Methicillin-resistant Staphylococcus aureus pneumonia in diabetics: a single-center, retrospective analysis

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Abstract

Background: Methicillin-resistant *Staphylococcus aureus* (MRSA) pneumonia is an important issue with significant morbidity and mortality in clinical practice, especially in diabetes mellitus (DM). Studies focusing on *S. aureus* pneumonia in DM is limited, we sought to make a relatively comprehensive exploration of clinical characteristics, antimicrobial resistance, and risk factors for mortality of *S. aureus* pneumonia in DM and non-diabetics mellitus (non-DM).

Methods: A retrospective study was conducted in Ruijin Hospital from 2014 to 2017. The characteristics of DM and non-DM patients were assessed, including demographics, comorbidities, using of invasive mechanical ventilation, Hemoglobin A1c (HbA1C), confusion, urea, respiratory rate, blood pressure, age ≥65 years (CURB-65) score, length of hospital stay, clinical outcomes, antimicrobial susceptibility. Independent risk factors for mortality were identified by univariate and multivariate logistic regression analysis.

Results: A total of 365 patients with *S. aureus* pneumonia were included in our study, including 144 with DM and 221 non-DM. DM patients were more susceptible to MRSA infection (65.3% *vs.* 56.1%, $P > 0.05$), suffered from much severer pneumonia with a higher CURB-65 score, invasive mechanical ventilation rate (46.5% *vs.* 28.1%, $P < 0.01$) and mortality rates (30.6% *vs.* 23.1%, $P > 0.05$); almost all DM patients had higher antimicrobial resistance than non-DM patients, the DM group had a higher co-infection rate (47.2% *vs.* 45.7%, $P > 0.05$), and *Acinetobacter baumannii* was the most common bacterium in DM, while *Klebsiella pneumoniae* ranked first in patients with non-DM. Independent risk factors for pneumonia-related mortality were MRSA and CURB-65. Higher HbA1c levels were linked to a higher MRSA infection and co-infection rate and more severe pneumonia, leading to an increase in mortality.

Conclusions: DM patients with poor glucose control are more susceptible to MRSA infection. They suffer from higher antimicrobial resistance, a higher co-infection rate, and much severer pneumonia than non-DM. MRSA itself is an independent risk factor for mortality in all patients.

Keywords: Methicillin-resistant S. *aureus*; Pneumonia; Diabetics mellitus; Co-infection; Risk factor; HbA1c

Introduction

Staphylococcus aureus (*S. aureus*), a gram-positive coccus, can cause a variety of diseases including skin and soft-tissue infections, necrotizing pneumonia, infective endocarditis, bacteremia, and osteomyelitis. Among its more than 200 different strains, methicillin-resistant *S. aureus* (MRSA) which was emergence shortly after the introduction of methicillin in 1960s, remains as the most serious infectious diseases in many hospitals and health care settings worldwide.[1-6] These MRSA strains have since become resistant to other antibiotics including macrolides, lincosamides, and all beta-lactams except the fifth generation of cephalosporine. More recently, multi-drug-resistant MRSA strains have acquired resistance against vancomycin.[7]

MRSA is highly prevalent in hospitals worldwide and particularly high rates (>50%) have been reported in Asia, Malta, North and South America, and the average detection of MRSA in China is 35.3% in 2017.

Because of their increased risk of hyperglycemia, decreased immunity, impaired lung function, and chronic complications such as heart disease, renal failure, and pulmonary microangiopathy, diabetes mellitus (DM) subjects are susceptible to infection, especially pneumonia.[8] In some small-scale studies, DM has been associated with increased *S. aureus* nasal carriage. Considering the susceptibility to *S. aureus* in subjects with poor immunity and the decreased immunity in DM subjects, it is important to explore the incidence, clinical characteristics, outcomes,

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antibiotic sensitivity, and risk factors of *S. aureus* in patients with DM.

Methods

Setting

Ruijin Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, is a comprehensive large hospital, consisting of medical, surgical, intensive care units, pediatrics, obstetrics, and gynecology.

Inclusion criteria

We performed retrospective cohort study that included 365 individuals in Ruijin Hospital from April 21, 2014 to December 31, 2017. The strains were isolated from sputum; therefore, all the patients' sputum cultures are *S. aureus* positive and from airway infections.

Clinical data collection

The patients' demographic and clinical data including age, gender, body mass index, comorbidities, the use of invasive mechanical ventilation, hemoglobin A1c (HbA1C), confusion, urea, respiratory rate, blood pressure, age ≥65 years (CURB-65) score, length of hospital stay, clinical outcomes, and so on were collected from the hospital's electronic medical record management system.

Antimicrobial susceptibility testing

Antimicrobial susceptibility testing results based on *E*-test were collected from the hospital's microbiology diagnostic laboratory. The interpretation was done according to Clinical and Laboratory Standards Institute guidelines. The susceptibility of *S. aureus* to Penicillins, Cephalosporins, Quinolones, Aminoglycosides, Macrolides, Lincosamides, Tetracyclines, Vancomycin, Linezolid, and other antibiotics were collected and analyzed.

Statistical analysis

Data are presented as number (%) or mean ± standard deviation (SD) unless otherwise stated. Continuous variables were compared using Student's *t* test for normally distributed variables and the Mann-Whitney *U* test for non-normally distributed variables. Characteristics of patients in different groups were compared using Chi-square or Fisher exact tests for categorical variables. Risk factors for mortality were explored using univariate and multivariate logistic regression in a Forward stepwise (likelihood ratio) manner, and the results were listed as odds ratios (ORs) (95% confidence interval [CI]). A $P \leq 0.05$ (two-tailed) was considered statistically significant. SPSS, version 24.0 (IBMSPSS, IBM Corporation, Somers, NY, USA) was used for all statistical analyses.

Results

Clinical characteristics

A total of 365 patients were enrolled during the study period, including 144 DM patients with pneumonia. The culture results indicated that there were 94 patients (65.3%) with MRSA infection in DM patients and 124 (56.1%) in non-diabetic (non-DM) groups; Therefore, MRSA infection was more common in DM patients.

Table 1 shows the baseline characteristics of each group. The average age of the DM group was 70.6 years and this was higher than that of the non-DM group (64.0 years; $P < 0.01$). There was no difference in the sex ratio between the two groups. In terms of comorbidities, the DM group was

Table 1: Baseline characteristics of patients admitted with pneumonia.

Items	DM (*N* = 144)	Non-DM (*N* = 221)	*P*
Age (years)	70.6 ± 1.3	64.0 ± 1.4	**<0.01**
Male	100 (69.4)	147 (66.5)	>0.05
BMI (kg/m^2)	23.7 ± 4.9	21.9 ± 3.9	**<0.01**
MRSA	94 (65.3)	124 (56.1)	>0.05
Comorbidities			**<0.01**
0–1	27	99	
2–4	95	117	
≥5	22	5	
Invasive MV			**<0.01**
Yes	67 (46.5)	62 (28.1)	
No	77 (53.5)	159 (71.9)	
Co-infection			>0.05
Yes	68 (47.2)	101 (45.7)	
No	76 (52.8)	120 (54.3)	
CURB-65			**<0.05**
0–2	95 (65.9)	172 (77.8)	
3–5	49 (34.0)	49 (22.2)	
LOHS (days)	191.36	171.12	**<0.05**
Die	44 (30.6)	51 (23.1)	>0.05

Data are presented as *n*, *n* (%) or mean ± standard deviation. BMI: Body mass index; CURB-65: Confusion, urea respiratory rate, blood pressure, age ≥65 years; LOHS: Length of hospital stay; MRSA: Methicillin-resistant *Staphylococcus aureus*; MV: Mechanical ventilation.

more/heavier than the non-DM group. Invasive MV was observed in 62 (28.1%) patients in non-DM groups, but in 67 (46.5%) patients in DM patients ($P < 0.01$). The rate of co-infection with other pathogens was higher in the DM group, but no statistically significant difference was present. The CURB-65 scores, which are a severity index for pneumonia, was also higher in the DM group (34.1% *vs.* 22.2%, $P < 0.05$). Meanwhile, a longer length of hospital stay in DM patients was observed (191.36 *vs.* 171.12, $P = 0.112$), which also reflects the severity of the disease. In addition, the DM group showed a trend toward a higher total in-hospital mortality rate than the non-DM group, although without statistical significance (30.6% *vs.* 23.1%, $P = 0.112$).

Antimicrobial susceptibility

The susceptibility of *S. aureus* to β-lactam antibiotics, quinolones, aminoglycosides, macrolides, tetracyclines, lincosamides, rifamycins, sulfonamides, polypeptide, and other antibiotics were collected in Table 2. All isolates were susceptible to vancomycin, teicoplanin, and linezolid. The percentage of resistance to both penicillin and oxacillin were 65.3% (94/144) in DM group, which is higher than non-DM patients 56.1% (124/221). Almost all DM patients had higher antimicrobial resistance than non-DM groups, including ampicillin/sulbactam, ciprofloxacin, moxifloxacin, levofloxacin, gentamicin, erythromycin, tetracycline, clindamycin, sulfamethoxazole, nitrofurantoin, and quinupristin.

Co-infection with other pathogens

In addition to *S. aureus*, we also analyzed other microorganisms that were positive in sputum culture. The three most common bacteria are *Acinetobacter baumannii*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*. Then we further analyzed their distribution in different group and found *A. baumannii* had the highest presence in sputum culture in DM, while *K. pneumoniae* in non-DM patients. In terms of mortality, we found an interesting phenomenon: although *Acinetobacter baumannii* ranked first in terms of co-infections in the DM group, co-infection with *Klebsiella pneumoniae* led to an increase in mortality (44%); in non-DM patients, *S. aureus* co-infection with *Pseudomonas aeruginosa* instead of *Klebsiella pneumoniae* resulted in higher mortality rates (59.3%).

Risk factors for mortality

Univariate and multivariate regression analyses of risk factors related to mortality were conducted in all the patients [Table 3]. The univariate regression analyses revealed that the risk factors for mortality were age (OR: 1.031, 95% CI 1.023–1.046, $P < 0.001$), comorbidities (OR: 1.489, 95% CI 1.250–1.773, $P < 0.001$), co-infection (OR: 1.620, 95% CI 1.293–2.031, $P < 0.001$), and CURB-65 (OR: 2.072, 95% CI 1.727–2.485, $P < 0.001$). While in multivariate regression analyses, only MRSA (OR: 2.080, 95% CI 1.037–4.173, $P = 0.039$) and CURB-65 (OR: 2.470, 95% CI 1.968–3.101, $P < 0.001$) were positively related to mortality.

Table 2: Antimicrobial susceptibility and resistance rate of 365 *Staphylococcus aureus* isolated.

| Items | DM | | Non-DM | | P |
	R	S	R	S	
β-lactam					
Efazolin	33 (60)	22 (40)	57 (62.6)	34 (37.4)	0.751
Ampicillin/sulbactam	32 (60.4)	21 (39.6)	55 (57.3)	41 (42.7)	0.715
Quinolones					
Ciprofloxacin	46 (62.2)	28 (37.8)	43 (45.7)	51 (54.3)	0.034
Moxifloxacin	27 (49.1)	28 (50.9)	30 (35.3)	55 (64.7)	0.105
Levofloxacin	83 (63.8)	47 (36.2)	104 (53.9)	89 (46.1)	0.075
Aminoglycosides					
Gentamicin	70 (53.4)	61 (46.6)	83 (42.8)	111 (57.2)	0.059
Macrolides					
Erythromycin	97 (74.6)	33 (25.4)	136 (70.5)	57 (29.5)	0.415
Tetracyclines					
Tetracycline	40 (54.1)	34 (45.9)	47 (50.0)	47 (50.0)	0.602
Lincosamides					
Clindamycin	83 (65.4)	44 (34.6)	112 (60.9)	72 (30.1)	0.421
Rifamycins					
Rifampicin	9 (7.0)	119 (93.0)	14 (7.2)	180 (92.8)	0.950
Sulfonamides					
Sulfamethoxazole	8 (6.2)	122 (93.8)	9 (4.5)	189 (95.5)	0.520
Nitrofurans					
Nitrofurantoin	2 (2.7)	72 (97.3)	0 (0)	89 (100.0)	0.119
Other antibiotics					
Fosfomycin	15 (28.8)	37 (71.2)	33 (33.7)	65 (66.3)	0.546
Quinupristin	2 (2.7)	72 (97.3)	2 (2.1)	94 (97.9)	0.792

DM: Diabetics; Non-DM: Non-diabetics; R: Resistance; S: Susceptibility.

Table 3: Univariate and multivariate analysis of factors related to mortality in pneumonia.

Items	Univariate analysis		Multivariate analysis	
	Odds ratio (95% CI)	P	Odds ratio (95% CI)	P
Age	1.031 (1.023–1.046)	<0.001		
Gender	0.914 (0.548–1.526)	0.731		
BMI,	1.012 (0.956–1.072)	0.672		
Diabetes mellitus	0.682 (0.425–1.094)	0.112		
MRSA	0.985 (0.611–1.587)	0.950	**2.080 (1.037–4.173)**	**0.039**
Invasive MV	0.763 (0.471–1.235)	0.270		
Comorbidities,	1.489 (1.250–1.773)	<0.001		
Co-infection	1.620 (1.293–2.031)	<0.001		
CURB-65	2.072 (1.727–2.485)	<0.001	**2.470 (1.968–3.101)**	**<0.001**

CI: Confidence interval; BMI: Body mass index; MRSA: Methicillin-resistant Staphylococcus aureus; MV: Mechanical ventilation; CURB-65: Confusion, urea respiratory rate, blood pressure, age ≥65 year.

Influence of HbA1c on the prognosis of disease

The infection rates of MRSA were 50.0% (11/22), 55.6% (5/9) and 60.0% (3/5) in the ≥4%–<7% group, the ≥7%–8% group and >8% group, respectively. The co-infection rates were 36.4% (8/22) for the ≥4%–<7% group and 60.0% for the >8% group, respectively. The CURB-65 scores in the three groups were 1.68 (≥4%–<7% group), 2.00 (≥7%–8% group) and 3.20 (>8% group), and mortalities were 22.7% (≥4%–<7% group), 33.3% (≥7%–8% group) and 60.0% (>8% group).

Discussion

This retrospective cohort study provides comprehensive information on patient demographics, co-infection, antimicrobial susceptibility, and risk factors of *staphylococcal* pneumonia, and highlights certain similarities and key differences between the two group patients admitted in our study. We found that (1) DM patients were more susceptible to infection MRSA, suffered from much severer pneumonia with a much higher CURB-65 score, invasive MV rate, and mortality. (2) Almost all DM patients had higher antimicrobial resistance than no-DM groups, all isolates *S. aureus* were susceptible to vancomycin, teicoplanin, and linezolid. (3) The DM group had a higher co-infection rate, and *A. baumannii* was the most common bacterium in DM, while *K. pneumoniae* ranked first in non-DM patients. (4) Independent risk factors for pneumonia-related mortality were MRSA and CURB-65. (5) Higher HbA1c levels were linked to a higher MRSA infection and co-infection rate and more severe pneumonia, leading to an increase in mortality.

For the past few years, some studies found DM subjects were susceptive to pneumonia. In 2007, a cohort study including 10,063 subjects followed for 7 years found that each 1 mmol/L increase in baseline plasma glucose was associated with a 6% increase in the relative risk of pneumonia.[9] A population-based, case-control study in the Denmark found that type 1 DM was associated with a 4.4 fold increased risk of a pneumonia-related hospitalization, and type 2 DM was associated with a 1.2-fold in non-DM subjects ($n = 513,749$ in each group).[10] While based on the research described above, our study further

found that DM patients were more likely to develop MRSA pneumonia than non-DM subjects, with a higher CURB-65 score, invasive MV rate, and mortality. Add to some prior researches, we can get that DM is a risk factor for pneumonia, especially *S. aureus* infection. Decreased immunity, impaired lung function, pulmonary micro-angiopathy, increased risk of aspiration, hyperglycemia, and coexisting morbidity may contribute to this susceptibility. Several investigators have reported high level of antibiotic resistance among the DM patients isolates.[11,12] Nevertheless, in our study, we found DM group's antibiotic resistance rate was higher than non-DM, but there were no statistical differences, which is in concurrence with the studies done by Meiland *et al*[13] and Bonadio *et al*.[14] Compared with that reported by the China Antimicrobial Surveillance Network, the overall antibiotic resistance rate in our study was higher than that presented, showing the grim situation of drug resistance in tertiary hospitals, but, it is gratifying that all *S. aureus* were susceptible to vancomycin, teicoplanin, and linezolid in this study. Differences in antibiotic resistance may be related to antibiotic exposure following infection in DM patients.

Acinetobacter is considered to be a low-grade pathogen and can remain on or in the human body without causing illness. Nosocomial infections are usually seen in patients who are subjected to an invasive procedure, especially in the intensive care unit setting, community-acquired infections are commonly seen as acute pneumonia generally in patients with a history of diabetes, alcohol abuse, cancer, or bronchopulmonary disease.[15] A variety of virulence mechanisms have been identified in *A. baumannii*, including biofilm formation, siderophore-mediated iron acquisition systems, adherence and outer membrane porins, the lipopolysaccharide, capsular polysaccharides, and quorum-sensing.[16-18] Some previous researches[19-21] have shown that hyperglycaemia causes the appearance of glucose in airway secretions, and glucose is known to be required for biofilm formation, We speculated that glucose in airway secretions may facilitate the formation of biofilm to *A. baumannii*. In addition, a higher invasive MV rate of DM patients in our study may also further explains why DM are more likely to co-infection with *A. baumannii*. *K. pneumoniae* is an

important human pathogen that can cause bacteraemia, urinary infections, and abscesses, these infections may be nosocomial, healthcare related, or community acquired. Ever since the recognition of hypervirulent *K. pneumonia* (hvKP) infection, DM has been speculated as a significant risk factor.[22-26] Importantly, when compared with *S. pneumoniae*, hvKP infected patients experienced a higher mortality (55.1% *vs.* 27.3%) with, unsurprisingly, septic shock and respiratory failure being independent predictors of death. In our study, although *A. baumannii* ranked first in co-infections in DM group, whereas co-infection with *K. pneumoniae* would lead to an increase in mortality (44%), despite not further identify the phenotype.

In our study, univariate logistic regression analysis identified four risk factors related to mortality, age (OR 1.031, 95% CI 1.023–1.046; $P < 0.001$), comorbidities (OR 1.489, 95% CI 1.250–1.773; $P < 0.001$), co-infection (OR 1.620, 95% CI 1.293–2.031; $P < 0.001$), CURB-65 (OR 2.072, 95% CI 1.727–2.485; $P < 0.001$), while in multivariate regression analyses, only MRSA (OR 2.080, 95% CI 1.037–4.173, $P = 0.039$) and CURB-65 (OR 2.470, 95% CI 1.968–3.101, $P < 0.001$) were associated with increased risk for mortality in all patients. In a previous study performed by Ishiguro et al, to explore risk factors for the severity and mortality of pneumococcal pneumonia, they found that age (≥65 years), DM, and poor performance status were independent factors associated with severity.[10,27] However, in our study, we did not conclude DM itself was an independent predictor for mortality. The small sample size and did not die from the infection itself may lead to our results different from others. Therefore, we further stratified and analyzed the factors related to disease severity in DM patients.

HbA1c levels reflect blood glucose control in DM patients over a 3 month period, so we performed a hierarchical analysis of HbA1c levels and found a link between HbA1c levels and the MRSA infection rate and co-infection rate, whereby higher levels of HbA1c were linked with more severe pneumonia, leading to an increase in mortality.

Our findings are consistent with previous studies, in 2008, a population-based case-control study in Denmark found that DM combined with an HbA1c level >9% is associated with a 60% increased risk of pneumonia-related hospitalization, while diabetes combined with an HbA1c level <7% was associated with a 22% increased risk, compared with subjects without diabetes.[33]

Although our research has yielded some meaningful results, there are still several limitations. First, co-infection with other bacteria and some comorbidities may have an impact on severity of pneumonia and mortality. Second, it is indeed difficult to distinguish colonization from infection, so there might be some misclassification of colonization and infection. Third, our study was retrospective, and some of the findings cannot be explained, for example, co-infection with different bacteria would lead to a different mortality in different groups. With regard to the co-infection, we only described the co-existence of pathogen in sputum culture, so co-existence pathogen may be more accurate. Fourth, it was a single center small

sample size study and the sample size in stratified analysis of HbA1c is especially smaller, so they may lead to a bias in the results.

In conclusion, our data, combined with previous results, provide strong evidence that DM patients with poor glucose control are more susceptible to infection MRSA, they suffer from a higher antimicrobial resistance, a higher co-infection rate and a much severer pneumonia than non-DM. More importantly, we conclude MRSA itself is an independent risk factor for mortality in all patients.

Conflicts of interest

None.

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