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ORIGINAL ARTICLE

Clinical predictors of methicillin-resistant *Staphylococcus aureus* in nosocomial and healthcare-associated pneumonia: a multicenter, matched case–control study

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Abstract The situations in which coverage for methicillin-resistant *Staphylococcus aureus* (MRSA) in the empirical treatment of nosocomial pneumonia (NP) or severe healthcare-associated pneumonia (HCAP) is needed are poorly defined, particularly outside intensive care units (ICUs). Our aim was to characterize if the risk of MRSA NP/HCAP can be defined by clinical variables. We designed an observational, retrospective, multicenter, case–control study to analyze the association between defined clinical variables and risk of MRSA NP/HCAP in non-ICU patients using conditional multivariable logistic regression. Cases and controls (1:2) with microbiological diagnosis were included. Controls were matched for hospital, type of pneumonia (NP or HCAP), and date of isolation. A total of 140 cases (77 NP and 63 HCAP) and 280 controls were studied. The variables associated with the risk of MRSA pneumonia were: (i) respiratory infection/colonization caused by MRSA in the previous year [odds ratio (OR) 14.81, 95% confidence interval (CI) 4.13–53.13, $p < 0.001$]; (ii) hospitalization in the previous 90 days (OR 2.41, 95% CI 1.21–4.81, $p = 0.012$); and (iii) age (OR 1.02, 95% CI 1.001–1.05, $p = 0.040$). The area under the receiver operating characteristic (ROC) curve for the multivariable model was 0.72 (95% CI 0.66–0.78). The multivariate model had a sensitivity of 74.5% (95% CI 65.3–83.6), a specificity of 63.3% (95% CI 56.0–70.6), a positive predictive value of 52.5% (95% CI 43.9–61.2), and a negative predictive value of 82.0% (95% CI 75.3–88.8) for the observed data. Clinical predictors of MRSA NP/HCAP can be used to define a low-risk population in whom coverage against MRSA may not be needed.

Introduction

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a common cause of nosocomial pneumonia (NP) and healthcare-associated pneumonia (HCAP) [1–4]. Although incidence is higher in ventilator-associated pneumonia (VAP) [1], that observed in non-ventilated patients is not negligible in areas with a high prevalence of MRSA [3–6]. Mortality in this patient population is high (40–60%) and, therefore, MRSA should be considered when designing empirical therapy regimens. Despite the remarkable efforts made in recent years to improve prognosis in these patients [2–4, 7], the clinical settings that warrant additional coverage against MRSA are poorly defined outside the context of VAP [4]. Therefore, the identification of predictors for MRSA would be helpful in selecting patients that might benefit from including anti-MRSA drugs in empirical therapy. In this context, this study aimed to characterize if the odds of MRSA etiology in certain non-ventilated hospitalized patients with NP/HCAP could be defined by clinical predictors that can be valuable for empirical treatment.

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Materials and methods

Study subjects and design

This is a retrospective, observational, multicenter, case–control study (SENECA study, Pfizer Protocol NRA5950067), performed in 15 university hospitals in Spain. The case patient population included non-ventilated adult patients hospitalized for > 48 h with NP or HCAP caused by MRSA over a period of 5 years (from January 2008 to December 2013). Patients admitted to the intensive care unit (ICU) were excluded. Table 1 shows the clinical criteria used to diagnose pneumonia. We considered that pneumonia was nosocomial when it debuted at least 48 h after hospital admission. HCAP was defined as community-onset pneumonia in patients with any of the following: intermediate care facility residents (e.g., nursing home or rehabilitation centers), hospitalization for > 48 h in the 90 days prior to the current admission, or reception of home intravenous therapy or dialysis in the previous month [8]. MRSA was defined as an oxacillin minimum inhibitory concentration (MIC) ≥ 4 μg/mL, according to the guidelines of the Clinical and Laboratory Standards Institute (CLSI) [9].

The cases were identified from the records of the local microbiology services databases. Patients from whom MRSA was isolated from valid sputum (> 25 neutrophils and < 10 epithelial cells per field), quantitative bronchial aspirate (BAS)/bronchoalveolar lavage (BAL), brush catheter, pleural fluid, or blood cultures were eligible. Medical records were reviewed in search of patients meeting the diagnostic criteria for pneumonia.

Two controls were included for each case, matched by hospital and type of pneumonia (NP or HCAP). Patients with NP or HCAP and with microbiological isolation of bacteria other than MRSA from respiratory samples, pleural fluid, or blood cultures were eligible as controls; those dated immediately before or after the respective case in the same hospital were selected. Controls of NP cases were not matched for healthcare exposure before present admission.

Table 1 Clinical criteria for pneumonia diagnosis

Group	Diagnostic criteria
I	– Onset or worsening of cough – Onset of purulent sputum production or worsening in character of sputum – Auscultation of rales or symptoms of consolidation – Dyspnea or tachypnea (≥ 30 breaths/min) – Hypoxemia with a PO2 < 60 mmHg while breathing room air
II	– Fever ≥ 38.4 °C (axillary) – Systolic blood pressure < 90 mmHg – Altered mental status consistent with sepsis – Leukocytosis > 10,000/mm^3 or > 15% immature neutrophils regardless of total leukocyte count or leukopenia < 4500/mm^3 – Positive culture in respiratory sample obtained by invasive* or non-invasive** procedures or blood cultures
III	– Onset of purulent sputum or worsening in character of sputum and at least one of the following criteria: – Fever ≥ 38.4 °C (axillary) – Leukocytosis > 10,000/mm^3

At least two Group I criteria associated with at least two Group II criteria or, alternatively, one Group III criterion were required for the clinical diagnosis of pneumonia. Radiological evidence of pneumonia was also required

*Invasive procedures: bronchoalveolar lavage (BAL), brush catheter or pleural puncture

**Non-invasive procedures: high-quality sputum (> 25 neutrophils and < 10 epithelial cells per field) or quantitative bronchial aspirate (BAS)

Ethics

The ethics committee of the Hospital Universitario Reina Sofía approved the use and analysis of clinical data needed to conduct the study and waived the need for informed consent due to the retrospective design of the study (code NRA 5950067, reference 1893). The database used for the analysis was anonymized. The study was classified by the Spanish Agency of Medicaments, Ministry of Health, as an "observational study" (No-EPA).

Clinical variables and definitions

Clinical variables and definitions are shown in Table 2.

Calculation of sample size

To estimate an odds ratio (OR) ≥ 1.6 with a 95% significance level, a two-sided test power of 80%, and assuming a 60% exposure rate in the control group, we estimated that 761 patients should be included (254 cases and 507 controls). Estimating a replacement rate of 10%, a sample size of 837 patients (279 cases and 558 controls) was calculated and aimed.

Statistical analysis

Quantitative variables were expressed as mean ± standard deviation (SD). We calculated univariate ORs and the 95% confidence intervals (CIs) for all the potential risk factors of MRSA pneumonia using univariate logistic regression. For all analyses, patients without respiratory sample cultures in the previous 12 months were considered to have no MRSA isolates. All variables with $p < 0.25$ in the univariate conditional logistic regression analysis were included in a multivariate conditional logistic regression model [10] and selected using a stepwise backward process. The area under the receiver operating characteristic (AUROC) curve for the final multivariable model was determined; the sensitivity, specificity, and predictive values of the model with respect to observed

Table 2 Univariate and multivariate analysis of risk factors for methicillin-resistant *Staphylococcus aureus* (MRSA) pneumonia in non-ventilated hospitalized patients

	Case (n = 140)	Control (n = 280)	Univariate model		Multivariate model			
			OR_{crude}	p-Value	$OR_{adjusted}$	95% CI L_lower	95% CI L_upper	p-Value
Demographic variables								
- Age, mean (SD)	74.9 (13.2)	71.6 (15.0)	1.017	0.025	1.02	1.001	1.05	0.040
- Female sex, number (%)	40 (28.6%)	82 (29.3%)	0.966	0.879				
Clinical variables								
- Dependent patient	82 (58.6%)	135 (48.2%)	1.517	0.046				
- Diabetes mellitus	45 (32.1%)	74 (26.4%)	1.312	0.235				
- Underlying respiratory disease	69 (49.3%)	123 (43.9%)	1.241	0.299				
- Neoplasm	44 (31.4%)	88 (31.4%)	1.034	0.881				
- Liver disease	20 (14.3%)	26 (9.3%)	1.504	0.203				
- Chronic renal insufficiency/dialysis	22 (15.7%)	48 (17.1%)	0.907	0.734				
- Isolation of MRSA in the previous 12 months	25 (17.9%)	4 (1.4%)	15.625	0.000	14.81	4.13	53.13	0.000
- Dementia	30 (21.4%)	46 (16.4%)	1.304	0.318				
- Charlson index, mean (SD)	2.4 (1.5)	2.2 (1.5)	1.081	0.264				
Variables related to hospitalization								
- Parenteral nutrition	5 (3.6%)	11 (3.9%)	0.899	0.846				
- Surgery during admission	6 (4.3%)	19 (6.8%)	0.611	0.304				
- Hospitalization in the last 90 days	98 (70.0%)	159 (56.8%)	1.639	0.027	2.41	1.21	4.81	0.012
Variables related to immunosuppression								
- Neutropenia (< 500 neutrophils/mm^3)	6 (4.3%)	11 (3.9%)	1.087	0.872				
- HIV	6 (4.3%)	12 (4.3%)	0.967	0.948				
- Chemotherapy	20 (14.3%)	31 (11.1%)	1.274	0.433				
- Steroids (prednisone ≥ 20 mg/day or equivalent)	51 (36.4%)	98 (35.0%)	0.991	0.968				
- Biological treatment	2 (1.4%)	3 (1.1%)	1.357	0.740				
- Transplant	6 (4.3%)	15 (5.4%)	0.785	0.625				
Variables related to the severity of pneumonia								
- Septic shock	24 (17.1%)	53 (18.9%)	0.838	0.518				
- Pleural effusion/empyema	23 (16.4%)	64 (22.9%)	0.644	0.107				
Variables related to prior medication								
- Antibiotic therapy for at least 48 h in the 10 days prior to diagnosis	73 (52.1%)	133 (47.5%)	1.250	0.307				
- Aminoglycosides	4 (2.9%)	8 (2.9%)	1000	1.000				
- Carbapenems	14 (10.0%)	24 (8.6%)	1.185	0.631				
- Cephalosporins	16 (11.4%)	25 (8.9%)	1.316	0.417				
- Penicillin	21 (15.0%)	36 (12.9%)	1.196	0.546				
- Quinolones	33 (23.6%)	58 (20.7%)	1.181	0.503				
- Cotrimoxazole	5 (3.6%)	11 (3.9%)	0.906	0.857				
- Proton pump inhibitors for at least one week in the previous month	112 (80.0%)	192 (68.6%)	1.996	0.016				
- Statins for at least one week in the previous month	30 (21.4%)	68 (24.3%)	0.814	0.421				

Data are expressed as number (%) or as mean (standard deviation, SD)

Underlying respiratory disease includes chronic obstructive respiratory disease, interstitial lung disease, and cystic fibrosis

The area under the receiver operating characteristic (AUROC) curve for the multivariable model was 0.725 (0.662–0.787). Hosmer–Lemeshow test P = 0.091

data were calculated. The goodness-of-fit of the model was determined by the Hosmer–Lemeshow test.

All analyses were conducted with SPSS software. *p*-Values < 0.05 were considered to be statistically significant. All reported *p*-values are two-tailed.

Results

Description of cases and controls

A total of 140 cases and 280 controls were included in the study. The 140 cases of MRSA pneumonia in non-ventilated patients were identified in the selected centers: 77 cases of NP (55%) and 63 cases of HCAP (45%); 12 cases of NP (15.6%) and 18 cases of HCAP (28.6%) were residents of a long-term care facility. The median (range) of the proportion of methicillin resistance among *S. aureus* isolates in the hospitals in which the participating patients were admitted was 32% (16–47). A full description of the clinical and demographic variables of cases and controls is shown in Table 2. The etiologies of the 280 controls are shown in Table 3.

Risk factors for MRSA pneumonia

The variables that were significantly associated with the risk of MRSA pneumonia in the univariate analysis were age, dependency, MRSA respiratory infection/colonization within the previous year, hospitalization in the previous 90 days, and the use of proton pump inhibitors in the previous month. For the analysis, patients without cultures in the 12 months prior to diagnosis were considered to have no MRSA infection/colonization (25/140 [17.9%] vs. 4/280 [1.4%]). The variables associated with the risk of MRSA pneumonia in the conditional multivariate logistic regression model were: (i) MRSA infection/colonization in the previous year (OR 14.81, 95% CI 4.13–53.13, $p < 0.001$); (ii) hospitalization in the previous 90 days (OR 2.41, 95% CI 1.21–4.81, $p = 0.012$); and (iii) older age (OR per year, 1.02, 95% CI 1.001–1.05, $p = 0.040$) (Table 2). The AUROC curve for the multivariable model was 0.72 (95% CI, 0.66–0.78). The multivariate model predicted MRSA pneumonia for the observed data with a sensitivity of 74.5% (95% CI 65.3–83.6), a specificity of 63.3% (95% CI 56.0–70.6), a positive predictive value of 52.5% (95% CI 43.9–61.2), and a negative predictive value of 82.0% (95% CI 75.3–88.8) (Table 2).

Discussion

We have studied whether some clinical variables can define the risk of MRSA NP/HCAP in order to characterize the situations in which coverage for MRSA in the empirical treatment of NP or HCAP is needed. Our major findings are: (1) MRSA respiratory infection/colonization within the previous year, hospitalization in the previous 90 days, and older age are associated with the risk of MRSA pneumonia; (2) These risk factors are applicable to both HCAP and NP in settings with a high prevalence of MRSA; and (3) The identified clinical variables define a low-risk population in whom coverage for MRSA could be avoided.

Other studies have reported risk factors for community-acquired pneumonia due to MRSA [8] or other multidrug-resistant bacteria [11–14]. The primary risk factors in the "Aliberti Score" [11, 12] included hospitalization in the previous 3 months and residence in a nursing home. Other specific MRSA risk factors are related to dependence on the health system (advanced age, parenteral antibiotic therapy, or neurological impairment) [15–17], which may be surrogate risk factors for respiratory colonization.

Our study confirms the above risk factors for patients in the community, such as advanced age and hospitalization in the previous 3 months. However, a further contribution of our study is that MRSA colonization/infection in the previous year is a risk factor for MRSA HCAP and NP. The value of

Table 3 Etiology of pneumonia in the 280 control patients

Microorganisms	Number of cases	%
Pseudomonas aeruginosa	69	24.6
Streptococcus pneumoniae	54	19.3
Escherichia coli	45	16.1
Klebsiella pneumoniae	22	7.9
Methicillin-sensitive *Staphylococcus aureus*	19	6.8
Acinetobacter baumannii	14	5.0
Haemophilus influenzae	10	3.6
Stenotrophomonas maltophilia	9	3.2
Enterobacter cloacae	6	2.1
Enterococcus faecalis	5	1.8
Serratia marcescens	3	1.1
Proteus mirabilis	3	1.1
Klebsiella oxytoca	3	1.1
Enterobacter aerogenes	3	1.1
Bacteroides fragilis	3	1.1
Enterococcus faecium	3	1.1
Achromobacter xylosoxidans.	2	0.7
Providencia stuartii	1	0.4
Pseudomonas putida	1	0.4
Prevotella oralis	1	0.4
Legionella pneumophila	1	0.4
Haemophilus parainfluenzae	1	0.4
Citrobacter freundii.	1	0.4
Moraxella catarrhalis	1	0.4
Total	280	

the isolation of MRSA to guide the empirical treatment of NP/HCAP has been discussed. Although the 2005 Infectious Diseases Society of America (IDSA)/American Thoracic Society (ATS) guidelines recognize the value of MRSA colonization to guide empirical therapy [4], no prospective study has evaluated the use of MRSA screening to guide the empirical treatment, so there is not enough evidence to consider this as a definitive risk factor for MRSA pneumonia. The 2016 IDSA/ATS guidelines insist on the negative predictive value of the MRSA screening only when the prevalence of MRSA is low [18]. Our results should be understood and interpreted within the framework of the high MRSA prevalence (32%) observed in the centers included in the study. In this context, our multivariate model has a high negative predictive value (82%) and permits identifying patients at low risk in whom colonization studies at admission or empirical coverage for MRSA could be avoided. It is difficult to make a recommendation in the remaining patients, since the model has a positive predictive value of 52.5%.

This study has some limitations which have to be pointed out, mainly its retrospective design and a much lower recruitment rate than previously estimated. This was due to the fact that the actual incidence of NP/HCAP in the centers included in the study was lower than expected. Furthermore, to avoid inclusion of a non-diagnosed MRSA pneumonia, the controls used in the study were patients with pneumonia of known etiology, and, therefore, the results cannot be applied to patients in whom the etiology of pneumonia is not known. Finally, our results would be mainly applicable to centers with a similar epidemiology of MRSA.

In summary, our study establishes a set of clinical predictors of MRSA NP/HCAP that can be used to identify patients at low risk for MRSA pneumonia. Given the scarce available information to take decisions with regard to coverage against MRSA in HCAP and NP outside ICUs, our findings may be clinically valuable in helping to optimize the diagnosis and empirical treatment of MRSA pneumonia.

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Compliance with ethical standards

Conflict of interest All investigators' institutions have received financial support from Pfizer Spain to conduct this study. JT-C has received funding or honoraria for lectures and training activities from Pfizer and Novartis. JR-B was speaker for Astellas, AstraZeneca, Merck, Novartis, and Pfizer, and was scientific advisor for AstraZeneca, Merck, Pfizer, Novartis, InfectoPharm, Roche, and Basilea. Francisco Mesa is an employee and shareholder of Pfizer. Mladen Trikic is a former Pfizer employee.

Ethical approval All procedures performed in this study were in accordance with the ethical standard of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Due to the retrospective design of the study, informed consent is not required.

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