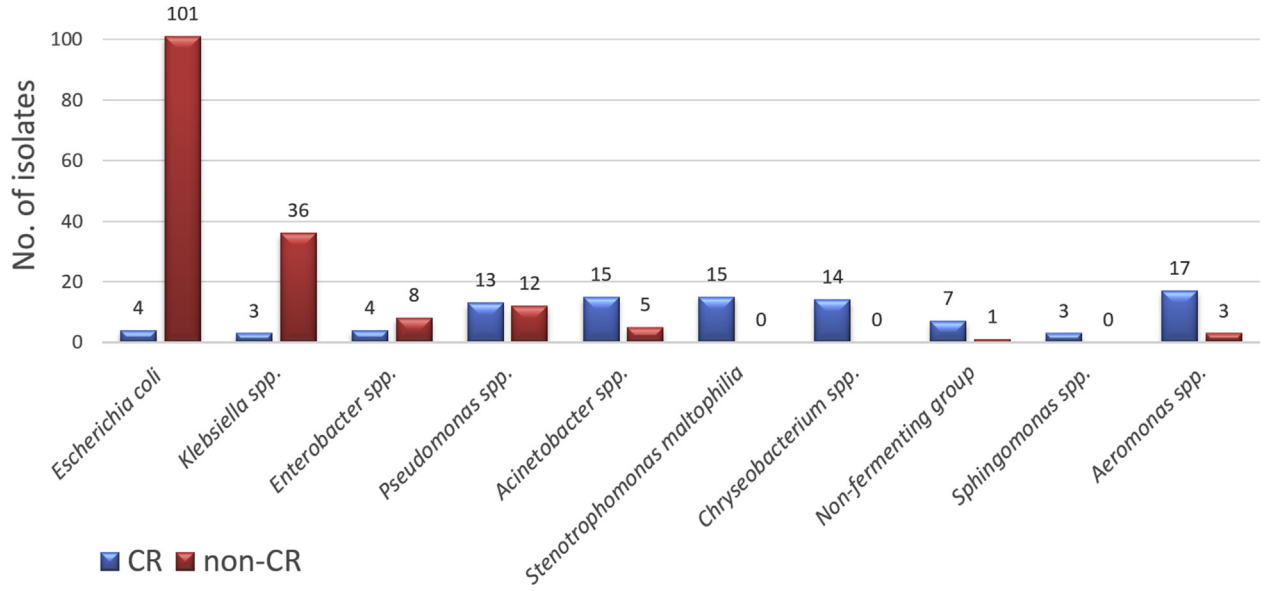

Figure 2. Major non-carbapenem-resistant (non-CR) and carbapenems-resistant (CR) Gram-negative bacilli found in this bacteremic patient cohort.

Table 1 Distribution of microorganism in this propensity score-matched cohort.

Microorganism in PSM cohort	Total (N = 285)	CR GNB (N = 95)	Non-CR GNB (N = 190)
Enterobacteriaceae, n (%)	174 (61.1)	11 (11.6)	163 (85.8)
Escherichia coli	105 (36.8)	4 (4.2)	101 (53.2)
Klebsiella spp.	39 (13.7)	3 (3.2)	36 (19.0)
K. pneumoniae	36 (12.6)	3 (3.2)	33 (17.4)
Enterobacter spp.	12 (4.2)	4 (4.2)	8 (4.2)
Salmonella spp.	6 (2.1)	0	6 (3.2)
Proteus mirabilis	4 (1.4)	0	4 (2.1)
Citrobacter spp.	5 (1.8)	0	5 (2.6)
Serratia marcescens	3 (1.1)	0	3 (1.6)
Glucose non-fermenting GNB, n (%)	85 (29.8)	67 (70.5)	18 (9.5)
Pseudomonas spp.	25 (8.8)	13 (13.7)	12 (6.3)
P. aeruginosa	20 (7.0)	10 (10.5)	10 (5.3)
Acinetobacter spp.	20 (7.0)	15 (15.8)	5 (2.6)
A. baumanni	12 (4.2)	10 (10.5)	2 (1.1)
Stenotrophomonas maltophilia	15 (5.3)	15 (15.8)	0
Chryseobacterium spp.	14 (4.9)	14 (14.7)	0
Chryseobacterium meningosepticum	10 (3.5)	10 (10.5)	0
Non-fermenting group	8 (2.8)	7 (7.4)	1 (0.5)
Sphingomonas spp.	3 (1.1)	3 (3.2)	0
Vibrionaceae, n (%)	21 (7.4)	17 (17.9)	4 (2.1)
Aeromonas spp.	20 (7.0)	17 (17.9)	3 (1.6)
Vibrio vulnificus	1 (0.4)	0	1 (0.5)
Others, n (%)	5 (1.8)	0	5 (2.6)
Bacteroides fragilis	2 (0.7)	0	2 (1.1)
Shewanella putrefaciens	1 (0.4)	0	1 (0.5)
Pantoea spp.	1 (0.4)	0	1 (0.5)
Agrobacterium radiobacter	1 (0.4)	0	1 (0.5)

Comparisons between demographics, clinical characteristics and outcomes between propensity-score matched groups

Among the overall 285 patients, the most common underlying disease and invasive procedure were neoplasm (35.4%) and Foley catheterization (14.7%), respectively. PSM-group 1 was found to have a significantly higher mechanical ventilatory supporting rate (12.6% vs. 4.7%; $p = 0.016$) at the emergence of GNB bacteremia, longer length of hospital stay prior to the development of GNB bacteremia (24 days vs. 1 day; $p < 0.001$), and higher

Table 2 Demographics, clinical characteristics, and outcomes of the GNB bacteremic patients in the propensity-score matched cohort and comparisons between CR GMB bacteremic patients (PSM-group 1) and non-CR GNB bacteremic patients (PSM-group 2).

Variable	Overall patients (N = 285)	PSM-group 1 (N = 95)	PSM-group 2 (N = 190)	*p* value[a]
Age (yrs), mean ± SD	65.5 ± 14.7	65.6 ± 14.9	65.5 ± 14.6	0.948
Gender (male), n (%)	180 (63.2)	60 (63.2)	120 (63.2)	1.000
Charlson comorbidity index, mean ± SD	2.92 ± 2.2	2.93 ± 2.2	2.91 ± 2.2	0.954
<3, n (%)	167 (58.6)	55 (57.9)	112(58.9)	0.865
3–5, n (%)	64 (22.5)	23 (24.2)	41(21.6)	0.616
≥6, n (%)	54 (18.9)	17 (17.9)	37 (19.5)	0.748
Comorbidity, n (%)				
Diabetes mellitus	44 (15.4)	16 (16.8)	28 (14.7)	0.643
Hypertension	47 (16.5)	16 (16.8)	31 (16.3)	0.910
Congestive heart failure	26 (9.1)	13 (13.7)	13 (6.8)	0.059
ESRD	17 (6.0)	9 (9.5)	8 (4.2)	0.077
COPD	10 (3.5)	5 (5.3)	5 (2.6)	0.255
Liver cirrhosis	43 (15.1)	17 (17.9)	26 (13.7)	0.349
Malignancy	101 (35.4)	35 (36.8)	66 (34.7)	0.726
Organ transplantation	4 (1.4)	1 (1.1)	3 (1.6)	0.722
Neutropenia	12 (4.2)	6 (6.3)	6 (3.2)	0.211
Immuno-suppressants	44 (15.4)	17 (17.9)	27 (14.2)	0.417
Steroid	41 (14.4)	16 (16.8)	25 (13.2)	0.403
Prior invasive procedures, n (%)				
Central venous catheterization	19 (6.7)	4 (4.2)	15 (7.9)	0.240
Foley catheterization	42 (14.7)	15 (15.8)	27 (14.2)	0.723
Endotracheal intubation	17 (6.0)	8 (8.4)	9 (4.7)	0.216
Mechanical ventilation	21 (7.4)	12 (12.6)	9 (4.7)	0.016*
Previously used antibiotic,[b] n (%)				
Penicillin/β-lactamase inhibitor	27 (9.5)	14 (14.7)	13 (6.8)	0.032*
Antipseudomonal penicillins	34 (11.9)	26 (27.4)	8 (4.2)	<0.001*
Antipseudomonal cephalosporins	35 (12.3)	29 (30.5)	6 (3.2)	<0.001*
Cephalosporins	99 (34.7)	37 (38.9)	62 (32.6)	0.291
1st generation	41 (14.4)	19 (20.0)	22 (11.6)	0.056
2nd generation	13 (4.6)	2 (2.1)	11 (5.8)	0.160
3rd generation	62 (21.8)	21 (22.1)	41 (21.6)	0.919
Carbapenems	52 (18.2)	38 (40.0)	14 (7.4)	<0.001*
Fluoroquinolones	36 (12.6)	22 (23.2)	14 (7.4)	<0.001*
Glycopeptide	36 (12.6)	25 (26.3)	11 (5.8)	<0.001*
Aminoglycoside	12 (4.2)	7 (7.4)	5 (2.6)	0.061
Others[c]	9 (3.2)	8 (8.4)	1 (0.5)	<0.001*
LOS **prior** to isolation of GNB pathogens, mean day ± SD	9 ± 26	24 ± 38	1 ± 10	<0.001*
Overall admission, mean day ± SD	30 ± 35	51 ± 49	16 ± 16	<0.001*
Outcomes				
LOS **after** GNB bacteremia, mean day ± SD	21 ± 17	27 ± 22	18 ± 14	<0.001*
Mortality, n (%)				
14-day	24 (8.4)	18 (18.9)	6 (3.2)	<0.001*
30-day	37 (13.0)	26 (27.4)	11 (5.8)	<0.001*

SD = standard deviation; ESRD = end-stage renal disease; COPD = chronic obstructive pulmonary disease; LOS = length of stay.
* Statistically significant, $p < 0.05$.
[a] For comparisons between PSM-group 1 and PSM-group 2.
[b] Antibiotic used for >48 h within 30 days.
[c] Including macrolides and tigecycline.

frequency in prior exposure to penicillins/β-lactamase inhibitors, antipseudomonal penicillins, antipseudomonal cephalosporins, glycopeptides, carbapenems, and/or fluoroquinolones. Of note, carbapenems were found to be the most frequent prior exposure antibiotics among patients in the PSM-group 1 (38/95 [40%]) (Table 2).

Patients in the PSM-group 1 was found to have a significantly longer length of hospitalization (51 days vs. 16 days; $p < 0.001$), longer length of hospital stay after emerging CR-GNB bacteremia (27 days vs. 18 days; $p < 0.001$), and higher 14-day (18.9% vs. 3.2%; $p < 0.001$) and 30-day (27.4% vs. 5.8%; $p < 0.001$) mortality rates.

Independent risk factors for acquisition of CR GNB bacteremia

After eliminating confounding, independent risk factors for acquisition of CR GNB bacteremia included previous exposure to antipseudomonal penicillins (odds ratio [OR] = 3.58; 95% confidence interval [CI] = 1.30—9.90), antipseudomonal cephalosporins (OR = 3.49; 95% CI = 1.09—11.24), carbapenems (OR = 3.60; 95% CI = 1.37—9.47) and a longer length of stay before development of GNB bacteremia (OR = 1.03; 95% CI = 1.01—1.05) (Table 3).

Fatalities in CR GNB bacteremic patients who received an immediate appropriate antibiotic therapy and those who did not

Among a total of 95 patients in the PSM-group 1, 27 (28.4%) received AAT, while 68 (71.6%) received IAT, and a significant difference in 30-day mortality rate was found between these subgroups (3/27 patients [11.1%] vs. 23/68 patients [33.8%]; $p = 0.025$). Of note, IAT was the only significant risk for the fatality difference in univariate analysis.

Table 3 Independent risk factors for acquisition of carbapenems-resistant Gram-negative bacillus bacteremia among patients with Gram-negative bacteremia in the propensity-score matched cohort.

Risk factor	Adjusted odds ratio (95% confidence interval)	*p* Value
Mechanical ventilatory support	2.42 (0.84—6.95)	0.101
Recent exposure to[a]		
Penicillins/β-lactamase inhibitor	2.28 (0.90—5.76)	0.081
Antipseudomonal penicillins	3.58 (1.30—9.90)	0.014*
Antipseudomonal cephalosporins	3.49 (1.09—11.24)	0.036*
Carbapenems	3.60 (1.37—9.47)	0.010*
Fluoroquinolones	0.66 (0.22—1.99)	0.462
Glycopeptides	0.74 (0.23—2.34)	0.602
Other antibiotics	8.86 (0.61—128.39)	0.110
Length of stay **before** isolation of GNB bacteremia	1.03 (1.01—1.05)	0.013*

*Statistically significant, $p < 0.05$. Hosmer and Lemeshow Test, p = 0.541; the goodness-of-fit test showed good agreement between observed and predicted values of the model.

[a] Antibiotics were previously used (>48 h) within 30 days before sampling blood for culture.

Discussion

Sepsis is one of the leading causes of death among hospitalized patients.[19—21] The invading culprit bacteria are capable of producing a variety of virulence factors that enable them to escape the immune defenses and disseminate to remote organs, and toxins that interact with host cells via specific receptors on the cell surface and trigger a dysregulated immune response.[22] It has been well documented that the earlier the starting an AAT, the lower the mortality rate[23,24]; our data suggest that there is no exception for patients suffering CR GNB bacteremia in terms mandating a timely AAT. Kumar A et al. reported an increase in mortality of 7.6% for every hour by which antimicrobials were delayed in septic shock.[25] With the backdrop of increasing multidrug-resistance microbes and aging population in Taiwan,[6,26,27] increasing number of elderly patients with multiple comorbidities after completing medical treatment at hospitals are released to nursing homes; the aging-inherent vulnerability makes them subject to high chances of repeatedly seeking medical treatment for recurrent bacterial infection, mandating empirical antibiotic therapy at their hospital presentations. In these circumstances, the line between a hospital-acquired infection and a community-acquired infection is often blurred; our data suggested the patients with prior exposure (within 30 days) to an anti-pseudomonal penicillin, antipseudomonal cephalosporin and/or a carbapenem are at risk for CR GNB bacteremia upon their arrival at hospital. The underlying comorbididy/ies and prior antibiotic exposure suggest that bacteremias due to CR GNB resulting from the selective antibiotic pressure, which is consistent with other reports.[10,28]

Immediately notifying clinicians of the preliminary blood culture results was part of efforts in providing an earliest AAT for septic patients at KSCGMH. The drawback of this practice is the lack of antimicrobial susceptibility profile at the immediate notification of preliminary blood culture result. One may argue broad-spectrum antimicrobial coverage under these circumstances, and deescalate antimicrobial(s) later if it is indicated by the subsequently isolated bacterium and the susceptibility testing results.[29] However, in the era of increasing prevalence of MDR bacterial infections, it is more often than not that a diverse antibiotic resistance pattern exists when it comes to the etiologic GNBs in infections acquired from a hospital setting,[5,6,30] and type 2 carbapenems are no longer regarded as omnipotent antibiotics for empirical therapy for suspected sepsis due to GNB, and this is particularly true when septic shock develops. The predicament makes decision on chosen empirical antibiotic(s) difficult and challenging, and highlights the importance of identifying risk factors for acquisition of CR GNB infections. In consistent with other series, most of the CR GNBs isolated from blood in ours were GNF GNBs,[10,31,32] underscoring that clinicians

should be familiar with the epidemiology of antibiotic resistance for the etiologic GNBs (especially for GNF GNBs) in hospital-acquired infections in their facilities.

Conducting at a single medical center, potential biases inherent to the retrospective study, inevitable missing data and small sample size are limitations of this study. Nevertheless, independent risk factors for CR GNB bacteremia among patients suffering GNB bacteremia identified in this cohort, including a longer hospital stay before the emergence of the GNB bacteremia and prior exposure to an antipseudomonal penicillin, antipseudomonal cephalosporin and/or a carbapenem, each may serve as a reminder alerting clinicians to hospitalized patients at risk for CR GNB bacteremia, and to minimize mischoosing antibiotic(s) in these situations, combined antibiotics may be used until antimicrobial de-escalation/adjustment is clearly indicated by the identified GNB pathogen and its antibiotic susceptibility profile.

Acknowledgement

The authors would like to thank epidemiologist Prof. Sheng-Nan Lu from the Statistical Consulting Center at KSCGMH for the statistical consultation.

References

1. Allegranzi B, Bagheri Nejad S, Combescure C, Graafmans W, Attar H, Donaldson L, et al. Burden of endemic health-care-associated infection in developing countries: systematic review and meta-analysis. *Lancet* 2011;**377**:228—41.
2. de Kraker ME, Jarlier V, Monen JC, Heuer OE, van de Sande N, Grundmann H. The changing epidemiology of bacteraemias in Europe: trends from the European Antimicrobial Resistance Surveillance System. *Clin Microbiol Infect* 2013;**19**:860—8.
3. Cerceo E, Deitelzweig SB, Sherman BM, Amin AN. Multidrug-resistant Gram-negative bacterial infections in the hospital setting: overview, implications for clinical practice, and emerging treatment options. *Microb Drug Resist* 2016;**22**:412—31.
4. Metan G, Demiraslan H, Kaynar LG, Zararsız G, Alp E, Eser B. Factors influencing the early mortality in haematological malignancy patients with nosocomial Gram negative bacilli bacteraemia: a retrospective analysis of 154 cases. *Braz J Infect Dis* 2013;**17**:143—9.
5. Lee CH, Su LH, Li CC, Chien CC, Tang YF, Liu JW. Microbiologic and clinical implications of bacteremia due to extended-spectrum-β-lactamase-producing *Klebsiella pneumoniae* with or without plasmid-mediated AmpC β-lactamase DHA-1. *Antimicrob Agents Chemother* 2010;**54**:5395—8.
6. Liu JW, Ko WC, Huang CH, Liao CH, Lu CT, Chuang YC, et al. Agreement assessment of tigecycline susceptibilities determined by the disk diffusion and broth microdilution methods among commonly encountered resistant bacterial isolates: results from the Tigecycline In Vitro Surveillance in Taiwan (TIST) study, 2008 to 2010. *Antimicrob Agents Chemother* 2012;**56**:1414—7.
7. Zhang D, Micek ST, Kollef MH. Time to appropriate antibiotic therapy is an independent determinant of postinfection ICU and hospital lengths of stay in patients with sepsis. *Crit Care Med* 2015;**43**:2133—40.
8. Raman G, Avendano E, Berger S, Menon V. Appropriate initial antibiotic therapy in hospitalized patients with Gram-negative infections: systematic review and meta-analysis. *BMC Infect Dis* 2015;**15**:395.
9. Paterson DL. Impact of antibiotic resistance in Gram-negative bacilli on empirical and definitive antibiotic therapy. *Clin Infect Dis* 2008;**15**(47 Suppl 1):S14—20.
10. Peleg AY, Hooper DC. Hospital-acquired infections due to Gram-negative bacteria. *N Engl J Med* 2010;**362**:1804—13.
11. Moghnieh R, Estaitieh N, Mugharbil A, Jisr T, Abdallah DI, Ziade F, et al. Third generation cephalosporin resistant Enterobacteriaceae and multidrug resistant Gram-negative bacteria causing bacteremia in febrile neutropenia adult cancer patients in Lebanon, broad spectrum antibiotics use as a major risk factor, and correlation with poor prognosis. *Front Cell Infect Microbiol* 2015;**5**:11.
12. Huttner A, Harbarth S, Carlet J, Cosgrove S, Goossens H, Holmes A, et al. Antimicrobial resistance: a global view from the 2013 World Healthcare-Associated Infections Forum. *Antimicrob Resist Infect Control* 2013;**2**:31.
13. Rosenbaum PR, Rubin DB. Reducing bias in observational studies using subclassification on propensity score. *J Am Stat Assoc* 1984;**79**:516—24.
14. Ternavasio-de la Vega HG, Mateos-Díaz AM, Martinez JA, Almela M, Cobos-Trigueros N, Morata L, et al. A propensity score analysis shows that empirical treatment with linezolid does not increase the thirty-day mortality rate in patients with Gram-negative bacteremia. *Antimicrob Agents Chemother* 2014;**58**:7025—31.
15. Wimmer JL, Long SW, Cernoch P, Land GA, Davis JR, Musser JM, et al. Strategy for rapid identification and antibiotic susceptibility testing of gram-negative bacteria directly recovered from positive blood cultures using the Bruker MALDI Biotyper and the BD Phoenix system. *J Clin Microbiol* 2012;**50**:2452—4.
16. Clinical and Laboratory Standards Institute. *Performance standards for antimicrobial susceptibility testing; 21st informational supplement. CLSI document M100-S21*. Wayne, PA: Clinical and Laboratory Standards Institute; 2011.
17. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;**40**:373—83.
18. Li WS, Lee CH, Liu JW. Antifungal therapy did not improve outcomes including 30-day all-cause mortality in patients suffering community-acquired perforated peptic ulcer-associated peritonitis with Candida species isolated from their peritoneal fluid. *J Microbiol Immunol Infect* 2015 Jul 31. pii: S1684-1182(15)00807-5. [Epub ahead of print].
19. Visintin A, Halmen KA, Latz E, Monks BG, Golenbock DT. Pharmacological inhibition of endotoxin responses is achieved by targeting the TLR4 coreceptor, MD-2. *J Immunol* 2005;**175**:6465—72.
20. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. *Crit Care Med* 2001;**29**:1303—10.
21. Daniels R. Surviving the first hours in sepsis: getting the basics right (an intensivist's perspective). *J Antimicrob Chemother* 2011;**66**(Suppl 2):ii11—23.
22. Ramachandran G. Gram-positive and gram-negative bacterial toxins in sepsis: a brief review. *Virulence* 2014;**5**:213—8.
23. Gaieski DF, Mikkelsen ME, Band RA, Pines JM, Massone R, Furia FF, et al. Impact of time to antibiotics on survival in patients with severe sepsis or septic shock in whom early goal-directed therapy was initiated in the emergency department. *Crit Care Med* 2010;**38**:1045—53.
24. Ibrahim EH, Sherman G, Ward S, Fraser VJ, Kollef MH. The influence of inadequate antimicrobial treatment of bloodstream infections on patient outcomes in the ICU setting. *Chest* 2000;**118**:146—55.

25. Kumar A, Roberts D, Wood KE, Light B, Parrillo JE, Sharma S, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. *Crit Care Med* 2006;**34**:1589—96.
26. Lee CH, Liu JW, Li CC, Chien CC, Tang YF, Su LH. Spread of ISCR1 elements containing blaDHA-1 and multiple antimicrobial resistance genes leading to increase of flomoxef resistance in extended-spectrum-beta-lactamase-producing *Klebsiella pneumoniae*. *Antimicrob Agents Chemother* 2011 Sep;**55**:4058—63.
27. Chien HJ, Chen YF. Rejuvenate Taiwan: time to act now: strategies of fewer children and population aging in Taiwan. *J Formos Med Assoc* 2016 Aug 18. pii: S0929-6646(16)30082-1. [Epub ahead of print].
28. Davidson Ross J, Davis Ian, Willey Barbara M, Rizg Keyro, Bolotin Shelly, Porter Vanessa, et al. Antimalarial therapy selection for quinolone resistance among *Escherichia coli* in the absence of quinolone exposure in tropical South America. *PLoS One* 2008;**3**(7):e2727.
29. Niederman MS. Use of broad-spectrum antimicrobials for the treatment of pneumonia in seriously ill patients: maximizing clinical outcomes and minimizing selection of resistant organisms. *Clin Infect Dis* 2006;**42**(Suppl. 2):S72—81.
30. Chen IL, Lee CH, Su LH, Tang YF, Chang SJ, Liu JW. Antibiotic consumption and healthcare-associated infections caused by multidrug-resistant gram-negative bacilli at a large medical center in Taiwan from 2002 to 2009: implicating the importance of antibiotic stewardship. *PLoS One* 2013;**8**: e65621.
31. Gupta E, Mohanty S, Sood S, Dhawan B, Das BK, Kapil A. Emerging resistance to carbapenems in a tertiary care hospital in north India. *Indian J Med Res* 2006;**124**:95—8.
32. Marchenay P, Blasco G, Navellou JC, Leroy J, Cholley P, Talon D, et al. Acquisition of carbapenem-resistant gram-negative bacilli in intensive care unit: predictors and molecular epidemiology. *Med Mal Infect* 2015;**45**:34—40.