Analysis of Pathogen and Host Factors Related to Clinical Outcomes in Patients with Hospital-Acquired Pneumonia Due to Methicillin-Resistant *Staphylococcus aureus*

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Methicillin-resistant *Staphylococcus aureus* (MRSA) is a major cause of nosocomial pneumonia. To characterize pathogen-derived and host-related factors in intensive care unit (ICU) patients with MRSA pneumonia, we evaluated the Improving Medicine through Pathway Assessment of Critical Therapy in Hospital-Acquired Pneumonia (IMPACT-HAP) database. We performed multivariate regression analyses of 28-day mortality and clinical response using univariate analysis variables at a *P* level of <0.25. In isolates from 251 patients, the most common molecular characteristics were USA100 (55.0%) and USA300 (23.9%), SCCmec types II (64.1%) and IV (33.1%), and *agr* I (36.7%) and II (61.8%). Panton-Valentine leukocidin (PVL) was present in 21.9%, and vancomycin heteroresistance was present in 15.9%. Mortality occurred in 37.1% of patients; factors in the univariate analysis were age, APACHE II score, AIDS, cardiac disease, vascular disease, diabetes, SCCmec type II, PVL negativity, and higher vancomycin MIC (all *P* values were <0.05). In multivariate analysis, independent predictors were APACHE II score (odds ratio [OR], 1.090; 95% confidence interval [CI], 1.041 to 1.141; *P* < 0.001) and age (OR, 1.024; 95% CI, 1.003 to 1.046; *P* = 0.02). Clinical failure occurred in 36.8% of 201 evaluable patients; the only independent predictor was APACHE II score (OR, 1.082; 95% CI, 1.031 to 1.136; *P* = 0.002). In summary, APACHE II score (mortality, clinical failure) and age (mortality) were the only independent predictors, which is consistent with severity of illness in ICU patients with MRSA pneumonia. Interestingly, our univariate findings suggest that both pathogen and host factors influence outcomes. As the epidemiology of MRSA pneumonia continues to evolve, both pathogen- and host-related factors should be considered when describing epidemiological trends and outcomes of therapeutic interventions.

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a major cause of hospital-acquired pneumonia (HAP), ventilator-associated pneumonia (VAP), and health care-associated pneumonia (HCAP) (26). These infections are associated with significant morbidity, mortality, and cost burdens (3, 20, 25).

While previous studies have attempted to identify risk factors for morbidity and mortality in patients with MRSA infections, they have typically focused on either the pathogen or the host. For example, severity of underlying illness, septic shock, age, comorbidities, and other selected host-related factors appear to be independent predictors of poor outcomes (5–7, 10, 14). MRSA features associated with poor prognosis in a variety of infection types include increases in vancomycin MIC, vancomycin heteroresistance, presence of Panton-Valentine leukocidin (PVL), *agr* group I, individual genes, and persistent colonization (1, 9, 11, 27). Because the outcomes of MRSA pneumonia are probably due to a combination of factors, studies are needed to evaluate the combined roles of MRSA-derived and host-related factors in a large sample of patients with HAP, VAP, or HCAP due to MRSA.

The objective of this study was to evaluate the influence of both pathogen-derived and host-related factors on mortality and clinical response in intensive care unit (ICU) patients diagnosed with MRSA HAP, including VAP and HCAP. To characterize the roles of these factors, we analyzed information from patients enrolled in the Improving Medicine through Pathway Assessment of Critical Therapy in Hospital-Acquired Pneumonia (IMPACT-HAP) study. This performance improvement project was intended to

offer better, standardized treatment across centers and which was compliant with guidelines. For example, patients at risk for resistant organisms were to receive broad-spectrum empirical therapy that included an agent active against MRSA. The development and implementation of this performance improvement project have been described previously (16).

(Preliminary results were presented by S. M. Donabedian, N. Haque, M. Perri, C. Moore, P. Peyrani, R. Ramirez, T. File, Jr., D. H. Kett, J. E. Mangino, E. Scerpella, K. D. Ford, and M. Zervos in 2010 at the 48th Annual Meeting of the Infectious Diseases Society of America in Vancouver, Canada.)

MATERIALS AND METHODS

Study design. This was a retrospective, observational study of ICU patients with HAP, VAP, or HCAP who were treated in five medical centers in the United States: University of Louisville (Louisville, KY), Ohio State University Medical Center (Columbus, OH), Henry Ford Health System (Detroit, MI), University of Miami/Jackson Memorial Hospital (Miami, FL), and Summa Health System (Akron, OH). Data were collected from

Received 14 December 2011 Returned for modification 18 January 2012

Accepted 6 February 2012

Published ahead of print 15 February 2012

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doi:10.1128/JCM.06701-11

February 2006 through November 2009. Nonconsecutive adult ICU patients who met American Thoracic Society/Infectious Diseases Society of America (ATS/IDSA) definitions for HAP, VAP, or HCAP (2) were entered into the database. For each case, investigators completed a data collection form and internally validated the information before transferring it via the internet to the IMPACT-HAP coordinating center at the University of Louisville. Validation of data quality was also performed at the coordinating center. The project was approved by the institutional review board at each participating institution; each board waived the need for informed consent.

Inclusion criteria. To be eligible for the IMPACT-HAP study, adult patients (≥ 18 years of age) in participating ICUs had to have clinical suspicion of evolving pneumonia with new or progressive infiltrates on chest radiograph and at least two of the following: new or increased cough or sputum production, fever, hypothermia, leukocytosis, left shift, leukopenia, or deterioration of pulmonary function. To be eligible for this analysis, patients also had to have at least one positive culture for MRSA isolated from blood or a respiratory site which was available for additional testing and had a known vital status (alive or dead) on day 28 after study admission.

Study variables. The following data were collected: patient demographic characteristics, comorbidities, physical examination, laboratory findings, severity of illness, including APACHE II (Acute Physiology and Chronic Health Evaluation) score, diagnostic procedures, and treatment data, including all antibiotics received for the treatment of pneumonia. Data were collected from the time of pneumonia diagnosis (day zero) until hospital discharge, death, or 28 days after the diagnosis of pneumonia, whichever occurred first. Laboratory values were collected during the index hospitalization.

Variables selected for the current analysis included age, sex, place of residence before the index infection, comorbidities, APACHE II score, 28-day clinical response, and 28-day all-cause mortality. Comorbidities included end-stage renal disease, end-stage liver disease, cardiac disease (systolic or diastolic heart failure), renal disease (history of chronic renal disease or abnormal blood urea nitrogen [BUN] and creatinine concentrations), vascular disease (history of peripheral or central vascular disease), diabetes, chronic obstructive pulmonary disease, presence of malignancies, and AIDS. Data on previous hospitalizations within 90 days, nursing home residence, receipt of home intravenous infusion treatment, home wound care treatment, steroids, active chemotherapy, or active radiotherapy, and outpatient hemodialysis were also collected.

Laboratory analysis. Initial identification of isolates and *in vitro* susceptibilities were determined using clinical microbiology laboratory tests with automated susceptibility testing methods at each participating center. Isolates were then stored and shipped to the IMPACT-HAP microbiology reference laboratory at Henry Ford Hospital for further evaluation. *In vitro* susceptibilities were determined by broth microdilution using Clinical and Laboratory Standards Institute (CLSI) criteria. Isolates were further characterized by pulsed-field gel electrophoresis (PFGE) for USA typing, PCR subtyping of staphylococcal cassette chromosome *mec* element (SCC*mec*), accessory gene regulator (*agr*) typing by PCR using *agr* group-specific primers, and PCR detection of the PVL toxin gene as described previously (4, 19). Isolates were screened for vancomycin heteroresistance by the Etest macromethod (AB bioMérieux, Solna, Sweden), which uses a higher inoculum to detect the presence of a less-susceptible subpopulation (28).

Outcome definitions. The primary outcome of interest was 28-day all-cause mortality, defined as any death that occurred between days 0 and 28. The secondary outcome of interest was the 28-day clinical response, defined as success (cure or improvement) or failure. Cure required complete resolution of signs and symptoms of pneumonia, while improvement involved partial resolution of signs and symptoms of pneumonia. Failure was defined as deterioration of signs and symptoms of pneumonia, relapse, or new infection.

Statistical analysis. In the univariate analysis, we compared baseline characteristics of ICU patients with MRSA HAP, VAP, or HCAP with and without the outcomes of interest. Categorical variables were compared using a chi-square test, or Fisher's exact test where sample sizes were small. Continuous variables were compared using the Wilcoxon rank sum test and the two-sample *t* test. All variables with *P* values of <0.25 from the univariate analysis were included in the multivariate analyses. A full model logistic regression analysis was performed to evaluate the independent association of each variable with the outcome of interest at day 28 (all-cause mortality, clinical response). For all variables, independence was assumed both between and within institutions. *P* values of <0.05 were considered statistically significant. Data were analyzed with SAS software version 9.2 (SAS Institute Inc., Cary, NC).

RESULTS

We identified a total of 251 patients with MRSA HAP, VAP, or HCAP. When we examined the general characteristics of our study population, we found that the mean age was 60.5 years and the mean APACHE II score was 20.6. The most common MRSA PFGE types were USA100 (55.0%) and USA300 (23.9%). Of 60 unique isolates of USA300, 53 were PVL positive and 7 were PVL negative. The most common SCC*mec* types were II (64.1%) and IV (33.1%). The most common *agr* groups were I (36.7%) and II (61.8%). The presence of the PVL toxin gene was detected in 55 isolates (21.9%), including 53 with USA300 and 2 with strains that were not USA100 to USA1100. Vancomycin heteroresistance was detected in 40 MRSA isolates (15.9%).

Mortality analysis. All-cause 28-day mortality was documented in 93 of 251 patients (37.1%). Patients who died were older (mean age, 67.7 versus 56.2 years; $P < 0.001$) and had higher APACHE II scores (mean score, 23.6 versus 18.8; $P < 0.001$) (Table 1). They also had higher rates of AIDS (3.2% versus 0%; $P = 0.05$), cardiac disease (49.5% versus 29.9%; $P = 0.002$), vascular disease (49.5% versus 34.8%; $P = 0.02$), and diabetes mellitus (36.6% versus 24.1%; $P = 0.03$).

Laboratory testing revealed differences in the distribution of molecular and microbiological characteristics of MRSA isolates between patients who died and those who survived (Table 1). MRSA isolates from patients who died were characterized by higher rates of SCC*mec* type II (73.1% versus 58.9%) and lower rates of SCC*mec* type IV (23.7% versus 38.6%; $P = 0.04$ for SCC*mec* type), as well as a lower frequency of PVL positivity (12.9% versus 27.2%; $P = 0.008$). MRSA strains from patients who died also had higher vancomycin MIC values (mean, 0.85 versus 0.74 $\mu\text{g/ml}$; $P = 0.001$).

In the multivariate analysis, higher APACHE II score (odds ratio [OR] for each 1-point increase in score, 1.090; 95% confidence interval [CI], 1.041 to 1.141; $P < 0.001$) and older age (OR for each year, 1.024; 95% CI, 1.003 to 1.046; $P = 0.02$) were independently associated with mortality. The only other factors with *P* values of <0.1 were presence of the PVL toxin gene (OR, 0.178; 95% CI, 0.032 to 1.004; $P = 0.051$) and vancomycin MIC (OR, 3.348; 95% CI, 0.879 to 12.743; $P = 0.077$). The following factors had *P* values of ≥ 0.1 : female sex, malignancy, end-stage liver disease, cardiac disease, renal disease, vascular disease, diabetes mellitus, USA300 (versus USA100), USA600 (versus USA100), USA other (versus USA100), SCC*mec* IV (versus SCC*mec* II), SCC*mec* other (versus SCC*mec* II), *agr* I (versus *agr* II), and *agr* other (versus *agr* II).

Clinical response analysis. Of 251 patients, 50 were excluded from the clinical response analysis because of incomplete or miss-

TABLE 1 Characteristics of patients with MRSA HAP, VAP, or HCAP, stratified by 28-day mortality

Variable	No. (%) of patients ^a		P value
	Survived (n = 158)	Died (n = 93)	
Host-related characteristics			
Age (yrs)	56.2 ± 18.1	67.7 ± 16.2	<0.001
Sex, female	45 (28.5)	33 (35.5)	0.247
APACHE II score	18.8 ± 7.1	23.6 ± 7.0	<0.001
Previous hospitalization within 90 days	68 (43.3) ^b	37 (39.8)	0.585
Nursing home resident	24 (15.2)	19 (20.4)	0.287
Hemodialysis	9 (5.7)	7 (7.5)	0.575
Home infusion	13 (8.2)	9 (9.7)	0.695
Home wound care	14 (9.0) ^b	7 (7.5)	0.680
Malignancy	20 (12.7)	17 (18.5) ^b	0.219
AIDS	0 (0.0)	3 (3.2)	0.050
End-stage renal disease	11 (7.0)	7 (7.5)	0.867
End-stage liver disease	5 (3.2)	6 (6.5)	0.220
Steroid therapy	21 (13.4) ^b	14 (15.1)	0.712
Active chemotherapy	6 (3.8)	5 (5.4)	0.542
Active radiotherapy	2 (1.3)	3 (3.2)	0.363
Cardiac disease	47 (29.9) ^b	46 (49.5)	0.002
Renal disease	27 (17.1)	22 (23.7)	0.205
Vascular disease	55 (34.8)	46 (49.5)	0.022
Diabetes mellitus	38 (24.1)	34 (36.6)	0.034
Chronic obstructive pulmonary disease	39 (24.8) ^b	24 (25.8)	0.865
Severe sepsis	115 (72.8)	72 (77.4)	0.416
Pathogen-related characteristics			
PFGE type			0.137
USA100	86 (54.4)	52 (55.9)	
USA300	44 (27.8)	16 (17.2)	
USA600	10 (6.3)	11 (11.8)	
Other	18 (11.4)	14 (15.1)	
SCCmec type			0.043
II	93 (58.9)	68 (73.1)	
IV	61 (38.6)	22 (23.7)	
Other	4 (2.5)	3 (3.2)	
agr group			0.742
I	60 (38.0)	32 (34.4)	
II	95 (60.1)	60 (64.5)	
Other	3 (1.9)	1 (1.1)	
PVL toxin gene	43 (27.2)	12 (12.9)	0.008
Vancomycin MIC (μg/ml)	0.74 ± 0.25	0.85 ± 0.26	0.001
Vancomycin heteroresistance	25 (15.8)	15 (16.1)	0.949

^a For patient age and APACHE II score and the vancomycin MIC for the pathogen, the means ± the standard deviations are reported rather than the number (and percentage) of patients in the category.

^b Percentage based on patients with available data (excludes those with missing data).

TABLE 2 Characteristics of patients with MRSA HAP, VAP, or HCAP, stratified by 28-day clinical response

Variable	No. (%) of patients ^a		P value
	Success (n = 127)	Failure (n = 74)	
Host-related characteristics			
Age (yrs)	56.6 ± 16.9	64.2 ± 20.1	0.005
Sex, female	38 (29.9)	25 (33.8)	0.569
APACHE II score	19.2 ± 7.0	23.4 ± 7.8	<0.001
Previous hospitalization within 90 days	63 (50.0) ^b	33 (44.6)	0.460
Nursing home resident	20 (15.7)	16 (21.6)	0.295
Hemodialysis	8 (6.3)	6 (8.1)	0.627
Home infusion	14 (11.0)	5 (6.8)	0.319
Home wound care	12 (9.7) ^b	5 (6.8)	0.478
Malignancy	18 (14.3) ^b	14 (19.2) ^b	0.365
AIDS	0 (0.0)	2 (2.7)	0.134
End-stage renal disease	10 (7.9)	7 (9.5)	0.697
End-stage liver disease	5 (3.9)	6 (8.2) ^b	0.214
Steroid therapy	18 (14.3) ^b	12 (16.2)	0.712
Active chemotherapy	4 (3.1)	6 (8.1)	0.177
Active radiotherapy	2 (1.6)	3 (4.1)	0.360
Cardiac disease	42 (33.3) ^b	39 (52.7)	0.007
Renal disease	24 (18.9)	18 (24.3)	0.361
Vascular disease	50 (39.4)	35 (47.3)	0.273
Diabetes mellitus	32 (25.2)	23 (31.1)	0.367
Chronic obstructive pulmonary disease	32 (25.4) ^b	21 (28.4)	0.645
Severe sepsis	94 (74.0)	60 (81.1)	0.254
Pathogen-related characteristics			
PFGE type			0.137
USA100	70 (55.1)	40 (54.1)	
USA300	36 (28.3)	14 (18.9)	
USA600	5 (3.9)	8 (10.8)	
Other USA	16 (12.6)	12 (16.2)	
SCCmec type			0.031
II	73 (57.5)	54 (73.0)	
IV	51 (40.2)	17 (23.0)	
Other	3 (2.4)	3 (4.1)	
agr group			0.434
I	45 (35.4)	27 (36.5)	
II	78 (61.4)	47 (63.5)	
Other	4 (3.1)	0 (0.0)	
PVL toxin gene	34 (26.8)	12 (16.2)	0.086
Vancomycin MIC (μg/ml)	0.74 ± 0.25	0.81 ± 0.28	0.112
Vancomycin heteroresistance	14 (11.0)	17 (23.0)	0.024

^a For patient age and APACHE II score and the vancomycin MIC for the pathogen, the means ± the standard deviations are reported rather than the number (and percentage) of patients in the category.

^b Percentage based on patients with available data (and excludes those with missing data).

ing data. Clinical failure was documented in 74 of 201 patients (36.8%). Patients who experienced clinical failure were older (mean age, 64.2 versus 56.6 years; *P* = 0.005) and had higher APACHE II scores (mean score, 23.4 versus 19.2; *P* < 0.001) (Table 2). They also had higher rates of underlying cardiac disease (52.7% versus 33.3%; *P* = 0.007).

Laboratory testing revealed differences in the distributions of molecular and microbiologic characteristics of MRSA isolates between patients with and without clinical success (Table 2). MRSA isolates from patients who experienced clinical failure were char-

acterized by higher rates of SCCmec type II (73.0% versus 57.5%) and lower rates of SCCmec type IV (23.0% versus 40.2%; *P* = 0.03 for SCCmec type). These isolates also presented a higher frequency of vancomycin heteroresistance (23.0% versus 11.0%; *P* = 0.02).

In the multivariate analysis, the only variable independently associated with clinical failure was APACHE II score (OR for each 1-point increase in score, 1.082; 95% CI, 1.031 to 1.136; *P* = 0.002). The only other factors with *P* values of <0.1 were SCCmec IV versus SCCmec II (OR, 0.275; 95% CI, 0.067 to 1.137; *P* = 0.075) and cardiac disease (OR, 1.828; 95% CI, 0.894 to 3.740; *P* =

0.098). The following factors had P values of ≥ 0.1 : age, end-stage liver disease, active chemotherapy, USA300 (versus USA100), USA600 (versus USA100), USA other (versus USA100), *SCCmec* other (versus *SCCmec* II), PVL toxin gene, vancomycin MIC, and vancomycin heteroresistance.

DISCUSSION

The results of this study showed that mortality and clinical failure each occurred in approximately one-third of ICU patients with MRSA HAP, VAP, or HCAP. Both host-related and pathogen-derived factors, individually and combined, were predictors of clinical outcomes in the univariate analysis. Factors associated with 28-day clinical failure included age, higher APACHE II score, cardiac disease, MRSA isolate carrying the *SCCmec* type II complex, and heteroresistance to vancomycin. The list of factors associated with 28-day mortality included additional host-related factors, specifically, vascular disease, diabetes mellitus, and AIDS. While the presence of *SCCmec* type II complex was also associated with mortality, a higher vancomycin MIC, but not vancomycin heteroresistance, was also associated. Therefore, host and pathogen factors, such as age, APACHE II score, cardiac disease, and presence of the *SCCmec* type II element, appeared to be the common predictors in the univariate analysis for both mortality and clinical failure in patients with hospital-acquired pneumonia due to MRSA.

The results of multivariate analyses revealed that APACHE II score was an independent predictor of both mortality and clinical failure, a finding that is consistent with previous studies of VAP (5, 6), including MRSA VAP (14). The high APACHE II scores observed in this group of ICU patients (mean score, 23.6 for nonsurvivors and 23.4 for patients with clinical failure) may have allowed this variable to carry more weight than others. The other independent predictor of mortality was age, which has already been associated with 28-day mortality in patients with nosocomial pneumonia in the ICU (10), those with VAP (5), and specifically in patients with MRSA VAP (6).

In this study, molecular markers usually associated with nosocomial MRSA infection were highly prevalent (e.g., *SCCmec* type II, USA100, and *agr* group II); however, markers associated with community-acquired MRSA were detected in at least 20% of patients and included *SCCmec* type IV, USA300, and the PVL toxin gene. These results are consistent with those from previous studies showing that community-acquired MRSA strains are becoming etiological agents of nosocomial infections (17, 22), including pneumonia, surgical site infections, and bacteremia (11, 13). We collected isolates from the period 2006 to 2009, whereas isolates described in previous reports (11, 13, 17, 22) were obtained before 2006. Therefore, our study provides one of the most recent indications that community-acquired MRSA strains continue to take the place of the more-traditional hospital-acquired MRSA strains as etiological agents of pneumonia in hospital and health care settings.

We found that patients with USA300, *SCCmec* IV, PVL-positive infections were overrepresented among those who survived or achieved clinical success. This is a significant observation, as previous reports suggested increased virulence of USA300 strains. Prior studies provided little information on the association between multiple microbiologic molecular characteristics and clinical outcome, or they did not focus on pneumonia *per se*. Hota et al. (12) recently reported that USA300 infection was negatively

associated with severe clinical courses in patients with community-onset infections, but theirs was a single-center study, and only 18% of all patients had pneumonia in the case-control analysis. Similarly, Seybold et al. (23) reported that crude in-hospital mortality was lower for MRSA USA300 than other MRSA strains in patients with bloodstream infections, including 17% with pulmonary infections. In contrast, a recently published study showed that patients with vancomycin-treated MRSA USA300 bloodstream infections had poor outcomes compared with those with non-USA300 strains; however, this finding was specific to patients with higher severity of illness and catheter-related infections and did not apply to those with high-risk sources, like the 10% with pneumonia (18).

There is little information from prior studies on the association between MRSA strain molecular characteristics and outcomes in MRSA pneumonia. While receiving substantial attention, studies about the clinical significance of PVL on pneumonia have been inconclusive. Lopez-Aguilar et al. (15) reported higher mortality for PVL-positive MRSA nosocomial pneumonia or bronchitis patients; however, this study evaluated only 24 patients, including 5 with PVL-positive MRSA. In contrast, a study of patients with MRSA HCAP found that patients with PVL-positive MRSA pneumonia had a mortality rate that was nominally (albeit not significantly) lower than the rate among patients with PVL-negative strains (24). In a more recent publication, severity of disease and clinical outcomes in patients with HAP or VAP due to MRSA were not influenced by the presence of the PVL gene (21). Although *agr* dysfunction has been linked to persistent MRSA bacteremia (8), our results do not provide compelling evidence for its role in severity of illness and outcomes. On the other hand, although USA600 strains accounted for less than 10% of MRSA PFGE types, they were preferentially found in patients who experienced clinical failure and in those who died, a finding that is consistent with a recent observation in patients with bloodstream infections in the United States (19).

Our study has several strengths, including a well-characterized study population with clinical and laboratory information available for analysis (16). IMPACT-HAP is a performance improvement project designed to better the management of ICU patients with HAP (including VAP and HCAP), which allowed us to explore the effect of a variety of pathogen- and host-related factors that can influence the clinical outcome of MRSA pneumonia. As part of the study procedures, investigators completed a data collection form and validated the information locally before transferring it to the IMPACT-HAP coordinating center, where it underwent a second validation step. We used a central reference laboratory for microbiology and molecular testing of all available MRSA isolates. Our study also has important limitations. IMPACT-HAP was not a randomized controlled trial, and a major weakness of every observational study of nonconsecutive patients is sampling error. The etiological diagnosis of MRSA infection was based on respiratory samples, including sputum and tracheal aspirates. IMPACT-HAP did not dictate prescribing practice, so we may have overlooked other treatment or patient characteristics that could have had an influence on outcome. We did not include type of empirical antibiotic therapy in the analyses, because the majority of patients received vancomycin and because we did not capture specific information on concomitant therapy (e.g., Gram-negative coverage). Finally, our patients were adults in the ICU who were diagnosed with HAP, VAP, or HCAP, an inherently

complex group for analysis; however, they were a more homogeneous group than those in previous studies that included patients with mixed infections in widely varied settings.

In summary, mortality and clinical failure occurred in approximately one-third of ICU patients with MRSA HAP, VAP, or HCAP. APACHE II score (clinical failure, mortality) and age (mortality) were the only independent predictors, reflecting the severity of illness and presence of comorbidities in these ICU patients. In the univariate analysis, we identified both pathogen and host factors that warrant further study. MRSA isolates with molecular characteristics of community-acquired strains are increasingly recognized as etiological agents of nosocomial pneumonia. As the epidemiology of MRSA continues to evolve, both geographically and temporally, combinations of pathogen-, host-, and therapy-related factors should be considered when describing changing epidemiological trends and the outcomes of therapeutic interventions.

ACKNOWLEDGMENTS

This study was supported by Pfizer Inc. US Medical.

The University of Louisville Foundation was responsible for project oversight and distribution of funds to participating institutions. Editorial and medical writing support was provided by Cindy Hamilton from Hamilton House and was funded by Pfizer Inc.

N.Z.H., P.P., S.A., M.B.P., K.R., and G.J. have no conflicts of interest to disclose. K.D.F. and E.G.S. are employees and stockholders of Pfizer, Inc. J.A.R. has received research support from Pfizer and Astellas, is a consultant for Pfizer, Cubist, and Forest, and has received honoraria from Pfizer and Astellas for lectures. M.J.Z. is a consultant for Cubist and has received grant support from Pfizer and Cubist.

As our collaborators, we thank the IMPACT-HAP Study Group, especially the following principal investigators: Julie E. Mangino, The Ohio State University, Columbus, OH, and Daniel H. Kett, University of Miami/Jackson Memorial Hospital, Miami, FL. We also thank the following collaborators for their contributions to IMPACT-HAP: Susan M. Donabedian and Carol L. Moore, Henry Ford Health System/Wayne State University School of Medicine, Detroit, MI, and Thomas File, Jr., Summa Health System, Akron, OH.

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