MAJOR ARTICLE

Gram-Negative Bacteremia upon Hospital Admission: When Should *Pseudomonas aeruginosa* Be Suspected?

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Background. *Pseudomonas aeruginosa* is an uncommon cause of community-acquired bacteremia among patients without severe immunodeficiency. Because tension exists between the need to limit unnecessary use of anti-pseudomonal agents and the need to avoid a delay in appropriate therapy, clinicians require better guidance regarding when to cover empirically for *P. aeruginosa*. We sought to determine the occurrence of and construct a model to predict *P. aeruginosa* bacteremia upon hospital admission.

Methods. A retrospective study was conducted in 4 tertiary care hospitals. Microbiology databases were searched to find all episodes of bacteremia caused by gram-negative rods (GNRs) ⩽48 h after hospital admission. Patient data were extracted from the medical records of 151 patients with *P. aeruginosa* bacteremia and of 152 randomly selected patients with bacteremia due to Enterobacteriaceae. Discriminative parameters were identified using logistic regression, and the probabilities of having *P. aeruginosa* bacteremia were calculated.

Results. *P. aeruginosa* caused 6.8% of 4114 unique patient episodes of GNR bacteremia upon hospital admission (incidence ratio, 5 cases per 10,000 hospital admissions). Independent predictors of *P. aeruginosa* bacteremia were severe immunodeficiency, age >90 years, receipt of antimicrobial therapy within past 30 days, and presence of a central venous catheter or a urinary device. Among 250 patients without severe immunodeficiency, if no predictor variables existed, the likelihood of having *P. aeruginosa* bacteremia was 1:42. If ⩾2 predictors existed, the risk increased to nearly 1:3.

Conclusions. *P. aeruginosa* bacteremia upon hospital admission in patients without severe immunodeficiency is rare. Among immunocompetent patients with suspected GNR bacteremia who have ⩾2 predictors, empirical anti-pseudomonal treatment is warranted.

Pseudomonas aeruginosa is a leading nosocomial pathogen, causing infections that usually occur late during hospital stay [1]. Affected patients are often hospitalized in an intensive care unit, have multiple invasive devices, undergo surgical procedures, and are immunocompromised as a result of disease and treatment [2]. Community-acquired *P. aeruginosa* infection is a rare condition that mostly affects patients with specific predisposing factors, such as neutropenia and chronic structural lung diseases (e.g., cystic fibrosis and bronchiectasis). However, it may occur occasionally among other patient populations [3].

For serious infections, timely, adequate empirical antibiotic therapy is an important determinant of improved outcomes [4–9]. Because treatment of *P. aeruginosa* requires the use of a limited number of antibiotic agents, the clinical decision regarding whether the causative organism of a serious infection is likely to be *P. aeruginosa* is of vast importance; failure to use an anti-pseudomonal agent for empirical treatment when *P. aeruginosa* is the causative pathogen may lead to delay in administration of effective therapy and cause severe adverse outcomes [10–13]. However, overuse of these

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anti-pseudomonal agents leads to increased resistance rates and limits future treatment options [14–16]. Thus, for clinical decision-making regarding the choice of appropriate empirical therapy, it is important to differentiate between patients at risk of developing *P. aeruginosa* infection and those with infections likely due to other gram-negative bacilli.

Our study was aimed to determine the occurrence of *P. aeruginosa* bacteremia upon hospital admission among patients with gram-negative bacteremia. We preferred to address this unambiguous and neutral term, denoting any bacteremia identified ≤48 h after hospital admission, rather than community-acquired infection, which suggests (often erroneously) that the infection and or the organisms originated in the community. We also aimed to characterize the clinical features of patients with *P. aeruginosa* bacteremia upon hospital admission and to offer a simple and useful model to discriminate between patients at risk of *P. aeruginosa* bacteremia from those with bacteremia due to other gram-negative pathogens upon hospital admission. We intended to provide clinicians with data regarding the probability of *P. aeruginosa* infection among patients with gram-negative bacteremia upon hospital admission, and to allow them to better direct empirical therapy against bloodstream infections at admission.

METHODS

Site, study design, and patients. We conducted a retrospective study at 4 tertiary care teaching hospitals: Beth Israel Deaconess Medical Center, a 740-bed hospital in Boston, Massachusetts; Duke University Hospital, a 750-bed hospital in Durham, North Carolina; Geneva University Hospital, a 1200-bed hospital in Geneva, Switzerland; and Tel Aviv Sourasky Medical Center, a 1200-bed hospital in Tel Aviv, Israel.

The occurrence of *P. aeruginosa* bacteremia upon hospital admission was determined using electronic microbiology databases. Each center examined a 3–5-year period during 2000–2005 to identify all cases of bacteremia due to gram-negative bacilli that occurred ≤48 h after hospital admission (defined as bacteremia upon hospital admission). Each patient admission was included once, and all gram-negative bacilli isolates were included in the analysis. In all centers, specimens were processed in accordance with the CLSI guidelines [17], and isolates were identified using the Vitek II system (bioMérieux).

A retrospective case-control study was conducted to characterize patients affected with *P. aeruginosa* bacteremia upon hospital admission. Medical records of a random sample of 151 patients with *P. aeruginosa* bacteremia (defined as case patients) and 152 patients with bacteremia caused by Enterobacteriaceae (defined as control subjects) were reviewed for specific underlying conditions and contacts with the health care system. The following data were collected: age, sex, activities of daily living status [18], nursing home residency, specific comorbidities, severe immunodeficiency (defined as receipt of a solid organ or bone marrow transplant, presence of neutropenia [neutrophil count, <1000 cells/μL], receipt of recent chemotherapy [≤30 days before bacteremia], AIDS [CD4 cell count, <200 cells/μL, or other evidence of AIDS], or receipt of treatment with high-dose corticosteroids [≥20 mg/day prednisone equivalent for >5 days], azathioprine sodium, or cyclosporine), admitting syndrome and source of bacteremia, recent hospitalization, antimicrobial use during the previous 30 days, invasive procedures performed during the previous 2 weeks, and invasive devices present at the time of admission.

Statistical analysis. Continuous variables were compared using the unpaired *t* test. Categorical variables were compared using the Pearson χ^2 test or Fisher's exact test, as appropriate. Differences in distribution of populations were compared using Kruskal-Wallis equality-of-populations rank test. *P* values ≤.05 were considered to indicate a statistically significant difference between groups. To find discriminative parameters between patients with *P. aeruginosa* bacteremia and patients with other gram-negative bacteremia, stepwise multivariable logistic regression was used. All variables with a *P* value ≤.10 in the univariate analysis were considered for inclusion in the multivariable logistic regression analysis, and variables for which $P < .05$ in the multivariable analysis were retained in the final model. The statistical software Stata, version 9, (Stata), was used for analysis.

In addition to logistic regression, we used decision tree analysis for classification of patients with *P. aeruginosa* bacteremia as a function of a set of predictors that were statistically significant in the multivariate model with logistic regression [19, 20]. We randomly divided the data into in-sample (training) data with 180 cases and out-sample (testing) data with the rest of the cases. We fit the decision tree over the in-sample data using the procedure "treefit" with Matlab (Mathwork) and evaluated the prediction of the decision tree model obtained over the out-sample data using the procedure "treeval." In addition, we used the "treeprune" procedure to avoid overfitting. We repeated this procedure 100 times and evaluated the best model for classification using area under the receiver-operating-characteristics curves and the log likelihood. To compare the logistic regression model with decision tree models, we used, in addition, 2 recently published criteria [21]: the net reclassification improvement and integrated discrimination improvement.

Among all evaluated criteria, logistic regression revealed similar classification capability. Thus, in our next step, we used logistic regression modeling to discriminate between patients with *P. aeruginosa* bacteremia and patients with other gram-negative bacteremia. For each case, with use of the logistic regression estimations, we calculated the probability of having *P. aeruginosa* bacteremia.

Table 1. Baseline and clinical characteristics of 151 case patients with *Pseudomonas aeruginosa* bacteremia upon hospital admission and of 152 control subjects with Enterobacteriaceae bacteremia upon hospital admission.

Variable	Case patients	Control subjects	*P*
Age, mean years ± SD	67 ± 16	66 ± 19	.5
Female sex	44.4	56.6	.034
Dependent ADL	31.1	17.1	.004
Chronic care	13.2	5.3	.016
Comorbidity			
Malignancy	47.0	24.3	<.001
Solid tumor	29.8	21.0	.08
Hematological malignancy	19.2	6.6	.001
Solid-organ transplantation	6.6	4.6	.446
Cardiovascular disease	37.7	40.8	.588
Diabetes mellitus	27.8	20.4	.13
Chronic lung disease	19.2	12.5	.11
Cystic fibrosis	0.7	0.0	.5
Bronchiectasis	1.3	1.3	>.99
Neurological disease	19.2	23.7	.342
Hepatobiliary disease	13.9	12.5	.717
Renal disease	26.5	19.1	.124
Nephrolithiasis	0.7	5.9	.02
Admitting syndrome			
Sepsis	35.1	27.0	
Neutropenic fever	18.5	2.6	<.001
Source of bacteremia			<.001
Urinary tract	23.2	64.5	
Abdominal	11.9	13.8	
Skin and skin structures	7.3	3.9	
Respiratory	19.2	2.0	
Intravenous catheter	15.2	4.6	
Bone	0.7	0.7	
Unknown	22.5	10.5	
Coexisting conditions			
Decubitus ulcers	2.6	3.3	.743
Diabetic foot infection	2.0	0.66	.37
Immunodeficiency			
All	38.4	15.8	<.001
Neutropenia	21.2	3.9	<.001
Recent chemotherapy	21.2	7.9	.001
Corticosteroids	9.3	5.9	.271
Severe AIDS	0.0	0.0	
Invasive devices			
Urinary devices			
All	15.9	3.9	<.001
Foley catheter	8.0	1.3	.006
Other urinary device [a]	8.0	2.6	.039
NGT	1.3	0.7	.62
Feeding enterostomy	1.3	2.6	.68
Central line in place	23.8	11.2	.004
Contact with the health care system			
Hospitalization during the previous 30 days	44.4	25.0	<.001
Hospitalization during the previous 90 days	64.9	36.2	<.001

(continued)

Table 1. ***(Continued.)***

Variable	Case patients	Control subjects	*P*
Invasive procedures in previous 14 days			
Endoscopy	2.0	2.0	>.99
Bronchoscopy	0.0	0.6	>.99
Cystoscopy	2.6	0.0	.06
Surgery	4.6	5.9	.80
Dialysis	3.3	1.3	.28
Trans-rectal prostatic biopsy	0.0	3.3	.06
Antimicrobial use in previous 30 days			
All	36.4	13.2	<.001
Fluoroquinolone	6.6	5.3	.617
β-Lactam	23.2	5.9	<.001
Macrolide	2.0	0.7	.37

NOTE. Data are percentage of patients, unless otherwise indicated. ADL, activities of daily living; NGT, nasogastric tube.

[a] Other urinary devices include pigtail and nephrostomy.

RESULTS

Study population. In the 4 participating centers, a total of 4114 unique patient gram-negative rods (GNRs) were isolated from cultures of blood specimens obtained at admission (i.e., ≤48 h after hospital admission). *Escherichia coli* was the most common isolate (51%; range, 41%–63%), followed by *Klebsiella* species (16%; range, 12%–21%), *P. aeruginosa* (6.8%; range, 5.3%–8.4%), *Enterobacter* species (4.9%; range, 2.7%–7.8%), and *Proteus* species (5%; range, 2.7%–6.2%). *Serratia, Morganella,* and *Citrobacter* species together contributed 5% of the cases. The incidence of *P. aeruginosa* bacteremia was calculated to be 5 cases per 10,000 hospital admissions.

For the case-control study, 151 patients with *P. aeruginosa* bacteremia upon hospital admission (case patients) and 152 subjects with bacteremia due to Enterobacteriaceae upon hospital admission (control subjects) were randomly chosen for inclusion. Blood isolates recovered from control subjects included *E. coli,* 110 subjects (72%); *Klebsiella* species, 22 subjects (14%); *Enterobacter* species, 9 subjects (6%); and *Proteus* species, 4 subjects (3%). *Citrobacter, Serratia,* and *Providentia* species together accounted for isolates in 6 patients (4%). Polymicrobial bacteremia *(E. coli* and *K. pneumoniae)* was documented in only 1 patient.

Demographic characteristics and comorbidities. The mean age of subjects was 67 years and did not differ between the 2 groups (table 1); however, age >90 years tended to be more prevalent among case patients than control subjects (14 of 151 vs. 6 of 152; OR 2.49; $P = .062$). Case patients were more often male (55.6% vs. 44.4%; $P = .034$), and more frequently had poor functional status, as evidenced by dependence on assistance with the activities of daily living (31% vs. 17%; $P = .004$). Case patients had more comorbidities than did control subjects (mean number of comorbidities ± SD, 2 ± 1.2 vs.1.6 ± 1.1; $P = .002$). Malignancy was the most common underlying illness among case patients: 47% of case patients had a malignant disease (of which 40% were hematological), compared with 24% of control subjects ($P < .001$). Nephrolithiasis was the only comorbidity that was significantly more prevalent among control subjects (5.9% vs. 0.7%; $P = .02$).

Clinical characteristics. Case patients were more often immunocompromised at presentation than were control subjects, mostly because of recent chemotherapy and neutropenia (table 1). Case patients also presented more often with febrile neutropenia than did control subjects (18.6% vs. 2.6%; $P < .001$).

The source of bacteremia differed between the 2 groups ($P < .001$) (table 1). Among the control subjects, the urinary tract was the most common focus, with a urinary tract infection documented in 65% of patients. Intra-abdominal infections were next most common focus of infection (14% of control patients), and 10.5% of control subjects had no known focus of infection. Among the case patients, the distribution of sources differed; urinary tract infections were less predominant (23% of patients) as the source of infection than in control subjects. Other foci of infection in case patients included lower respiratory tract infection and intravenous catheter-related infection (in 19% and 15% of patients, respectively). In 22% of case patients, no source of bacteremia was identified. Invasive devices at presentation—specifically, central venous catheters and urinary devices—were more often found among case patients.

Contact with the health care system. Few patients in either group (19 case patients [13%] and 15 control subjects [10%]) underwent an invasive procedure during the 2 weeks preceding

Table 2. Independent predictors of *Pseudomonas aeruginosa* bacteremia upon hospital admission among patients without severe immunodeficiency on the basis of multivariate logistic regression analysis.

Variable	OR (95% CI)	*P*
Presence of a urinary device[a]	6.80 (2.53–18.26)	<.001
Age >90 years	5.39 (1.91–15.17)	.001
Recent antimicrobial use[b]	3.70 (1.87–7.36)	<.001
Presence of a central venous catheter	2.97 (1.31–6.73)	.009

NOTE. Variables with a *P* value of ⩽.10 in the univariate analysis were considered for inclusion in multivariable logistic regression analysis.

[a] Includes Foley catheter, pigtail, and nephrostomy.

[b] Receipt of antimicrobial therapy during the previous 30 days.

the index hospitalization (table 1). Cystoscopy tended to be more prevalent among case patients, and prostatic biopsy tended to be more prevalent among control subjects; however, statistical significance was not reached in group-to-group comparisons for either procedure ($P = .06$).

Recent hospitalization and prior antimicrobial therapy were more common characteristics of case patients than control subjects. Forty-four percent of case patients had been hospitalized during the preceding 30 days, and 65% had been hospitalized during the preceding 90 days, whereas these figures were 25% and 36.2%, respectively, among control subjects ($P < .001$). Case patients more often received antimicrobial therapy (mostly β-lactam agents) during the month before hospitalization than did control subjects (36% vs 13.6%; $P < .001$).

Discriminative model. An initial multivariate logistic regression analysis identified 5 variables as independent predictors of *P. aeruginosa* bacteremia: severe immunodeficiency (including solid organ or bone marrow transplantation, neutropenia, recent chemotherapy, or treatment with high-dose corticosteroids for >5 days, azathioprine sodium, or cyclosporine), age >90 years, receipt of antimicrobial therapy during the prior 30 days, having a central venous catheter, or having a urinary device.

Because empirical coverage of *P. aeruginosa* is the standard of care in severely immunocompromised patients with signs of sepsis, we excluded patients with severe immunodeficiency from further analysis. After exclusion of patients with severe immunodeficiency, logistic regression analysis revealed that the same 4 variables (age >90 years, receipt of antimicrobial therapy during the previous 30 days, having a central venous catheter, and having a urinary device) were independently associated with being a case patient. Accordingly, the diagnostic accuracy of the logistic regression model, as given by the area under the receiver-operating-characteristics curves, was 0.726 (moderately good prediction) (table 2).

Among the 250 patients without severe immunodeficiency (109 case patients and 141 control subjects), a prediction model was constructed, and the probability of *P. aeruginosa* bacteremia was calculated. Subclassification of patients and probabilities based on the total number of independent predictors found for each patient is presented in table 3, including the number of total patients needed to treat to effectively treat a single case of *P. aeruginosa* bacteremia in each category. We found that the probability of bacteremia due to *P. aeruginosa* was 2.3% if none of the predictors was documented, 8.84% (range, 7%–14%) in the presence of 1 predictor, 28.1% (range, 21%–47%) in the presence of 2 predictors, and ⩾59% in the presence of 3 or 4 predictors. Having none of the predictors above was associated with a likelihood of *P. aeruginosa* bacteremia of 1:42, whereas having ⩾2 predictors increased the likelihood to nearly 1:3.

DISCUSSION

Prudent use of antibiotics requires that clinical decision-making take into account both the risk of the individual patient if not covered appropriately for a certain pathogen and the risk associated with overuse of antibiotics—in the context of this study, overuse of anti-pseudomonal agents. Thus, a clinician

Table 3. Risk classification for *Pseudomonas aeruginosa* bacteremia among 250 patients without severe immunodeficiency, according to the total number of independent predictors, and the number of patients needed to treat in each group to effectively treat a single case of *P. aeruginosa* bacteremia.

No. of predictors (risk category)	Occurrence based on data, %	Probability of *P. aeruginosa* bacteremia, %	No. of patients needed to treat		
			Per risk group[a]	For risk group or higher risk[b]	For risk group or lower risk[c]
0	71.77	2.36	42.4	20.00	42.4
1	24.39	8.84	11.3	8.55	25.0
2	3.75	28.13	3.55	3.35	20.4
3	0.09	100.00	1.00	1.00	20
4	0.00	…	…	…	…

[a] For treatment of only patients with gram-negative bacteremia in the specific risk category.

[b] For treatment of all patients with gram-negative bacteremia in the specific risk category or higher.

[c] For treatment of all patients with gram-negative bacteremia in the specific risk category or lower. This provides an estimate of limiting the overuse of anti-pseudomonal agents per 1 missed case of *P. aeruginosa* bacteremia.

must consider both the number of patients not covered effectively by a certain antibiotic regimen and the number of patients who are treated but do not have the condition.

In the present study, we found *P. aeruginosa* bacteremia upon hospital admission to be a rare condition, occurring in 5 of 10,000 hospital admissions. Yet it was the third-leading GNR isolate to cause bacteremia at the time of admission (6.8% of 4114 unique patient cases of GNR bacteremia). Affected patients often had severe immunodeficiency, a malignant condition, recent hospitalization, prior antibiotic treatment, and invasive devices at presentation. Kang et al. [22] reported similar results. In their study, *P. aeruginosa* caused 4.4% of all community-acquired cases of gram-negative bacteremia, and clinical features of affected patients were alike; in particular, there was a high proportion of patients with cancer (solid tumors, 41%; and hematological malignancy, 18%).

To provide a simple clinical decision-making tool, a discriminative model was created. We intended this tool to be applied when bacteremia is suspected at hospital admission, to help the clinician decide whether to treat low-risk patients (i.e., those without severe immunodeficiency) with an anti-pseudomonal agent. A previous prediction model for *P. aeruginosa* bacteremia included mostly hospital-acquired infections (91%), and most predictors were related to a long duration of hospitalization [23). Thus, this model is not applicable to patients with bacteremia at the time of admission. We omitted patients with severe immunodeficiency from the model, because anti-pseudomonal coverage for these patients is accepted as standard medical practice [24].

We based the model on the occurrence of 4 predictors of *P. aeruginosa* bacteremia among patients without severe immunodeficiency: age >90 years, receipt of antimicrobial therapy ⩽30 days before hospital admission, having a central venous catheter, and having a urinary device. We found that the probability of *P. aeruginosa* bacteremia was 2.3% if none of the predictors was present, almost 9% if only 1 predictor was present, and >28% if ⩾2 predictors were present.

Table 3 provides estimates of risk of *P. aeruginosa* bacteremia generated by the discriminative model. These may guide the clinician regarding the implications of the choice of empirical therapy. Two scenarios are presented: (1) treatment of only patients in the same risk category as the index patient, and (2) treatment of patients on the basis of the threshold level (i.e., if we administer an anti-pseudomonal agent to a patient in a specific risk category, we should also treat patients in a higher risk category, and conversely for not treating). Treatment of every patient with GNR bacteremia upon hospital admission with an anti-pseudomonal agent will result in unnecessary treatment of 20 patients to cover 1 case of *P. aeruginosa* bacteremia (number needed to treat, 20). According to the risk stratification model, if no predictor is present, the number needed to treat is 42; if 1 predictor is present, the number needed to treat is 11; and if ⩾2 predictors are present, the number needed to treat is <4. We must remember that, when empirical therapy is instituted, the presence of GNR bacteremia is suspected, but in only a minority of cases (likely <10%) does GNR bacteremia truly exist. Thus, the numbers needed to treat for suspected GNR bacteremia are in reality much higher than those reported by us. Nevertheless, as shown in table 3, patients can be divided into 3 risk groups with respect of to *P. aeruginosa* bacteremia: patients with ⩾2 predictors are at high risk, patients with no predictors are at extremely low risk, and those with 1 predictor are at intermediate risk. In our study, 96% of the total population of patients with gram-negative bacteremia belonged to the lower-risk groups (i.e., they had <2 predictors). Because the number needed to treat for this group of patients is 25, not treating them will spare anti-pseudomonal treatment for 96% of patients who are admitted to the hospital with GNR bacteremia while taking the risk of 1:25 that 1 case of *P. aeruginosa* bacteremia will be missed.

In several studies, inadequate empirical treatment of *P. aeruginosa* bacteremia has been associated with increased mortality [10, 25]. However, others have not found this association [26]. The difference in study results may be related, at least in part, to differences in the patients studied; delay in effective therapy was linked to increased mortality, mostly in patients with hematological malignancies and neutropenia. Overuse of anti-pseudomonal agents also has unwarranted consequences—mainly, the emergence of resistance in *P. aeruginosa* isolates with subsequent limited treatment options and adverse outcomes [15, 27]. The question of when to cover and when not to cover *P. aeruginosa* remains a clinical decision that has to take into account various parameters, including the severity of the infection, the risk imparted to the patient by delaying appropriate therapy, and other medical and social parameters. Such decisions go beyond the consideration of *P. aeruginosa* and include the need to cover gram-positive bacteria, various drug-resistant organisms, and nonbacterial pathogens. However, we believe that the model presented here provides support for the decision not to administer anti-pseudomonal agents to patients with no predictors and to treat those with ⩾2 predictors. For patients with 1 predictor, we recommend consideration of the risks and benefits on an individual basis.

Our study has several limitations: first, it is a retrospective study; thus, some of the data recorded in the medical charts may have not been complete. We do not believe that this is a major problem, because the data included in the study are routinely recorded in the patient chart. Second, the study represents 4 tertiary care centers, and the results may not be generalizable to non–tertiary care centers. On the other hand, the international character of this study is a clear strength that makes it more easily generalizable. We recommend additional

study of this topic and validation of the model that we have suggested in additional settings. Third, and most importantly, our study refers to patients with documented GNR bacteremia, and the true question that the clinicians face regards all patients with suspected bacteremia: who is at risk of having *P. aeruginosa* bacteremia. We believe that future studies should focus on this question and that our model will be validated in a prospective group of patients who present with infection.

On the basis of the model we have created, the clinician can estimate the probability of *P. aeruginosa* bacteremia for each clinical case of suspected gram-negative bacteremia, and make an educated decision whether an anti-pseudomonal therapy should be included in the empirical therapy.

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