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 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 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 are 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.
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 staphyloccocal 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 *SCCmec* 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 *SCCmec* type II (73.1% versus 58.9%) and lower rates of *SCCmec* type IV (23.7% versus 38.6%; *P = 0.04 for *SCCmec* type), as well as a lower frequency of PVL positivity (12.9% versus 27.2%; *P = 0.008). MRSA strains from patients who died had higher vancomycin MIC values (mean, 0.85 versus 0.74 μg/ml; *P = 0.001).

In the multivariate analysis, higher APACHE II score (odds ratio [OR] for each 1-point increase in score, 1.09; 95% confidence interval [CI], 1.041 to 1.141; *P < 0.001) and older age (OR for each year, 1.024; 95% CI, 1.103 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), *SCCmec* IV (versus *SCCmec* II), *SCCmec* other (versus *SCCmec* 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-
RESULTS

Characteristics of Patients with MRSA HAP, VAP, or HCAP, Stratified by 28-Day Mortality and Clinical Response

Table 1 shows the characteristics of patients with MRSA HAP, VAP, or HCAP, stratified by 28-day mortality. The table includes variables such as age, sex, APACHE II score, and previous hospitalization within 90 days. The data is presented as the number of patients (%) and includes statistical significance values for the comparison between survived and died groups.

Table 2 provides the characteristics of patients with MRSA HAP, VAP, or HCAP, stratified by 28-day clinical response. Similar to Table 1, the table includes various variables and their associated statistical significance values.

In summary, the results indicate that patients with MRSA HAP, VAP, or HCAP had different clinical outcomes based on various patient characteristics and pathogen-related variables. The tables highlight the importance of identifying risk factors associated with clinical failure and potential targets for intervention.

For patient age and APACHE II score and the vancomycin MIC for the pathogen, the means± standard deviations are reported rather than the number (and percentage) of patients in the category. For patient age, APACHE II score, and the vancomycin MIC for the pathogen, the percentage values are based on patients with available data (excludes those with missing data).

For patient age and APACHE II score and the vancomycin MIC for the pathogen, the percentage values are based on patients with available data (excludes those with missing data).
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 etiologic 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 homogenous 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.

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