The aim of this study was to define risk factors associated with mortality in Pseudomonas aeruginosa bacteraemia and to combine them in a clinical index predicting the risk of death. The study investigated 125 consecutive episodes of P. aeruginosa bacteraemia at this hospital. Crude mortality was 34%, corresponding to 43 patients who died, with 67% of deaths, directly attributable to bacteraemia. A regression logistic model identified five variables that were independently and significantly associated with an increased risk of death: 1) hospitalisation in the intensive care unit; 2) coagulopathy; 3) septic shock; 4) age > 65 years; and 5) the clinical condition of the patient. These variables were as recorded at the time that the first positive blood culture was obtained. The sensitivity and specificity of a prediction of death based on the model were 84% and 85%, respectively. An index score, calculated from these variables, divided patients into three groups with increasing likelihood of mortality resulting from P. aeruginosa bacteraemia.

Introduction

Pseudomonas aeruginosa bacteraemia usually occurs in patients with serious underlying diseases [1]. It is frequently hospital-acquired and may be polymicrobial in nature [1, 2]. Despite all the advances in medical practice in recent years, pseudomonal bacteraemia continues to have a high associated mortality, ranging from 18% to 61% [2–11]. Therefore, investigators have attempted to define those factors that influence the outcome of this infection. These analyses have emphasised the deleterious impact of underlying diseases [3, 8, 10], septic shock [2, 5, 6, 8, 10, 11] and the development of septic metastasis [2, 5, 6] on the outcome of bacteraemia. The availability of potent antimicrobial agents as well as high technology support for therapy of P. aeruginosa bacteraemia has barely modified the mortality rate [9]. Factors frequently associated with higher mortality from bacteraemia include certain sources and patient types, particularly those with pneumonia [2–6, 8, 11], neutropenia [2–6, 11] and inappropriate antibiotic therapy [2, 4–7, 10, 11]. Although these studies have added much to our understanding of bloodstream pseudomonas infections, difficulties remain in ascertaining the relationship between mortality and both the infection episode itself and the clinical factors that influence prognosis.

Clearly, there is a need for evaluation of novel therapeutic approaches. To evaluate these, there is also a need for predictive models of high-risk patients with P. aeruginosa sepsis. Thus, the purpose of the present study was to determine those variables which are readily identifiable at the bedside and that predict mortality in patients with P. aeruginosa bacteraemia. The influence of specific epidemiological, laboratory and clinical variables on the outcome of episodes of pseudomonas bacteraemia were analysed.

Materials and methods

Patients

The clinical records of all patients with blood cultures positive for P. aeruginosa at this hospital in the period from Jan. 1996 to Dec. 1998 were reviewed retrospectively. This centre is a 1200-bed tertiary care institution, serving as a primary facility for a rural and urban area of nearly 500,000 inhabitants. Blood cultures were performed at the request of the attending physicians, who made the decisions concerning the patients' diagnosis or treatment.
Microbiology

Three blood culture sets were usually drawn from an antecubital vein. Blood cultures were performed with a colorimetric blood culture analyser, with FAN-TM culture bottles (Bact/Alert; Organon Teknika, Durham, SC, USA) incubated routinely for 5 days. Antimicrobial susceptibility tests were performed by a commercial broth microdilution method (PASCO MIC/ID panel; Difco Laboratories, Detroit, MI, USA). The bacteremia was considered polymicrobial if micro-organisms other than P. aeruginosa were also isolated from blood culture, except that diphtheroids, Bacillus spp. and coagulase-negative staphylococci were considered to be contaminants, unless they grew in two or more blood cultures. All isolates were identified to species level by standard microbiological techniques [12].

Clinical definitions

A patient was considered to have had two separate episodes of bacteraemia if the first and second episode were at least 30 days apart, and the patient had been treated appropriately for \( \geq 10 \) days, with evidence of a clinical response to this treatment [3].

Bacteremia was considered to be community-acquired when P. aeruginosa was isolated from blood cultures taken within 48 h of hospital admission and the patient had not been hospitalised in the previous 2 weeks. Bacteremia was defined as nosocomial if positive blood cultures were obtained after 48 h or more had elapsed since hospital admission, and if there was no evidence of pseudomonas infection at the time of hospitalisation.

The severity of underlying disease was classified according to the system of Kreger et al. [13] and the patient’s condition as outlined by Winston et al. [14]. On this latter basis, the patient’s condition before the bacteremia was classified as ‘critical’ (condition rapidly deteriorating with death in a short period of time not unlikely), poor (condition deteriorating but death not likely) or good (condition stable).

The following predisposing factors for bacteremia were considered: i) intravenous drug abuse; ii) surgical procedures requiring general anaesthesia, cytotoxic agents or radiation therapy within the previous month; iii) use of antibiotics or corticosteroids within 10 days before the episode of bacteremia; and iv) instrumental manipulation (intravenous catheter, indwelling Foley catheterisation, endotracheal intubation and endoscopy) within the week preceding the pseudomonas bacteremia.

The source of the bacteremia was determined if a localised infection was present before, or coincident with, the detection of the bacteremia; otherwise, the portal of entry was categorised as unknown. Septic shock was defined as the presence of severe sepsis accompanied by a sustained decrease in systolic blood pressure to \(< 90 \text{mmHg}\) or a drop of 40 mmHg from baseline, for at least 1 h, despite adequate fluid resuscitation, or any such decrease that required vasoactive drugs [15]. The presence of coagulopathy was considered when there was clotting or bleeding or alterations in blood coagulation tests as follows: a decline in fibrinogen levels to \(< 150 \text{mg/dL}\), an increase in fibrin split products to \(> 10 \text{mg/dL}\), thrombocytopenia with a platelet count \(< 100,000/\mu \text{L}\), or a prolonged prothrombin time or activated partial thromboplastin time \(> 80\%\) of the control. Patients in whom these laboratory measurements were not performed were excluded from analysis of coagulopathy. All these clinical variables were recorded for the day on which the initial positive blood culture was obtained.

Any microbiologically or clinically documented infection, other than the source of bacteremia, and not present at the time bacteremia was detected, was interpreted as septic metastasis. Therapy was deemed appropriate if there was use of one or more antibiotic(s) active in vitro against all the organisms found in the bloodstream, and if the dose and route of administration was in accordance with standard recommendations [16]. Therefore, antibiotic therapy was assessed critically only after the results of susceptibility tests became available to the attending physician.

Overall mortality was used for statistical analysis, taking the view that when bacteremia was the primary cause of death, mortality was directly related; whereas mortality was indirectly related if another cause of death was present.

Statistical analysis

Fisher’s exact test was used to assess statistical significance for various outcome measures. The odds ratio and its confidence intervals were calculated. A backwards stepwise logistic regression procedure was used to establish which variables were significantly and independently associated with mortality. The dependent binary variable was mortality, and the independent variables were the monitored clinical factors and the in-vitro test results. p values \(< 0.05\) were taken as the limit for entering variables in the model. All variables were entered in the regression analysis as categorical variables within two categories: present or absent. The sensitivity and specificity of the model were determined with an estimated probability of dying of 50% as the cut-off point. The regression coefficients of the final logistic model were used to compile a linear model for predicting mortality due to pseudomonal bacteremia. All tests of significance were two-tailed. Statistical
Results

In all, 125 episodes of *P. aeruginosa* bacteraemia in 123 patients were studied. To allow easier interpretation, episodes are approximated to patients and, on this basis, there were 90 male and 35 female patients. Their mean (SD) age was 55 (22) years (range: 1 month–87 years); there were nine paediatric patients. The overall incidence of *P. aeruginosa* bacteraemia at the hospital was 1.06 episodes/1000 admissions; 110 (88%) of the episodes were hospital-acquired and 15 (12%) were community-acquired. Different services were associated with different rates of bacteraemia; 76 episodes occurred in the intensive care unit (ICU), 37 in medical wards and 12 in surgical wards. No pseudomonads were isolated from obstetric/gynaecological services. Bacteraemia involved only *P. aeruginosa* in 103 cases, but was polymicrobial in 22 cases (18%). Most of the patients had serious underlying diseases at the time of the bacteraemia; 63 patients (50%) were receiving assisted ventilation. The underlying conditions are summarised in Table 1.

All 15 patients with community-acquired bacteraemia were male. Three had fever and positive blood cultures although they were admitted to the hospital for reasons unrelated to infection. The sources of the infections in these three patients were unknown. Three other patients had indwelling urinary catheters because of prostate disease. Five patients were intravenous drug users infected with HIV. One community patient had two separate episodes of bacteraemia along with chronic pseudomonal pneumonia. Of the remaining four patients, one had chronic airways disease and pneumonia, one had prostate carcinoma and two patients had leukaemia in addition to a teratoma and aplastic anaemia.

A primary source of bacteraemia was identified in 81 episodes, as confirmed either by culture or by clinical evidence of a primary focus. The most common focus was the respiratory tract, recorded for 29 patients (36%); other sources were intravenous catheters (22%), the urinary tract (18%), skin infections (14%) and intra-abdominal foci (10%). The source of the bacteraemia was considered unknown in 40 episodes, and data were unavailable for 4 patients.

Eighty-two patients (66%) survived to be discharged from the hospital. Of the 41 patients who died, 29 (67%) did so directly from the bacteraemia, whereas 14 (33%) died of causes not directly related to the infection.

Table 2 shows the clinical, epidemiological, laboratory and therapeutic factors that were evaluated and their influence on mortality in patients. Univariate risk factor analysis showed that the risk of death increased with the following variables: age ≥65 years (p = 0.001), nosocomial bacteraemia (p = 0.01), admission to the ICU (p <0.001), invasive procedures carried out before the bacteraemia (p = 0.03), previous antibiotic therapy (p = 0.05), the respiratory tract as the source of the bacteraemia (p <0.001), a critical or poor clinical condition (p <0.001), septic shock (p <0.001), coagulopathy (p <0.001) and the presence of septic metastases (p = 0.01). Conversely, a urinary focus for the bacteraemia represented a low-risk source for mortality (p = 0.01).

Bacteraemia was treated only with antimicrobial agents in 116 patients. In five patients, surgical drainage of a localised infection was performed in addition to antibiotics. Four patients received no therapy. Antibiotic therapy was assessed critically only at the time when the results of susceptibility tests became available to the primary physician. One hundred (80%) of the episodes were treated appropriately, and 25 (20%) inappropriately. No statistical significance was observed when comparing mortality in these two groups of patients (p >0.05).

Based on an analysis of the individual factors listed in Table 2, a multivariate analysis was performed. Five variables were associated with a significantly increased risk of death independent of the influence of possibly confounding concurrent variables, i.e., (1) hospitalisation in an ICU (OR 17; CI 95%, 2.59–109.80; p = 0.003); (2) presence of coagulopathy (OR 14; CI 95%, 2.38–81.92; p = 0.003); (3) septic shock (OR 13; CI 95%, 3.40–51.15; p <0.001); (4) age ≥65 years (OR 9; CI 95%, 2.32–38.29; p = 0.001); and (5) a critical or poor clinical condition (OR 5; CI 95%,

<table>
<thead>
<tr>
<th>Underlying condition*</th>
<th>Number (%) of episodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Surgery</td>
<td></td>
</tr>
<tr>
<td>Cardiac</td>
<td>21 (17)</td>
</tr>
<tr>
<td>Abdominal</td>
<td>18 (14)</td>
</tr>
<tr>
<td>Other</td>
<td>18 (14)</td>
</tr>
<tr>
<td>Ventilator-associated pneumonia(^1)</td>
<td>26 (21)</td>
</tr>
<tr>
<td>Nosocomial pneumonia</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Polytumoura</td>
<td>9 (7)</td>
</tr>
<tr>
<td>Leukaemia/lymphoma</td>
<td>8 (6)</td>
</tr>
<tr>
<td>Carcinoma</td>
<td>17 (14)</td>
</tr>
<tr>
<td>Acute myocardial infection</td>
<td>9 (7)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>6 (2)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>9 (7)</td>
</tr>
<tr>
<td>HIV infection</td>
<td>10 (8)</td>
</tr>
<tr>
<td>Chronic airways disease</td>
<td>14 (11)</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>6 (2)</td>
</tr>
<tr>
<td>Haemorrhagic shock</td>
<td>5 (4)</td>
</tr>
<tr>
<td>Other</td>
<td>24 (19)</td>
</tr>
</tbody>
</table>

\(^1\) Some patients had more than one underlying condition.
\(^2\) Another four patients developed ventilator-associated pneumonia while in hospital.
The present study examined a large cohort of patients with \( P. \) \( \text{aeruginosa} \) bacteraemia and included a complete clinical assessment and a precise follow-up to hospital discharge or death. Five variables were significantly and independently associated with mortality from pseudomonal bacteraemia: detection of the episode in the ICU, septic shock, coagulopathy, advanced age and a poor clinical condition of the patient when bacteraemia was detected. An index incorporating these risk factors allowed the allocation of patients to one of three groups with an increasing risk of death from bacteraemia due to \( P. \) \( \text{aeruginosa} \). \( P. \) \( \text{aeruginosa} \) bacteraemia accounted for 1.06 episodes per 1000 admissions at this institution from Jan. 1996 to Dec. 1998. This prevalence is lower than that published in previous series [2, 3, 5, 6, 8, 9], with the exception of that reported by Vázquez and colleagues in which the incidence of pseudomonas bacteraemia was 0.7 episodes per 1000 admissions [17]. This differential may reflect, at least in part, a current trend of decreasing incidence of \( P. \) \( \text{aeruginosa} \) infection among selected categories of immunocompromised patients [1, 11].

A somewhat surprising finding in two recent papers \[3, 18\] was that nearly 40% of \( P. \) \( \text{aeruginosa} \) bacteraemias were community-acquired. However, the present study, like other large series from the literature underlined the importance of nosocomial acquisition [2, 4–11]: 88% of our patients developed the infection in hospital. As in other series [3, 4, 11], preceding procedures and therapies were common in the patients in the present study, and are indicative of the number and severity of concomitant illnesses seen in these patients.

One-third of the patients had no recognisable source of the infection. This proportion is consistent with findings in earlier and recent papers on bacteraemia, many of which indicate a high percentage of patients in whom the portal of entry of infection remains unknown.
Mortality from P. aeruginosa bacteraemia has remained high over the past few decades [9]. Except for two recent reviews [8, 11] with reported mortality rates of 18% and 20%, most workers have found that rates range from 33% to 61% among the generality of P. aeruginosa bacteraemia patients [2–7, 9, 10]. The case-fatality rate in the present study is in accordance with previous investigations. Univariate analysis of risk factors associated with mortality from P. aeruginosa bacteraemia revealed several high-risk variables. Some, such as septic shock and septic metastases, have been emphasised in other investigations [2, 5, 6, 8, 10, 11]. In contrast to earlier investigations [2–6], neither leukopenic nor neutropenic patients were found to have a significantly higher mortality rate from P. aeruginosa bacteraemia [8], probably indicating the need for more aggressive treatment now used for these patients. Several series [3, 8], including the present one, have failed to show a difference in mortality between those receiving appropriate and inappropriate antibiotics for pseudomonas bacteraemia. However, other groups have demonstrated a decrease in mortality when appropriate antibiotics are used [2, 4–7, 10, 11]. We have no straightforward explanation for this discrepancy, but it may be attributable to the criteria for defining ‘appropriate’ treatment. Our definition of ‘appropriate’ therapy allows at least a possible 48 h before laboratory results and appropriate therapy becoming available.

Certain limitations to the study are acknowledged. Foremost, the relatively small sample size, with only 43 deaths, may not have sufficient statistical power to identify all the important variables influencing the outcome of P. aeruginosa bacteraemia. Furthermore, multiple statistical significance testing was performed, and caution should be exercised in interpreting the P values. Because of these limitations, we are going to validate our index in an independent cohort of patients, but, on the basis of this study, it is concluded that the use of simple clinical and laboratory data, known within hours of detection of a bacteraemic episode, can define those groups of patients at high and low risk of death from P. aeruginosa bacteraemia.

References