MAJOR ARTICLE

Factors Predicting Mortality in Necrotizing Community-Acquired Pneumonia Caused by *Staphylococcus aureus* Containing Panton-Valentine Leukocidin

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Background. Necrotizing pneumonia due to Panton-Valentine leukocidin–producing strains of *Staphylococcus aureus* is associated with a high mortality rate. We sought factors associated with vital outcome in 50 cases occurring from 1986 through 2005.

Methods. We compared the clinical and biological characteristics of 50 patients according to their vital outcome and examined the characteristics of the corresponding *S. aureus* isolates.

Results. The overall mortality rate was 56%, and the median survival time was 10 days. All of the deaths were attributed to *S. aureus* infection and were secondary to refractory shock and/or respiratory failure. Fatal outcome was associated with classical severity factors, such as the need for mechanical ventilation or inotrope support, and with onset of the acute respiratory distress syndrome. Airway bleeding was strongly associated with fatal outcome ($P = .002$). Patients who had focal staphylococcal infection before the onset of pneumonia had a significantly lower mortality rate ($P = .002$). The main biological feature associated with death was leukopenia ($P < .001$). In multivariate analysis, leukopenia and erythroderma occurring within the first 24 h after admission to the hospital were independently associated with fatal outcome. Erythroderma was not associated with toxic shock syndrome toxin.

Conclusions. Airway bleeding, erythroderma, and leukopenia are associated with fatal outcome from Panton-Valentine leukocidin–positive *S. aureus* necrotizing pneumonia. More work is needed to develop more efficacious therapy against this highly lethal disease.

Staphylococcus aureus expresses a variety of virulence factors, including Panton-Valentine leukocidin (PVL), a cytotoxin. PVL is expressed by major methicillin-resistant *S. aureus* clones, which have now spread throughout the world [1]. PVL is specifically associated with primary skin and soft-tissue infections and causes severe necrotizing pneumonia through its direct toxic activity and the indirect up-regulation of surface proteins [2–4]. Necrotizing *S. aureus* pneumonia has long been recognized, but the association with PVL was made in 2002 [2], and numerous cases have since been reported worldwide [5–24]. Contrary to PVL-negative *S. aureus* pneumonia, PVL-positive *S. aureus* pneumonia is often preceded by influenza-like symptoms and is mainly characterized by hemoptysis, pleural effusion, rapid onset of acute respiratory distress, and leukopenia [2].

PVL-positive *S. aureus* necrotizing pneumonia is associated with a high fatality rate. Among 41 cases reported in the literature, 25 patients (61%) died, usually rapidly [2, 6, 7, 9–17, 19–24]. No independent factors associated with vital outcome have thus far been described. We examined 50 cases of PVL-associated necrotizing pneumonia that were reported from 1986 through 2005 to identify determinants of vital outcome.

Received 2 February 2007; accepted 18 April 2007; electronically published 15 June 2007.

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Clinical Infectious Diseases 2007; 45:315–21

1058-4838/2007/4503-0007$15.00
DOI: 10.1086/519263

PATIENTS AND METHODS

Since completing the first study of 16 cases of PVL-associated necrotizing pneumonia [2], we have prospectively collected case reports of documented *S. aureus* pneumonia caused by strains shown by the French National Reference Center for Staphylococci (Lyon, France) to harbor the PVL genes (*luk*-PV). All of these cases were spontaneously referred to the Reference Center by hospitals in France and elsewhere, and only minimal clinical data were provided in most cases. When the case matched the inclusion criteria (see below), a standardized data collection form was immediately sent to the referring clinician. The diagnostic criteria for community-acquired pneumonia were those used in the above-mentioned princeps study [2].

Definitions. Pneumonia was defined by signs and symptoms of lower respiratory tract infection (e.g., cough, expectoration, and chest pain) and pulmonary infiltrates on the chest radiograph that were not attributable to other causes, coinciding with isolation of *S. aureus* as the only potential pathogen, by at least 1 of the following procedures: (1) puncture of a pleural effusion or lung abscess; (2) culture of bronchoalveolar lavage fluid ($\geqslant 10^4$ CFU/mL), Wimberley brushing ($\geqslant 10^3$ CFU/mL), or protected tracheal aspiration ($\geqslant 10^3$ CFU/mL); and (3) blood culture yielding the same *S. aureus* strain as that found in tracheal secretions. Pneumonia was classified as nosocomial when respiratory symptoms started at least 48 h after hospitalization, and all such cases were excluded from the study.

Microbiological studies. *S. aureus* isolates were tested for toxin production and antimicrobial susceptibility. Gene sequences encoding PVL and superantigenic toxins (e.g., enterotoxins A–C and toxic shock syndrome toxin–1) were detected using PCR-based methods [25]. Isolates were tested for antimicrobial susceptibility by broth microdilution, using the interpretive criteria of the Clinical and Laboratory Standards Institute (formerly the National Committee for Clinical Laboratory Standards) [26]. The following antimicrobial agents were tested: penicillin, oxacillin, kanamycin, tobramycin, gentamicin, erythromycin, clindamycin, tetracycline, ofloxacin, fusidic acid, rifampin, vancomycin, teicoplanin, fosfomycin, trimethoprim-sulfamethoxazole, and linezolid. In addition, the *mec*A gene, which codes for methicillin resistance, was detected by PCR, as described elsewhere [27]. Only cases caused by PVL-positive *S. aureus* strains were included in the study.

Data. The following data were recorded in each case: demographic data, medical history (including risk factors for infection and history of personal or familial abscesses or furuncles), signs and symptoms, radiological findings, and laboratory results during the first 48 h of hospitalization. Severity was rated using the Pediatric Risk of Mortality (PRISM) 3 score [28] for patients aged <18 years and using the Simplified Acute Physiology Score (SAPS) II [29] for patients aged ⩾18 years, when available. Some biological or radiological results were missing because of death shortly after admission to the hospital.

Statistical analysis. The population was subdivided into patients who survived and patients who died in the hospital. Baseline characteristics of the 2 subgroups were compared with the χ^2 test or Fisher's exact test for categorical variables and Student's *t* test or the Mann-Whitney *U* test for continuous variables.

The endpoint was death of all causes, and the survival probability was estimated using the Kaplan-Meier method. Baseline was the day of admission to the hospital for pneumonia, and patients who survived were censored at discharge from the hospital. When patients died within 24 h after admission, the observation period was rounded to 1 day. Survival distributions were compared with the log-rank test. Variables independently associated with survival were identified with a Cox regression model based on hazard ratios. Variables with *P* values from .10 through .15 were entered in a multivariate model. *P* values <.05 (2-tailed) were considered to indicate statistical significance. Statistical analyses were performed using SPSS software, version 11.0 (SPSS).

RESULTS

Fifty-seven case reports of PVL-positive *S. aureus* pneumonia were collected from 39 different hospitals, but 7 case reports were excluded because of missing data. No cases of hospital-acquired necrotizing pneumonia were reported and excluded during the study. Therefore, the study involved 50 cases (table 1). The cases occurred in France (32 cases), French Polynesia (10 cases), the French West Indies (2 cases), and the United States (2 cases), as well as in Algeria, Germany, Singapore, and Switzerland (1 case each). The male-to-female sex ratio was 1.3 (28 males and 22 females), and the median age was 14.5 years (interquartile range [IQR], 1.8–36 years).

Medical History

Risk factors for infection and/or respiratory disease were identified in 20% of patients. The most frequent risk factor was smoking, which was reported for 7 patients and was associated with alcohol abuse for 2 patients. Common risks factors for staphylococcal infection, such as diabetes, steroid therapy, and immunosuppressive drug therapy, were recorded for only 1 patient each. Among the 34 patients for whom data were available, 6 (17.6%) had a personal history of furuncles or skin abscess, and another patient had a history of familial furunculosis.

Presentation

The median duration of symptoms before hospitalization was 3.0 days (IQR, 2.0–5.0 days). Influenza-like symptoms occurred before hospital admission in 33 (67.3%) of 49 patients. Viro-

Table 1. Baseline characteristics of 50 patients with Panton-Valentine leukocidin–positive *Staphylococcus aureus* pneumonia.

Characteristic	Patients
Demographic information	
Age, median value (range)	14.5 years (1 month–78 years)
Sex, M:F (ratio)	28:22 (1.27)
Medical history	
Risk factors for respiratory disease	
Smoking	7/50 (14)
Smoking and alcohol abuse	2/50 (4)
Diabetes	1/50 (1.9)
Steroid treatment	1/49 (2)
Immunosuppressive treatment	1/50 (1.9)
Any	10/50 (20)
Personal history of furuncles	6/34 (17.6)
Before admission to the hospital	
Period between onset of symptoms and admission, median days (IQR)	3 (2.0–5.0)
Influenza-like illness	33/49 (67.3)
Influenza virus A infection[a]	4
Cytomegalovirus infection[a]	1
Other sites of *S. aureus* infection	12/50 (24)
Skin abscess	6
Deep-seated infection	4
Skin abscess and deep-seated infection	2
Clinical features during the first 48 h after hospital admission	
Median PRISM score (IQR)[b]	15 (5.8–20.5)
Median SAPS II score (IQR)[c]	53.5 (28.0–72.0)
Fever, temperature >39°C	38/50 (76)
Generalized rash	5/48 (10.4)
Airway hemorrhage	
Any	22/50 (44)
Lower airway hemorrhage	17
Upper airway hemorrhage	1
Both upper and lower airway hemorrhage	4
Respiratory failure requiring intubation	39/50 (78)
Chest radiography at hospital admission[d]	
Unilobar consolidation	9/48 (18.1)
Multilobar consolidation	38/48 (79.1)
Pleural effusion	25/47 (53.1)
Laboratory findings within the first 48 h after hospital admission	
Lowest blood leukocyte count, median leukocytes/mL (IQR)[d]	3900 (1230–10,700)
Lowest platelet count, median platelets/mL (IQR)[d]	145,000 (50,000–242,000)
Median lowest PaO2:FiO2 ratio (IQR)[e]	69 (47.5–103.3)
Treatment and outcome	
Mechanical ventilation	39/50 (78)
Antibiotic treatment during the first 24 h after hospital admission[d]	45/48 (91.8)
Antibiotic active[f] against the isolate introduced <24 h after hospital admission	37 (82.2)
Active[f] treatment introduced 24–72 h after hospital admission	5
No active[f] antibiotic ⩽72 h after hospital admission	6
ARDS	24/47 (51.1)
Mortality	28/50 (56)
Percentage of deaths attributed to *S. aureus* infection	100
Survival time, median days[g]	10

NOTE. Data are no. of patients or no. of patients/no. of patients for whom data were available (%), unless otherwise indicated. ARDS, acute respiratory distress syndrome; IQR, interquartile range; PRISM, Pediatric Risk of Mortality; SAPS II, Simplified Acute Physiology Score II.

[a] Virological studies were performed for only 9 patients.
[b] For patients aged <18 years ($n = 14$).
[c] For patients aged ⩾18 ($n = 18$).
[d] Values are for 48 patients, because 2 patients died before antibiotic treatment was administered and paraclinical investigations were performed.
[e] Available only for patients who received mechanical ventilation with known FiO2 values ($n = 22$).
[f] In vitro activity.
[g] Determined using Kaplan-Meier analysis.

logical tests were performed for 9 patients: 4 patients had influenza type A infection, 1 had cytomegalovirus infection, and 4 had negative results. Twelve patients (24%) had preexisting focal staphylococcal infections, which consisted of skin abscesses in 6 patients, deep abscesses in 4 patients, and both skin and deep abscesses in 2 patients. Four of the 6 patients with skin abscesses only had previously had furuncles, and the other 2 patients had no known history of skin infections. None of the 4 patients with deep abscesses only had previously had skin infections or abscesses.

The clinical course during the first 48 h after hospital admission was usually severe, as reflected by the severity scores (PRISM 3 or SAPS II), which were available at admission for 31 patients. The median SAPS II value was 53.5 (IQR, 28.0–72.0), and the median PRISM 3 value was 15 (IQR, 5.8–20.5). Fever (temperature, >39°C) was reported in 38 (76%) of 50 patients. The most remarkable feature was airway bleeding, which was present in 22 (44%) of 50 patients. The lower airways were involved in 21 patients (presenting with hemoptysis or bloody tracheal aspirate), 4 of whom also experienced nasal hemorrhage. One patient experienced only nasal hemorrhage.

Most patients had marked respiratory distress, and 39 (78%) of 50 patients required intubation and mechanical ventilation. The severity of respiratory failure was reflected by the low PaO2:FiO2 ratio in intubated patients (median PaO2:FiO2 ratio, 69; IQR, 47.5–103.3). Generalized rash was present in 5 (10.4%) of 48 patients, and 8 patients (17%) had diarrhea.

Chest radiographic examination was performed for only 48 of 50 patients, because 2 patients died very shortly after hospital admission. The radiographs showed multilobar consolidation in 38 (79.1%) of 48 patients and unilobar consolidation in 9 (18.1%) of 48 patients. Pleural effusion was associated with consolidation in 24 (50%) of 48 patients and was isolated in

1 patient (2%). Bubbles, excavation, and pyopneumothorax were reported in 4, 2, and 2 patients, respectively.

Biological Features

Because of the rapid death of 2 patients, biological data were available for only 48 patients. The median minimal leukocyte count during the first 48 h of hospitalization was 3900 leukocytes/mL (IQR, 1230–10,700 leukocytes/mL), and 26 (54.1%) of 48 patients had a leukocyte count <5000 leukocytes/mL. The minimal platelet count was also low, with a median of 145,000 platelets/mL (IQR, 50,000–242,000 platelets/mL); 10 (21.2%) of 47 patients had a platelet count <50,000 platelets/mL.

S. aureus was recovered by blood culture in 31 (62%) of 50 patients, in pleural fluid from 15 (30%) of 50 patients, and in bronchoalveolar lavage fluid or brushing specimens from 17 (34%) of 50 patients. All *S. aureus* isolates were fully characterized. Six (12%) of the 50 isolates were methicillin resistant. Methicillin resistance was always associated with kanamycin resistance. Thirteen isolates were resistant to tetracycline, 9 to erythromycin, 6 to trimethoprim-sulfamethoxazole, 6 to fusidic acid, and 3 to tobramycin. Resistance to gentamicin, clindamycin, ofloxacin, and rifampin was sporadic. All isolates were susceptible to glycopeptides, fosfomycin, and linezolid. In addition to the presence of the *luk*-PV genes encoding PVL, 11 isolates harbored at least 1 of the toxin genes associated with nonmenstrual toxic shock syndrome; *sea* (encoding SEA), *seb* (encoding SEB), and *sec* (encoding SEC) were detected in 6 isolates, 5 isolates, and 1 isolate, respectively. The *tst* gene (encoding toxic shock syndrome toxin–1) was not detected in any isolate.

Treatment and Outcome

Intubation and mechanical ventilation were required for 39 (78%) of 50 patients (table 1). Among the patients who survived, the median duration of mechanical ventilation was 6.5 days. The frequencies of other treatments are given for 48 patients, because 2 patients died before receiving any other treatment.

Antibiotic therapy was initiated on the first hospital day in 45 of 48 patients. During the first 24 h, at least 1 of the prescribed drugs was active against *S. aureus* in 37 (82.2%) of 45 patients. Among the 11 patients in whom initial antibiotic treatment was inappropriate or absent, active antibiotics were introduced between 24 and 72 h to 5 patients and after 72 h to 2 patients; the remaining 4 patients died without receiving appropriate antibiotic treatment. High-dose intravenous immunoglobulins were administered to 2 patients who survived but presented with the main features associated with death.

Respiratory status was characterized by the onset of signs consistent with acute respiratory distress syndrome with diffuse bilateral infiltrates in 24 (51.1%) of 47 patients. In addition to the 25 patients who initially had pleural effusion, 4 patients developed purulent pleural effusion after hospital admission. Serial radiological studies were not available for 3 patients because of early death.

The overall in-hospital mortality rate was 56%, and the median survival time was 10 days. All of the deaths were attributed to *S. aureus* infection and were secondary to refractory shock and/or respiratory failure.

Factors Associated with Vital Outcome

Clinical characteristics. The need for artificial ventilation or inotrope support and acute respiratory distress syndrome onset were associated with death. Airway bleeding was strongly associated with fatal outcome and was also associated with more rapid death (figure 1). All 5 of the patients who developed erythroderma within 24 h after hospital admission died, and erythroderma never occurred in the patients who survived ($P = .059$).

Features associated with survival included probable hematogenous infection of the lungs from a focus of infection (such as skin abscesses or deep abscesses). The presence of pleural effusion at hospital admission was also associated with survival. The mortality rate was significantly higher among female patients.

Biological factors. The main biological feature associated with death was leukopenia (table 2). The platelet count was also lower in patients who died but was not markedly below the normal limit. The PaO2:FiO2 ratio in patients receiving mechanical ventilation was low in both patients who survived and patients who died, but it was significantly lower in patients who died.

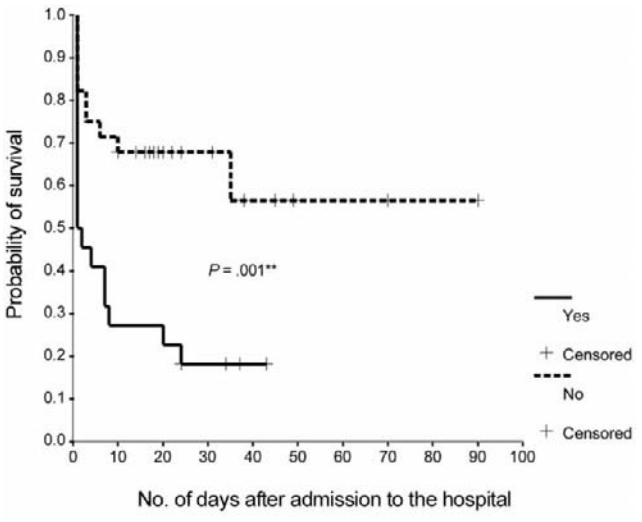

Figure 1. Probability of survival among patients with Panton-Valentine leukocidin–positive *Staphylococcus aureus* pneumonia, according to airway bleeding.

Table 2. Comparison of patients who survived with patients who died.

Characteristic	Patients who survived (n = 22)	Patients who died (n = 28)	P
Age, median years (IQR)	8.75 (0.7–29.8)	17 (13.0–37.5)	.465
Male sex (%)	16/22 (72.7)	12/28 (42.9)	.035
Furuncles (%)	5/18 (27.8)	1/16 (6.3)	.180
Initial presentation			
Time from onset of symptoms to hospital admission, median days (IQR)	3.5 (1–5.25)	3 (2–4)	.959
Influenza-like syndrome	13/22 (59.1)	20/27 (74.1)	.266
Hematogenous spread	10/22 (45.5)	2/28 (7.1)	.002
Rash	0/22 (0)	5/27 (18.5)	.059
Airway hemorrhage	4/22 (18.2)	18/28 (64.3)	.002
Multilobar consolidation	16/21[a] (76.2)	22/26[b] (84.6)	.486
Pleural effusion	15/22 (68.2)	9/27 (33.3)	.022
ARDS	6/19 (31.6)	18/28 (64.3)	.028
Median PRISM 3 score (IQR)[c]	12 (4–15)	22 (18–35)	.008
Median SAPS II (IQR)[d]	28 (24–39)	67 (50–77)	.026
Biological features[b]			
Lowest leukocyte count, median leukocytes/mL (IQR)	9550 (4900–17,000)	1450 (800–3000)	<.001
<1000 leukocytes/mL	1	11	
1000–3000 leukocytes/mL	1	10	
>3000–5000 leukocytes/mL	9	3	
>5000 leukocytes/mL	10	2	
Superantigen expressed by the *S. aureus* isolate	6	5	.332
Lowest platelet count, median platelets/mL (IQR)	178,500 (142,000–302,000)	92,000 (40,000–194,000)	.006
Median PaO2:FiO2 ratio (IQR)[e]	88 (82–200)	53 (39–76)	.009
Treatment			
Appropriate antibiotics administered ⩽24 h after hospital admission	16/22 (76.2)	20/26[b] (76.9)	.289
Mechanical ventilation	14/22 (63.6)	25/28 (89.3)	.042

NOTE. Data are no. (%) of patients, unless otherwise indicated. ARDS, acute respiratory distress syndrome; IQR, interquartile range; PRISM, Pediatric Risk of Mortality; SAPS II, Severe Acute Physiology Score II.

[a] One patient had only pleural effusion.
[b] Data are for 48 patients, because 2 patients died before antibiotic treatment was administered and paraclinical investigations were performed.
[c] For patients aged <18 years (n = 14).
[d] For patients aged ⩾18 years (n = 18).
[e] For patients who received mechanical ventilation with available FiO2 values (n = 22).

Multivariate analysis. Multivariate analysis revealed that the only factors independently associated with fatal outcome were onset of leukopenia and erythroderma within 24 h after hospital admission (table 3).

DISCUSSION

In this series of 50 cases of necrotizing pneumonia, the overall mortality rate was slightly lower than that in the initial study [2]—probably because of better diagnosis and treatment—but was, nonetheless, very high (overall mortality rate, 56%), especially considering that most of the patients were young, immunocompetent, and otherwise healthy.

Factors associated with fatal outcome. In univariate analysis, the need for inotrope support, onset of acute respiratory distress syndrome, a low PaO2:FiO2 ratio, and high severity scores were associated with fatal outcome, but these characteristics are generally found in studies of severe infectious respiratory diseases. In contrast, hemoptysis, which is uncommon in children and adolescents with severe pneumonia, occurred very frequently in our series (in 44% of patients) and was associated with rapid death [figure 1]. Thus, hemoptysis appears to be both a major diagnostic sign of necrotizing pneumonia and an important predictor of fatal outcome. Airway hemorrhage, in this context, likely reflects necrosis of the respiratory mucosa as a consequence of the direct toxic effect of PVL, coupled with the indirect up-regulation of the lung proinflammatory factor protein A [4].

Erythroderma occurred in only 10% of the patients, but it is noteworthy that all 5 of the patients with erythroderma died. This could have occurred because staphylococcal toxic shock syndrome–related toxins, such as enterotoxins SEA, SEB, and SEC [30], and the corresponding toxin genes were detected in

Table 3. Multivariate analysis of factors associated with death among patients with Panton-Valentine leukocidin–positive *Staphylococcus aureus* pneumonia.

Variable	Adjusted Relative Hazard (95% CI)
Leukocyte count at hospital admission, leukocytes/mL	
11,000–74,000	1.0
4000–10,000	1.29 (0.21–7.80)
>1000–3000	7.99 (1.66–38.43)
0–1000	7.38 (1.60–34.02)
Erythroderma ⩽24 h after hospital admission	2.84 (0.94–8.56)

NOTE. Cox regression model, in which both variables were included in the model, and no other covariables were analyzed.

11 isolates. However, only 2 of the isolates from the 5 patients with rash harbored these toxin genes, and several patients whose isolates contained these toxin genes remained free of cutaneous disorders.

With regard to biological data, leukopenia was independently associated with mortality in multivariate analysis. Not only was there a significant difference in the median leukocyte count between patients who survived and patients who died, but the relation between the leukocyte count and the risk of death appeared to be linear: the survival rate was <10% when the leukocyte count was <1000 leukocytes/mL and exceeded 85% when the leukocyte count was >10,000 leukocytes/mL. The leukocyte count was ⩽5000 leukocytes/mL in 35 patients and >15,000 leukocytes/mL in only 7 patients. This suggests that leukopenia is a specific feature of staphylococcal necrotizing pneumonia and that it is strongly associated with fatal outcome. This is in agreement with in vitro data showing that PVL induces both apoptosis and necrosis of human leukocytes [31].

Features and outcome of the disease. Initial influenza-like symptoms were present in 75% of the patients in the princeps study [2] and in 67% of the patients in the present study; no correlation was detected between influenza seasons and occurrence of necrotizing pneumonia cases. Viral infections were reported for only 5 patients, but only 9 patients had virological studies performed. Viral infections of the respiratory tract are known to facilitate the onset of bacterial pneumonia, both by impairing local defenses and by enhancing bacterial adhesion to damaged epithelia [32].

The initial presentation was always severe, with marked respiratory distress, hypoxemia, high fever, and extensive bilateral consolidations often associated with pleural effusion on chest radiography. Most of our patients received aggressive treatment, with 78% of patients receiving mechanical ventilation. Antibiotic therapy was started promptly after hospital admission and, based on in vitro activity, the initial antibiotics (those started during the first 24 h after admission) were effective against the *S. aureus* isolate in 82.2% of the patients. However, there was no difference between patients who survived and patients who died with regard to the in vitro efficacy of initial antibiotic therapy, suggesting that fatal outcome was not due to antibiotic treatment failure.

A personal history of furuncles appears to be protective. Unfortunately, this information was only available for 34 of the 50 patients, and the difference between patients who survived and patients who died did not reach statistical significance (27.8% of patients who survived and 6.3% of patients who died had a personal history of furuncles; $P = .18$). It is conceivable that patients with such a history had previously been exposed to PVL and had developed a degree of protective immunity, because anti-PVL antibodies found in human immunoglobulin preparations have been found to neutralize the action of the toxin [33].

Certain limitations of this study need to be addressed. Patient recruitment might have been biased toward hospitals specializing in pediatric infectious diseases. Certain data were lacking when death occurred shortly after hospital admission, meaning that strong early predictors may not have been available in some cases. Another limitation is a potential selection bias if the characteristics of patients are hospital-dependent and, then, if the documentation of cases (or quality of information) is related to the hospital. However, no major differences in the frequency of missing data were found among the participating hospitals.

Acknowledgments

We thank David Young, for editing the manuscript, and the following clinicians for sending clinical information: C. Alonso-Tarres (de la Creu Roja Hospital, Barcelona, Spain); M. Auburtin (Bichat-Claude Bernard Hospital, Paris, France); H. Ben Mansour (Institut Montsouris, Paris, France); J. C. Berthier (Debrousse Hospital, Lyon, France); E. Bonnieux, M. P. de Barthez, V. Boussaud, M. Levy, M. Papouin-Rauzy, and V. Quenee (Centre Hospitalier Territorial de Polynésie, Papeete, French Polynesia); C. P. Cartwright (Hennepin County Medial Center, Minneapolis, MN); M. Chalumeau (Saint Vincent de Paul Hospital, Paris, France); J. Cotting (CHU Vaudois, Lausanne, Switzerland); J. L. Daigre and F. Joly (St. Laurent du Maroni Hospital, St. Laurent du Maroni, French Guyana); O. Delastre (Centre Hospitalier d'Elboeuf, Elboeuf, France); Y. Domart (Centre Hospitalier de Compiègne, Compiègne, France); B. François (Dupuytren Hospital, Limoges, France); D. Gendrel (Saint Vincent de Paul Hospital, Paris, France); W. Hamis, N. Ramdani, and M. Tazir (Mustapha Pacha Hospital, Algiers, Algeria); F. Hornig, B. Kahl, and C. von Eiff (Universitatsklinikum, Muenster, Germany); P. Hubert (Necker Enfants Malades Hospital, Paris, France); V. Jounieaux (Centre Hospitalier Sud, Amiens, France); A. Lahlou (Hautepierre Hospital, Strasbourg, France); E. Laporte-Turpin (Hôpital des Enfants, Toulouse, France); H. Le Loch, H. Mentec, and J. P. Sollet (Victor Dupouy Hospital, Argenteuil, France); F. Leclerc (Jeanne de Flandre Hospital, Lille, France); M. Lorrot (Robert Debré Hospital, Paris, France); B. Melon (Francois Mitterand Hospital, Pau, France); A. Metton (Georges Pianta Hospital, Thonon-les-Bains, France); F. Molenat (Centre Hospitalier, Aix-en-Provence, France); J. M. Perez (Centre Hospitalier, Pointe-à-Pitre, French West Indies); D. Plantaz (Hospital de la Tronche, Grenoble, France); A. Reynaud (Hôtel-Dieu, Nantes, France); A. Rousson (Debrousse Hospital, Lyon, France); P. Schoeffler (Hôtel-Dieu, Clermont-Ferrand, France); B.

Spellerberg (University of Ulm, Ulm, Germany); and L. Y. Hsu (Singapore General Hospital, Singapore City, Singapore).

Potential conflicts of interest. All authors: no conflicts.

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