Improved Prognosis of *Pseudomonas aeruginosa* Bacteremia in 127 Consecutive Neutropenic Patients with Hematologic Malignancies

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ABSTRACT

Objectives: Although decreasing in frequency, *Pseudomonas aeruginosa* bacteremia is still a major challenge for neutropenic cancer patients. In patients with hematologic malignancies, the prognosis of *P. aeruginosa* bacteremia is particularly poor due to the prolonged and severe neutropenia, mucosal damage, and other defects in immunity related both to the underlying disease and to the cytotoxic therapy.

Methods: To verify the outcome of *P. aeruginosa* bacteremia and to try to define possible prognostic factors, the authors reviewed the medical records of 127 consecutive episodes of *P. aeruginosa* bacteremia observed in the hematologic unit of the Verona University School of Medicine.

Results: Presence of pneumonia and septic shock, persistence and severity of neutropenia, delayed and inappropriate antibiotic therapy, and unresponsive underlying disease had negative impact on clinical outcome of *P. aeruginosa* bacteremia.

Conclusions: With recognition of the risk factors and more careful management, the prognosis of *P. aeruginosa* bacteremia in neutropenic patients with hematologic malignancies has improved in recent years.

Key Words: *bacteremia, neutropenia*, Pseudomonas aeruginosa

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Infections due to aerobic gram-negative organisms and in particular to *Pseudomonas aeruginosa* cause a high rate of mortality in immunocompromised hosts.[1-8] Among *P. aeruginosa* infections, bacteremia is the most challenging to the patients and implies a high mortality rate, especially if associated with organ invasion. In a previous study on gram-negative bacteremias at the Verona University School of Medicine Department of Hematology, a disturbingly high mortality rate was noted in granulocytopenic patients with *Pseudomonas* septicemia.[9] Since then, diagnostic and therapeutic approaches have been improved, with early implementation of diagnostic maneuvers and early initiation of empirical antibacterial therapy, based on the study of the commonly offending pathogens. Highly active antipseudomonal drugs, in particular amikacin; third generation cephalosporins, notably ceftazidime; and more recently, imipenem-cilastatin, have been routinely combined in the ensuing years.

To verify whether these new modalities of treatment have had an impact on clinical outcome of *P. aeruginosa* bacteremia in patients with hematologic malignancies and if there are particular prognostic factors, the authors analyzed 127 consecutive episodes of *P. aeruginosa* bacteremia that occurred in the hematologic unit between April 1976 and December 1995.

The literature reports a variety of studies, most of which originate in the United States, on *P. aeruginosa* bacteremia in patients with malignancies.[7,8,10-24] However, few of these reports relate exclusively to patients with hematologic malignancies which are known to imply frequently an association of risk factors.[18,19,22,23]

MATERIAL AND METHODS

The medical records of all patients who experienced *P. aeruginosa* bacteremia in the hematologic unit between April 1976 and December 1995 were reviewed. All patients who had appropriate signs and symptoms of systemic infection in association with one or more ante mortem positive blood specimens for *P. aeruginosa* are included in this study.

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Definitions

Associated infection was defined a microbiologically or clinically proven site of infection concomitant to positive blood cultures. At the onset of bacteremia, the patients were classified in four groups according to the neutrophil count: less than 100/μL, between 100 and 500/μL, between 501 and 1000 μL, and more than 1000/μL. The neutrophil count was considered to have increased if at the end of the episode the count was in a higher group compared to the initial count. The patient was considered in septic shock if his or her previous normal blood pressure fell under 90/60 mmHg in presence of oliguria or anuria. The bacteremia was considered nosocomial if it occurred after 5 days of hospitalization. Patients were considered to be cured of their infection if they became afebrile and all the clinical and laboratory signs of infection disappeared. Death occurring within 21 days after the first positive blood culture was considered to be due to *P. aeruginosa* bacteremia, even if other causes of death were present, such as other infections, hemorrhage, or progression of disease. Empirical antibiotic therapy was defined appropriate if it included at least an antipseudomonal beta lactam or an aminoglycoside antibiotic administered at appropriate dosage for at least 24 hours.[20] Antibiotic sensitivity tests were performed in vitro on positive subcultures with antibiotic-impregnated disks, using the Kirby-Bauer technique.

Delay in antibiotic therapy was defined as an interval of 12 or more hours between the onset of the signs of infection and the start of antibiotic therapy. To evaluate the outcome in relation to the antibiotic therapy, the patients were divided into two groups: those treated before 1984, who received a broad-spectrum antibiotic without third generation cephalosporin or imipenem-cilastatin, and those treated since 1984 with third generation cephalosporin or imipenem-cilastatin alone or associated with aminoglycoside. The two groups of patients were compared. The first group included 38 episodes observed between 1976 and 1983; the second, 89 episodes seen between 1984 and 1995.

Statistical Analysis

Statistical analysis was performed using chi-square test and Fisher's exact test.

RESULTS

One hundred and twenty-seven consecutive episodes of *P. aeruginosa* bacteremia were diagnosed among 119 patients (52 females, 67 males) at the University of Verona Hematologic Unit. The mean age of patients was 47 years (range = 12–80 y). All but one patient had a hematologic malignancy. The majority of episodes of bacteremia occurred in patients with acute leukemia: 85 of 127 (67%) (acute nonlymphocytic leukemia: n = 47; acute lymphocytic leukemia: n = 31; blastic transformation of chronic myelogenous leukemia: n = 7). The remaining episodes occurred in patients with non-Hodgkin lymphoma (n = 26), Hodgkin disease (n = 4), chronic lymphocytic leukemia (n = 4), multiple myeloma (n = 6), malignant histiocytosis (n = 1), severe aplastic anemia (n = 1). Twelve patients each had two episodes of *P. aeruginosa* bacteremia, 8 of the 12 during different periods of hospitalization. Fifty-three episodes (42%) occurred in patients with hematologic disease in relapse or not responsive to chemotherapy.

Table 1. Relation between Pneumonia and Outcome in Episodes of *Pseudomonas aeruginosa* Bacteremia

	Episodes (n = 127)	*Mortality (n = 49) (38.5%)*
Bacteremia with pneumonia	61	35/61 (57)
Bacteremia without pneumonia	66	14/66 (21)*

*Bacteremia with pneumonia vs. bacteremia without pneumonia = P < 0.0001, chi-square.

Associated Infections

In 78 of 127 episodes (61%), the bacteremia was associated with other microbiologically or clinically documented sites of infection. Bacteremia alone was diagnosed in the remaining 49 episodes. Pneumonia, alone or associated with some other site of infection, was the most common type of concomitant infection (61/127, 48%), and it was related to a high mortality (Table 1). Cutaneous lesions defined as ecthyma gangrenosum were observed in 12 of 127 episodes (9.5%).

Mortality

The overall mortality was 49 of 127 (38%) and decreased from 27 of 38 (71%) in the first period of the study to 22 of 89 (25%) in the second period (P < 0.0001, chi-square).

Granulocytopenia

During the bacteremia, in all but eight episodes the patients experienced neutropenia (polymorphonuclear cells [PMN] <1000/μL), including six patients not

Table 2. Relation between Neutropenia and Outcome in Episodes of *Pseudomonas aeruginosa* Bacteremia

		Deaths/Episodes	
Initial Count (PMN/μL)	*Deaths/Episodes (49/127) (38.5%)*	*PMN Decrease (42/66) (64%)*	*PMN Rise* (7/61) (11.5%)*
<100	16/57 (28)	14/22	2/35
100–500	15/37 (40.5)	13/21	2/16
501–1000	11/19 (58.0)	11/17	0/2
>1000	7/14 (50.0)	4/6	3/8

PMN = polymorphonuclear cells.
*Deaths/Episodes: PMN decrease vs. PMN rise = P < 0.0001, chi-square.

Table 3. Relation between Septic Shock and Outcome in Episodes of *Pseudomonas aeruginosa* Bacteremia

	Patients (n = 127) (100%)	*Deaths (49/127) (38.5%)*
Septic shock	46 (36)	30/46 (65.0)
No septic shock	81 (64)	19/81 (23.0)*

*Deaths: septic shock vs. no septic shock = P < 0.0001, chi-square.

neutropenic at the onset but who became neutropenic soon thereafter. The neutrophil count at the onset of the episode, the evolution of neutropenia during the episode, and its relation with death are reported in Table 2. At the onset of the bacteremia, 94 of 127 (74%) patients had less than 500 PMN/μL; among these (57/127, 45%) had less than 100 PMN/μL. Of the neutropenic patients, 61 of 113 (54%) subsequently had a granulocyte recovery to above 1000 PMN/μL. The mortality was 11.5% in patients with granulocyte recovery, as opposed to 64% in patients who remained neutropenic (P < 0.0001, chi-square).

Shock

Forty-six of 127 (36%) episodes of bacteremia were complicated by septic shock (Table 3). The mortality rate in episodes with septic shock was 65% (30/46) whereas in the 81 episodes without shock it was 23% (19/81) (P < 0.0001, chi-square). The majority of the episodes with shock were observed in the first period of the study (1976–1983) (Table 4).

Polymicrobial Bacteremia

Twenty-six of 127 (20.5%) episodes of bacteremia were polymicrobial, with a fatal outcome in 11 of 26 (42%), similar to the outcome observed in monomicrobial bacteremias (38/101, 38%) (P = not significant, chi-square). In the first period (1976–1983), polymicrobial bacteremias were found in 9 of 38 cases (24%) with a mortality rate of 67% (6/9). In the second period (1984–1995), polymicrobial bacteremias were found in 17 of 89 cases (19%) with a fatal outcome in 5 of 17 (29%). The results are comparable to those observed in monomicrobial bacteremias in the corresponding period of time (first period: episodes 29/38 [76%], mortality 21/29 [72%]; second period: episodes 72/89 [81%], mortality 17/72 [23%], respectively) (P = not significant, chi-square).

The most frequently associated organisms were: *Staphylococcus aureus* (n = 10), *Streptococcus* spp (n = 5), *Escherichia coli* (n = 4), *Klebsiella* (n = 3), *Staphylococcus epidermidis* (n = 3), non-*aeruginosa Pseudomonas* (n = 1), *Micrococcus* (n = 1). Some episodes involved more than two organisms.

Age

The patients under and over 50 years of age were in comparable number. The mortality rate was 47% (29/62) in patients over age 50 compared to 35% (20/57) in patients under age 50 (P = not significant, chi-square).

Status of Underlying Disease

The status of hematologic malignancy significantly affected the prognosis. The mortality rate in patients in relapse was 47% (25/53) compared to a mortality rate of 32% (24/74) in patients not in relapse (P = 0.02, chi-square).

Antibiotic Therapy

Table 4 analyzes the relations among inappropriate antibiotic therapy, delayed antibiotic therapy, pneumonia, shock, and clinical outcome. The two groups of patients were again those treated before the introduction of third generation cephalosporin or imipenem-cilastatin and those who received these antibiotics. In the first group of patients (A) the empirical antibiotic therapy was inappropriate in 11 of 38 episodes (29%). The incidence of pneumonia, shock and death were respectively 27 of 38 (71%), 29 of 38 (76%), and 27 of 38 (71%). In the second group (B), including 89 episodes, the cases with inappropriate antibiotic therapy were significantly reduced (2/89, 2%, P < 0.0001). Similarly, the mortality was significantly reduced (22/89, 25%, P < 0.0001).

The delay in starting the antibiotic therapy was important for the clinical outcome (see Table 4). A delay between the onset of fever that subsequently was proven to be due to *P. aeruginosa* and starting of antibiotic

Table 4. Relation among Inappropriate Antibiotic Therapy, Septic Shock, Pneumonia, and Delayed Antibiotic Therapy, in Episodes of *Pseudomonas aeruginosa* Bacteremia

	Episodes	*Deaths*	*Inappropriate Antibiotic Therapy*	*Shock*	*Pneumonia*	*Delay*	*Deaths**	
							Delay	*No Delay*
1976–1983 (A)	38	27/38 (71%)	11/38 (29%)	29/38 (76%)	27/38 (71%)	18/38 (47%)	15/18 (83%)	12/20 (60%)
1984–1995 (B)	89	22/89 (25%)	2/89 (2%)	17/89 (19%)	34/89 (38%)	5/89 (5%)	4/5 (80%)	18/84 (21%)
P-Value (A vs. B)		< 0.0001	< 0.0001	< 0.0001	< 0.001	< 0.0001	NS	0.0003
Total	127	49/127 (38%)	13/127 (10%)	46/127 (36%)	61/127 (48%)	23/127 (18%)	19/23 (83%)	30/104 (29%)

*Delay vs. no delay, P < 0.0001.

Table 5. Relation between Antibiotic Therapy and Outcome in Episodes of *Pseudomonas aeruginosa* Bacteremia

Antibiotics	*1976–1983*	*1984–1995*	*Mortality*(%)*
Broad-spectrum penicillin + aminoglycoside	7	2	6/9 (67)
Others antibiotics	11	2	7/13 (53)
Second generation cephalosporin + aminoglycoside	20	–	15/20 (75)
Ceftazidime	–	13	5/13 (38)
Ceftazidime + aminoglycoside	–	53	15/53 (28)
Imipenem-cilastatin	–	6	0/6 (–)
Imipenem-cilastatin + aminoglycoside	–	13	1/13 (8)

*Ceftazidime vs. ceftazidime + aminoglycoside, P = not significant; imipenem vs. imipenem-cilastatin + aminoglycoside, P = not significant; ceftazidime ± aminoglycoside vs. imipenem-cilastatin + aminoglycoside, $P < 0.002$.

therapy was observed in 23 of 127 (18%) episodes. During the study, the number of patients starting with delay the empirical antibiotic therapy progressively decreased from 47% in the first group to 5% of the second group ($P < 0.0001$).The overall mortality at 48 and 96 hours was 21% and 30%, respectively. The time of institution of antibiotics had an effect on survival. At 48 and 96 hours, 83% and 74% of patients treated without delay were alive, respectively, in contrast to 56.5% ($P = 0.01$, chi-square) and 43.5% ($P = 0.01$, chi-square) of patients who received delayed antibiotic therapy.

The various antibiotic therapies employed throughout the study period are reported in Table 5. Of note, third generation cephalosporins and imipenem-cilastatin, alone or combined with aminoglycoside, have been routinely used since 1984. In patients treated with these drugs, the mortality decreased (see Table 5).

DISCUSSION

Pseudomonas aeruginosa bacteremia is considered the most life-threatening of bacteremias. Its mortality rate in most series approaches 45 to 50%, but it often reaches 60 to 70% in neutropenic patients with neoplastic diseases, with the highest fatality rate observed in patients with hematologic malignancies.[6-8,11,13,21,25,26] In more recent years, the mortality rate due to *P. aeruginosa* in neutropenic patients has ranged between 31% and 42%.[27,28]

The 127 consecutive episodes here reported occurred in a homogeneous population of adult patients with hematologic malignancies, most of them being affected by acute leukemia, often in relapse, and characterized by severe and prolonged neutropenia.

The overall cure rate found in this study (61.5%) is similar to that previously reported in neutropenic patients.[19] In a large 10-year study reported by Bodey et al,[20] patients with hematologic malignancies had a cure rate of 62%, without significant variations of mortality in the last 5 years compared to the first 5 years of the study. In the present study, the authors observed a reduction in the rate of mortality in recent years from 71% in the first period to 25% in the last period (see Table 4), which compares favorably with recently published data.[27-29] This improvement may be related to a combination of factors: physicians' previous experience, earlier diagnosis, and prompt starting of the empirical antibiotic treatment with antipseudomonal activity at the onset of clinical signs of infection. Moreover, the recent introduction of newer antibiotics may have played a role in the improved results.

The present study demonstrates that the following factors have unfavorable prognostic significance: pneumonia, septic shock, persistent and profound neutropenia, hematologic malignancy in relapse, delay in starting the antibiotic therapy, inappropriate empirical therapy. Concomitant pneumonia, as previously observed,[10,19,20] was associated with a high rate of mortality. Significantly better results have been obtained with bacteremia alone or associated with affected sites other than lung (see Table 1). In patients presenting septic shock, the mortality rate was high, confirming the severity of this event.[3,5-8,20,28-34] The role of neutropenia as a risk factor was also confirmed in the present series.[35] Granulocyte recovery was important for a favorable outcome (see Table 2). *Pseudomonas aeruginosa* bacteremia has a rapid evolution, with a mortality rate, ranging between 31% and 40% in the first 36 hours.[10,12] This study confirms its rapid course in neutropenic patients. However, important differences in prognosis were observed, depending on the interval between the onset of fever and the start of the antibiotic therapy. Probably the improvement of results is partly connected with the shortening of the interval between onset of infection and antipseudomonal therapy in recent years (see Table 4). An appropriate treatment was of great importance for the prognosis. In the last years, the number of patients receiving an inappropriate empirical treatment sharply decreased (see Table 4). Obviously, the definition of appropriate empirical treatment is theoretic, and it does not take into account the actual in vitro efficacy against the offending pathogen (with the diagnostic methods presently available, the initial therapy remains truly empirical). Nevertheless, this definition was of practical value

as a prognostic factor, in that deaths occurred considerably more frequently in patients receiving an inappropriate therapy (see Table 4).

The introduction in more recent years of ceftazidime and imipenem-cilastatin, alone or associated with aminoglycosides, improved the results (see Table 5). The more frequently used combination has been ceftazidime plus amikacin. The results are similar to those reported by the EORTC International Antimicrobial Therapy Cooperative Group.[36] No differences in outcome were found between patients who received either ceftazidime or imipenem-cilastatin alone versus the same drugs in combination with aminoglycosides. These data concur with findings reported by Pizzo et al with initial ceftazidime monotherapy.[37] Although no significant advantage was observed with the addition by aminoglycosides, combinations of active agents are recommended in prolonged neutropenia by many investigators, owing to the intrinsic aggressiveness of *P. aeruginosa*, and to avoid the development of antibiotic resistance.[38] Moreover, recent studies support the use of initial combination therapy to reduce the duration of antibiotic therapy.[39] A particularly low rate of mortality has been observed after the introduction of imipenem-cilastatin.

Results show that early and more effective antibiotic therapy is able to improve the outcome of this formerly devastating complication in neutropenic patients. Recent reports on the re-emergence of *P. aeruginosa* in Europe and in Japan suggest that a continuous surveillance should be kept against this organism.[28,40]

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