ABSTRACT • BACKGROUND: Pseudomonas aeruginosa bacteremia (PAB) is associated with high mortality and morbidity rates, but the outcome for patients with PAB has not been recently well evaluated.

METHODS: Between 1997 and 1999, all episodes of PAB at the Hôtel-Dieu de France University Hospital, Lebanon, were analyzed to evaluate the outcome for patients with PAB.

RESULTS: Fifty-five episodes of PAB in 53 patients (26 episodes in men and 29 in women) were analyzed. The mean age of the patients in the cohort was 60.7 years (range: 18-89 years). The mean time between the onset of hospitalization and the first episode of PAB was 21 days (range: 0-77 days). Most of the tested isolates showed favorable in vitro susceptibility to ceftazidime (85%), amikacin (77%) and imipenem (67%). The overall in-hospital cumulative survival was 89% at one week and 49% at 2 months. Among the variables analyzed, four were statistically associated with a higher mortality rate: prior use of antimicrobials (85% vs 54%), use of systemic steroids (49% vs 36%), intubation (67% vs 32%), and admission to the intensive care unit (74% vs 39%) (P < .05).

CONCLUSION: Hospitalized patients with PAB have low survival rates. Newer strategies for prevention and treatment are crucial.

The excessive use of antimicrobials, systemic steroids, and immunosuppressive therapy, led to a progressive increase in the incidence of Pseudomonas aeruginosa infections in hospitals in the last thirty years [1-3]. According to the Centers for Disease Control and Prevention National Nosocomial Infections Surveillance System [4], between 1986 and 1996, P. aeruginosa caused 9% of all nosocomial infections. It was ranked as the fifth most common cause of nosocomial infections overall, the second most common gram-negative bacillus after Escherichia coli, the second most common cause of nosocomial pneumonia, the third most common cause of urinary tract infections, and the fourth most common cause of surgical wound infections. Immuno-compromising conditions [5-8], surgery [9-10], diabetes mellitus [11-12], burns [13], and transplantation [14] have all been considered predisposing factors. Mortality rates attributed to P. aeruginosa bacteremia (PAB) can reach 80% [15-17]. Despite the low overall incidence of PAB in the past decade, higher rates were reported in patients with comorbid conditions such as septic shock, neutropenia, sequelae of inappropriate treatment, septic metastasis, renal insufficiency, and bacteremia of pulmonary or skin origin [11, 18-20].

For unknown reasons, the frequency of multidrug-

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Sfeir PF, Choucair JE, Berbari EF. Les bactériémies à Pseudomonas aeruginosa (BPA) sont une cause majeure de morbidité et de mortalité, mais l’étude de ces bactériémies et des facteurs de risques associés à la mortalité n’a pas été récemment réalisée.


RÉSULTATS DE L’ÉTUDÉ: Cinquante-cinq épisodes retrouvés chez 53 patients ont été analysés, dont 26 hommes et 29 femmes. L’âge moyen est de 60,7 ans (18-89 ans). Le délai entre l’admission et le premier épisode de BPA est de 21 jours (0-77 jours). Les souches isolées étaient sensibles à la ceftazidime dans 85% des cas, l’amikacine dans 77% des cas et l’imipénème dans 67% des cas. La survie cumulative intrahospitalière était de 89% à une semaine et de 49% à 2 mois. Parmi les variables analysées, 4 facteurs de risque de mortalité étaient statistiquement significatifs : l’utilisation préalable d’antibiotiques (85% vs 54%), l’intubation (67% vs 32%), la corticothérapie (49% vs 36%) et l’admission aux soins intensifs (74% vs 39%) (P < 0,05).

CONCLUSION: La mortalité intrahospitalière associée aux BPA reste élevée. Une nouvelle approche de prévention et de traitement est primordiale.

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resistant *P. aeruginosa* nosocomial infections remains high in Lebanon [21]. We analyzed the epidemiology and outcome for all patients with PAB hospitalized at the Hôtel-Dieu de France (HDF) University Hospital between 1997 and 1999.

**PATIENTS AND METHODS**

**Study design and subjects**
This study was a retrospective cohort study of all patients admitted to the HDF University Hospital with PAB between January 1, 1997, and December 31, 1999. Patients under 18 years of age were excluded from the study. Patients were identified through the registers of the Department of Clinical Microbiology at the HDF University Hospital. Data were abstracted from the patients’ medical records in the medical archives of the hospital by use of a standardized data collection tool.

**Statistics**
Descriptive statistics are reported as number and percentage for discrete variables and as mean and range for continuous variables. Proportions were compared using the χ² test and the Fisher exact test. The survival curve of intrahospital mortality was estimated using the Kaplan-Meier method.

**Definitions**
- **P. aeruginosa bacteremia** - Any positive blood culture growing *P. aeruginosa* during the study period. A second episode was noted if a second blood culture in the same patient, from a blood sample drawn at least 48 hours after the first isolate, grew *P. aeruginosa*.
- **Nosocomial bacteremia** - If the blood culture yielded an organism at least 48 hours after admission of the patient or on admission if the patient was hospitalized in the previous 14 days.
- **Multidrug-resistant *P. aeruginosa* strain** - When the *P. aeruginosa* strain is resistant to 2 or more antimicrobials (piperacillin, piperacillin/tazobactam, ceftazidime, cefepime, aminoglycoside, and imipenem).
- **Recent surgery** - Surgery within 2 weeks before the onset of bacteremia.
- **Recent use of antimicrobials** - Use of any systemic antimicrobial within 2 weeks before the onset of bacteremia.
- **Neutropenia** - An absolute neutrophil count of less than 500/µL within 2 days before the onset of bacteremia.
- **Prior hospitalization** - Any hospitalization within 2 weeks before the onset of bacteremia.
- **Initial treatment** - Any systemic antimicrobial therapy initiated before results of the in vitro antimicrobial susceptibilities are available.
- **Final therapy** - Any systemic antimicrobial therapy initiated after the results of the in vitro antimicrobial susceptibilities are available.
- **Combination therapy** - When the antimicrobial regimen includes more than one effective antimicrobial agent and is used for more than 50% of the total time of treatment.

**Intrahospital mortality** - Death documented by the treating physician and thought to be related to bacteremia during hospitalization.

**RESULTS**

**Study Population**
During the study period, PAB was diagnosed in 53 patients. Two patients had 2 episodes. Therefore, we analyzed 55 episodes of PAB: 46 of the 55 episodes (84%) were nosocomial. The gender ratio was slightly unequal: 29 episodes (53%) occurred in females while 26 (47%) occurred in males. The mean age at the time of the diagnosis of PAB was 60.7 years (range: 18-89 years) and the median was 63 years. The mean duration of the hospital stay was 34.4 days (range: 2-124 days), and the mean time between admission and diagnosis of PAB was 21 days (range: 0-77 days), with 20 of the 55 episodes (36%) admitted to the oncology ward. Thirty-one out of 55 episodes (56%) had a malignancy and 9 of the 55 (16%) had neurologic diseases. Thirty-one out of 55 episodes (56%) were admitted to the intensive care unit during hospitalization and 23 of the 31 (74%) were diagnosed with PAB during their stay in the intensive care unit.

**Microbiology**
Based on internal data from previous reviews of the microbiology records at the HDF University Hospital, *P. aeruginosa* was the third most common cause after Coagulase Negative *Staphylococcus* and *Escherichia coli*. In vitro antimicrobial susceptibilities were not available in 7 of the 55 episodes. Results of the in vitro antimicrobial susceptibilities are shown in Table I. *P. aeruginosa*...
nosha strains were susceptible to piperacillin/tazobactam (93%), ceftazidime (85%), and amikacin (77%). Imipenem showed favorable susceptibility in only 67% of the episodes. Ciprofloxacin and cefepime were not added to the antimicrobial susceptibility panel until June 1998. Among the 48 P. aeruginosa isolates analyzed, 16 (33%) were multidrug-resistant.

Source of PAB
Seventeen of the 55 episodes (31%) had isolated bacteremia, with no documented positive culture at other sites. Urine cultures positive for P. aeruginosa were associated with PAB in 18 of 55 episodes (33%); pulmonary infections were another common cause (24%). Infections from intravascular catheters were associated with PAB in 12 of 55 episodes (22%). In 11 of 55 episodes (20%), patients were thought to be colonized with P. aeruginosa because the bacterium was recovered in nonsterile sites with nasal, axillary, and rectal swabs.

Predisposing factors and comorbid conditions
A significant number of patients had associated malignancies; 14 (25%) had hematological malignancies and 17 (31%) had solid malignancies, and they were receiving chemotherapy when PAB was diagnosed. Urinary catheters were placed in 38 (69%) of the cases, and a similar number had prior use of antimicrobials. Arterial vascular catheters were encountered in 30 (54%) cases and venous catheters in 32 (58%) cases. Twenty-eight (51%) of the cases were on systemic steroids and 27 (49%) were intubated. Twenty-one (38%) of the episodes were subject of recent surgery, 8 (14%) had diabetes, while one patient received a kidney transplant and was on immunosuppressive therapy for 40 days before the diagnosis of PAB.

Antimicrobial therapy
The duration of antimicrobial therapy varied between 0 and 25 days, as some patients died on the first day of hospitalization. In 7 of 55 episodes (13%), no initial therapy was administered, and the results were inconclusive in 6 of the 55 episodes (11%). The initial therapeutic regimen was considered adequate if the P. aeruginosa strain was susceptible to the antimicrobials started upon diagnosis in each case; this was applicable in 46 of the 55 episodes (84%). Only one antimicrobial agent was used in 27% of the episodes. Combination therapy was used in 49%: 38% received 2 antimicrobials and 11% received 3 antimicrobials. No difference in mortality rate was noted between patients receiving combination therapy and those receiving monotherapy (29.3% vs 26.7% respectively). The highest percentage of mortality rate was among those who received no therapy (50%). Among the 48 episodes treated with effective antimicrobials, amikacin (33%) and ceftazidime (27%) were the two most commonly used, and the most frequent combination therapy was ceftazidime with amikacin (19%).

Survival Analysis
The overall crude mortality rate among patients with PAB in this cohort was 49% (27/55). Only 6 deaths among 55 episodes (11%) were thought to be directly related to a septic cause. Analysis of intrahospital survival showed that 89% of the patients were alive 7 days after the diagnosis of PAB, 74% after one month, and 49% after 2 months (Figure 1). Variables associated with higher mortality are shown in Table II. Four variables were statistically associated with increased mortality: steroid therapy (49% vs 36%), previous antimicrobial use (85% vs 54%), tracheal intubation (67% vs 32%), and admission to the intensive care unit (74% vs 39%).

<table>
<thead>
<tr>
<th>VARIABLES</th>
<th>Mortality rate*</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous antimicrobial use</td>
<td>23 (85%)</td>
<td>.02</td>
</tr>
<tr>
<td>Intensive care unit</td>
<td>20 (74%)</td>
<td>.01</td>
</tr>
<tr>
<td>Intubation</td>
<td>18 (67%)</td>
<td>.02</td>
</tr>
<tr>
<td>Systemic steroids</td>
<td>18 (67%)</td>
<td>.04</td>
</tr>
<tr>
<td>Previous hospitalization</td>
<td>15 (56%)</td>
<td>.9</td>
</tr>
<tr>
<td>Solid malignancy</td>
<td>10 (37%)</td>
<td>.8</td>
</tr>
<tr>
<td>WBC** count &lt; 1,000 cells/mcl</td>
<td>10 (37%)</td>
<td>.7</td>
</tr>
<tr>
<td>Multidrug-resistant P. aeruginosa</td>
<td>8 (30%)</td>
<td>.5</td>
</tr>
<tr>
<td>Hematologic malignancy</td>
<td>5 (19%)</td>
<td>.39</td>
</tr>
</tbody>
</table>

* A total of 27 patients who died. **White blood cells
P. aeruginosa infections are an important cause of nosocomial mortality and morbidity. The virulence of this bacterium depends on its capacity to invade and damage tissues by producing toxins, such as elastase and protease, which are responsible for the tissue necrosis and hemorrhage. In addition, P. aeruginosa produces endotoxins and exotoxins that are implicated in septic shock and resistance to many antimicrobials [2, 22-23].

P. aeruginosa was the third most common cause of bacteremia at the HDF University Hospital, ranking second after E. coli among the gram-negative bacteria. The higher incidence of PAB in this cohort may be due to several factors, including longer hospitalization periods mostly in the intensive care unit, use of deep venous catheters, and a high proportion of immunocompromised patients in this tertiary care center. However, since several Coagulase Negative Staphylococcus bacteremias are attributed to contaminated cultures, we believe that the actual incidence of nosocomial PAB is underestimated.

The rate of community-acquired P. aeruginosa infections in this cohort is higher than in the National Nosocomial Infections Surveillance System. The reason for this difference is unclear but likely related to the differences in infection control measures and patient’s characteristics.

The patients demographic data in this study are comparable to other published data, such as young age (50% were younger than 63 years), prolonged hospital stay and gender. Patients were hospitalized in the oncology and neurology wards in 72% of the 55 episodes of PAB and this is likely a confounding factor for patients with malignancy and other comorbid conditions. Admission to the intensive care unit was not only a predisposing factor for PAB (for 56% of our patients), but it was also associated with a higher mortality. This also likely represents a confounding variable in sicker patients undergoing multiple invasive procedures. The results of our study concur with previous reports that the main sources of the bacteremias are the urinary and respiratory tracts. They also correlate with the relatively increased number of patients who had urinary and tracheal catheters.

Initial therapy was an effective antimicrobial regimen in 84% of the episodes. Optimal initial therapy is crucial as the risk of mortality is highest in the first 48 hours [1, 11, 24-25]. The initial regimen should take into account the local in vitro susceptibility data as it varies by location among communities and hospitals [26]. In this cohort, the outcome of patients treated with one drug was similar to patients treated with combination therapy. Although significant selection bias might have existed between the two groups, we advocate the use of monotherapy over combination therapy in patients who are hemodynamically stable. However, we believe that it is appropriate to administer a 2-drug regimen to patients with hemodynamic instability, when the burden of microorganisms is high, or in the initial period in patients with risk factors while awaiting the in vitro sensitivity results [27-28]. In this cohort, the most commonly used combination was ceftazidime and amikacin, most likely reflecting the synergistic effect and favorable toxicity profile of this combination [29].

Four variables were associated with a higher mortality rate: steroid therapy, previous antimicrobial use, tracheal intubation, and admission to the intensive care unit. These variables confound each other and may represent surrogate markers for high morbidity and mortality.

Part of the study limitations is that the sources of bacteremias are speculative, since data collection is based on the authors’ best clinical correlation from retrospective chart review of patients with PAB. In this retrospective analysis, patients may have been treated differently by different providers. The possibility of undetectable associated and confounding variables is inherent to this type of study.

CONCLUSION

Episodes of PAB occur frequently at the HDF University Hospital, in contrast to the data from oncological hospitals. Even though adequate antimicrobial therapy was initiated in the majority of patients, the mortality rate was still high at 49%. Clinicians should be aware of the associated risk factors and consider the possibility of PAB in those patients in order to institute an optimal initial therapeutic regimen. We believe that the results of this study will help physicians recognize and treat PAB early in hospitalized patients. Further prospective studies looking at the reasons for the increased incidence of PAB at HDF University Hospital are needed and advised. Implementing new strategies intended for prevention and treatment of PAB are also warranted.

REFERENCES


