Recent Experience With *Pseudomonas aeruginosa* Bacteremia in Patients With Cancer

Retrospective Analysis of 245 Episodes

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**Background:** *Pseudomonas aeruginosa* bacteremia is a serious and possibly fatal condition in patients with cancer.

**Objectives:** To ascertain the frequency, demographics, and predisposing factors for *P aeruginosa* bacteremia in patients with cancer and to determine the efficacy of various therapeutic regimens.

**Subjects and Methods:** Patient records of the Clinical Microbiology Laboratory, The University of Texas, M. D. Anderson Cancer Center, Houston, were reviewed. From January 1, 1972, through December 31, 1995, 245 eligible cases of *P aeruginosa* bacteremia were identified. We examined the patient records for the underlying malignant neoplasm and its management, symptoms and signs of infection, culture results of appropriate specimens, antibiotic therapy, and outcome. We also compared our present experience with a previous analysis from this institution covering the period from January 1, 1972, to December 31, 1981.

**Results:** The incidence of *P aeruginosa* bacteremia has decreased compared with the previous study (2.8 vs 4.7 cases per 1000 admissions). It was most common in patients with acute leukemia (55 of 1000 registrations), and the frequency in this disease has not changed. Half of the patients were not in the hospital when they developed their infection. The overall cure rate was 80%, which was a significant (P<.001) increase compared with the 62% cure rate in the previous study. In this study, no significant difference in the cure rates was observed between monotherapy with a β-lactam and combination therapy overall (P = .72), and in patients with shock (P = 1.0) and those with pneumonia (P = .60). The patients' initial neutrophil counts were not of prognostic value; however, the cure rate depended on subsequent changes in neutrophil count during therapy.

**Conclusions:** The frequency rate of *P aeruginosa* bacteremia has decreased in patients with solid tumors but has remained unchanged in patients with acute leukemia. Antibiotic regimens for empirical therapy of neutropenic patients and especially patients with acute leukemia should still provide coverage against *P aeruginosa*.

*Arch Intern Med. 2000;160:501-509*

SEUDEMONAS AERUGINOSA emerged as a common cause of gram-negative bacteremia during the 1960s, especially among immunocompromised hosts. At that time, the mortality was approximately 90% and the only available antipseudomonal antibiotics, the polymixins, were ineffective in patients with persistent neutropenia. Therapy of these infections was improved somewhat with the introduction of gentamicin sulfate, but its efficacy in neutropenic patients was limited. The era of effective therapy for *P aeruginosa* infections began with the introduction of carbencillin and gentamicin and improved with the discovery of other antipseudomonal penicillins, cephalosporins, carbapenems, and fluoroquinolones. Despite these advances, *P aeruginosa* continues to cause serious infections and represents a significant threat to immunocompromised patients and especially to those with severe neutropenia.

An analysis of the 410 cases of *Pseudomonas* bacteremia occurring at the M. D. Anderson Cancer Center, Houston, Tex, from January 1, 1972, to December 31, 1981, found the cure rate to be 62%. Since that time, several antibiotics have been discovered that have potent antipseudomonal activity, including cefazidime, aztreonam, ciprofloxacin, and imipenem. Also, major changes have occurred in the management of patients with malignant diseases, including intensive chemotherapeutic regimens, bone marrow transplantation, antimicrobial prophylaxis for neutropenic patients, and widespread use of long-term intravascular catheters.
PATIENTS AND METHODS

Patient records of the Clinical Microbiology Laboratory, The University of Texas, M. D. Anderson Cancer Center, from January 1, 1991, through December 31, 1995, were reviewed, and a total of 304 episodes of P aeruginosa bacteremia, occurring in 299 patients, were identified. In 9 of these episodes, P aeruginosa was isolated only from the heart blood culture at the autopsy examination. Only those 2 episodes in which the patients manifested clinical signs and symptoms of infection plus evidence of organ infection at the autopsy examination were included. The remaining 7 episodes were excluded because the possibility of postmortem contamination could not be eliminated. Forty-six episodes of polymicrobial bacteremia were excluded, and an additional 6 episodes were excluded because of inadequate information. Hence, 245 episodes occurring in 240 patients were included in the analysis. Although 5 patients had multiple episodes of P aeruginosa bacteremia, for ease of presentation the terms episode and patient will be used interchangeably.

Patient records were examined for details concerning the underlying malignant neoplasm and its management, symptoms and signs of infection, laboratory and roentgenologic abnormalities, culture results of blood and other specimens, antibiotic therapy, and outcome. Pneumonia was defined as any new infiltrate arising within 48 hours before or after the onset of Pseudomonas bacteremia that could not be attributed to other causes, such as pulmonary edema or hemorrhage. The presence of microbiologic evidence was not necessary for the definition given. Patients were considered to have septic shock if they displayed signs and symptoms of hemodynamic instability (systolic blood pressure of <90 mm Hg in a previously normotensive patient or a reduction of ≥40 mm Hg) that were related to the onset of bacteremia and unrelated to other possible causes of hypotension.17 Other concomitant sites of infection identified during the episode of Pseudomonas bacteremia were considered to be due to P aeruginosa only if the organism was isolated from appropriate cultures. The date of onset of bacteremia was considered to be that date when P aeruginosa was isolated from cultures of the patient’s blood for the first time. Pseudomonas aeruginosa was identified with the use of an automated method (VITEK-GNI cards; bio-Mérieux, Hazelwood, Mo).

Appropriate antibiotic therapy was considered to be any therapy that included an antipseudomonal β-lactam (antipseudomonal penicillins, cephalosporins, imipenem, and aztreonam), an antipseudomonal aminoglycoside, or ciprofloxacin. Results of in vitro susceptibility testing were not included in the definition of appropriate antibiotic therapy because they were not available to the physicians when they were prescribing the therapy at the onset of these infections and, therefore, could not influence their choice of antibiotic therapy. Persistent bacteremia was considered to be the isolation of P aeruginosa from blood culture specimens for at least 18 hours after the onset of appropriate antimicrobial therapy. Cure was considered to be the eradication of all signs and symptoms of Pseudomonas infection, the resolution of fever for at least 72 hours, and the absence of evidence of recurrence of signs and symptoms of Pseudomonas infection for at least 7 days after the discontinuation of the antibiotic therapy. Patients who died of other causes during therapy were considered to be cured if the signs and symptoms of infection had resolved and there was no evidence of Pseudomonas infection at the autopsy examination (if performed). The overall cure rates were determined as the ultimate outcome of the infections and included those patients responding to initial therapy and those requiring changes in antibiotic therapy due to failure of the initial regimen. However, in the analysis of response to initial antibiotics, those patients whose antibiotic regimens were altered were considered as failures even if they responded to subsequent regimens. Fever was considered to be a temperature of 38.3°C or higher that was recorded when the initial blood culture specimen was collected. Initial neutrophil counts were categorized as follows: less than 0.10 X 10^9/L, 0.10 to 0.50 X 10^9/L, 0.50 to 1.00 X 10^9/L, and more than 1.00 X 10^9/L.18 The neutrophil count was considered to have changed during therapy if the count at the end of the infection was in a different category than the initial count.

Univariate analyses were done to demonstrate the relation of individual prognostic factors to the outcome of P aeruginosa bacteremia. Frequencies and descriptive statistics of the demographic and clinical characteristics were performed. The χ² test or the Fisher exact test was used, as appropriate, to compare the different proportions.

Since few studies11-16 on Pseudomonas bacteremia have been reported in recent years, we conducted an analysis of 245 episodes occurring at the M. D. Anderson Cancer Center between 1991 and 1995 and have compared this experience with a previous study from this institution.8 The results of this study indicate that P aeruginosa continues to be a significant cause of bacteremia, especially among patients with acute leukemia.

RESULTS

During the 5-year period from January 1, 1991, through December 31, 1995, 245 episodes of P aeruginosa bacteremia occurred in 240 patients (144 males and 101 females) whose median age was 51 years (range, <1-89 years). Among the 5 patients who had 2 episodes of P aeruginosa bacteremia, the median interval between episodes was 42 days (range, 20-61 days). All signs and symptoms of the initial infection were eradicated before the second episode. There were 88 319 hospital admissions during this period; hence, there were 2.8 cases of P aeruginosa bacteremia per 1000 admissions. The distribution of underlying malignant diseases is listed in Table 1. Patients with multiple episodes of bacteremia were included only once in this table. Most (54%) patients had hematologic malignant diseases, with variants of acute leukemia being the most common. Information was not available regarding the number of hospital admissions by diagnosis during this period. Since the number of new patient registrations could be determined, these figures were used to estimate the frequency of P aeruginosa bacteremia. This infection occurred most often in patients with acute leukemia, and it was 27 times more frequent in these patients than in
patients with solid tumors. Of the patients, 64% had neutrophil counts of less than 1.00 × 10^9/L at the onset of their infection and 53% had neutrophil counts of less than 0.10 × 10^9/L.

During the 2 weeks before the onset of P aeruginosa bacteremia, most patients (89%) underwent some type of antineoplastic therapy. Chemotherapy alone or in combination with other therapeutic modalities was given to 89% of these 219 patients. Of the 219 patients, 15% underwent a surgical procedure and 11% underwent radiotherapy.

One hundred twenty-three patients (50%) were not in the hospital when they developed their infection. However, 11 (9%) of these patients had been discharged from the hospital during the preceding 3 days, and an additional 31 (25%) had been discharged during the preceding week. Sixty-six (27%) of the total 245 patients had not been hospitalized within 2 weeks preceding the onset of their infection, although many of these patients were visiting hospital clinics regularly. The 122 patients who did not present with fever at the onset of Pseudomonas bacteremia, 19 had other signs and symptoms of infection. Of the remaining 17 patients, 11 had community-acquired infection and experienced fever before examination at the hospital but were not febrile at the time that the positive blood culture results were collected. For the remaining 6 patients, there was no information in the patient record to indicate the reason for obtaining the positive blood culture specimen. The median interval between the onset of fever and the collection of the first positive blood culture result was 0 days (range, 0-11 days). Fever first occurred on the same day in 72% of the patients and preceded the first positive blood culture result by 1 to 2 days in 17% of the patients. The remaining 9% of the patients had a fever for 3 to 11 days before the onset of bacteremia.

Of the 245 patients, 13 (5%) had major hemorrhage associated with their infections, and an additional 3 (1%) had minor hemorrhages; however, only 5 patients (2%) had hematologic abnormalities consistent with the diagnosis of disseminated intravascular coagulation. A total of 52 patients (21%) developed shock as a manifestation of their infection. Ecthyma gangrenosum was observed in only 4 patients.

At the onset of Pseudomonas bacteremia, 97 patients (40%) had pneumonia (not always caused by P aeruginosa) and 18 (7%) had significant pleural effusions. Pseudomonas aeruginosa was isolated from the sputum culture specimens of only 6 patients and from the bronchoalveolar lavage specimens of 10 patients. Twenty-seven patients had soft tissue infections, but P aeruginosa was cultured from the infected site of only 7 patients. In 74 patients (30%), the organism was cultured from specimens obtained from various sites immediately before or at the onset of infection. The following were considered to be the portal of entry: sputum (n = 6), bronchoalveolar lavage (n = 10), soft tissue (n = 7), urine (n = 20), skin lesions (n = 16), perirectal area (n = 3), device related (n = 4), cerebrospinal fluid (n = 2), mouth (n = 4), ear (n = 1), and eye (n = 1). An additional 101 patients (41%) had concomitant sites of infection, but P aeruginosa was never cultured from specimens collected from these sites. In the remaining 70 patients, a possible portal of entry could not be identified.

The overall cure rate in these 245 patients was 80%. Only 11% of the patients had bacteremia persisting for more than 1 day. There was not a significant annual variation in the cure rate (range, 75%-88%) during this study period. Among those patients who were cured of

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**Table 1. Underlying Malignant Neoplasms in Patients With Pseudomonas aeruginosa Bacteremia**

<table>
<thead>
<tr>
<th>Malignant Neoplasm</th>
<th>No. of Patients Infected</th>
<th>New Patient Registrations With the Diagnosis*</th>
<th>Rate per 1000 Registrations</th>
<th>Cure, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematologic</td>
<td>129</td>
<td>6895</td>
<td>19</td>
<td>79</td>
</tr>
<tr>
<td>Leukemia†</td>
<td>68</td>
<td>1239</td>
<td>55</td>
<td>77</td>
</tr>
<tr>
<td>Acute</td>
<td>29</td>
<td>1286</td>
<td>23</td>
<td>86</td>
</tr>
<tr>
<td>Chronic</td>
<td>20</td>
<td>3306</td>
<td>6</td>
<td>67</td>
</tr>
<tr>
<td>Lymphoma†</td>
<td>12</td>
<td>1064</td>
<td>11</td>
<td>100</td>
</tr>
<tr>
<td>Other</td>
<td>111</td>
<td>47820</td>
<td>2</td>
<td>82</td>
</tr>
<tr>
<td>Solid tumors</td>
<td>36</td>
<td>12745</td>
<td>3</td>
<td>86</td>
</tr>
<tr>
<td>Gastrointestinal tract</td>
<td>21</td>
<td>7264</td>
<td>3</td>
<td>86</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>18</td>
<td>1342</td>
<td>13</td>
<td>83</td>
</tr>
<tr>
<td>Breast†</td>
<td>12</td>
<td>7264</td>
<td>2</td>
<td>77</td>
</tr>
<tr>
<td>Other</td>
<td>24</td>
<td>19205</td>
<td>1</td>
<td>75</td>
</tr>
<tr>
<td>Total</td>
<td>240</td>
<td>54715</td>
<td>4</td>
<td>80</td>
</tr>
</tbody>
</table>

*Patient population identified through a search of the database maintained by Medical Informatics.
†Patients with 2 episodes were counted only once.
Among patients whose highest temperature was 37.0°C or less (P < .001).

The outcome among the 230 patients who received appropriate antibiotic therapy was related to the duration of bacteremia (Table 3). The cure rate was similar among patients with bacteremia for 1 to 3 days (85%), but among the remaining patients with more than 3 days of bacteremia the cure rate was only 50%. The duration of bacteremia before the institution of appropriate antibiotic therapy also was of prognostic significance. Only 10% of the patients had persistent bacteremia after receiving appropriate antibiotic therapy.

Recovery from Pseudomonas bacteremia was examined with respect to the patients’ initial neutrophil counts and changes in neutrophil counts during their infections (Table 4). Complete data were available for 223 patients. The patients’ initial neutrophil counts were not of prognostic significance; however, their outcome did depend on the subsequent changes in neutrophil count during therapy. Irrespective of their initial neutrophil counts, the cure rate was 89% for all patients whose neutrophil counts increased or remained above 1.00 × 10⁹/L and 62% for all patients whose neutrophil counts decreased or remained below 0.10 × 10⁹/L (P < .001). Considering only those patients whose initial neutrophil counts were 0.10 × 10⁹/L or less, there was a significant difference in survival among those patients whose neutrophil counts increased compared with those whose neutrophil counts remained at 0.10 × 10⁹/L or less throughout their treatment.

There was a significant difference in the cure rates depending on whether the patients received appropriate (overall) antibiotic therapy (83% vs 53%; P = .01). Fifteen patients received either inappropriate or no therapy. Nine of these patients survived, 7 of whom had a single temperature elevation of 38.7°C or less, no other signs of infection, and a single positive blood culture result.

Three had central venous catheters removed. Of the 9 patients, 1 had severe neutropenia, had a single temperature elevation of only 37.7°C, experienced no other
signs of infection, and was discharged from the hospital the same day that trimethoprim-sulfamethoxazole was administered. The remaining survivor was not neutropenic, had multiple temperature elevations to 38.5°C, and had a single positive blood and urine culture result. He was discharged from the hospital before the culture results became available and returned 10 days later when he was treated appropriately for his persistent urinary tract infection. Of the 6 nonsurvivors, 5 were severely neutropenic and died within 1 day of the onset of their infection. The remaining patient was terminally ill and was given no therapy.

Various antibiotic regimens were used as therapy (Table 5). Ceftazidime was the most commonly used cephalosporin, although a few patients received cefoperazone sodium. The most commonly used antipseudomonal penicillin was ticarcillin alone or in combination with clavulanic acid; fewer patients received piperacillin sodium and mezlocillin. Amikacin was the most widely used aminoglycoside; gentamicin and tobramycin were less frequently used with approximately equal frequency. Most of these patients (64%) received a single agent, predominantly ceftazidime or imipenem. Only 3% each received an aminoglycoside or ciprofloxacin, and only 17% received one of these in combination with a β-lactam. There was no statistically significant difference in the cure rates for initial therapy with a single β-lactam vs combination therapy (P = .72) or 2 β-lactams vs combination therapy (P = .68).

Of these patients (64%) received a single agent, predominantly ceftazidime or imipenem. Only 3% each received an aminoglycoside or ciprofloxacin, and only 17% received one of these in combination with a β-lactam. There was no statistically significant difference in the cure rates for initial therapy with a single β-lactam vs combination therapy (P = .72) or 2 β-lactams vs combination therapy (P = .68). Only 7 patients received an aminoglycoside alone, and none responded. Despite the small number, this was a significantly poorer cure rate than for a single β-lactam (0% vs 58%; P < .001). Among the single β-lactam antibiotics, antipseudomonal penicillins or aztreonam were less effective than an antipseudomonal cephalosporin or imipenem (46% vs 61%; P = .17).

All patients who failed to respond to aminoglycoside monotherapy subsequently received combination therapy with a β-lactam and ciprofloxacin, and 6 of the 7 responded. One hundred two patients failed initial therapy, and 30 (29%) of these died (most often within 48 hours) without receiving other therapy. Of the 72 patients who received subsequent therapy, 60 (83%) were cured. Various regimens were used as subsequent therapy.

Because of the small numbers, no definite conclusions could be drawn regarding the efficacy of each of these antibiotic regimens.

Among the 230 patients who received appropriate antibiotic therapy, only 24 (10%) had persistent bacteremia. Twenty-one (88%) of these 24 patients were receiving a single β-lactam; 1, an aminoglycoside; and 2, a combination agent. Only 1 patient experienced persistent bacteremia because the organism was resistant to therapy (aztreonam).

Thirty (12%) of the 245 patients developed a superinfection while receiving antipseudomonal therapy. Nine patients were receiving β-lactam monotherapy; 9, a combination of a β-lactam and an aminoglycoside; 5, a combination of a β-lactam and ciprofloxacin; and 7, a combination of all 3 antibiotic families. Five superinfections were caused by gram-positive organisms, 5 by gram-negative bacilli, 10 by fungi, and 4 by viruses; 3 were polymicrobial, and 3 had an unknown cause.

The outcome among patients with shock and pneumonia was related to the initial therapeutic regimen (Table 6). Among patients with shock, there was no difference in cure between patients who were initially treated with β-lactam monotherapy and patients

### Table 5. Cure Related to Antibiotic Therapy: A Comparison Between 2 Periods in the Same Institution*

<table>
<thead>
<tr>
<th>First Regimen</th>
<th>No. (%) of Patients</th>
<th>Cure With the Initial Regimen, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminoglycoside only</td>
<td>128 (34)</td>
<td>7 (3)</td>
</tr>
<tr>
<td>β-Lactams only</td>
<td>90 (24)</td>
<td>176 (77)</td>
</tr>
<tr>
<td>Single β-lactam</td>
<td>90 (24)</td>
<td>148 (64)</td>
</tr>
<tr>
<td>Penicillin only</td>
<td>72 (19)</td>
<td>11 (5)</td>
</tr>
<tr>
<td>Cephalosporin only</td>
<td>18 (5)</td>
<td>70 (30)</td>
</tr>
<tr>
<td>Imipenem only</td>
<td></td>
<td>52 (23)</td>
</tr>
<tr>
<td>Aztreonam only</td>
<td></td>
<td>15 (7)</td>
</tr>
<tr>
<td>Double β-lactam</td>
<td></td>
<td>28 (12)</td>
</tr>
<tr>
<td>Ciprofloxacin only</td>
<td></td>
<td>7 (3)</td>
</tr>
<tr>
<td>β-Lactam and aminoglycoside</td>
<td>156 (42)</td>
<td>33 (14)</td>
</tr>
<tr>
<td>β-Lactam and ciprofloxacin</td>
<td></td>
<td>7 (3)</td>
</tr>
</tbody>
</table>

*Ellipses indicate data not applicable.
†P = .008.

### Table 6. Cure in Patients With Shock or Pneumonia Related to the Initial Therapeutic Regimen

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Shock*</th>
<th>Pneumonia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Patients</td>
<td>Cure, %†</td>
</tr>
<tr>
<td>Aminoglycoside</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>β-Lactam</td>
<td>36</td>
<td>47</td>
</tr>
<tr>
<td>Imipenem or ceftazidime</td>
<td>31</td>
<td>48</td>
</tr>
<tr>
<td>Penicillin or aztreonam</td>
<td>5</td>
<td>20</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Combination</td>
<td>7</td>
<td>28</td>
</tr>
<tr>
<td>β-Lactam, an aminoglycoside,</td>
<td>6</td>
<td>50</td>
</tr>
<tr>
<td>and/or ciprofloxacin</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Three patients received no therapy.
†Ellipses indicate data not applicable.
who received a combination of a β-lactam, an aminoglycoside, and/or ciprofloxacin. Patients who received imipenem or ceftazidime had higher cure rates than patients who were treated with antipseudomonal penicillins or aztreonam (P = .36). Similarly in patients with pneumonia, β-lactam monotherapy was as effective as combination therapy (P = .53). The cure rate was higher among patients who received imipenem or ceftazidime compared with patients who received antipseudomonal penicillins or aztreonam (P = .10). It is recognized that the sample sizes for patients with shock and pneumonia are not adequate to provide a definite conclusion. A sample size of at least 90 patients (45 on each arm) would have been necessary to derive firm conclusions.

In vitro susceptibility testing was conducted by using the Kirby-Bauer technique. Information on the in vitro susceptibility of the infecting strains of *P aeruginosa* to the antibiotics used as initial therapy was available in 204 of the 245 infections (Table 7). Only 17 (8%) of the isolates were resistant to any antibiotic in the initial therapeutic regimen, and 7 of these infections responded to this therapy. Among the 144 patients who received monotherapy, only 13 (9%) of the isolates were resistant to the antibiotic administered. None of the infections treated with a cephalosporin were caused by a resistant strain even though ceftazidime was the antibiotic used most often during this period. Six (13%) of the 48 isolates tested were resistant to imipenem, and 3 of the infections failed to respond to this antibiotic. Although only a few patients received aztreonam, an antipseudomonal penicillin, or an aminoglycoside alone, approximately 20% of the infections treated with these antibiotics failed to respond because the organism was resistant. Among the 60 infections treated with an antibiotic combination, 4 strains were resistant to at least 1 antibiotic selected for therapy. Two of these infections responded to the therapy; 1 infection responded despite resistance to imipenem, amikacin, and ticarcillin. One responded although the organism was resistant to ticarcillin but susceptible to gentamicin. One infection caused by a strain resistant to ciprofloxacin and aztreonam failed to respond to therapy. The other failure was an infection treated with amikacin and ticarcillin. The organism was susceptible to both drugs initially but developed resistance during therapy.

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Isolates Tested</th>
<th>Resistant Isolates</th>
<th>Failures Due to Resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monotherapy</td>
<td>144</td>
<td>13</td>
<td>8</td>
</tr>
<tr>
<td>Cephalosporin</td>
<td>63</td>
<td>0</td>
<td>. . .</td>
</tr>
<tr>
<td>Imipenem</td>
<td>48</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Aztreonam</td>
<td>12</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Penicillin</td>
<td>8</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>7</td>
<td>0</td>
<td>. . .</td>
</tr>
<tr>
<td>Aminoglycoside</td>
<td>6</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Combinations</td>
<td>60</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>204</td>
<td>17</td>
<td>9</td>
</tr>
</tbody>
</table>

*Ellipses indicate data not applicable.*

For many years, *P aeruginosa* has been recognized as a cause of serious infections, especially among patients with cancer. In several previous reviews of *Pseudomonas* bacteremia in patients with cancer, the frequency was highest among patients with acute leukemia and lymphoma. In these studies, most of the infections were nosocomial and associated with substantial mortality. The presence of neutropenia was a poor prognostic sign, and prompt administration of appropriate antibiotic therapy was crucial for a favorable outcome.

In recent years, most of the infections in neutropenic patients with cancer have been caused by gram-positive organisms. The decline in the frequency of gram-negative infections has led some physicians to use empirical antibiotic regimens that do not provide optimum coverage against *P aeruginosa*. The decreased frequency of *Pseudomonas* bacteremia is confirmed in this study. In the previous study, there were 4.7 cases per 1000 hospital admissions compared with 2.8 cases in the present study. However, the frequency among patients with acute leukemia remains unchanged; 58 per 1000 registrations previously and 55 per 1000 registrations during the present study. Hence, the decline in frequency has occurred only among patients with solid tumors and lymphomas. It is not clear what has caused this decreased frequency. Antimicrobial prophylaxis with ciprofloxacin cannot be the explanation since this is used mostly in patients with acute leukemia. Despite this decrease in *P aeruginosa* bacteremia at our institution, *P aeruginosa* remains one of the 3 most frequently isolated gram-negative bacilli from sites of infection. Recent reports from other institutions, in the United States and Europe, confirm the continued high frequency of *P aeruginosa* as a cause of infections in patients with cancer. Consequently, it is inappropriate to use empirical antibiotic regimens that do not provide adequate antipseudomonal coverage, especially for patients with acute leukemia.

A striking difference between the 2 studies is the increased proportion of *Pseudomonas* bacteremia that occurred in patients who were not in the hospital. From 1972 to 1981, only 19% of the infections occurred in patients who were in the community, and 76% of these infected patients had been discharged from the hospital during the preceding week. In the present study, half of the patients were in the community when they developed their infection, and only 32% of these patients had been hospitalized during the preceding week. A major factor responsible for this change is the great increase in the outpatient administration of cancer chemotherapy and in outpatient surgical procedures. Since the patients received their cancer therapy at the hospital clinics, they may have been exposed to nosocomial organisms. Also, it has been found that *P aeruginosa* can be readily cultured from fresh fruits and vegetables, and since it survives in moist environments, it may be present in sinks and other areas in the home. Historically, *Pseudomonas* bacteremia has been considered to be almost entirely nosocomially acquired. Many of our patients also may have acquired the organism from a hospital source. The important point is that physicians caring for pa-
Patients with cancer cannot conclude that infection is unlikely to be due to *P. aeruginosa* simply because the patient developed infection while in the community.

Disseminated intravascular coagulation has been associated with *P. aeruginosa* bacteremia. Interestingly, in this study, only 2% of the patients had any evidence of disseminated intravascular coagulation and only 5% of the patients had major hemorrhage associated with their infection. Ecthyma gangrenosum is a skin manifestation highly suggestive of *P. aeruginosa* bacteremia, although occasionally it can be caused by other bacteria or fungi. In the past, it has been found in as many as 28% of patients with *Pseudomonas* bacteremia, but in the present study it was found in only 2% of patients. This low frequency may be due to the prompt institution of appropriate and more potent antibiotics at the onset of infections before ecthyma can develop in many of these patients.

**FACTORS ASSOCIATED** with an unfavorable outcome include the presence of shock and pneumonia. Other studies have reported the poor prognosis of patients who develop shock. In the present study, we failed to repeat the previous observation of the greater efficacy of the combination of a β-lactam plus an aminoglycoside compared with a β-lactam alone in patients who developed shock. The use of imipenem or cefazidime as monotherapy had a similar effect on the outcome as the combination of a β-lactam, an aminoglycoside, and/or ciprofloxacin, although the number of patients who received combination therapy was small. In the present study, patients with shock had a significantly better cure rate than in the previous one (60% vs 25%; *P* < .001).

*Pseudomonas* pneumonia almost always occurs in hospitalized patients, especially in intensive care units. Patients who are susceptible to *Pseudomonas* pneumonia include those with malignant neoplasms, diabetes mellitus, bronchiectasis, emphysema, and congestive heart failure. Bacteremic *P. aeruginosa* pneumonia occurs predominantly in neutropenic patients after cancer chemotherapy. It is a fulminant disease and notoriously difficult to treat. In the present study, and in the previous one, the presence of pneumonia at the onset of bacteremia was an ominous sign (even if it was not caused by *P. aeruginosa*). In the present study, patients with pneumonia had a significantly poorer cure rate than those without pneumonia (63% vs 92%; *P* < .001), but there was a significantly better cure rate for the patients with pneumonia in this study than for those in the previous study (63% vs 49%; *P* = .03).

The availability of more potent antipseudomonal regimens has had a major impact on the outcome of *Pseudomonas* bacteremia in patients with cancer. The overall cure rate increased to 80% in the present study compared with 62% in the previous study. Likewise, the survival at 1 week was substantially improved (84% vs 66%). The antipseudomonal antibiotics that became available since the previous study from 1972 to 1981 include cefazidime, aztreonam, imipenem, and ciprofloxacin. Cefazidime and imipenem were more effective than the older antipseudomonal penicillins and aztreonam. This greater efficacy, however, was not due to a much higher frequency of resistance to the older antibiotics but probably due to the greater potency of these newer antibiotics. There are some studies that indicate that the greater the serum activity, the greater the efficacy of antibiotics, especially in neutropenic patients.

There has been considerable debate for many years regarding whether gram-negative bacteremia can be treated with a single β-lactam or requires a combination (usually a β-lactam plus an aminoglycoside). This issue has been of special concern in treating neutropenic patients. Some randomized trials have found single-agent therapy to be as effective as combination therapy, whereas others have supported the superior efficacy of combination therapy. Single-agent therapy with an aminoglycoside is suboptimal in neutropenic patients. Most investigators have indicated that combination therapy is especially essential in treating *Pseudomonas* infections, although the present and previous studies have found single β-lactams to be as effective as combination agents when administered at optimum doses and schedules.

The acceptance of single-agent therapy at the M. D. Anderson Cancer Center is reflected by the increased frequency of its use in the present study compared with the previous study (77% vs 24%). In a review of 909 cases of bacteremia, Elting et al found that combination therapy was not more effective than single-agent therapy, but defervescence occurred more rapidly with combination therapy. Also, the use of combination therapy may reduce the likelihood of the emergence of antibiotic resistance.

The study by Elting et al demonstrated that factors other than therapy had a major impact on the outcome of gram-negative bacteremias. Bacteremias were categorized as simple or complex. Simple bacteremias included those without any associated site or those associated with a minor infection such as cellulitis, cystitis, or bronchitis. Complex bacteremias were associated with major infections such as pneumonia, necrotizing cellulitis, or meningitis. The cure rate for simple bacteremias was 94% compared with 73% for complex bacteremias. In the present study of *Pseudomonas* bacteremias, the cure rates were 96% and 68%, respectively, confirming their observation.

More than 30 years ago, it was demonstrated that the risk of acquiring infection and the outcome for patients with acute leukemia was related to the level of circulating neutrophils. With the availability of more effective antibiotic therapy, outcome has not been associated with the patients’ neutrophil counts at the onset of infection. However, outcome continues to be related to whether the neutrophil count of neutropenic patients increases during therapy, and this is especially true among patients with initial neutrophil counts of less than 0.10 × 10⁹/L.

In this study, the cure rate was 97% among patients whose neutrophil count increased above 0.10 × 10⁹/L during therapy but was 62% if their neutrophil count persisted below 0.10 × 10⁹/L during therapy. Even in the latter group, however, the cure rate was better than the 41% found in the previous study.
The results of this study are encouraging. The frequency of Pseudomonas bacteremia is decreasing among most patients with cancer. The more potent antibiotics introduced in recent years are more effective even in neutropenic patients and in patients with other poor prognostic factors. Antibiotic regimens used for empirical therapy in neutropenic patients should still provide coverage against P aeruginosa, even among patients who develop their infection as outpatients. Physicians do not associate P aeruginosa with community-acquired infections, but this study has demonstrated that a substantial proportion of Pseudomonas infections occur in this setting. Most of these “community-acquired” infections occur in patients who have been hospitalized recently or visit hospital clinics frequently. Increasingly, many febrile patients with neutropenia are being treated with antibiotics without being admitted to the hospital. Since these patients are not being supervised as closely as patients who are treated in the hospital, it becomes especially important that they receive antibiotic regimens with substantial antipseudomonal activity. Although Pseudomonas infections caused by antibiotic-resistant strains have been reported with increasing frequency in recent years, in this study antibiotic resistance was not a major factor responsible for antibiotic therapy. Although the retrospective nature of this study precludes an accurate comparison of different antibiotic therapies, the data provide some general conclusions. Single-agent therapy with a β-lactam antibiotic given in an appropriate dose and schedule is as effective as a combination of a β-lactam plus an aminoglycoside, confirming the results of previous studies.3,16-50 β-Lactams with more potent antipseudomonal activity, such as the antipseudomonal cephalosporins and carbapenems, are more effective than the less potent antipseudomonal penicillins when used alone. It is likely that patients with complex infections, such as bacteremia with pneumonia, necrotic cellulitis, and typhilitis, may respond better to combination therapy.36 Ciprofloxacin is probably as effective as an aminoglycoside in combination with a β-lactam. Whatever regimen is selected, it is most effective if administered promptly after the onset of infection, especially in neutropenic patients.

Accepted for publication May 6, 1999.

This study was supported in part by a grant from the Amphiaracea Foundation for Chemotherapeutic Studies, Athens, Greece.

We thank Maria Vlachou, RN, and Catherine S. Cooksley, MPH, for their contribution in the data collection and provision of patient population information, respectively.

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