Pseudomonas aeruginosa nosocomial pneumonia: Impact of pneumonia classification

Scott T. Micek  
*St. Louis College of Pharmacy*

Marin H. Kollef  
*Washington University School of Medicine in St. Louis*

Antoni Torres  
*University of Barcelona*

Catherine Chen  
*Washington University School of Medicine in St. Louis*

Jordi Rello  
*Hospital Vall D’Hebron*

*See next page for additional authors*

Follow this and additional works at: [http://digitalcommons.wustl.edu/open_access_pubs](http://digitalcommons.wustl.edu/open_access_pubs)

**Recommended Citation**

Micek, Scott T.; Kollef, Marin H.; Torres, Antoni; Chen, Catherine; Rello, Jordi; Chastre, Jean; Antonelli, Massimo; Welte, Tobias; Clair, Bernard; Ostermann, Helmut; Calbo, Esther; Wunderink, Richard; Menichetti, Francesco; Schramm, Garrett; and Menon, Vandana, “Pseudomonas aeruginosa nosocomial pneumonia: Impact of pneumonia classification.” Infection Control & Hospital Epidemiology.36,10. 1190-1197. (2015).  
[http://digitalcommons.wustl.edu/open_access_pubs/4679](http://digitalcommons.wustl.edu/open_access_pubs/4679)
Pseudomonas aeruginosa Nosocomial Pneumonia: Impact of Pneumonia Classification

Scott T. Micek, Marin H. Kollef, Antoni Torres, Catherine Chen, Jordi Rello, Jean Chastre, Massimo Antonelli, Tobias Welte, Bernard Clair, Helmut Ostermann, Esther Calbo, Richard Wunderink, Francesco Menichetti, Garrett Schramm and Vandana Menon

Infection Control & Hospital Epidemiology / Volume 36 / Issue 10 / October 2015, pp 1190 - 1197
DOI: 10.1017/ice.2015.167, Published online: 20 July 2015

Link to this article: http://journals.cambridge.org/abstract_S0899823X15001671

How to cite this article: Scott T. Micek, Marin H. Kollef, Antoni Torres, Catherine Chen, Jordi Rello, Jean Chastre, Massimo Antonelli, Tobias Welte, Bernard Clair, Helmut Ostermann, Esther Calbo, Richard Wunderink, Francesco Menichetti, Garrett Schramm and Vandana Menon (2015). Pseudomonas aeruginosa Nosocomial Pneumonia: Impact of Pneumonia Classification. Infection Control & Hospital Epidemiology, 36, pp 1190-1197 doi:10.1017/ice.2015.167

Request Permissions: Click here
**Pseudomonas aeruginosa** Nosocomial Pneumonia: Impact of Pneumonia Classification

Scott T. Micek, PharmD; Marin H. Kollef, MD; Antoni Torres, MD; Catherine Chen, MD; Jordi Rello, MD; Jean Chastre, MD; Massimo Antonelli, MD; Tobias Welte, MD, PhD; Bernard Clair, MD; Helmut Ostermann, MD, PhD; Esther Calbo, MD; Richard Wunderink, MD; Francesco Menichetti, MD; Garrett Schramm, PharmD; Vandana Menon, MD

**Objective.** To describe and compare the mortality associated with nosocomial pneumonia due to *Pseudomonas aeruginosa* (Pa-NP) according to pneumonia classification (community-onset pneumonia [COP], hospital-acquired pneumonia [HAP], and ventilator-associated pneumonia [VAP]).

**Design.** We conducted a retrospective cohort study of adults with Pa-NP. We compared mortality for Pa-NP among patients with COP, HAP, and VAP and used logistic regression to identify risk factors for hospital mortality and inappropriate initial antibiotic therapy (IIAT).

**Setting.** Twelve acute care hospitals in 5 countries (United States, 3; France, 2; Germany, 2; Italy, 2; and Spain, 3).

**Patients/Participants.** A total of 742 patients with Pa-NP.

**Results.** Hospital mortality was greater for those with VAP (41.9%) and HAP (40.1%) compared with COP (24.5%) ($P < .001$). In multivariate analyses, independent predictors of hospital mortality differed by pneumonia classification (COP: need for mechanical ventilation and intensive care; HAP: multidrug-resistant isolate; VAP: IIAT, increasing age, increasing Charlson comorbidity score, bacteremia, and use of vasopressors). Presence of multidrug resistance was identified as an independent predictor of IIAT for patients with COP and HAP, whereas recent antibiotic administration was protective in patients with VAP.

**Conclusions.** Among patients with Pa-NP, pneumonia classification identified patients with different risks for hospital mortality. Specific risk factors for hospital mortality also differed by pneumonia classification and multidrug resistance appeared to be an important risk factor for IIAT. These findings suggest that pneumonia classification for *P. aeruginosa* identifies patients with different mortality risks and specific risk factors for outcome and IIAT.


Nosocomial pneumonia (NP) can occur in a diverse spectrum of patients and can be attributed to varied etiologic pathogens. NP is typically classified according to the location and conditions of infection onset (community-onset usually with healthcare-associated risk factors [COP], hospital-acquired pneumonia [HAP], or pneumonia acquired during mechanical ventilation). Few studies have attempted to evaluate NP according to the location and conditions of infection or to compare outcomes among these categories of NP. Notably, recent trends show an increase in the prevalence of NP caused by multidrug-resistant (MDR) gram-negative bacteria, most commonly *Pseudomonas aeruginosa*. Mortality associated with *P. aeruginosa* NP (Pa-NP) is among the highest of any bacteria owing to both the virulence of *P. aeruginosa* as well as the administration of inappropriate initial antibiotic therapy (IIAT) in MDR isolates.

The escalating prevalence of antibiotic resistance in *P. aeruginosa*, along with the development and availability of novel antimicrobial therapies, requires a precise understanding of how the various categories of Pa-NP influence outcome. A comparison of mortality of Pa-NP, as well as risk factors for mortality, according to pneumonia classification


Received April 3, 2015; accepted June 20, 2015; electronically published July 20, 2015

© 2015 by The Society for Healthcare Epidemiology of America. All rights reserved. 0899-823X/2015/3610-0009. DOI: 10.1017/ice.2015.167
has not previously been performed. Pneumonia classification of *P. aeruginosa* may have important clinical implications, especially from treatment and infection control perspectives where typically ventilator-associated pneumonia (VAP) is primarily evaluated. Therefore, we set out to perform an analysis of a multinational study of *Pa-NP* with the following objectives: first, to describe and compare the mortality associated with *Pa-NP* according to pneumonia classification; second, to identify and compare risk factors for hospital mortality and IIAT according to pneumonia classification.

**METHODS**

**Study Design and Ethical Standards**

We conducted a retrospective cohort study in 12 hospitals in 5 countries (United States, 3; France, 2; Germany, 2; Italy, 2; and Spain, 3). Eligible consecutive patients were aged 18 years or older and admitted for their index hospitalization within 36 months prior to study initiation in 2013. All eligible patients met a clinical diagnosis of NP defined as new or progressive infiltrates consistent with pneumonia on chest radiograph or computed tomography and either a temperature higher than 38.3°C or leukocytosis greater than 10,000 cells/mm³ or both. To be eligible patients had to have *P. aeruginosa* cultured from blood or a respiratory specimen collected from the following: sputum, pleural fluid, flexible bronchoscopy with protected specimen brush, bronchoalveolar, or transbronchial biopsy, “mini-bronchoalveolar” sample, and tracheobronchial aspirate in intubated patients. Microbiologic cultures had to be obtained within the 24-hour period surrounding initiation of antibiotics. *Pa-NP* was classified as COP, HAP, and VAP according to the location and conditions of the onset of infection (COP: prior to hospital admission; HAP: developing during the hospital stay; VAP: developing while receiving mechanical ventilation). Patients with COP had to have 1 or more of the following characteristics to be included: hospitalized in an acute care hospital for 2 or more days within 90 days of infection; resided in a nursing home or long-term care facility; received recent intravenous antibiotic therapy, chemotherapy, or wound care in the past 30 days; or attended a hospital or hemodialysis clinic. Each investigator obtained approval from an independent ethics committee or institutional review board at his or her institution.

**End Points and Covariates**

The primary end point examined was hospital mortality. We also examined other important covariates to include demographic characteristics, MDR status of the *P. aeruginosa* isolate, and comorbidities (acute coronary syndrome, valvular heart disease, hypertension, venous thromboembolism, chronic obstructive pulmonary disease, asthma, other chronic respiratory diseases, and diabetes mellitus). Patients were also classified according to whether they received IIAT.

**Definitions**

To be classified as MDR, the *P. aeruginosa* isolate had to be nonsusceptible to at least 1 agent in at least 3 of the following antimicrobial categories: aminoglycosides, antipseudomonal carbapenems, antipseudomonal cephalosporins, antipseudomonal fluoroquinolones, antipseudomonal penicillins plus β-lactamase inhibitors, monobactams, phosphonic acids, and polymixins. Antimicrobial treatment was deemed to represent IIAT if the initially prescribed antibiotic regimen was not active against the identified isolate on the basis of in vitro susceptibility testing or was administered more than 24 hours following respiratory specimen collection. Microbiology laboratories determined antimicrobial susceptibility of the isolates using disk diffusion or automated testing methods according to established guidelines and breakpoints.

**Statistical Analyses**

Continuous variables were reported as means with standard deviations. Differences between mean values were tested via the *t* test. Categorical data were summarized as proportions, and the χ² test or Fisher exact test for small samples was used to examine differences between groups. We developed several multiple logistic regression models to identify clinical risk factors associated with hospital mortality and IIAT. Risk factors that were significant at *P* ≤ .20 in the univariate analyses, as well as all biologically plausible factors even if they did not reach this level of significance, were included in the corresponding multivariable analyses. All variables entered into the models were examined to assess for collinearity, and interaction terms were tested. The most parsimonious models for the predictors of hospital mortality and IIAT respectively were computed and their fit was tested with the area under the receiver operating curve and the Hosmer-Lemeshow goodness-of-fit test. All tests were 2-tailed, and a *P* value < .05 was deemed a priori to represent statistical significance. On the basis of our prior experience and available publications, we estimated that the hospital mortality for COP would be approximately 20% and the hospital mortality for HAP and VAP would be between 35% and 40%. Using a 2-sided estimate with a *P* value of .05 and 80% power required at least 138 patients per pneumonia type to yield statistically meaningful estimates. Thus our goal prior to performing the study was to have at least 150 patients per pneumonia type during study recruitment and data collection to ensure that our mortality analysis would be valid. All analyses were performed with SPSS software, version 19.0 (IBM).
made most commonly via bronchoalveolar lavage (35%), tracheobronchial aspirate (28%), mini-bronchoalveolar (18%), and sputum samples (15%). VAP was most common (339 [45.7%]) followed by COP (241 [32.5%]) and HAP (162 [21.8%]). Significant differences in subject location prior to hospital admission, underlying comorbidities, and vital signs were observed by pneumonia classification (Table 1). Patients with VAP had the lowest Charlson comorbidity scores and prevalence of secondary bacteremia, but VAP was associated with the greatest use of vasopressors following pneumonia onset. The antibiotic susceptibility of the \textit{P. aeruginosa} isolates was comparable for COP, HAP, and VAP (Table 2). Similarly, the prevalence of MDR isolates and the rate of IIAT were equivalent for all 3 pneumonia categories.

Overall hospital mortality was 35.8% (n = 266) and ranged across centers from 12% to 60%. Hospital mortality was greater for VAP (41.9%) and HAP (40.1%) compared with COP (24.5%) \( (P < .001) \). This was confirmed in a Kaplan-Meier analysis (Figure 1). Hospital length of stay, uncensored for survival, was significantly longer for VAP compared with HAP (Table 3). However, total durations of mechanical ventilation and intensive care progressively increased going from COP to HAP and VAP. Hospital readmission was similar across pneumonia types. Among the HAP patients, 97 (59.9%) developed HAP while in the intensive care unit (ICU) setting. Hospital mortality was higher for HAP within the ICU compared with HAP occurring outside of the ICU (45.4% vs 32.3%; \( P = .097 \)). However, median (interquartile range) hospital length of stay was similar for HAP within the ICU and HAP occurring outside of the ICU (28 days [11.5–45.0 days] vs 23.0 days [12.0-37.0 days]; \( P = .414 \)).

Table 4 shows the results of the logistic regression model derivations examining the variables associated with hospital mortality for each pneumonia category. Among subjects with

### Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Community-onset pneumonia (n = 241)</th>
<th>Hospital-acquired pneumonia (n = 162)</th>
<th>Ventilator-associated pneumonia (n = 339)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ± SD, y</td>
<td>57.8 ± 17.7</td>
<td>61.2 ± 17.2</td>
<td>59.7 ± 15.6</td>
</tr>
<tr>
<td>Male sex</td>
<td>155 (64.3%)</td>
<td>111 (68.5%)</td>
<td>238 (70.2%)</td>
</tr>
<tr>
<td>Location prior to admission</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Community</td>
<td>119 (49.4%)</td>
<td>98 (60.5%)</td>
<td>172 (50.7%)^c</td>
</tr>
<tr>
<td>Skilled nursing facility</td>
<td>29 (12.0%)</td>
<td>21 (13.0%)</td>
<td>4 (1.2%)^b,c</td>
</tr>
<tr>
<td>Long-term care facility</td>
<td>16 (6.6%)</td>
<td>5 (3.1%)</td>
<td>6 (1.8%)^b</td>
</tr>
<tr>
<td>Assisted living</td>
<td>4 (1.7%)</td>
<td>2 (1.2%)</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td>Inpatient rehabilitation</td>
<td>36 (14.9%)</td>
<td>6 (3.7%)</td>
<td>5 (1.5%)^b</td>
</tr>
<tr>
<td>Other</td>
<td>36 (14.9%)</td>
<td>27 (16.7%)</td>
<td>147 (43.4%)^b,c</td>
</tr>
<tr>
<td>Medical history</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospitalized in the previous 6 months</td>
<td>173 (74.6%)</td>
<td>88 (57.9%)^a</td>
<td>111 (42.5%)^b,c</td>
</tr>
<tr>
<td>Sepsis</td>
<td>50 (21.8%)</td>
<td>28 (19.0%)</td>
<td>41 (13.5%)^b</td>
</tr>
<tr>
<td>HIV</td>
<td>4 (1.8%)</td>
<td>3 (2.1%)</td>
<td>2 (0.7%)</td>
</tr>
<tr>
<td>Acute coronary syndrome</td>
<td>38 (17.3%)</td>
<td>20 (13.6%)</td>
<td>31 (10.3%)^b</td>
</tr>
<tr>
<td>Valvular heart disease</td>
<td>34 (15.2%)</td>
<td>16 (10.9%)</td>
<td>31 (10.3%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>115 (49.4%)</td>
<td>70 (44.0%)</td>
<td>152 (47.1%)</td>
</tr>
<tr>
<td>Venous thromboembolic disease</td>
<td>30 (13.2%)</td>
<td>16 (10.8%)</td>
<td>11 (3.6%)^b,c</td>
</tr>
<tr>
<td>Asthma/COPD</td>
<td>77 (33.5%)</td>
<td>40 (26.1%)</td>
<td>61 (20.1%)^b</td>
</tr>
<tr>
<td>Other respiratory disease</td>
<td>107 (48.4%)</td>
<td>44 (30.3%)^a</td>
<td>49 (16.3%)^b,c</td>
</tr>
<tr>
<td>Charlson comorbidity score, mean ± SD</td>
<td>3.8 ± 2.9</td>
<td>3.3 ± 2.7</td>
<td>2.4 ± 2.3^b,c</td>
</tr>
<tr>
<td>ICU admission</td>
<td>117 (48.5%)</td>
<td>108 (66.7%)^a</td>
<td>324 (95.6%)^b,c</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>169 (70.1%)</td>
<td>131 (80.9%)^a</td>
<td>339 (100%)^b,c</td>
</tr>
<tr>
<td>Vasopressor administration</td>
<td>126 (52.3%)</td>
<td>95 (58.6%)</td>
<td>235 (69.3%)^b,c</td>
</tr>
<tr>
<td>Bacteremia</td>
<td>88 (36.5%)</td>
<td>47 (29.0%)</td>
<td>47 (13.9%)^b,c</td>
</tr>
<tr>
<td>Polymicrobial respiratory specimen</td>
<td>47 (19.5%)</td>
<td>46 (28.4%)^a</td>
<td>87 (25.7%)</td>
</tr>
</tbody>
</table>

**NE**. Data are no. (%) unless otherwise specified. COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus; ICU, intensive care unit.

^a\( P < .05 \) comparing hospital-acquired pneumonia and community-onset pneumonia.

^b\( P < .05 \) comparing ventilator-associated pneumonia and community-onset pneumonia.

^c\( P < .05 \) comparing ventilator-associated pneumonia and hospital-acquired pneumonia.
COP the need for mechanical ventilation and the ICU were independent predictors of hospital death. For subjects with HAP only the presence of an MDR isolate was independently associated with hospital death. Administration of IIAT, vasopressor use, increasing Charlson comorbidity scores and age, and secondary bacteremia were identified as independent predictors of hospital mortality for VAP. MDR and bacteremia were independent predictors of IIAT for COP (Table 5). MDR was also an independent predictor of IIAT for HAP, whereas increasing Charlson comorbidity scores predicted IIAT in VAP and recent antibiotic administration was found to be protective against IIAT.

**Discussion**

We found that hospital mortality varied among patients with *Pa-NP* according to their pneumonia classification. Those with VAP and HAP had significantly greater risk of hospital death compared with patients with COP. Moreover, the risk factors for hospital death also varied by pneumonia classification.
Among patients with COP, severity of illness markers including the need for mechanical ventilation and intensive care predicted death. For the HAP cohort, infection with an MDR isolate was found to be the most important predictor of outcome. Patients with VAP had both severity of illness markers (need for vaso-pressors, bacteremia, 1-point increments in the Charlson comorbidity score) and IIAT identified as risk factors for death.

Interestingly, the rates of antibiotic resistance, multidrug resistance, and inappropriate therapy were similar for COP, HAP, and VAP, suggesting that a similar pathogen phenotype was responsible for infection regardless of pneumonia classification.

We also found that MDR status was an important risk factor for IIAT among patients with COP and HAP.

Kollef et al previously examined a large US pneumonia database and showed that mortality rates associated with healthcare-associated pneumonia (HCAP) and HAP were both significantly higher than that for community-acquired pneumonia and lower than that for VAP. Similarly, hospital length of stay and hospitalization charges varied significantly with pneumonia category in order of ascending values for community-acquired pneumonia, HCAP, HAP, and VAP. These findings were confirmed in a subsequent single-center study from the United States. However, several authors have criticized the use of the term HCAP, suggesting that it could result in the needless administration of broad-spectrum antibiotics to individuals with COP not infected with antibiotic-resistant pathogens. An alternative approach for classifying patients with COP is to identify the number of risk factors for MDR infection they have in order to better direct the use of broad-spectrum antibiotics. Our study found that

### Table 3. Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Community-onset pneumonia (n = 241)</th>
<th>Hospital-acquired pneumonia (n = 162)</th>
<th>Ventilator-associated pneumonia (n = 339)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital mortality, no. (%)</td>
<td>59 (24.5%)</td>
<td>65 (40.1%)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>142 (41.9%)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Hospital length of stay, days, all subjects</td>
<td>Mean ± SD 42.4 ± 52.4</td>
<td>31.9 ± 30.1&lt;sup&gt;c&lt;/sup&gt;</td>
<td>40.1 ± 40.7&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>ICU duration, days</td>
<td>Mean ± SD 13.6 ± 17.9</td>
<td>19.9 ± 19.0&lt;sup&gt;a&lt;/sup&gt;</td>
<td>29.6 ± 25.7&lt;sup&gt;b,c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Duration of mechanical ventilation, days</td>
<td>Mean ± SD 12.3 ± 14.6</td>
<td>23.2 ± 34.3&lt;sup&gt;a&lt;/sup&gt;</td>
<td>27.1 ± 24.2&lt;sup&gt;b,c&lt;/sup&gt;</td>
</tr>
<tr>
<td>30-day hospital readmission among hospital survivors, no. (%)</td>
<td>8.7 (3.5–15.2)</td>
<td>11.1 (4.8–27.2)</td>
<td>20.9 (11.7–34.2)</td>
</tr>
</tbody>
</table>

**NOTE.** ICU, intensive care unit.

<sup>a</sup>P < .005 comparing hospital-acquired pneumonia and community-onset pneumonia.

<sup>b</sup>P < .005 comparing ventilator-associated pneumonia and community-onset pneumonia.

<sup>c</sup>P < .05 comparing ventilator-associated pneumonia and hospital-acquired pneumonia.

### Table 4. Independent Predictors of Mortality

<table>
<thead>
<tr>
<th>Variable</th>
<th>Community-onset pneumonia</th>
<th>Hospital-acquired pneumonia</th>
<th>Ventilator-associated pneumonia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AOR 95% CI</td>
<td>P value</td>
<td>AOR 95% CI</td>
</tr>
<tr>
<td>Inappropriate initial antibiotics</td>
<td>1.86 1.40–2.45</td>
<td>.026</td>
<td>2.04 1.54–2.70</td>
</tr>
<tr>
<td>Vasopressor administration</td>
<td>3.27 1.85–5.76</td>
<td>.037</td>
<td>5.50 3.56–8.51 &lt;.001</td>
</tr>
<tr>
<td>Charlson comorbidity score (increasing increments of 1)</td>
<td>1.14 1.08–1.20</td>
<td>.018</td>
<td>1.02 1.01–1.03</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>5.00 3.56–8.51 &lt;.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multidrug-resistant isolate</td>
<td>2.88 1.78–4.68</td>
<td>.029</td>
<td></td>
</tr>
<tr>
<td>Age (increasing increments of 1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bacteremia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICU admission</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**NOTE.** Factors excluded from the model for collinearity: aminoglycoside resistance, carbapenem resistance, cephalosporin resistance, fluoroquinolone resistance, penicillin-beta-lactamase inhibitor resistance (collinear with multidrug-resistant isolate). Variables included but not retained in the model at the P < .05 in addition to those shown: corticosteroids for the ventilator-associated pneumonia analysis. Hosmer-Lemeshow/ area under the receiver operating curve: community-onset pneumonia, 0.452/0.642; hospital-acquired pneumonia, 0.866/0.679; ventilator-associated pneumonia, 0.698/0.620. AOR, adjusted odds ratio; ICU, intensive care unit.
almost one-third of Pa-NP had onset in the community setting and that the rates of MDR and IIAT were similar for COP compared with HAP and VAP, being approximately one-third and one-quarter respectively. Moreover, patients with COP had the highest rates of previous hospitalization, placing them at greater risk for infection with healthcare-associated pathogens. This highlights the importance of correctly identifying patients at risk for Pa-NP, regardless of the location and conditions of their pneumonia, in order to provide optimal medical treatment for potentially antibiotic-resistant isolates.

Our study is unique in providing the largest cohort to date of Pa-NP in order to assess the impact of pneumonia classification on outcomes. By focusing on a single pathogen we have a more homogeneous population in order to minimize pathogen-related confounders. Nevertheless, our findings are consistent with those from studies examining NP attributed to heterogeneous pathogens. Quartin et al performed a post hoc analysis of a randomized antibiotic treatment trial in 1,184 patients. Compared with patients with HAP or VAP, patients with COP were older, had slightly higher severity scores, and were more likely to have comorbidities. P. aeruginosa was the most common gram-negative organism isolated in all pneumonia classes (COP, 11.1%; HAP, 7.4%; VAP, 9.4%). Piskin et al examined 348 patients with HAP or VAP and found that risk factors for IIAT varied by their pneumonia type. Multiple logistic regression analysis revealed that the risk factors for inappropriate initial therapy in HAP were late-onset infection and greater APACHE II scores whereas in VAP antibiotic usage in the previous 3 months and admission to a surgical unit were found to be independent risk factors for IIAT. Taken together with our data, these studies highlight the difficulty in identifying consistent clinical markers for outcome in NP across pneumonia categories.

A large volume of research has emphasized the importance of early appropriate antimicrobial therapy for serious infections in order to minimize the risk of death. It has also been shown that escalation of treatment from IIAT to an appropriate antibiotic regimen in response to culture results fails to mitigate this increase in the risk of death. Our findings generally confirm these relationships. IIAT was found to be a predictor of hospital death in VAP where patients with VAP had the greatest severity of illness and prevalence of septic shock. The potential practical implications of these findings are illustrated by a recent large epidemiologic study from the United States that identified 205,526 patients with P. aeruginosa infections (187,343 pneumonia; 18,183 bloodstream infection) and 95,566 patients with Enterobacteriaceae infections (58,810 pneumonia; 36,756 bloodstream infection). The prevalence of MDR P. aeruginosa was approximately 15-fold higher than carbapenem-resistant Enterobacteriaceae and there was a net rise in MDR P. aeruginosa as a proportion of all P. aeruginosa infections from 2000 to 2009. A recent meta-analysis also demonstrated that MDR status was an important determinant of mortality due to nosocomial infections attributed to gram-negative bacteria, where P. aeruginosa and Acinetobacter species were the most common isolates. It is also interesting that the observed mortality for COP was lower than that observed more than 10 years ago despite the high rate of bacteremia, suggesting that these may have been less virulent strains of gram-negative bacteria.

The high rates of MDR and IIAT in Pa-NP for all pneumonia types mandate that clinicians have therapeutic strategies in place to optimize therapy. Scoring systems to identify patients with MDR infections, including MDR P. aeruginosa, are available but limited in their overall ability to predict MDR infection. A number of novel methods aimed at improving the early identification of pathogens and related antibiotic susceptibilities are also entering the diagnostic arena. Such technological advances offer a strategy that could potentially maximize the administration of appropriate antibiotic therapy while minimizing unnecessary antibiotic exposure. One such approach employs advanced automated microscopy techniques that allow the identification of bacterial species, the determination of the presence of antibiotic resistance genes, and bacterial killing by specific antibiotics within 4 to 6 hours using direct specimen inoculation.

Our study has a number of limitations. First, it was limited to an evaluation of Pa-NP and the findings may not be applicable to NP attributed to other pathogens. Second, the criteria for establishing a diagnosis of Pa-NP varied across centers. Therefore, our study cohort could have included patients without true pneumonia. Third, by analyzing each category of pneumonia separately we have limited our ability to identify all important factors for inappropriate initial therapy in HAP were late-onset infection and greater APACHE II scores whereas in VAP antibiotic usage in the previous 3 months and admission to a surgical unit were found to be independent risk factors for IIAT. Taken together with our data, these studies highlight the difficulty in identifying consistent clinical markers for outcome in NP across pneumonia categories.

A large volume of research has emphasized the importance of early appropriate antimicrobial therapy for serious infections in order to minimize the risk of death. It has also been shown that escalation of treatment from IIAT to an appropriate antibiotic regimen in response to culture results fails to mitigate this increase in the risk of death. Our findings generally confirm these relationships. IIAT was found to be a predictor of hospital death in VAP where patients with VAP had the greatest severity of illness and prevalence of septic shock. The potential practical implications of these findings are illustrated by a recent large epidemiologic study from the United States that identified 205,526 patients with P. aeruginosa infections (187,343 pneumonia; 18,183 bloodstream infection) and 95,566 patients with Enterobacteriaceae infections (58,810 pneumonia; 36,756 bloodstream infection). The prevalence of MDR P. aeruginosa was approximately 15-fold higher than carbapenem-resistant Enterobacteriaceae and there was a net rise in MDR P. aeruginosa as a proportion of all P. aeruginosa infections from 2000 to 2009. A recent meta-analysis also demonstrated that MDR status was an important determinant of mortality due to nosocomial infections attributed to gram-negative bacteria, where P. aeruginosa and Acinetobacter species were the most common isolates. It is also interesting that the observed mortality for COP was lower than that observed more than 10 years ago despite the high rate of bacteremia, suggesting that these may have been less virulent strains of gram-negative bacteria.

The high rates of MDR and IIAT in Pa-NP for all pneumonia types mandate that clinicians have therapeutic strategies in place to optimize therapy. Scoring systems to identify patients with MDR infections, including MDR P. aeruginosa, are available but limited in their overall ability to predict MDR infection. A number of novel methods aimed at improving the early identification of pathogens and related antibiotic susceptibilities are also entering the diagnostic arena. Such technological advances offer a strategy that could potentially maximize the administration of appropriate antibiotic therapy while minimizing unnecessary antibiotic exposure. One such approach employs advanced automated microscopy techniques that allow the identification of bacterial species, the determination of the presence of antibiotic resistance genes, and bacterial killing by specific antibiotics within 4 to 6 hours using direct specimen inoculation.

Our study has a number of limitations. First, it was limited to an evaluation of Pa-NP and the findings may not be applicable to NP attributed to other pathogens. Second, the criteria for establishing a diagnosis of Pa-NP varied across centers. Therefore, our study cohort could have included patients without true pneumonia. Third, by analyzing each category of pneumonia separately we have limited our ability to identify all important factors for inappropriate initial therapy in HAP were late-onset infection and greater APACHE II scores whereas in VAP antibiotic usage in the previous 3 months and admission to a surgical unit were found to be independent risk factors for IIAT. Taken together with our data, these studies highlight the difficulty in identifying consistent clinical markers for outcome in NP across pneumonia categories.

A large volume of research has emphasized the importance of early appropriate antimicrobial therapy for serious infections in order to minimize the risk of death. It has also been shown that escalation of treatment from IIAT to an appropriate antibiotic regimen in response to culture results fails to mitigate this increase in the risk of death. Our findings generally confirm these relationships. IIAT was found to be a predictor of hospital death in VAP where patients with VAP had the greatest severity of illness and prevalence of septic shock. The potential practical implications of these findings are illustrated by a recent large epidemiologic study from the United States that identified 205,526 patients with P. aeruginosa infections (187,343 pneumonia; 18,183 bloodstream infection) and 95,566 patients with Enterobacteriaceae infections (58,810 pneumonia; 36,756 bloodstream infection). The prevalence of MDR P. aeruginosa was approximately 15-fold higher than carbapenem-resistant Enterobacteriaceae and there was a net rise in MDR P. aeruginosa as a proportion of all P. aeruginosa infections from 2000 to 2009. A recent meta-analysis also demonstrated that MDR status was an important determinant of mortality due to nosocomial infections attributed to gram-negative bacteria, where P. aeruginosa and Acinetobacter species were the most common isolates. It is also interesting that the observed mortality for COP was lower than that observed more than 10 years ago despite the high rate of bacteremia, suggesting that these may have been less virulent strains of gram-negative bacteria.

The high rates of MDR and IIAT in Pa-NP for all pneumonia types mandate that clinicians have therapeutic strategies in place to optimize therapy. Scoring systems to identify patients with MDR infections, including MDR P. aeruginosa, are available but limited in their overall ability to predict MDR infection. A number of novel methods aimed at improving the early identification of pathogens and related antibiotic susceptibilities are also entering the diagnostic arena. Such technological advances offer a strategy that could potentially maximize the administration of appropriate antibiotic therapy while minimizing unnecessary antibiotic exposure. One such approach employs advanced automated microscopy techniques that allow the identification of bacterial species, the determination of the presence of antibiotic resistance genes, and bacterial killing by specific antibiotics within 4 to 6 hours using direct specimen inoculation.

Our study has a number of limitations. First, it was limited to an evaluation of Pa-NP and the findings may not be applicable to NP attributed to other pathogens. Second, the criteria for establishing a diagnosis of Pa-NP varied across centers. Therefore, our study cohort could have included patients without true pneumonia. Third, by analyzing each category of pneumonia separately we have limited our ability to identify all important
risk factors for hospital mortality and IIAT. Larger cohorts might show more-similar risk factors for these outcomes. Fourth, our definition of COP included patients who previously would have been classified as HCAP. However, given the controversies surrounding the HCAP definition we chose to simply define patients acquiring Pa-NP outside of the hospital as community-onset. In addition, we did not assess the type of prior antibiotics administered nor did we assess how clinicians made decisions regarding the selection of empirical antibiotic therapy in this cohort. This may have been important, especially if the administration of prior antibiotics gave rise to broader subsequent empirical therapy resulting in less IIAT as suggested by the VAP analysis. Finally, we did not require the study sites to provide information on the overall number of patients screened or the number of patients with possible Pseudomonas pneumonia that were excluded for not meeting the entry criteria. We recognize that this is a potential bias of our study, potentially selecting out a cohort of patients with Pseudomonas pneumonia that may not be representative of all patients with this infection.

In summary, our study found that for Pa-NP, pneumonia classification identified patients with different risks for hospital mortality. Risk factors for hospital mortality also differed by pneumonia classification and multidrug resistance appeared to be a common risk factor for IIAT. These findings suggest that pneumonia classification for P. aeruginosa identifies patients with different mortality risks and specific risk factors for outcome and IIAT.

ACKNOWLEDGMENTS

Financial support. Cubist Pharmaceuticals.

Potential conflicts of interest. S.T.M. reports that he has received research funding from Cubist, Astellas, Pfizer, and Pfizer. M.H.K. reports that he has served as a consultant to and/or received research funding from Cubist, Astellas, Pfizer, and Pfizer, the Academy of Infection Management, and Theravance. J.C. reports that he has received consulting or lecture fees from Bayer, Pfizer, Basilea, Astellas, Cubist-Trius, and Kenta-Aridis. H.O. reports that he has served as a consultant and/or speaker and/or received research grants from Astellas, AstraZeneca, Cubist, Gilead, MSD, and Pfizer. All other authors report no conflicts of interest relevant to this article.

Address correspondence to Scott T. Micek, PharmD, St. Louis College of Pharmacy, 4588 Parkview Pl, St. Louis, Missouri 63110-1088 (scott.micek@stlcop.edu).

REFERENCES


34. Vardakas KZ, Rafailidis PI, Konstantelias AA, Falagas ME. Predictors of mortality in patients with infections due to multidrug resistant gram negative bacteria: the study, the patient, the bug or the drug? *J Infect* 2013;66:401–414.


**APPENDIX I. Number of Subjects Enrolled at each Center and Corresponding Hospital Mortality Rate (%)**

Groupe Hospitalier Pitie-Salpetriere, France, n = 100 (38%)
Hospital Raymond Poincare, France, n = 41 (37%)
University Hospital of Munich, Germany, n = 41 (12%)
Medizinische Hochschule Hannover, Germany, n = 79 (57%)
Polclinica Universitario A Gemelli, Italy, n = 83 (46%)
Azienda Ospedaliera Universitaria Pisana, Italy, n = 25 (48%)
Hospital Universitari Mutua De Terrassa, Spain, n = 27 (26%)
Hospital Vall D’Hebron, Spain, n = 62 (60%)
Hospital Clinic De Barcelona, Spain, n = 26 (42%)
Barnes-Jewish Hospital, United States, n = 100 (15%)
Northwestern Memorial Hospital, United States, n = 78 (19%)
Mayo Clinic, United States, n = 80 (36%)