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Brief report

The impact of multidrug resistance on outcomes in ventilator-associated pneumonia

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Pseudomonas aeruginosa

Multidrug-resistant (MDR) organisms in ventilator-associated pneumonia were found in 49 of 107 patients and were associated with home antibiotics, pre-ventilator-associated pneumonia hospital stay, and health care exposure. Overall, MDR organisms were associated with increased mortality ($P = .006$). On multivariate analysis, MDR status was modulated by organism class. In nonfermenting gram-negative rods, no association between MDR and mortality was found, but, in all other organisms, MDR was associated with increased mortality risk (hazard ratio, 6.15; 95% confidence interval: 1.80-21.05, $P = .004$).

Ventilator-associated pneumonia (VAP) is an important infectious complication of mechanical ventilation and remains a major cause of morbidity and mortality in critically ill patients.[1,2] Microbial pathogens in VAP are frequently multidrug-resistant (MDR) organisms (MDR-O) and have been identified as an independent risk factor for mortality.[3-5] *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Klebsiella* spp, and *Acinetobacter baumanii* are common MDR-O.[6] It is debatable whether the higher mortality in this population is specifically linked to certain pathogens.[7,8] Different types of pathogens have different virulence factors and pathogenic potential, and the association between MDR status and mortality risk may vary as well.

PATIENTS AND METHODS

Setting and study design

This retrospective study was conducted at a tertiary care referral center with 1,200 beds and 209 adult intensive care unit beds from January 1, 2008, to December 31, 2010. The Institutional Review Board approved the study.

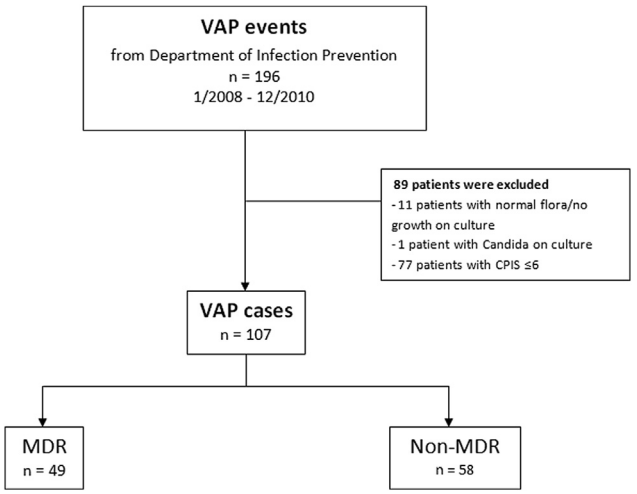

Fig 1. Flow diagram.

Definitions

Patients met Centers for Disease Control and Prevention (CDC)/National Healthcare Safety Network (NHSN) VAP criteria, had a pathogen isolated in respiratory culture, and a modified Clinical Pulmonary Infection Score >6.[9,10] Patients with respiratory cultures

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Table 1
Baseline patient characteristics and risk factors

	All	MDR	Non-MDR	*P* value*	OR (95% CI)	*P* value†
No.	107	49	58	-		
Age in years, mean ± SD	62 ± 14	60 ± 16	64 ± 13	.14		
Male	59 (55)	29 (59)	30 (52)	.56		
White race	79 (74)	34 (69)	45 (78)	.38		
Comorbidities						
Cardiovascular disease	59 (55)	24 (49)	35 (60)	.25		
Pulmonary disease	26 (24)	10 (9)	16 (15)	.50		
Diabetes mellitus	29 (27)	13 (27)	16 (28)	1		
Chronic kidney disease	30 (28)	14 (29)	16 (28)	1		
End-stage liver disease	10 (9)	6 (12)	4 (7)	.51		
Immunocompromised	12 (11)	8 (16)	4 (7)	.14		
Malignancy	10 (9)	4 (8)	6 (10)	.75		
Intensive care unit						
Medical	29 (27)	15 (31)	14 (24)	.51		
Surgical	25 (23)	17 (35)	8 (14)	.01*		
Cardiovascular	37 (35)	13 (27)	24 (42)	.11		
Coronary	4 (4)	1 (2)	3 (5)	.62		
Neurologic	12 (11)	3 (6)	9 (16)	.21		
CPIS, median (range)	8 (7-11)	8 (7-11)	8 (7-11)	1		
Days intubation to VAP, median (IQR)	13 (6-20)	16 (9-24)	10 (4-18)	.012		
Days hospital admission to VAP, median (IQR)	17 (10-28)	25 (16-34)	14 (7-21)	<.0001	1.04 (1.01-1.08)‡	.02
Days ICU admission to VAP, median (IQR)	15 (8-24)	20 (14-28)	12 (6-19)	<.0001		
Duration of MV, days, median (IQR)	25 (15-36)	26 (17-37)	22 (13-31)	.08		
Prior home antibiotics in the past 30 days	25 (23)	18 (37)	7 (12)	.0031	2.96 (1.06-8.91)	.04
Prior antibiotics 7 days before VAP diagnosis	88 (82)	45 (92)	43 (74)	.0219		
Prior admission in the past 90 days	39 (36)	26 (53)	13 (22)	.0013		
Health care exposure prior to admission§	71 (66)	41 (84)	30 (52)	.0005	3.82 (1.51-10.47)	.004

CPIS, Clinical Pulmonary Infection Score; *ICU*, intensive care unit; *IQR*, interquartile range; *MV*, mechanical ventilation.
NOTE. All data expressed as n (%) unless otherwise stated.
*Univariate analysis.
†Multivariate regression, backward stepwise approach was used, retaining only variables that remained significant at $\alpha \leq .05$.
‡Per day increase.
§Health care exposures include skilled nursing facility, long-term care facility, and outside hospitals.

of *Candida* species, normal flora, or no growth were excluded. Patients who were less than 18 years old were excluded.

MDR pathogens definitions were adapted from Magiorakos et al.[11] They include methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus* spp, *Enterobacteriaceae*, *Pseudomonas aeruginosa*, and *Acinetobacter* spp that are resistant to more than 3 antimicrobial classes. Nonfermenting gram-negative rods (NF GNR) included *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and *Stenotrophomonas maltophilia*. Patients with polymicrobial VAP, with at least 1 NF GNR were classified as NF GNR. Adequate empiric antibiotic therapy was defined as antibiotics with in vitro susceptibility started within 48 hours of first positive culture.

Data collection

Clinical data were recorded from electronic medical records. Isolated organisms from qualitative tracheal secretions, quantitative (mini) bronchoalveolar lavage, or (mini) bronchoalveolar lavage at the time of VAP diagnoses along with their corresponding sensitivities to antimicrobials were obtained.

Statistical analysis

All comparisons were unpaired, and all tests of significance were 2-tailed with P value $< .05$. Categorical variables were analyzed using the Pearson χ^2 test or Fisher exact test where appropriate. Continuous variables were reported as means ± standard deviation and were analyzed using the Student t test for normally distributed samples. Other non-normally distributed continuous variables were reported as medians and interquartile range (IQR) and analyzed using the Wilcoxon rank-sum test. All the variables measured were subjected to univariate analyses. Multivariate logistic regression analysis was performed for analysis of risk factors. Backward stepwise approach was used, retaining only variables that remained significant at $\alpha = .05$. The risk factors were reported as odd ratios (OR) with 95% confidence interval (CI). The same strategy was used and entered into Cox proportional hazard model to predict the independent predictors for hospital mortality, and the predictors were reported as hazard ratio (HR) with 95% CI. The proportion of VAP patients having a 28-day survival time was estimated by Kaplan-Meier analysis comparing subjects with MDR and non-MDR pathogens. Patients who were discharged out of the hospital were censored. All statistics were performed using JMP and SAS software (both SAS Institute, Cary, NC).

RESULTS

During the study period, a total of 196 VAP events met the Centers for Disease Control and Prevention/National Healthcare Safety Network criteria for VAP. Of these patients, 89 were excluded; 77 patients had a Clinical Pulmonary Infection Score less than 6, and 12 patients did not have a respiratory pathogen isolated. MDR-O were isolated in 49 (46%) of the remaining 107 patients with VAP (Fig 1). All of our patients were late-onset VAP. The baseline characteristics for the study cohort are shown in the Table 1.

NF GNR were over-represented in the MDR-O group; 60% of NF GNR were MDR-O as compared with 40% of other organisms (Table 2). In multivariate regression analysis, 3 independent risk factors for MDR-O were identified, and they were prior home antibiotic therapy (OR, 2.96; 95% CI: 1.06-8.91, $P = .04$), hospital days prior to VAP diagnosis (OR per additional day, 1.04; 95% CI: 1.01-1.08, $P = .02$), and health care exposure prior to admission (OR, 3.82; 95% CI: 1.51-10.47, $P = .004$).