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Factors influencing mortality in hospital-acquired pneumonia caused by Gram-negative bacteria in China

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ABSTRACT

Background: Hospital-acquired pneumonia (HAP) remains an important cause of morbidity and mortality despite advances in antimicrobial therapy. The emergence of Gram-negative bacteria (GNB) is of major concern. The objective of this study was to describe the epidemiology, microbiology, and predictors of infection-related 30-day mortality in HAP with GNB.
Methods: We performed a retrospective, single-center analysis of HAP patients with GNB occurring from January 2014 and December 2017. Univariate and multivariate analyses were performed to identify the risk factors for mortality.
Results: During the observational period, there were 1472 cases of HAP; 314 cases were bacterial culture-positive, 269 cases were caused by GNB, with a predominance of *Acinetobacter baumannii* and *Pseudomonas aeruginosa*. The mortality related to GNB was 14.5% (39 deaths).In the multivariate logistic regression analysis, the risk factors for mortality were age >70 years, intensive care unit (ICU) admission, blood lymphocyte count $< 0.8 \times 10^9$/L, multidrug-resistant Gram-negative bacteria(MDR-GNB) infection, and elevation of blood urea nitrogen(BUN) level. We identified these factors as significant predictors of GNB related mortality; the area under the receiver operating characteristic (ROC) curves was 0.836.
Conclusion: The results provided can help clinicians in identifying individuals who are at risk of infection-related 30-day mortality in HAP with GNB.

Background

Hospital-acquired pneumonia (HAP) is a common hospital-acquired infection resulting in prolonged hospital stay, increased burden, and high patient mortality [1]. In the United States, HAP is the second most common nosocomial infection, with the incidence ranging from 0.5–1% [2]. Studies in China have recorded the incidence of HAP to be 1.74–6.4% [3,4]. HAP was noted as the most common hospital-acquired infection in adult intensive care units in Vietnam [5]. Bacterial infection is the main cause of HAP, which means it is important to determine its etiology [2,6].Gram-negative bacteria are more prevalent than Gram-positive bacteria in HAP [6,7], resulting in longer hospital lengths of stay, increased costs, and high mortality [8,9].The objective of this study was to describe the epidemiology, microbiology, and predictors of infection-related 30-day mortality in HAP with Gram-negative bacteria (GNB).

Methods

Data related to all episodes of HAP caused by GNB that occurred in the third affiliated hospital of Sun Yat-sen University, Guangdong, China, between January 2014 and December 2017 were collected. All included patients were at least 18 years old. The criteria for a diagnosis of HAP [2] included a new pulmonary infiltrate confirmed by X-ray or computed tomography (occurred ≥48 h after admission) associated with at least one of the following: new or worsening cough with or without sputum production, fever (temperature >37.8 °C) or hypothermia (<35.6 °C), leukocy-

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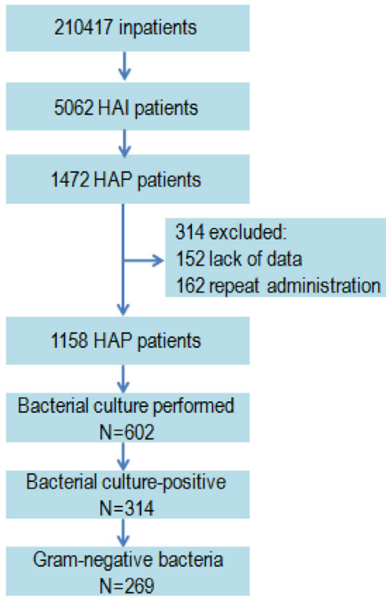

Fig. 1. Analysis plan.

tosis, left shift, or leukopenia based on local normal values. Cases of ventilator-associated pneumonia, acquired immune deficiency syndrome, and those missing key data were excluded.

Pathogenic organisms [10] were identified through quantitative culture ($\geq 10^4$ colony forming units/mL) of bronchoalveolar lavage specimen, semiquantitative culture (moderate or heavy growth) of bronchoscopic aspirate or bronchoalveolar lavage specimen of endotracheal aspirate with white blood cell count >25 cells/high power field on Gram stain, or adequate sputum with white blood cell count >25 cells/ high power field and <10 epithelial cells on Gram stain. Pathogenic organism susceptibility testing was performed by adopting the micro dilution method (MicroScan system; Baxter Health Care, West Sacramento, CA, USA), and the results were interpreted according to the National Committee for Clinical Laboratory Standards guidelines published in 2012 (Clinical and Laboratory Standards Institute, 2012).Here, multidrug-resistant Gram-negative bacteria(MDR-GNB)were defined as organisms resistant to at least one agent of three or more antimicrobial categories in susceptibility tests of isolates from patients with HAP. The antimicrobial categories used in this investigation were aminoglycosides, carbapenems, cephalosporins, fluoroquinolones, penicillin + β-lactamase inhibitors, and polymyxin [11]. Statistical analyses of parametric data were reported as frequency, percentage, mean value, and standard deviation. Nonparametric data were reported as frequency and percentage. Simple logistic regression analysis was used and each independent variable was analyzed together with the dependent variable pneumonia. This is reported as the *P* value and odds ratio (OR). A receiver operating characteristic (ROC) curve was used to analyze the probability of GNB-related mortality. The accepted level of significance was $P < 0.05$. Statistical analysis was performed using SPSS Statistics version 20 (IBM Corp., Armonk, NY, USA).

Results

During the observational period, 1472 cases of HAP occurred among 210,417 inpatients; 314 cases were bacterial culture-positive and 269 cases were due to GNB (Fig. 1), with a predominance of *Acinetobacter baumannii* (28.4%), *Pseudomonas aeruginosa* (24.6%) and *Klebsiella pneumonia* (18.2%) (Table 1) and164 (61.0%) were due to MDR-GNB. There were 107 cases

Table 1
Distribution of GNB.

Pathogenic organisms	n = 285 (%)
Acinetobacter baumannii	81 (28.4%)
Pseudomonas aeruginosa	70 (24.6%)
Klebsiella pneumonia	52 (18.2%)
Stenotrophomonas maltophilia	31 (10.9%)
Escherichia coli	16 (5.6%)
Enterobacter cloacae	10 (3.5%)
Others	25 (8.8%)

Table 2
Demographic, laboratory and clinical variables of 269 HAP with GNB.

Characteristics	Value
Age > 70, y	107 (39.8%)
Gender: male	194 (72.1%)
Smoke	60 (22.3%)
Diabetes mellitus	34 (12.6%)
COPD	24 (8.9%)
Antibiotics therapy in the preceding 90 days	184 (68.4%)
Prior endotracheal tracheostomy	64 (23.8%)
Stomach tube intubation	160 (59.5%)
Central venous catheterization	86 (32.0%)
Multi-lobular infiltration	228 (84.8%)
CRP	54.77 ± 39.05
WBC, *10e9/l	11.46 ± 6.90
Lymphocyte count < 0.8*10e9/l	83 (30.9%)
BUN	7.91 ± 6.67
MDR	164 (61.0%)
Use of PPI	188 (69.9%)
ICU admission	18 (6.7%)
Related mortality	39 (14.5%)

Abbreviations: COPD: chronic obstructive pulmonary disease; CRP: C-reactive protein; WBC: white blood cell; BUN: blood urea nitrogen; MDR: multidrug resistant; PPI: proton pump inhibitor; ICU: intensive care unit.

(39.8%) among patients older than 70 years; 184 (68.4%) patients had antibiotic therapy in the preceding 90 days. One hundred and sixty (59.5%) cases underwent gastric intubation and 18(6.7%) were admitted to the intensive care unit (ICU). Eighty-three (30.9%) had blood lymphocyte count $<0.8 \times 10^9$/L, and blood urea nitrogen (BUN) level 7.91 ± 6.67 mmol/L. The mortality rate related to GNB was 14.5% (39 deaths) (Table 2).

Logistic regression analysis identified independent risk factors for 30-day mortality: age > 70 years, ICU admission, blood lymphocyte count $<0.8 \times 10^9$/L, MDR-GNB infection, elevation of BUN level, C-reactive protein level, neutrophil-to-lymphocyte count ratio, and proton pump inhibitor use. In the multivariate logistic regression analysis, with $p < 0.20$ was considered as criterion for selection of variables, the risk factors for mortality were age > 70 years (odds ratio [OR] = 3.053, 95% confidence interval (CI): 1.291–7.221, P = 0.01), ICU admission(OR = 5.920, 95% CI: 1.586–22.100, P = 0.01), blood lymphocyte count < 0.8 × 109/L (OR = 2.503, 95% CI: 1.094–5.727, P = 0.03), MDR-GNB infection (OR = 6.025, 95%CI: 1.894–19.166, P < 0.001), and elevation of BUN level(OR = 1.080, 95% CI: 1.014–1.149, P = 0.02) (Table 3). We identified these factors as significant predictors of GNB-HAP related mortality; the area under the receiver operating characteristic (ROC) curve was 0.836 Fig. 2.

Discussion

In this study, we noted that GNB was the major pathogen of HAP similar to that seen in previous studies [6,7,12]. This occurred because warmer climates, increased prevalence of organisms in the environment and the developing world tend to have higher rates of

Table 3
Significant univariate and multivariate logistic regression analyses of risk factors associated with 30-day mortality.

Characteristics	Related mortality	Survival	Univariate			Multivariate		
	n = 39 (14.5%)	n = 230 (85.5%)	OR	95% CI	P	OR	95% CI	P
Age > 70, y	28 (71.8%)	79 (34.3%)	4.865	2.301–10.286	<0.001	3.053	1.291–7.221	0.01
Gender: male	27 (69.2%)	167 (72.6%)			0.664			
Smoke	7 (17.9%)	53 (23.0%)			0.481			
Diabetes mellitus	6 (15.4%)	28 (12.2%)			0.578			
COPD	5 (12.8%)	19 (8.3%)			0.36			
Antibiotics therapy in the preceding 90 days	32 (82.1%)	152 (66.1%)			0.053			
Prior endotracheal tracheostomy	6 (15.4%)	58 (25.2%)			0.188			
Stomach tube intubation	28 (71.8%)	132 (57.4%)			0.094			
Central venous catheterization	11 (28.2%)	75 (32.6%)			0.586			
Multi-lobular infiltration	32 (82.1%)	196 (85.2%)			0.612			
CRP	68.87 ± 34.44	52.37 ± 39.35	1.009	1.001–1.016	0.02			
WBC, *10e9/l	10.67 ± 5.88	11.60 ± 7.06			0.569			
Lymphocyte count < 0.8*10e9/l	19 (48.7%)	64 (27.8%)	2.464	1.235–4.917	0.011	2.503	1.094–5.727	0.03
BUN	13.24 ± 12.21	6.97 ± 4.54	1.124	1.062–1.189	<0.001	1.08	1.014–1.149	0.02
MDR	35 (89.7%)	129 (56.1%)	6.851	2.358–19.908	<0.001	6.025	1.894–19.166	<0.001
Use of PPI	34 (87.2%)	154 (67.0%)	3.356	1.262–8.925	0.015			
ICU admission	9 (23.1%)	9 (3.9%)	7.367	2.711–20.016	<0.001	5.920	1.586–22.100	0.01

Notes: Data were presented by median (interquartile range), numbers (percentage), or mean ± standard deviation (x ± s) (continuous). Continuous variables were compared using student's t-test or Mann-Whitney U-test and categorical variables using Pearson's chi-square or Fisher's exact probability test. P-value <0.05 is considered significant. *Abbreviations*: COPD: chronic obstructive pulmonary disease; CRP: C-reactive protein; WBC: white blood cell; BUN: blood urea nitrogen; MDR: multidrug resistant; PPI: proton pump inhibitor; ICU: intensive care unit.

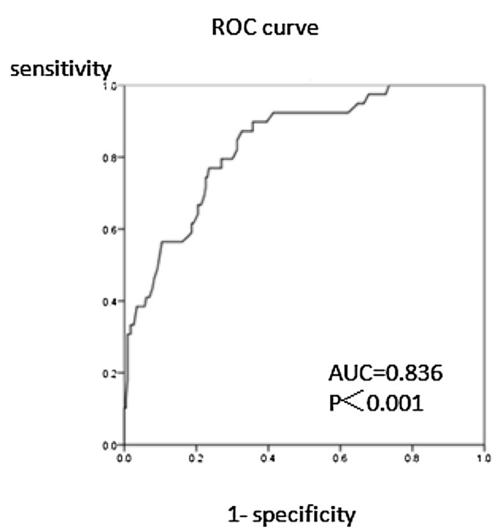

Fig. 2. The area under of the ROC curve for predicting 30-day mortality.
Abbreviation: AUC, area under curve.

infection with GNB, especially with *Acinetobacter* [6,13]. The most common organisms responsible for GNB-HAP were *A. baumannii*, *P. aeruginosa*, and *K. pneumoniae*. This finding was similar to that reported previously. Some reports have concluded that *P. aeruginosa*, *K. pneumoniae*, *Escherichia coli*, and *A. baumannii* are the key pathogenic bacteria involved in HAP [14,15]. The rate of MDR-GNB in this study was similar to that seen previously [16,17], thus indicating that MDR-GNB infection remains a challenging aspect of HAP etiology. Our 30-day mortality rate of 14.5% is consistent with the GNB-HAP mortality reported by other researchers [8,9]. This indicates that attention should be paid to the prevention and control of risk factors of GNB-HAP mortality in order to reduce the mortality and improve HAP prognosis.

Age>70 years was a risk factor for GNB-HAP 30-day mortality in this study. This is similar to previous studies that showed that increasing age is a predictive factor for mortality in pneumonia patients [9,18]. Aging is associated with a progressively weakened immune system and decreased lung performance [9]. Although there were only 18 patients with ICU admission, the 30-day mortality was still related to ICU admission in this study because antimicrobial resistance is an increasing concern in ICUs worldwide [19] and the illness maybe severer among patients who need ICU admission. A previous study had shown that lower lymphocyte count tended to be associated with higher mortality with GNB infection [20]. Peripheral blood lymphocyte count <0.8 × 10^9/L was also an independent risk factor for 30-day mortality in this study. Patients with peripheral blood lymphocyte count <0.8 × 10^9/L may have poor host response to GNB-HAP and with poor results [21]. Most GNB-HAP pathogens are MDR bacteria; in the current study, 61% were MDR bacteria. Some studies found that the rate of MDR bacteria among HAP pathogens was more than 46% [22,23]. Barbier et al. found that MDR bacteria have an increasing trend to cause HAP, especially multidrug-resistant Gram-negative bacteria [24].The prognosis for HAP caused by MDR bacteria is worse and has higher mortality [2]. BUN level plays an important role in pneumonia because patients with pneumonia often have hydration status resulting in increasing reabsorption of urea by the kidneys, and elevation of BUN level is frequently observed [25,26]. In the current study, severer pneumonia may reflect serious hydration status, and result in elevation of BUN level with high mortality. The area under the ROC curve of GNB-HAP related 30-day mortality was 0.836, showing that the predicted value was good.

There are several limitations of this study that may decrease the impact of the results presented. First, as a retrospective study, coding practices can vary over time due to policy and other systemic changes, which may introduce bias that we do not fully account for [27]. Second, the sample of this study was small resulting in sparse data bias. Third, the regression model was created based more on statistical approaches than prior knowledge, which was similar to the phenomenon mentioned by the researchers [28]. Fourth, this study is lack of bootstrapping conduct for checking internal validity, it meant the model may be along with degree of optimism [29]. We will try to enlarge the sample and take prospective study to reduce bias in future.

Conclusion

The results indicate that GNB was the main pathogenic bacteria of HAP, with a predominance of *A. baumannii* and *P. aeruginosa*. The findings highlight the risk factors of GNB-related 30-day mortality to enable clinicians identify individuals who are at risk of mortality.

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Competing interests

None declared.

Ethics approval

The study has been approved by the institutional review board of the hospital and the ethics committee of the third affiliated hospital of Sun Yat-sen University (No. 2018-295-01).

References

[1] Craven DE, Chroneou A. Nosocomial pneumonia. In: Mandell GL, Bennet JE, Dolin R, editors. Principles and practice of infectious diseases. 7th ed. Philadelphia [PA]: Elsevier Churchill Livingstone; 2010. p. 3717–25.
[2] Kalil AC, Metersky ML, Klompas M, Muscedere J, Sweeney DA, Palmer LB, et al. Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 clinical practice guidelines by the Infectious Diseases Society of America and the American Thoracic Society. Clin Infect Dis 2016;63(September (5)):e61–111, http://dx.doi.org/10.1093/cid/ciw353. Epub 2016 Jul 14.
[3] Tao XB, Qian LH, Li Y, Wu Q, Ruan JJ, Cai DZ, et al. Hospital-acquired infection rate in a tertiary care teaching hospital in China: a cross-sectional survey involving 2434 inpatients. Int J Infect Dis 2014;27:7–9, http://dx.doi.org/10.1016/j.ijid.2014.05.011.
[4] Zhu J, Zhang X, Shi G, Yi K, Tan X. Atrial fibrillation is an independent risk factor for hospital-acquired pneumonia. PLoS One 2015;10(7), http://dx.doi.org/10.1371/journal.pone.0131782, e0131782.
[5] Phu VD, Wertheim HFL, Larsson M, Nadjm B, Hanberger H. Burden of hospital acquired infections and antimicrobial use in vietnamese adult intensive care units. PLoS One 2016;11(1), e0147544.
[6] Enne VI, Personne Y, Grgic L, Gant V, Zumla A. Aetiology of hospital-acquired pneumonia and trends in antimicrobial resistance. Curr Opin Pulm Med 2014;20:252–8, http://dx.doi.org/10.1097/MCP.0000000000000042.
[7] Iwata K, Igarashi W, Honjo M, Oka H, Oba Y, Yoshida H, et al. Hospital-acquired pneumonia in Japan may have a better mortality profile than HAP in the United States: a retrospective study. J Infect Chemother 2012;18:734–40.
[8] Dehghan F, Zolghadri N, Boostani V, Shafii A, Eftekhaari TE. Resistance of gram negative bacteria in hospital acquired pneumonia: a prospective study. Braz J Infect Dis 2016;20(January–February (1)):113–4, http://dx.doi.org/10.1016/j.bjid.2015.11.006. Epub 2015 Dec 22.
[9] Kim T, Chong YP, Park SY, Jeon MH, Choo EJ, Chung JW, et al. Risk factors for hospital-acquired pneumonia caused by carbapenem-resistant gram-negative bacteria in critically ill patients: a multicenter study in Korea. Diagn Microbiol Infect Dis 2014;78(4):457–61, http://dx.doi.org/10.1016/j.diagmicrobio.2013.08.011.
[10] Elias J, Frosch M, Vogel U. Neisseria. In: Versalovic J, Carroll KC, Funke G, Jorgensen JH, Landry ML, Warnock DW, editors. Manual of clinical microbiology. 10th ed. Washington, DC: American Society of Microbiology; 2011. p. 677e91.
[11] Magiorakos AP, Srinivasan A, Carey RB, Carmeli Y, Falagas ME, Giske CG, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. Clin Microbiol Infect 2012;18(3):268–81, http://dx.doi.org/10.1111/j.1469-0691.2011.03570.x.
[12] Chung DR, Song JH, Kim SH, Thamlikitkul V, Huang SG, Wang H, et al. High prevalence of multidrug-resistant nonfermenters in hospital-acquired pneumonia in Asia. Am J Respir Crit Care Med 2011;184:1409–17.
[13] Reechaipichitkul W, Phondongnok S, Bourpoern J, Chaimanee P. Causative agents and resistance among hospital-acquired and ventilator-associated pneumonia patients at Srinagarind hospital, northeastern Thailand. Southeast Asian J Trop Med Public Health 2013;44:490–502.
[14] Torres A, Ewig S, Lode H, Carlet J, European HAP working group. Defining, treating and preventing hospital acquired pneumonia: European perspective. Intensive Care Med 2009;35:9–29, http://dx.doi.org/10.1007/s00134-008-1336-9.
[15] Pássaro L, Harbarth S, Landelle C. Prevention of hospital-acquired pneumonia in non-ventilated adult patients: a narrative review. Antimicrob Resist Infect Control 2016;5:43, eCollection 2016.
[16] Uvizl R, Hanulik V, Husickova V, Htoutou Sedlakova M, Adamus M, Kolar M. Hospital-acquired pneumonia in ICU patients. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub 2011;155:373–8, http://dx.doi.org/10.5507/bp.2011.067.
[17] Zhao T, Liu Y, Cao B, Wang H, Chen L, She D, et al. Prospective multicenter study of pathogen distributions in early-onset and late-onset hospital-acquired pneumonia in China. Antimicrob Agents Chemother 2013;57:6404–5, http://dx.doi.org/10.1128/AAC.01539-13.
[18] Sligl WI, Eurich DT, Marrie TJ, Majumdar SR. Age still matters: prognosticating short- and long-term mortality for critically ill patients with pneumonia. Crit Care Med 2010;38:2126–32.
[19] Cohen J. Confronting the threat of multidrug-resistant gram-negative bacteria in critically ill patients. J Antimicrob Chemother 2013;68:490–1.
[20] Qiao B, Wu J, Wan Q, Zhang S, Ye Q. Factors influencing mortality in abdominal solid organ transplant recipients with multidrug-resistant gram-negative bacteremia. BMC Infect Dis 2017;17(February (1)):171, http://dx.doi.org/10.1186/s12879-017-2276-1.
[21] Van Vught LA, Scicluna BP, Wiewel MA, Hoogendijk AJ, Klein Klouwenberg PM, Franitza M, et al. Comparative analysis of the host response to community-acquired and hospital-acquired pneumonia in critically ill patients. Am J Respir Crit Care Med 2016;194(December (11)):1366–74.
[22] Cardoso T, Almeida M, Carratalà J, Aragão I, Costa-Pereira A, Sarmento AE, et al. Microbiology of healthcare-associated infections and the definition accuracy to predict infection by potentially drug resistant pathogens: a systematic review. BMC Infect Dis 2015;15:565, http://dx.doi.org/10.1186/s12879-015-1304-2.
[23] Denys GA, Relich RF. Antibiotic resistance in nosocomial respiratory infections. Clin Lab Med 2014;34:257–70, http://dx.doi.org/10.1016/j.cll.2014.02.004.
[24] Barbier F, Andremont A, Wolff M, Bouadma L. Hospital-acquired pneumonia and ventilator-associated pneumonia: recent advances in epidemiology and management. Curr Opin Pulm Med 2013;19:216–28, http://dx.doi.org/10.1097/MCP.0b013e32835f27be.
[25] Woodford-Williams E. Respiratory tract disease. Diagnosis and management of pneumonia in the aged. Br Med J 1966;1:467–70.
[26] Kasper DL, Fauci AS, Longo DL, editors. Harrison's principles of internal medicine. 16th ed New York, NY: McGraw-Hill Professional; 2004.
[27] Gohil SK, Cao C, Phelan M, Tjoa T, Rhee C, Platt R, et al. Impact of policies on the rise in sepsis incidence, 2000–2010. Clin Infect Dis 2016;62(March (6)):695–703, http://dx.doi.org/10.1093/cid/civ1019. Epub 2016 Jan 19.
[28] Ayubi E, Sani M. Carotid atherosclerosis is associated with left ventricular diastolic function: methodological issue. J Echocardiogr 2016;14(December (4)):181. Epub 2016 Aug 26.
[29] Ashrafi-Asgarabad A, Ayubi E, Safiri S. Predictors of health-related quality of life in people with amyotrophic lateral sclerosis: Methodological issues. J Neurol Sci 2017;372(January):228, http://dx.doi.org/10.1016/j.jns.2016.11.063. Epub 2016 Nov 24.