American Journal of Infection Control ■■ (2016) ■■-■■

Contents lists available at ScienceDirect

American Journal of Infection Control

journal homepage: www.ajicjournal.org

Clinical Case Study

Predictors of mortality in bloodstream infections caused by multidrug-resistant gram-negative bacteria: 4 years of collection

Weiwei Wang MM [a], Ting Jiang MM [a], Weihong Zhang MD [b], Chunyu Li MM [a], Jun Chen MM [a], Dandan Xiang MPH [c], Kejiang Cao MD [d], Lian-Wen Qi PhD [e], Ping Li PhD [e], Wei Zhu MD [f], Wensen Chen MPH [b,*], Yan Chen MD [a,g,*]

[a] *Emergency Center, The First Affiliated Hospital of Nanjing Medical University, Nanjing, China*
[b] *Department of Infection Management Office, The First Affiliated Hospital of Nanjing Medical University, Nanjing, China*
[c] *Department of Epidemiology, School of Public Health of Nanjing Medical University, Nanjing, China*
[d] *Department of Cardiology, The First Affiliated Hospital of Nanjing Medical University, Nanjing, China*
[e] *State Key Laboratory of Natural Medicines, China Pharmaceutical University, Nanjing, China*
[f] *Department of Oncology, The First Affiliated Hospital of Nanjing Medical University, Nanjing, China*
[g] *Medical Department, Women and Children Health Care Hospital of Jiangsu Province, Nanjing, China*

Key Words:
Carbapenem-resistant
Gram-negative bacilli
Risk factor
Therapy

The study was undertaken to describe the profile of patients and the characteristics of all multidrug-resistant gram-negative bacteria (MDR-GNB) and to assess mortality. We examined 138 patients with bloodstream infections (BSIs) caused by MDR-GNB. Clinical characteristics, antibiotic therapy, and in-hospital mortality were analyzed. Survivor and nonsurvivor subgroups were compared to identify predictors of mortality. The in-hospital mortality rate was 25.4%. Univariate analysis revealed that comorbidities and inadequate initial antimicrobial treatment could increase risk of death. In Cox regression analysis, mortality was independently associated with the age ($P = .034$), hospitalization in an intensive care unit (ICU) ($P = .04$), invasive procedures ($P < .001$), and Acute Physiology and Chronic Health Evaluation II scores ($P < .001$), whereas combination therapy or monotherapy was not associated with mortality ($P = .829$). Postantibiogram therapy was associated with hospitalization in an ICU ($P = .006$), Charlson comorbidity index score ($P = .003$), and inadequate initial antimicrobial treatment ($P < .001$). MDR-GNB strains and antimicrobial regimens were not the major risk factors of mortality. Inadequate initial antimicrobial treatment, invasive procedures, high Acute Physiology And Chronic Health Evaluation II scores, hospitalization in an ICU, and comorbidities were the important factors responsible for mortality. Although there was no difference between combination therapy and monotherapy in mortality, combined treatment may be more effective than monotherapy for patients in an ICU, with a Charlson comorbidity index score < 4, or inadequate initial antimicrobial treatment.

Multidrug-resistant gram-negative bacteria (MDR-GNB) are gaining increasing importance in health care settings, especially in high-dependency units and among critical care patients.[1] Carbapenem-resistant Enterobacteriaceae (CRE), carbapenem-resistant *Acinetobacter baumannii* (CR-AB), and multidrug-resistant *Pseudomonas aeruginosa* (MDR-PA) are emerging frequently multidrug-resistant gram-negative pathogens that have spread worldwide in recent years. These bacteria are frequently resistant to all antibiotics except colistin, some aminoglycosides, and variably tigecycline, posing a serious challenge for treatment. Several observational clinical studies have claimed an advantage for colistin-based combination therapy and, as a consequence, combination therapy has become the standard of care employed by many physicians for infections caused by MDR-GNB.[2-5] But in the meta-analysis by Paul et al,[6] there was no evidence-based support for most

* Address correspondence to Yan Chen, MD, Emergency Center or Wensen Chen, MPH, Department of Infection Management Office, the First Affiliated Hospital of Nanjing Medical University, Nanjing 210029, China.
E-mail addresses: chenyandoc@163.com (Y. Chen); metrischen@126.com (W. Chen).

This work was supported by the National Natural Science Foundation of China (grant Nos. 81372035 and 81571873), the Priority Academic Program Development of Jiangsu Higher Education Institutions (grant No. JX10231081), the Foundation of the Health Department of Jiangsu Province (grant No. H201301), the Six Talents Peak Project of Jiangsu Province (grant No. 2013WSN035), the Open Project Program of State Key Laboratory of Natural Medicines, China Pharmaceutical University (grant Nos. SKLNMKF201311 and 201408), and Lijieshou intestinal barrier research fund (grant No. LJS-201306). General support was provided by the China Postdoctoral Science Foundation (grant No. 2014M561735), and the key project was supported by the Medical Science and Technology Development Foundation, Jiangsu (grant No. BL2014082) and Jiangsu Province Projects of Preventive Medicine Research (grant No. Y2013044).
WW and TJ contributed equally to this work.
Conflicts of interest: None to report.

0196-6553/
http://dx.doi.org/10.1016/j.ajic.2016.08.008

combination therapies against MDR-GNB, including colistin and carbapenem combination therapy. The most common CRE reported in the literature was *Klebsiella pneumoniae*, followed by *Escherichia coli* and/or *Enterobacter* species.[7,8] The estimated mortality rate ranged from 29%-52% in patients with CRE infections, and 40%-50% in bloodstream infection (BSI).[9,10] The worldwide spread of MDR-GNB now represents a significant threat to public health and requires immediate efforts toward early detection and infection control.

In this multicenter, hospital-based study, we attempted to pinpoint risk factors for mortality in a cohort of 138 patients with BSI caused by MDR-GNB. Particular attention was focused on the influence of antimicrobial regimens used in the definitive phase of treatment.

MATERIALS AND METHODS

Setting

This retrospective cohort study was performed at the First Affiliated Hospital of Nanjing Medical University in China, a large teaching and scientific research hospital that offers a full range of clinical services. Surveillance cultures were not routinely performed during the study period.[11]

Study design and patients

We searched the teaching hospital's central microbiology laboratory database to identify cases with all of the following characteristics: MDR-GNB BSI diagnosed between January 1, 2013, and December 31, 2016; adult patients (aged ≥18 years); absence of bloodstream isolates other than MDR-GNB; no evidence of MDR-GNB infections at other sites; and treatment of the BSI for at least 48 hours (empirically and/or based on antibiogram data) with ≥1 antimicrobial agent displaying in vitro activity against the MDR-GNB.[12] If the patient had multiple infections during the study period, only the initial BSI infection was included. Only true infections based on established systemic inflammatory response syndrome criteria were included, and cultures deemed to represent colonization were excluded. If the interval between previous discharge and next hospital admission was <48 hours for the same patient, it was regarded as a single hospital stay.[13]

The MDR-GNB included were CRE, CR-AB, and MDR-PA. The characteristics of each case were collected from the electronic medical records database by the first author. A retrospective cohort study design was employed. Clinical characteristics, antibiotic therapy, and in-hospital mortality of the first positive blood culture were analyzed. Survivor and nonsurvivor subgroups were compared to identify predictors of mortality. Most of the characteristics of our cohort of patients with BSIs are shown in Table 1.

Variables explored as possible predictors of mortality

Variables collected for each patient included demographic characteristics (including age and sex), microbiology data (including CRE, CR-AB, and MDR-PA), comorbid conditions (including Charlson comorbidity index score[14]), underlying diseases, BSI onset in an intensive care unit (ICU), history of previous hospitalization (≤12 months before BSI onset), hospital-acquired infection (the index blood culture had been collected >48 hours after hospital admission and no signs or symptoms of infection had been noted at admission), surgery (≤30 days before BSI onset), invasive procedures performed ≤72 hours before BSI onset (eg, indwelling central venous catheter, indwelling urinary catheter, or mechanical ventilation), Acute Physiology And Chronic Health Evaluation II (APACHE II) score[15] at the time of BSI onset, previous antimicrobial

Table 1
Univariate analysis of factors associated with death among patients with bloodstream infections due to carbapenem-resistant gram-negative bacteria

Variable	Patients		*P* value	Odds ratio (95% confidence interval)
	Nonsurvivors (n = 35)	Survivors (n = 103)		
Age (y)	71.17 ± 22.294	55.52 ± 19.78	<.001	
Intensive care unit	24 (68.6)	31 (30.1)	<.001	5.07 (2.21-11.61)
Bacteria strain				
CRE	9 (25.7)	24 (23.3)	.77	1.14 (0.47-2.76)
CR-AB	20 (57.1)	63 (61.2)	.68	.85 (0.39-1.84)
MDR-PA	6 (17.1)	16 (15.5)	.82	1.13 (0.40-3.15)
Previous hospitalization*	24 (68.6)	41 (39.8)	.00	3.30 (1.46-7.46)
Invasive procedures†	31 (88.6)	88 (85.4)	.86	1.32 (.41-4.28)
Comorbidities				
Cerebrovascular disease	16 (45.7)	20 (19.4)	.00	3.50 (1.53-7.98)
Dementia	7 (20)	6 (5.8)	.03	4.04 (1.26-13.01)
Chronic kidney disease	11 (31.4)	15 (14.6)	.03	2.69 (1.09-6.61)
Charlson comorbidity score	3 (1-4)	2 (1-3)	.00	
≤1	9 (25.7)	45 (43.7)	.06	0.45 (0.19-1.05)
2-3	13 (37.1)	41 (39.8)	.78	0.89 (0.41-1.97)
≥4	13 (37.1)	17 (16.5)	.01	2.99 (1.26-7.07)
APACHE II score	17 (16-18)	10 (8-12)	<.001	
≤10	3 (8.6)	59 (57.3)	<.001	0.07 (0.02-0.24)
11-14	1 (2.9)	34 (33)	<.001	0.06 (0.01-0.46)
≥15	31 (88.6)	10 (9.7)	<.001	72.08 (21.09-246.27)
Previous antibiotic therapy‡	30 (85.7)	67 (65.7)	.03	3.134 (1.12-8.79)
Inadequate initial antimicrobial treatment	19 (54.3)	28 (27.2)	.00	3.18 (1.44-7.04)
Postantibiogram antimicrobial regimens				
Monotherapy	15 (42.9)	42 (40.8)	.83	0.92 (0.42-2.00)
Combination therapy	20 (57.1)	61 (59.2)		
Hospital costs ($)	34,822 (15,034-119,367)	21,088 (8,773-40,095)	.01	

NOTE. Values are expressed as mean ± standard deviation, n (%), or median (interquartile range).
APACHE, Acute Physiology and Chronic Health Evaluation; *CR-AB*, carbapenem-resistant *Acinetobacter baumannii*; *CRE*, carbapenem-resistant Enterobacteriaceae; *MDR-PA*, multidrug-resistant *Pseudomonas aeruginosa*.
*During the 12 months preceding bloodstream infection onset.
†During the 72 hours preceding bloodstream infection onset.
‡During the 30 days preceding bloodstream infection onset.