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Differences in microbial etiology between hospital-acquired pneumonia and ventilator-associated pneumonia: a single-center retrospective study in Guang Zhou

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Purpose: Nosocomial pneumonia is a common nosocomial infection that includes hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia(VAP). It is an important cause of morbidity and mortality in hospitalized patients. This study aimed to evaluate the differences in microbial etiology and outcomes between HAP and VAP, particularly in related risk factors of multidrug-resistant organism (MDRO) causing HAP and VAP.

Patients and methods: This single-center retrospective, observational study included patients with HAP/VAP. Clinical and epidemiological data of nosocomial pneumonia confirmed by microbial etiology that occurred in the Third Affiliated Hospital of Sun Yat-sen University, China, from January 2014 to December 2017 were obtained.

Results: A total of 313 HAP cases and 106 VAP cases were included. The leading pathogens of HAP and VAP were similar, including *Acinetobacter baumannii, Pseudomonas aeruginosa*, and *Klebsiella pneumoniae*. Antimicrobial susceptibility of the pathogens was low, and *P. aeruginosa* in VAP was less susceptible. In the multivariate logistic regression analysis, the risk factors associated with MDRO-HAP were chronic obstructive pulmonary disease, antibiotic therapy in the preceding 90 days, and prior endotracheal tracheostomy. The risk factor of MDRO-VAP was ≥5 days of hospitalization. The 30-day mortality rates of HAP and VAP were 18.5% and 42.5%.

Conclusion: The leading pathogens were similar in both HAP and VAP, and antimicrobial susceptibility of the pathogens was low. The risk factors associated with MDRO infection in HAP and VAP have significant variability; hence, attention should be paid to improve prognosis. VAP was associated with poorer outcomes compared with HAP.

Keywords: hospital-acquired pneumonia, ventilator-associated pneumonia, epidemiology, microbial etiology

Introduction

Nosocomial pneumonia (NP), including hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP), is an important cause of morbidity and mortality in hospitalized patients despite advances in antimicrobial therapy and better supportive care modalities.[1,2] Comparing the 2005 version guideline with the 2016 version guideline of the Infectious Diseases Society of America and the American Thoracic Society, HAP had different definitions; in 2016 version, it emphasized that HAP was not associated with mechanical ventilation (MV), but remained a confusing area.[3,4] VAP is related to the

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duration of MV, intensive care unit (ICU) and hospital length of stay, and healthcare costs.[2] This demands a focus on the difference between HAP and VAP characteristics and prognosis. Clinical practice guidelines developed by international societies need to be tailored according to local epidemiology.[5] Meanwhile,bacterial infection is the main cause of NP, and multidrug-resistant organism(MDRO) has appeared in recent years;hence, the risk factors of MDRO must be identified to facilitate the accurate prescription of antibiotics and improve overall prognosis in cases of NP.[6,7] This study aimed to evaluate the differences in microbial etiology between HAP and VAP, especially in related risk factors and prognosis caused by MDRO.

Material and methods

This single-center retrospective, observational study included patients with HAP/VAP. Data on all episodes of NP that occurred in the Third Affiliated Hospital of Sun Yat-sen University, Guangdong, China, from January 2014 to December 2017 were collected. All patients were at least 18 years old. The criteria for a NPdiagnosis[4] includedthe presence of a new pulmonary infiltrate acquired in the hospital with two or more of the following: temperature >38.3 °C or <36 °C, leukocyte count $>10\times10^9$/L or $<4\times10^9$/L, and the presence of purulent respiratory secretions. HAP was defined as pneumonia that occurred ≥48h after admission, with no association with MV. VAP was defined as pneumonia that occurred 48–72 h after the intubation and initiation of MV. All cases were confirmed by microbial etiology. Cases with acquired immunodeficiency syndrome and those missing key data were excluded.

The simplified version of the clinical pulmonary infection score (CPIS), which determined temperature, blood leukocytes, tracheal secretions, PaO_2/FiO_2, and chest radiograph to assess the severity of NP, was used.

A microbiological strategy was then followed for the establishment of diagnosis: lower respiratory tract samples were obtained by bronchoalveolar lavage, endotracheal aspiration,or adequate sputum culture with WBCs >25 cells/HPF and epithelial cells <10 cells on Gram stain. Pathogenic bacteria were further characterized by conventional biochemical tests to identify the specific strain using standard microbiological methods. Pathogenic organism susceptibility testing was performed using the microdilution method (Micro ScanSystem; Baxter Healthcare, West Sacramento, CA, USA), and the results were interpreted using the National Committee for Clinical Laboratory Standards guidelines published in 2012 (Clinical & Laboratory Standards Institute, 2012). Here, MDROs were defined as organisms that were resistant to at least one agent from each of the three or more antimicrobial categories in susceptibility tests of isolates from patients with NP.[8] In the statistical analysis, the parametric data were reported as frequency, percentage, mean value, and standard deviation, while nonparametric data were reported as frequency and percentage. Simple logistic regression analysis was performed, and each independent variable was analyzed together with the dependent variable of NP. These were reported as the *P*-value and odds ratio (OR). The accepted level of significance was $P<0.05$. Statistical analysis was performed using IBM SPSS Statistics, version 20 (IBM Corp., Armonk, New York, America).

Results

A total of 1,158 patients had HAP, and only 313 cases were included because 556 patients did not undergo bacterial culture and 289 patients had a negative bacterial culture result. Among the 2,901 inpatients under MV, 106 patients had VAP, and they were included. By comparing the characteristics between HAP and VAP, we found that less VAP patients were aged >70years, and VAP patients had more antibiotic therapy in the preceding 90 days and prior endotracheal tracheostomy (Table 1). The leading pathogens were similar in both kinds of NP, including *Acinetobacter baumannii, Pseudomonas aeruginosa*, and *Klebsiella pneumoniae*, but *A.baumannii*was significantly abundant in VAP. *K.pneumonia and Staphylococcus aureus* were significantly predominant in HAP (Table 2). Of these, VAP had more MDROs (Table 1). Moreover, the antimicrobial susceptibility of *A.baumannii, K. pneumonia* and *Staphylococcus aureus* was similar in both groups (Table 3, Table 4). However, *P. aeruginosa* causing VAP was less susceptible than *P. aeruginosa* causing HAP (Table 3). A CPIS ≥6 was predominant in the VAP group. The 30-day mortality rates of HAP and VAP were 18.5% and 42.5%, respectively (Table 1).

To determine the distinction between HAP and VAP, this study analyzed the risk factors for MDRO-HAP and MDRO-VAP. The first logistic regression analysis identified the following risk factors for MDRO-HAP: chronic obstructive pulmonary disease (COPD), antibiotic therapy in the preceding 90 days, prior endotracheal tracheostomy, stomach tube intubation, and elevated blood urea nitrogen (BUN) level. Meanwhile, only ≥5 days of hospitalization and albumin level were considered the risk factors for MDRO-VAP. In the second multivariate analysis, COPD (P=0.023; OR, 3.006; 95% confidence interval [CI], 1.166–7.751), antibiotic therapy in the preceding 90 days (P=0.02; OR, 1.843; 95% CI,

Table 1 The characteristics difference between HAP and VAP

Characteristics	HAP n=313	VAP n=106	*P*
Age＞70, years	123(39.3%)	27(25.5%)	0.007
Gender: male	227(72.5%)	71(67.0%)	0.276
≥5 days of hospitalization	270(86.3%)	91(85.8%)	0.915
Smoke	69(22.0%)	17(16.0%)	0.186
Diabetes mellitus	45(14.4%)	12(11.3%)	0.428
Heart failure	41(13.1%)	16(15.1%)	0.605
Cerebrovascular disease	127(40.6%)	39(36.8%)	0.491
COPD	30(9.6%)	10(9.4%)	0.964
Antibiotics therapy in the preceding 90 days	217(69.3%)	101(95.3%)	＜0.001
prior endotracheal tracheostomy	71(22.7%)	36(34.0%)	0.021
Stomach tube intubation	179(57.2%)	86(81.1%)	＜0.001
Central venous catheterization	98(31.3%)	66(62.3%)	＜0.001
ALB,g/L	35.39±4.97	35.76±5.30	0.748
BUN, mmol/L	8.65±7.07	13.53±9.41	＜0.001
MDRO	193(61.7%)	78(73.6%)	0.026
CPIS≥6	162(51.8%)	83(76.9%)	＜0.001
30-day Mortality	58(18.5%)	45(42.5%)	＜0.001

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: HAP, hospital-acquired pneumonia; VAP, ventilator-associated pneumonia; COPD, chronic obstructive pulmonary disease; ALB, albumin; BUN, blood urea nitrogen; MDRO, multidrug resistant organism; CPIS, clinical pulmonary infection score.

Table 2 Distribution of pathogens between HAP and VAP

Pathogenic organisms	HAP n=327 (%)	VAP n=110 (%)	*P*
Acinetobacter baummannii	81(24.8%)	59(53.6%)	＜0.001
Pseudomonas aeruginosa	70(21.4%)	20(18.2%)	0.469
Klebsiella pneumonia	45(13.8%)	6(5.5%)	0.019
Staphylococcus aureus	45(13.8%)	4(3.6%)	0.003
Escherichia coli	14(4.3%)	3(2.7%)	0.579
Others	72(22.0%)	18(16.4%)	0.205

Abbreviations: HAP, hospital-acquired pneumonia;VAP, ventilator-associated pneumonia.

1.102–3.081), and prior endotracheal tracheostomy (*P*=0.033; OR, 1.932; 95% CI, 1.055–3.539) were still associated with MDRO-HAP (Table 5). Furthermore, only≥5 days of hospitalization (*P*=0.01; OR, 0.021; 95% CI, 0.065–0.685) was associated with MDRO-VAP (Table 6).

Discussion

In this study, we found that less VAP patients had age >70years. Although it was similar to HAP in that VAP incidence was lower in the elderly,[9] the causes of these observations in the elderly are imperfectly understood. Survival bias might be a factor, that is, because of the elderly's comorbid conditions, they died before or during VAP acquisition.[10,11] VAP patients had to undergo more antibiotic therapy in the preceding 90 days, because this kind of patients had comorbidities requiring antibiotic therapy or preventive medication before MV. The patients who had prior endotracheal tracheostomy were more likely to have VAP in the current study; this is because they could easily be exposed to bacterial colonization,[12] and changes to the airway structure are a further risk factor. As VAP often occurred in the ICU, it suggested that patients were in critical condition and frequently required stomach tube intubation and central venous catheterization. This was consistent with our research. We noted that the BUN level of VAP patients was higher than that of HAP patients. Because patients with pneumonia often had dehydrated status resulting in the increased reabsorption of urea by the kidneys, elevation of BUN level is frequently observed,[13,14] especially with VAP.

In the current study, the leading pathogens were similar in both kinds of NP, with a predominance of *A. baumannii, P. aeruginosa*, and *K. pneumonia*. But *A.baumannii* was significantly *abundant* in VAP, and *K. pneumonia* and *S. aureus* were commonly predominant in HAP. This is similar to the findings reported previously.[4,15,16] It suggested

Table 3 The antimicrobial susceptibility differences between HAP and VAP

Antibiotic	HAP	VAP	P1	HAP	VAP	P2	HAP	VAP	P3
	Acinetobacter baummannii (n=81)	Acinetobacter baummannii (n=59)		Pseudomonas aeruginosa (n=70)	Pseudomonas aeruginosa (n=20)		Klebsiella pneumonia (n=45)	Klebsiella pneumonia (n=6)	
PRL	10(12.3%)	5(8.5%)	0.465	58(82.9%)	12(60.0%)	0.03	14(31.1%)	0	1
CEF	13(16.0%)	7(11.9%)	0.485	56(80.0%)	12(60.0%)	0.066	25(55.6%)	2(33.3%)	0.402
CTR	11(13.6%)	4(6.8%)	0.425	43(61.4%)	1(5.0%)	<0.001	22(48.9%)	1(16.7%)	0.204
CFM	13(16.0%)	8(13.6%)	0.684	55(78.6%)	10(50.0%)	0.012	26(57.8%)	3(50.0%)	1
IMP	15(18.5%)	11(18.6%)	0.985	53(75.7%)	9(45.0%)	0.009	39(86.7%)	5(83.3%)	1
MER	14(17.3%)	13(22.0%)	0.482	55(78.6%)	8(40.0%)	0.001	37(82.2%)	5(83.3%)	1
TAZ	12(14.8%)	7(11.9&)	0.615	56(80.0%)	12(60.0%)	0.066	32(71.1%)	2(33.3%)	0.087
CIP	11(13.6%)	7(11.9&)	0.765	53(75.7%)	11(55.0%)	0.071	25(55.6%)	2(33.3%)	0.402
GEN	13(16.0%)	7(11.9&)	0.485	56(80.0%)	14(70.0%)	0.343	31(68.9%)	3(50.0%)	0.387
AMC	16(19.8%)	12(20.3%)	0.932	62(88.6%)	17(85.0%)	0.461	38(84.4%)	4(66.7%)	0.284
TGC	80(98.8%)	58(98.3%)	1	NA	NA	NA	45(100%)	6(100%)	1

Abbreviations: HAP, hospital-acquired pneumonia;VAP, ventilator-associated pneumonia; PRL, piperacillin; CEF, ceftazidime; CTR, ceftriaxone; CFM, cefepime; IMP:imipenem; MER, meropenem; TAZ, piperacillin/tazobactam; CIP, ciprofloxacin; GEN, gentamicin; AMC, amikacin; TGC, tigecycline; NA, not available.

Table 4 Antimicrobial susceptibility among Staphylococcus aureus of HAP and VAP

Antibiotic	HAP	VAP	*P*
	SA(n=45)	SA(n=4)	
PEN	5(11.1%)	0	1
OXA	7(15.6%)	0	1
TET	24(53.3%)	2(50.0%)	1
CLI	23(51.1%)	3(75.0%)	0.612
FOX	8(17.8%)	0	1
CHL	34(75.6%)	4(100%)	1
SXT	16(35.6%)	2(50.0%)	0.618
RIF	29(64.4%)	3(75.0%)	1
VAN	45(100%)	4(100%)	1
TEC	45(100%)	4(100%)	1
LNZ	45(100%)	4(100%)	1

Abbreviations: HAP, hospital-acquired pneumonia; VAP, ventilator-associated pneumonia; SA, Staphylococcus aureus; PEN, penicillin; OXA, oxacillin; TET, tetracycline; CLI, clindamycin; FOX, cefoxitin; CHL, chloramphenicol; SXT, Trimethoprim-sulfamethoxazole; RIF, rifampicin; VAN, vancomycin; TEC, teicoplanin; LNZ, linezolid.

that Gram-negative bacteria were the major NP pathogens in our center. This may be attributed to the warmer climate in our city, increased prevalence of organisms in the environment, and the higher prevalence of Gram-negative bacterial infections, especially *A.baumannii* infection in VAP, in the developing world.[17]Although *S. aureus* is the most common Gram-positive pathogen of NP,[18,19] it was still inferior to Gram-negative bacteria, especially in VAP. Our study demonstrated that VAP had more MDROs. Additionally, antimicrobial susceptibility of *P. aeruginosa* causing VAP was lower than that causing HAP, as in previous reports.[20,21] Meanwhile, this study found a higher rate of *A.baumannii* resistant to meropenem in these populations (82.7% in the HAP group and 78% in the VAP group).Similar resistance rates(79.5%–92.5%) to carbapenems were observed in previous studies of other hospitals,[22,23] indicating that MDRO infection remains a challenging aspect of NP etiology.

In this study, we assessed the risk factors associated with MDRO-NP. COPD was associated with MDRO-HAP because acute exacerbation of COPD usually requires antibiotic treatment.[24,25] Moreover, studies have shown that the colonization rates of Gram-negative bacteria such as *P. aeruginosa* and *A. baumannii* were higher in patients with COPD; therefore, it is easier for them to be repeatedly infected.[26,27] Antibiotics are crucial intreating infectious diseases including HAP. However, antibiotic resistance has increased, and the rise of MDR bacteria is threatening human health.[28] Antibiotic therapy in the preceding 90 days was an important risk factor for MDRO-HAP in the present study. This finding is similar to that of the previous studies that suggested the impact of virulence

Table 5 Significant univariate and multivariate logistic regression analyses of risk factors associated with HAP

Characteristics	Non-MDRO	MDRO	Univariate			Multivariate		
	n=120(%)	n=193(%)	OR	95%CI	*P*	OR	95%CI	*P*
Age＞70, years	41(34.2%)	82(42.5%)			0.101			
Gender: male	88(73.3%)	139(72.0%)			0.8			
≥5 days of hospitalization	106(88.3%)	164(85.0%)			0.402			
Smoke	23(19.2%)	46(23.8%)			0.334			
Diabetes mellitus	13(10.8%)	32(16.6%)			0.162			
Heart failure	11(9.2%)	30(15.5%)			0.108			
Cerebrovascular disease	45(37.5%)	82(42.5%)			0.383			
COPD	6(5.0%)	24(12.4%)	2.698	1.069–6.809	0.036	3.006	1.166–7.751	0.023
Antibiotics therapy in the preceding 90 days	71(59.2%)	146(75.6%)	2.144	1.313–3.501	0.002	1.843	1.102–3.081	0.02
prior endotracheal tracheostomy	20(16.7%)	51(26.4%)	1.796	1.009–3.198	0.047	1.932	1.055–3.539	0.033
Stomach tube intubation	61(50.8%)	118(61.1%)	1.522	0.960–2.411	0.074			
Central venous catheterization	40(33.3%)	58(30.1%)			0.543			
ALB,g/L	34.95±4.43	35.67±5.24			0.209			
BUN, mmol/L	7.66±5.79	9.34±7.73	1.04	1.000–1.082	0.05			

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. With $P<0.10$ was considered as criterion for selection of variables in the multivariate logistic regression analysis. *P*-value <0.05 is considered significant.

Abbreviations: HAP, hospital-acquired pneumonia; COPD, chronic obstructive pulmonary disease; ALB, albumin; BUN, blood urea nitrogen; MDRO, multidrug resistant organism.

Table 6 Significant univariate and multivariate logistic regression analyses of risk factors associated with VAP

Characteristics	Non-MDRO	MDRO	Univariate			Multivariate		
	n=28(%)	n=78(%)	OR	95%CI	*P*	OR	95%CI	*P*
Age>70, years	6(21.4%)	21(26.9%)			0.568			
Gender: male	19(67.9%)	52(66.7%)			0.909			
≥5 days of hospitalization	19(67.9%)	72(92.3%)	0.176	0.056–0.556	0.003	0.211	0.065–0.685	0.01
Smoke	7(25.0%)	10(12.8%)			0.139			
Diabetes mellitus	4(14.3%)	8(10.3%)			0.565			
Heart failure	6(21.4%)	10(12.8%)			0.28			
Cerebrovascular disease	11(39.3%)	28(35.9%)			0.75			
COPD	3(10.7%)	7(9.0%)			0.787			
Antibiotics therapy in the preceding 90 days	26(92.9%)	75(96.2%)			0.487			
prior endotracheal tracheostomy	9(32.1%)	27(34.6%)			0.813			
Stomach tube intubation	22(78.6%)	64(82.1%)			0.687			
Central venous catheterization	18(64.3%)	48(61.5%)			0.797			
ALB,g/L	33.96±3.86	36.40±5.63	1.116	1.009–1.235	0.033			
BUN, mmol/L	11.10±5.41	14.38±10.35			0.12			

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: VAP, ventilator-associated pneumonia; COPD, chronic obstructive pulmonary disease; ALB, albumin; BUN, blood urea nitrogen; MDRO, multidrug resistant organism.

and antibiotic tolerance.[24,29] Therefore, among patients with HAP who have been exposed to antibiotics, MDRO should be targeted to control the condition effectively and improve prognosis. Tracheotomy was also likely to lead to MDRO infection. This is because patients who had required MV or undergone tracheotomy can easily be exposed to MDRO colonization.[12] ICU admission or broad-spectrum antibiotic use also contributes to MDRO infection,[30] and changes to the airway structure are a further risk factor. Meanwhile, in our hospital, the rehabilitation department is famous in Guang Zhou, and there are many patients with tracheotomy coming to that department for rehabilitation treatment. Hence, tracheotomy became a risk factor of MDRO-HAP. The risk factor for MDRO with HAP or VAP was ≥5 days of hospitalization.[4,31] In this study, it was similar to VAP but not HAP, because VAP patients had long hospitalization, were easily exposed to antibiotics, and had induced bacterial resistance. In other words, the risk factors for MDRO in HAP and VAP were not the same.

The 30-day mortality rates of HAP and VAP were 18.5% and 42.5%, respectively, in this study. It was consistent with previous reports.[32,33] The reason why VAP had higher mortality rate was that the patients often had severe infection[34] or morbid state.[35] CPIS is a vital tool that evaluates the severity of pulmonary infection, and this score is positively correlated with the severity of pulmonary infection and prognosis.[36,37] The present study results support this finding, indicating an area for future research.

There are several limitations in our study. First, the sample size of this study was small, resulting in sparse data bias. Second, all clinical information related to the risk factors was collected retrospectively, which limits the generalization of our findings. Further prospective studies are warranted to reduce bias in the future.

Conclusion

HAP and VAP had similar pathogens, but antimicrobial susceptibility of VAP was lower, especially with *P. aeruginosa*. The risk factors associated with MDRO infection in HAP and VAP were different. VAP was associated with poorer outcomes compared with HAP.

Ethics approval and informed consent

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. The patient consent was written informed consent and their information has been kept confidential.

Data availability

The data used to support the findings of this study are available from the corresponding author upon request.

Abbreviation list

NP, Nosocomial pneumonia; HAP, hospital-acquired pneumonia; VAP, ventilator-associated pneumonia; MV, mechanical ventilation; ICU, intensive care unit; MDRO, multidrug-resistant organism; OR, odds ratio; COPD, chronic obstructive pulmonary disease; BUN, blood urea nitrogen; CPIS, clinical pulmonary infection score; CI, 95% confidence interval.

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Author contributions

All authors contributed toward data analysis, drafting and critically revising the paper, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors have no conflicts of interest to disclose in this work.

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