Health and Economic Outcomes of Antibiotic Resistance in Pseudomonas aeruginosa

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Background: Antimicrobial resistance is an increasing problem.

Objective: To examine the clinical and economic impact of antibiotic resistance in Pseudomonas aeruginosa.

Methods: In-hospital mortality, secondary bacteremia, length of stay, and hospital charges were examined in a cohort of 489 inpatients with positive clinical cultures for P aeruginosa. One hundred forty-four had a resistant baseline P aeruginosa isolate and 30 had resistance emerge during follow-up. Multivariable and survival analytic methods were used to adjust for confounding and effects of time.

Results: The overall in-hospital mortality rate was 7.6%, 7.7% in patients with a resistant isolate at baseline (relative risk [RR], 1.3; 95% confidence interval [CI], 0.6-2.8) and 27% in patients in whom resistance emerged (RR, 3.0; 95% CI, 1.2-7.8). Secondary bacteremia developed in 1.4% of patients in whom resistance did not emerge and in 14% of those in whom resistance emerged (RR, 9.0; 95% CI, 2.7-30). The median duration of hospital stay following the initial P aeruginosa isolate was 7 days. Emergence of resistance, but not baseline resistance, was significantly associated with a longer hospital stay (P<.001 and P = .71, respectively). The average daily hospital charge was $2059. Neither baseline resistance nor emergence of resistance had a significant effect on the daily hospital charge. In a matched cohort analysis, a trend was seen toward increased total charges in patients demonstrating emergence of resistance (difference, $7340; P = .14).

Conclusions: Emergence of antibiotic resistance in P aeruginosa results in severe adverse outcomes. Efforts should be directed toward early detection and prevention of emergence of antibiotic resistance.

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ANTIBIOTIC RESISTANCE is a recognized clinical problem and a major public health threat. Infections caused by antibiotic-resistant bacteria are believed to result in higher mortality, prolonged hospitalization, and higher health care costs relative to antibiotic-susceptible bacteria, but detailed data are lacking. The reason that antibiotic resistance leads to adverse outcomes is presumably due to an increased likelihood that ineffective or suboptimal antibiotic therapy will be given. The development of resistance to all available antibiotics in some organisms may preclude the effectiveness of any antibiotic regimen. Antibiotic resistance genes may also be associated with virulence factors. To help define the effect of antibiotic resistance on outcomes, we conducted a study of antibiotic-resistant Pseudomonas aeruginosa. Pseudomonas aeruginosa was chosen for this analysis since it is a leading cause of nosocomial infections, ranking second among the gram-negative pathogens reported to the National Nosocomial Infection Surveillance (NNIS) System from January 1990 through March 1996. Infections caused by P aeruginosa are frequently life-threatening and often difficult to treat because of the intrinsic susceptibility of P aeruginosa to a limited number of antimicrobial agents. Resistance to antipseudomonal antibiotics is an increasing problem, and emergence of antibiotic resistance during therapy occurs with relatively high frequency.

The objective of this study was to quantify the direct in-hospital clinical and economic impact of antibiotic resistance in a cohort of patients with clinical isolation of P aeruginosa. We examined both the effect of resistance detected in baseline cultures and the effect of resistance emerging during antibiotic treatment. Resistance to any of the following 4 major
METHODS

HOSPITAL SETTING, DATA COLLECTION, AND MICROBIOLOGY

The Deaconess Hospital (currently Beth Israel Deaconess Medical Center, West Campus) is a 320-bed urban tertiary-care teaching hospital in Boston, Mass. It has 24 intensive care units beds and approximately 11,000 admissions per year.

Data were extracted from administrative, accounting, and laboratory computerized databases and compiled into a single data set using a relational database management system (Access, Microsoft Corp, Redmond, Wash). The billing database contained itemized charges for each hospital service or product according to the date of service. This informatics system has been described elsewhere.19

Pseudomonas aeruginosa was identified by the Gram-Negative Identification Panel Type II (Dade International Inc, West Sacramento, Calif). Susceptibility was tested by microbroth dilution (MicroScan; Dade International Inc).

DEFINITIONS AND STUDY DESIGN

The study population consisted of all patients admitted between August 1, 1994, and July 31, 1996, from whom P aeruginosa was recovered in clinical culture and who were hospitalized for at least 2 days. Two subgroups were also analyzed: (1) patients treated with at least one of the study agents and in whom Pseudomonas infection was confirmed using the Centers for Disease Control and Prevention definitions for infection (modified to include community infections and to exclude asymptomatic bacteriuria) and (2) patients who had one or more additional positive cultures for P aeruginosa at least 48 hours after the baseline culture (persistent P aeruginosa infection).

Resistance to 4 antipseudomonal antibiotics was studied: piperacillin, ceftazidime, ciprofloxacin, and imipenem.15 The initial P aeruginosa isolate of each patient was considered the baseline isolate. Baseline resistance was defined as resistance of baseline isolate to any of the study antibiotics. Emergence of resistance was defined as the subsequent detection of P aeruginosa with at least a 4-fold increase (2 dilutions) in minimal inhibitory concentration relative to the baseline isolate and a change in the interpretive class. The minimal inhibitory concentrations used to determine susceptibility thresholds for the different drugs were according to the National Committee for Clinical Laboratory Standards guidelines (<128 µg/mL for piperacillin sodium, <16 µg/mL for ceftazidime sodium, <8 µg/mL for imipenem, and <2 µg/mL for ciprofloxacin hydrochloride). Isolates with intermediate susceptibility were considered resistant.

Four outcomes were examined: mortality, secondary bacteremia, length of hospital stay following the detection of the baseline isolate, and daily hospital charge following detection of the baseline isolate. The daily hospital charge was studied only for patients admitted after April 1, 1995, because these data were not available prior to this date.

Persistence of infection was defined as the recurrent isolation of P aeruginosa at least 48 hours after the date of the baseline isolate. Secondary bacteremia was defined as a first positive blood culture for P aeruginosa at least 24 hours after the baseline isolate.

The delay in effective treatment related to resistance was calculated as the number of days that a patient was treated with an antipseudomonal agent to which the organism was resistant and simultaneously not receiving antipseudomonal drugs was studied: ceftazidime sodium, ciprofloxacin hydrochloride, imipenem, and piperacillin sodium.

RESULTS

Four hundred eighty-nine patient admissions representing 421 unique individuals satisfied the criteria for entry into the study cohort. Demographic characteristics are shown in Table 1. The population was 42% female, with a mean age of 63 years. Many of the cohort patients had chronic underlying illnesses, as expressed by a high mean Charlson score of 2.9. The cohort also included many severely ill patients: 20% were transferred from another institution, 28% underwent a major surgical procedure, and 19% were admitted to an intensive care unit. A high proportion (49%) of patients had diabetes mellitus, a characteristic of the overall hospital population.

For 63% of the patients, the baseline isolate was obtained within 48 hours of admission and thus was not considered nosocomial. Three hundred forty-five (70%) of the baseline isolates were susceptible to all 4 study drugs; 94 (19%) were resistant to 1, 38 (8%) to 2, and 12 (3%) to 3 of the study antimicrobial agents. Baseline resistance resulted in delay of effective antibiotic treatment in 14 patients. In 9 cases the delay ranged from 24 to 48 hours, and in 5 cases more than 48 hours. Emergence of resistance to at least one of the study agents occurred in 30 patients (6.1%). For these patients, the median time between the baseline P aeruginosa isolate and emergence of resistance was 14 days. The cohort patients were evaluated for a total of 5122 days. The median follow-up period was 7 days (range, 1-72 days). A wound was the single most common site of Pseudomonas infection.

MORTALITY

Of the 489 patients, 37 died in hospital (case fatality rate [CFR], 7.6%): 26 of 345 patients with a susceptible baseline isolate, and 11 of 144 patients with a resistant baseline isolate (CFR, 7.5% vs 7.6%; RR, 0.94; P = .96). Eight of 30 patients in whom resistance emerged died, compared with 29 of 459 patients in whom resistance did not emerge (CFR, 26.6% vs 6.3%; RR, 2.9; P = .03).

Results of a crude analysis for the association of the cohort characteristics with mortality are shown in Table 2, and the results of a multivariable Cox model constructed to control for confounding are summarized in Table 3. Resistance of the baseline P aeruginosa isolate continued to lack an association with mortality in the adjusted model (RR, 1.3; P = .52). In contrast, even

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an antipseudomonal agent active against the baseline isolate.

STATISTICAL ANALYSIS

The patient admission represented the unit of analysis. Mortality and the length of hospital stay were examined using survival analytic methods in order to incorporate time into the models. Cox proportional hazard regression was used to address mortality, and an accelerated failure time model (Weibull) was used to examine length of stay. Time 0 was considered to be the date of the initial \( P \) aeruginosa isolate. In models of mortality, patients were censored at the time of discharge from the hospital; in models of length of stay, patients were censored at the time of death. Factors or exposures that occurred during follow-up, such as emergence of resistance, were introduced as time-dependent variables. Thus, for each day of follow-up, patients who demonstrated emergence of resistance were compared only with other patients remaining in the hospital on that day. Proportional hazard assumptions were tested using appropriate time-covariate interaction terms. Survivorship curves of hospital length of stay were examined and found to be appropriate for the accelerated failure time (Weibull) model. The Weibull model was parameterized in the form of logarithmic time, so that the exponentiated coefficients could be interpreted as multiplicative effects (MEs) on length of stay. This model was also used to estimate excess number of days in the hospital based on the value of the ME. Hazard ratios from the Cox proportional hazard model are presented as relative risks (RRs).

We developed linear regression models to analyze daily hospital charges, which were log-transformed because of their skewed distribution. Since these charges represented serial or longitudinal observations in a panel of subjects, the method of generalized estimating equations for model estimation was used. The within-subject correlation was modeled to be auto-regressive after examination of the correlation matrix. Robust SE estimators were specified. Charges for the last hospital day of each patient were much lower than charges for the other hospital days and therefore were excluded from the analysis. Coefficients from the generalized estimating equation model were exponentiated because of the log-transformation of the dependent variable and thus were also interpreted as MEs.

To control for confounding, variables with \( P < .2 \) in the crude analysis were considered candidates for multivariable analysis and added to a model in which the variables’ baseline resistance and emergence of resistance were forced. In addition to examining statistical significance, other variables were tested for confounding by adding them one by one to the model and looking at changes in the coefficient estimates for baseline resistance and emergence of resistance. In the case of substantial confounding (change in the coefficient estimate of 10% or more), the responsible variables were kept in the model. Effect modification between variables was evaluated by testing appropriate interaction terms for statistical significance.

To examine the effect on the total hospital charge of emergence of resistance, we performed a matched cohort study, matching a patient who had emergence of resistance with a patient who did not. Matching was performed on the day in hospital when emergence of resistance was detected and on the cumulative charges up to that day. The matched comparison was performed using a paired \( t \) test.

All statistical tests were 2-tailed; \( P \leq .05 \) was considered significant.

after adjustment for confounding, emergence of resistance was associated with a 3-fold higher risk of fatality (RR, 3.0; \( P = .02 \)).

SECONDARY BACTEREMIA

Secondary bacteremia developed in 10 of the 467 patients in whom blood was not the source of initial \( P \) aeruginosa culture, including 4 (14%) of 29 patients in whom resistance emerged, and in 6 (1.4%) of the other 438 patients (RR, 9.0; 95% confidence interval [CI], 2.7-30; \( P < .001 \)).

LENGTH OF HOSPITAL STAY

The median number of days between initial \( P \) aeruginosa isolation and discharge was 7 days (range 1-72 days) for the entire cohort, 7 days for patients with a resistant baseline isolate, and 24 days for patients in whom resistance emerged. The median number of days between emergence of resistance and discharge was 14 days. The ME on the duration of stay following initial \( P \) aeruginosa isolation was calculated using an accelerated failure time model. Results of the crude analysis are displayed in Table 2. A longer duration of stay was observed in patients with emergence of resistance (ME, 2.1; \( P < .001 \) but not in patients with baseline resistance (ME, 0.97; \( P = .72 \)). Similar results were seen in the multivariable model developed to control for confounding (baseline resistance: ME, 1.0; \( P = .71 \); emergence of resistance: ME, 1.7; \( P < .001 \)). We estimated that emergence of resistance was associated with an average adjusted increase of 5.7 days in length of hospital stay.

HOSPITAL CHARGE

The daily hospital charge was studied in 309 patients admitted after April 1, 1995. Two hundred seventeen patients had a baseline isolate that was susceptible to all 4 study agents, and 92 patients had a baseline isolate resistant to at least 1 agent. Resistance emerged in 17 patients. The overall average daily hospital charge was $2102. The average daily charge for patients with a sensitive baseline isolate was $2059; for patients with resistant baseline isolate, $2194. The average daily charge for patients in whom resistance emerged was $2822. In the crude analysis, neither resistance of the baseline isolate nor emergence of resistance was associated with significantly increased daily hospital charge (MEs, 1.04 and 1.1, respectively; \( P = .41 \) and \( P = .43 \)). The adjusted effects of resistance at baseline and emergence of resistance were similar in the multivariable model (Table 3).
The outcomes of mortality and length of hospital stay were also examined in 2 subgroups: (1) 271 patients treated with an antipseudomonal agent and in whom infection was confirmed using the Centers for Disease Control and Prevention criteria and (2) 150 patients who had one or more additional positive cultures for P aeruginosa at least 48 hours after the baseline culture (persistent P aeruginosa infection). The results were similar within each subgroup to those in the full study population. Among treated patients with confirmed infection, resistance at baseline did not affect mortality (RR, 1.3; P = .49) or length of stay (ME, 0.9; P = .32). In contrast, emergence of resistance had significant effects on both mortality (RR, 3.3; P = .01) and length of stay (ME, 1.5; P = .005). Similarly, among the patients who met criteria for persistent P aeruginosa infection, resistance at baseline did not affect mortality or length of stay (RR, 0.6; P = .41, and ME, 1.0; P = .78, respectively), whereas emergence of resistance continued to show significant associations with both outcomes (RR, 4.0; P = .01, and ME, 1.4; P = .02, respectively).

**COMMENT**

Antimicrobial resistance is a growing public health threat. Holenberg et al1 studied the impact of antibiotic resistance by reviewing 175 reports of investigations of outbreaks of Salmonella, Shigella, Serratia, and Staphylococcus aureus in the years 1971 to 1980. Antibiotic-resistant organisms were found to increase the mortality,
morbidly, and cost of infections compared with susceptible organisms. The national costs of antimicrobial resistance for the United States have been estimated between $100 million and $30 billion annually.21 The Office of Technology Assessment of the US Congress has estimated the minimal extra hospital cost associated with nosocomial infections caused by antibiotic-resistant bacteria to be $1.3 billion per year.3 However, despite the existence of these estimates, controlled studies that quantitatively examine the health and cost impact of resistant organisms in detail are lacking.

In this study, we examined in-hospital clinical and economic outcome measures in patients with clinical isolation of Pseudomonas aeruginosa. We used multivariable statistical methods to adjust for confounding and length of hospital stay, similar to the manner in which matching is used in other outcome studies to establish comparability. The use of time-dependent survival methods in our analyses ensured that the effect of emergence of resistance was always examined relative to other patients still hospitalized for the same follow-up interval.

Our principal finding was that emergence of resistance in P. aeruginosa during follow-up was associated with severe adverse outcomes. Emergence of resistance was associated with a 3-fold increase in mortality, a 9-fold higher rate of secondary bacteremia, and a 2.1-fold increase in hospital days. Emergence of resistance was associated with higher charges, whether calculating an effect on the basis of length of stay or estimating an effect in the matched cohort analysis, although the latter finding was not statistically significant. In striking contrast to the substantial effects associated with emergence of resistance, baseline resistance was not associated with increased mortality, secondary bacteremia, prolonged hospital stay, or increase in hospital charges.

The strong association between emergence of resistance and adverse outcomes even after adjustment for confounding is most consistent with a direct causal relationship. We hypothesize that emergence of resistance leads to adverse outcomes by rendering existing antibiotic therapy microbiologically ineffective, thus causing progressive or relapsing clinical infection. It is difficult to disengage the effects of emergence of resistance from the consequences of persistent or recurrent infection, since the latter may represent intermediate variables in the causal pathway. We examined this question further by testing the effects of emergence of resistance in the subcohort of patients with persistent infection, as indicated by culture positivity extending for at least 48 hours. Emergence of resistance was still associated with adverse outcomes in this group, supporting the causal link. Our data also suggest that emergence of resistance may result in inability to confine the infection to its original focus, as reflected by the observation of increased risk of secondary bacteremia. It is likely that the adverse consequences of emergence of resistance are amplified by a delay in clinical recognition of emergence of resistance, prolonging the period during which suboptimal therapy is administered. Thus, these results are compatible with previously reported analyses of Pseudomonas bacteremia22-26 that have found a relationship between inappropriate antibiotic therapy after reporting of culture results and poor outcome.

The lack of association between baseline resistance and adverse outcomes may be attributable to earlier recognition of resistance by clinicians and more timely adjustment in antibiotic therapy when the initial isolate is resistant. Furthermore, baseline resistance is probably less likely to specifically include resistance to the anti-infective drug in use. Indeed, baseline resistance led to delay in effective antipseudomonal treatment in only 14 of 144 patients with baseline resistance, and in 9 of these individuals the delay was less than 48 hours.

We have examined the associations between specific antibiotics and emergence of resistance in previous studies; emergence of resistance was more common during imipenem treatment than during treatment with other antipseudomonal agents.15 Further studies are needed to better define the relative merit of different antibiotic regimens with respect to clinical outcomes. Nonetheless, the data from this study suggest that strategies to prevent emergence of resistance should be a leading priority in any effort to improve outcomes from pseudomonal infection.

The results of this study should not be taken to imply that adverse consequences of antibiotic resistance are associated only with emergence of resistance during therapy, since there are a number of likely indirect effects of antibiotic resistance not accounted for in this study. For instance, the overall prevalence of antibiotic resistance in an institution or population has substantial effects on empirical antibiotic choices for those patients with suspected but not microbiologically documented infections (eg, the heavy use of vancomycin for suspected β-lactam-resistant staphylococcal infections). In this manner, antibiotic resistance probably increases total antibiotic costs within an institution. Failure of antibiotic prophylaxis, not addressed in this study, is another potential adverse effect of antibiotic resistance.

It was our intention for the a priori criteria for entry into the study cohort to be broadly inclusive, in part to maximize the power of the analyses and the generalizability of the results. However, applying more restrictive criteria to define the study population, such as limiting the analysis to only patients with confirmed infection, did not alter the results in any way.

Our study had limited power to examine the effect of emergence of resistance on hospital charges because daily

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Resistance at Baseline RR (95% CI) P</th>
<th>Emergence of Resistance RR (95% CI) P</th>
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</thead>
<tbody>
<tr>
<td>Mortality†</td>
<td>1.3 (0.6-2.8) .52</td>
<td>3.0 (1.2-7.8) .02</td>
</tr>
<tr>
<td>Length of hospital stay‡</td>
<td>1.0 (0.9-1.2) .71</td>
<td>1.7 (1.3-2.3) &lt;.001</td>
</tr>
<tr>
<td>Daily hospital charges§§</td>
<td>1.0 (1.0-1.4) .41</td>
<td>1.1 (0.9-1.3) .43</td>
</tr>
</tbody>
</table>

*RR indicates relative risk; CI, confidence interval.
†Variables included in the model: intensive care unit (ICU) stay (RR, 4.4), female (RR, 2.0), Charlson comorbidity score (RR, 1.2).
‡Variables included in the model: ICU stay (RR, 2.2), intensity of culturing (RR, 1.6), days in hospital before baseline culture (RR, 1.0), Pseudomonas aeruginosa isolated from urine (RR, 0.6).
§Variables included in the model: ICU stay (RR, 3.1), nosocomial isolate (RR, 0.9), major surgery (RR, 1.1).
∥The relative risk for this outcome is the multiplicative effect.
charge data were available only for part of the time studied and relatively few cases of emergence of resistance were included in this analysis. Another limitation of this study is that, similar to other observational epidemiologic analyses, there may be additional confounding factors not captured or included in the models. However, the outcome of antibiotic resistance and emergence of resistance are not amenable to randomized trial. Adjustment for severity of underlying illness is crucial. In the absence of an available gold standard method of risk adjustment for our study population, we elected to use a study-based method of adjustment by including information on variables such as age, sex, diagnosis related group, comorbidity, surgical procedures, intensive care unit stay, and frequency of microbiologic culturing. We considered that frequency of culturing was a particularly important control variable, in part because clinical cultures were the basis for detection of emergence of resistance.

We conclude that emergence of antibiotic resistance in P aeruginosa is associated with a significantly increased frequency of adverse outcomes. Efforts should be directed toward early detection and prevention of emergence of antibiotic resistance in P aeruginosa and other pathogenic organisms.

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