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Gram-negative Septicemia in Patients with Hematologic Malignancies

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Abstract—*The clinical records of* 66 *consecutive episodes of Gram-negative bacteremia occurring in* 60 *patients with hematologic malignancies during a* 66-*month period were reviewed to assess the major prognostic factors. The bacteremia-related mortality was* 53%. *Overall,* Pseudomonas aeruginosa (54%) *and* Escherichia coli (24%) *were the predominant isolates (fatality rate* 78 *and* 31% *respectively). The majority of patients* (58/66) *were granulocytopenic (PMN* $<1000/\mu l$). *Among the* 18 *patients whose circulating granulocytes increased by one* $\log_{10}$ *or to above* 1000/mmc *during therapy, the fatality rate was* 39%, *as opposed to* 70% *in the* 40 *patients without such an increase. Pneumonia-associated bacteremia* (56%) *had a high fatality rate* (73%) *compared to isolated bacteremias* (27%). *Septic shock and inappropriate antibiotic therapy accounted for the highest mortality. Our data suggest that* Pseudomonas *etiology, persistent neutropenia, associated pneumonia, septic shock and inappropriate antibiotic therapy account for a bad prognosis in Gram-negative bacteremia in hematologic malignancies.*

INTRODUCTION

GRAM-NEGATIVE septicemia is an acute, unpredictable event which remains a prevalent problem in cancer patients, especially those with hematologic malignancies, such as leukemia and lymphoma, who are undergoing vigorous chemotherapy [1–6]. Despite advances in antibiotic therapy, the mortality rate remains high, particularly in those patients in whom vascular collapse occurs. Prognosis seems to depend more on the severity of underlying disease or the proper selection of initial antimicrobial therapy than on the therapeutic measures employed when septicemia is found or shock occurs.

In an effort to define more clearly the clinical variables which influence prognosis, and to improve our therapeutic approach to septicemia and its complications, we reviewed all Gram-negative bacteremias diagnosed in our institution.

MATERIALS AND METHODS

The medical records of all patients who experienced Gram-negative bacteremia in our Section of Hematology between January 1976 and April 1982 were reviewed. All patients had hematologic malignancies; the underlying diseases were divided into rapidly fatal (RFD), ultimately fatal (UDF) and non-fatal disease (NFD), according to the McCabe–Jackson classification [6, 7].

Patients who had appropriate signs and symptoms of a systemic infection in association with one or more ante-mortem positive blood specimens for a Gram-negative bacillus were included in this study. Patients having two or more microorganisms cultured from one or more blood specimens during a single febrile episode were considered to have a single polymicrobial episode. The onset of the infectious episode was considered to coincide with the first day that a temperature above 38.5°C developed. Neutropenia was defined as less than 1000 neutrophils/μl and granulocyte recovery was defined as an increase of one $\log_{10}$ or to above $1000/\mu l$.

Patients were considered to be cured of their infection if they became afebrile and all previous clinical and laboratory signs of infection disappeared. The source of infection was determined by isolating the organism with the same antibiotic sensitivity from the blood and the suspect site before bacteremia. The bacteremia was considered 'nosocomial' if it occurred after 5

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days of hospitalization. A patient was considered to be shocked if his previously normal blood pressure fell under 90/60 mm Hg or if his previously high blood pressure decreased by more than 60 mm Hg.

Antibiotic sensitivity tests were performed *in vitro* on positive subcultures with antibiotic impregnated disks using the Kirby and Bauer technique. Therapy was considered appropriate if the organism cultured from the blood was sensitive to at least one of the antibiotics given according to usual dosage for these patients for at least 24 hr. Renal failure was considered to be present if creatininemia was over 1.5 mg/dl and/or BUN was over 35 mg/dl.

Statistical analysis were performed using the chi square method with Yates correction.

RESULTS

During a 66-month period 66 episodes of Gram-negative bacteremia were identified among 60 adult patients (26 females and 34 males) aged between 12 and 80 yr (mean 48 yr). All patients had hematologic malignancies and the majority had acute leukemia (35/60), including blastic transformation of myeloproliferative disorders (Table 1).

The great majority of the episodes (58/66, 88%) occurred in patients who were granulocytopenic at the onset of bacteremia (in 50 less than 500 PMN/μl; in 32 less than 100 PMN/μl). Overall, an increased production of granulocytes during bacteremia was observed in 18 episodes, the neutrophil count rising to above 1000/μl in only 8 (14%).

Causative organisms

Pseudomonas aeruginosa and *Escherichia coli* were the most common causative organisms in our Institution (Table 2). *Pseudomonas aeruginosa* was also found in most of the polymicrobial bacteremias (8/13). It should be pointed out that the incidence of shock and the fatality rate were significantly higher in patients with *P. aeruginosa* bacteremia than in all other patients ($P < 0.01$). We fail to observe a different prognosis in the polymicrobial bacteremias

Table 1. Underlying disease and fatality rate in 66 bacteremic episodes

Underlying disease	Episodes/ patients	Overall mortality (%)	Bacteremia-related mortality (%)
Acute non-lymphocytic leukemia	29/26	15 (52)	14 (48)
Acute lymphocytic leukemia	5/5	5 (100)	4 (80)
Blastic transformation of myeloproliferative disorders	4/4	3 (75)	3 (75)
RFD	38/35	23 (60.5)	21 (55)
Non-Hodgkin's lymphoma	14/12	5 (36)	5 (36)
Hodgkin's disease	6/6	5 (83)	5 (83)
Myeloproliferative disorders	4/4	2 (50)	2 (50)
Multiple myeloma	2/2	1 (50)	1 (50)
Aplastic anemia	2/1	1 (50)	1 (50)
UFD	28/25	14 (50)	14 (50)
Total	66/60	37 (56)	35 (53)

Table 2. Causative organisms and fatality rate in 66 bacteremias

Organisms	No. of episodes (%)	Overall mortality (%)
Pseudomonas aeruginosa	28 (42)	21 (75)
Escherichia coli	14 (21)	4 (29)
Klebsiella	3 (5)	2 (67)
Salmonella	3 (5)	2 (67)
Enterobacter	2 (3)	
Alcaligenes	1	
Proteus	1	1 (100)
Flavobacter	1	
Polymicrobial*	13 (20)	7 (54)
Total	66	37 (56)

*In 8/13 polymicrobial episodes and in all 7 deaths *Pseudomonas aeruginosa* was cultured.

(fatality rate 54%) than in monomicrobial bacteremias (57%).

Source of infection

In 35 of the 66 episodes we were able to ascertain the primary site of infection. The urinary and respiratory tracts were the sources for bacteremia in 60% of the evaluable cases. In our cases the source of bacteremia did not affect the outcome of the infectious episode.

Associated infections

In 51/66 episodes (77%) bacteremia was associated to other infections microbiologically and/or clinically documented; bacteremia alone occurred in 15 episodes (23%). The most common type of associated infection was pneumonia (56%), which accounted for the highest fatality rate (73%). Bacteremias plus infected sites other than pneumonia (21%) were responsible for a lower mortality (43%), whereas the lowest fatality rate was observed in episodes of bacteremia alone (27%).

Granulocytopenia

Patients were grouped according to the level of circulating granulocytes at onset of bacteremia (Table 3). The overall fatality rate was similar in the three groups of neutropenic patients (60%). Patients without evidence of granulocytes recovery during septicemia showed the highest incidence of mortality (70%). Among the non-neutropenic patients the fatality rate was 25%.

Shock

In 37/66 episodes the patients experienced shock. The fatality rate was very high in bacteremias with such a complication (84%). Three patients died after recovery from shock. Conversely, only 6/29 (20%) bacteremias without shock had a fatal outcome ($P<0.01$). We failed to observe any correlation between the initial neutrophil count or the underlying disease and the incidence or the outcome of shock. The number of patients with such a complication was too small to correctly evaluate the effectiveness of antibiotic or corticosteroid treatment in the outcome of septic shock.

Nosocomial bacteremias

Thirty-seven out of 66 episodes (56%) were defined as nosocomial. No difference in fatality rate between nosocomial (54%) and non-nosocomial (59%) episodes was observed.

Antibiotic therapy

During 57/66 episodes the patients received an association of antimicrobial agents, usually including a cephalosporin plus an aminoglycoside and carbenicillin. In six episodes monochemotherapy was used. In the remaining three episodes antibiotic therapy was so briefly administered that it was probably useless. The response rate related to the *in vitro* sensitivity to initially administered antibiotics is reported in Table 4: there was a significant difference in response rates between patients having bacteremia with antibiotic-resistant or -sensitive organisms ($P<0.01$). During 35 episodes the patients received appropriate antibiotic therapy as defined by either *in vitro* sensitivities or adequate dosage, and 22 (63%) were cured. During 25 episodes the patients were not treated with appropriate

Table 4. Response related to susceptibility to initially administered antibiotics (57 evaluable episodes)

Sensitivity to two or more (SS), one (S) or no (R) of given antibiotics	Episodes	Response (%)
SS	23	15 (65)
S	17	8 (47) $P<0.01$
R	17	1 (6)
Total	57	24 (42)

Table 3. Gram-negative bacteremia: neutropenia, granulocyte recovery and mortality

Initial neutrophil count/μl	No. of episodes	Overall fatality (%)	No. of deaths/No. of episodes (fatality rate %) No rise	Rise*
<100	32	20 (62.5)	15/20 (75)	5/12 (42)
101-500	18	11 (61)	9/14 (64)	2/4 (50)
501-1000	8	4 (50)	4/6 (67)	0/2
Total	58	35 (60)	28/40 (70)	7/18 (39)
>1000	8	2 (25)		

*Granulocyte increase of one $\log_{10}$ or to over 1000/μl. All patients with an increase of one $\log_{10}$ initially had less than 100 PMN/μl.

antibiotic therapy and only 3 (12%) were cured ($P < 0.01$).

DISCUSSION

The 66 episodes analyzed in this report occurred in a population consisting of patients with rapidly or ultimately fatal diseases. The majority of the patients had acute leukemias, and bacteremia most often occurred during severe and prolonged neutropenia (88%), neutrophil count rarely recovering above 1000/μl (14%).

The bacteremia-related mortality in our cases (53%) appears to be higher than that observed by other in different series [8–10]. Mortality rates for sepsis vary widely in the literature, depending on the underlying diseases considered, the causative organisms observed and the time during which the studies were conducted. The overall estimated mortality attributable to Gram-negative bacteremia in non-selected patients is 20–25% [2, 3, 11]. However, in most neoplastic series significantly higher mortality rates are reported, particularly in patients with leukemia or lymphoma [12–14]. Moreover, even worse prognosis is reported during severe neutropenia [2, 3, 14, 15] and *Pseudomonas* bacteremia [15–17]. *Pseudomonas aeruginosa* was the predominant causative organism in our series, unlike in other reports. Moreover, the higher incidence of shock developed during *Pseudomonas* bacteremia, as reported by others [10, 12, 14, 17, 18], could account for the high fatality rate.

The effect of shock on the outcome of patients with Gram-negative bacteremia is well established [10, 12, 17, 19]. The mortality for septicemia complicated by shock was 84%, in contrast to a mortality rate of 20% in episodes unaccompanied by shock ($P < 0.01$). Similar results were reported by Singer *et al.* [12] in patients with leukemia or lymphoma. Although shock was more frequent during the course of *Pseudomonas* bacteremia, no other factor predisposing to shock was identified; granulocytopenia does not seem to be related to either the development or the outcome of shock.

Although various authors have pointed out the role of source of infection, conflicting results have been reported [2, 4, 13]; in our experience the source of infection has little prognostic effect. On the contrary, little attention has been directed towards the prognostic significance of associated infections: the association of bacteremia with any other site of infection increased the mortality in our patients, pneumonia accounting for the highest fatality rate, whereas bacteremia alone does not appear to be an inordinately high risk factor.

The critical role of granulocytopenia in determining the outcome of septicemia has been emphasized in the literature [1, 3, 12, 14, 20, 21]. Among the neutropenic patients only 40% survived bacteremia whereas 75% of non-neutropenic patients survived. In our experience the neutrophil count recovery during bacteremia exerts a predominant role in determining the outcome of infection, in accordance with some previous reports [1, 22], rather than the level of neutropenia at the time of bacteremia, as suggested by others [23, 24]. As a matter of fact, an increasing fatality rate was observed in non-neutropenic patients (25%), in neutropenic patients with neutrophil count recovery (39%) and in persistently neutropenic patients (70%) respectively. Hence the overall mortality in our series is high, probably as a result of the large proportion of patients with either neutropenia (88%) or persistent neutropenia (69%).

The effectiveness of antibiotic therapy is the last but not the least factor which should be considered. Although the relative efficacy of individual agents or combinations of antibiotics remains unconsidered because of the various empiric regimens used, this study supports the usefulness of synergistic antibiotic association [25] and it clearly confirms that appropriate antibiotic treatment significantly reduces the number of fatalities, as previously reported [1, 3, 26]. Overall, appropriate therapy, as defined above, reduced the fatality rate to less than one-half that observed in patients who received ineffective therapy.

The findings of our data would suggest that *Pseudomonas* bacteremia, persistent neutropenia, shock, associated pneumonia and inappropriate antibiotic therapy are responsible for a poorer prognosis in Gram-negative bacteremia. Regrettably, however, identification of host and other factors associated with unfavorable outcome have a limited effect on the prospective identification of patients at high risk or on the development of an effective treatment. Therefore the empiric choice of initial antibiotic therapy will largely determine the ultimate chance for recovery from bacteremia. The appropriateness of antibiotic therapy should be supported by the results of surveillance cultures in each institution. It is likely that new antibiotics, immunoprophylaxis or immunotherapy can improve prognosis and the development of truly effective measures can prevent such complications. For the present, however, an appropriate antibiotic therapy and a better control of underlying disease remain the basic steps for treatment of Gram-negative bacteremias in hematologic malignancies.

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