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# BACTEREMIA IN PATIENTS WITH HEMATOLOGICAL MALIGNANCIES. ANALYSIS OF RISK FACTORS, ETIOLOGICAL AGENTS AND PROGNOSTIC INDICATORS

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**ABSTRACT**

**Background and Objective.** Patients with hematological malignancies are at increased risk for developing bacteremia. No previous study has investigated the risk and prognostic indicators of bacteremia in such patients using a statistical approach.

**Methods.** A case-control study was performed in 106 patients with hematological malignancies (group A). Two hundred and twelve patients were included as controls and divided into two groups: 106 patients with hematological malignancy without bacteremia (group B) and 106 HIV-infected patients with bacteremia (group C).

**Results.** At univariate analysis, bacteremia risk factors in group A were: neutropenia for more than six days (p=0.03 vs. group B), central venous catheter usage (p=0.04) and absence of antibiotic prophylaxis (p=0.03). At multivariate analysis, the use of CVC and neutropenia were independent bacteremia risk factors. The most frequent etiological agents were: *Staphylococcus epidermidis* and *Pseudomonas aeruginosa*. Comparing groups A and C, the distribution of *Staphylococcus spp.* was different, with *S. epidermidis* being prevalent in hematological patients only. As regards gram-negative organisms, it is of note that no episode of NT-Salmonella bacteremia was observed in group A, unlike group C, where they represent the second leading etiological agents. In group A, 14% of the patients died. Persistent neutropenia (p=0.01) and the presence of relapsed neoplasm (p=0.04) were prognostic indicators of bacteremia.

**Interpretation and Conclusions.** Our findings suggest that bacteremia in patients with hematological malignancies strictly correlates with the intensity and length of neutropenia and CVC usage. Although we observed a low mortality rate, we stress that this clinical condition requires special attention from the physician, who must recognize and treat it promptly.


*Key words: hematological malignancy, risk factors, prognostic indicators*

Patients with hematological malignancies are at increased risk for developing bacteremia.[1-7] The microorganisms responsible for this have changed over the last decade. In fact, while in the eighties there was a prevalence of gram-negative bacteria,[8,9] at present gram-positive microorganisms are the most frequently isolated agents of bacteremia.[2,5,7] Many factors account for this increase, including the widespread use of central venous catheters (CVC) and the application of more aggressive anti-neoplastic regimens that cause more severe and more prolonged neutropenia and oropharyngeal mucositis.[10] A controversial point remains whether this shift has been influenced by the relatively extensive use of prophylactic antibiotics with a spectrum of activity more effective against gram-negative bacteria.[11-13] It is, however, of note that a high frequency of gram-positive infections has also been documented in patients who have not even received antibiotic prophylaxis.

Since few studies in Italy have investigated the risk factors and prognostic indicators of bacteremia in hematological neoplasms using a statistical approach, we conducted a matched case-control study in order to identify the risk factors and variables that influence the prognosis of bacteremia in hematological patients, through univariate and multivariate statistical analysis. In addition, in order to better define the characteristics of bacteremia in hematological patients, we made a comparative analysis with another group of immunocompromized patients (i.e. HIV-infected patients) with bacteremia.

## *Materials and Methods*

A retrospective case-control study was conducted in the Division of Hematology of the Catholic University in Rome, Italy, of all patients with hematological malignancies admitted from January 1, 1990 to December 31, 1995. A diagnosis of bacteremia was based on fever associated with two or more cultures positive for the same micro-organism obtained on differ-

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ent occasions or on the same occasion from different sites. Community-acquired bacteremia was defined as bacteremia developing in a patientwho had not been treated in a hospital nor had lived in an institutional setting for at least 60 days before the onset of symptoms. A recurrence of bacteremia was considered the presence of positive blood cultures for the same microorganism responsible for an earlier episode occurring more than one month after the completion of successful treatment for the original bacteremia. Neutropenia was indicated by a concentration of circulating polymorphonuclear (PMN) cells below $0.5\times10^9$/L.

*Patients*

One hundred and twenty-five episodes of bacteremia were identified in 106 patients with hematological malignancies (group A). Two hundred and twelve patients were included as controls and divided into two groups (B and C). Group B comprized 106 patients matched for underlying hematological malignancy and stage of disease with the members of group A but without bacteremia. These patients were randomly selected from the same hospital ward as group A during the study period. Group C comprised 106 HIV-infected patients with 127 episodes of bacteremia but without hematological malignancies. The patients in this last group had been admitted to the Department of Infectious Diseases of the Catholic University during the study period and were randomly selected.

*Parameters evaluated*

For each patient (cases and controls) the following features were considered: age, sex, bacteremia risk factors, PMN cell count, concurrent opportunistic infections and antibiotic prophylaxis. The risk factors for bacteremia included: antineoplastic chemotherapy, corticosteroid therapy, total days of neutropenia, presence of CVC, medications (sucralfate, antacids, H2 antagonists), mucocutaneous lesions (i.e. mucositis, sinusitis, gingivitis, perianal lesions, cellulitis, gastritis, esophagitis), pneumonia, gastrointestinal and urinary infections. Sources of bacteremia were categorized according the following definitions: 1) pneumonia, gastrointestinal and urinary infections: if the patient showed indicative clinical manifestations and the microorganism isolated from other sites (broncho-alveolar lavage, stools, urine, biopsies, etc.) was the same as that isolated from the blood; 2) CVC-related infection: if the microorganism isolated from the catheter culture was the same as that isolated from the blood.

Antibiotic prophylaxis was performed in neutropenic patients with oral quinolones.

In patients with bacteremia we also analyzed the etiological agents and the clinical outcome of the episode.

*Specimen collection and handling*

For patients with suspected bacteremia, three blood cultures were aseptically collected at no less than hourly intervals. On each occasion a 10 mL blood sample from each patient was inoculated into a BACTEC NR6A vial for aerobic culture and a BACTEC NR7A vial for anaerobic culture (Becton Dickinson, Diagnostic Instrument System, Spark, MA, USA). Detection of bacterial growth was instrument-assisted and predicated on infrared spectroscopic analysis of air in the head space of the blood culture bottles for the presence of evolved $CO_2$. Samples of the contents of all instrument-positive vials were gram-stained and subcultured. Isolates were identified by means of microscope examination as well as biochemical and serological tests.

*Statistical methods*

Quantitative variables were tested for normal distribution and compared by means of Student's two tailed t-test. Differences in group proportions were assessed with the $\chi^2$ test or, for small numbers, Fisher's exact test. Potential risk factors and prognostic indicators for bacteremia were analyzed by univariate methods in order to determine possible inclusion in multivariate models. To facilitate the statistical analysis of the outcome, the fatalities directly or indirectly related to bacteremia were included in a single category when they occurred before the episode of bacteremia was considered resolved. Multivariate analysis was performed with logistic regression models, and 95% test-based confidence intervals (CI) were used to determine the statistical significance of the odds ratio (OR). Two-tailed tests of significance at the $p < 0.05$ level were used to determine statistical significance.

## Results

A total of 125 episodes of bacteremia occurred in 106 patients (58 males and 48 females with a mean age of 45±12.5 years), namely 41 patients (39%) with acute myeloid leukemia, 29 (27%) with non-Hodgkin's lymphoma, 13 (12%) with acute lymphoid leukemia, ten (9%) with Hodgkin's disease and five patients (5%) with multiple myeloma. Eight patients (8%) suffered from other hematological malignancies. Thirteen patients (12%) experienced two episodes of bacteremia and three (3%) three episodes.

The cumulative incidence of bacteremia in total yearly hematological malignancy-related admissions at our ward increased from 3.5% in 1990 to 6.8% in 1995. Sixty-eight (54%) episodes were community acquired, while 57 (46%) were nosocomial. CVC was the presumptive source of bacteremia in 34 episodes (27%), genitourinary infections in 12 (10%), respiratory, gastrointestinal and soft tissue infections in eight (6%), six (5%) and five (4%), respectively. A source of infection was not identified in 60 episodes (48%).

Gram-positive agents were responsible for 77 episodes of bacteremia (62%) and gram-negative for 38 episodes (30%). Ten episodes (8%) were polymicrobial. The most common etiological agents of bacteremia were: *Staphylococcus epidermidis* (36.8%), *Pseudomonas spp.* (9.6%), *Escherichia coli* (9.6%), *Staphylococcus aureus* (4%). *S. epidermidis* was also the most frequently isolated bacterium from patients with polymicrobial bacteremia. *Candida spp.* was isolated in seven episodes in association with various species of bacteria. Table 1 summarizes the detailed data and the comparison of etiological agents in group A (hematological patients with bacteremia), versus group C (patients with HIV infection and bacteremia).

The cumulative incidence of CVC-related bacteremia was 1.9 per 100 catheter days. The interval between the insertion of the CVC and the onset of bacteremia ranged from four to 21 days (mean 12±7.8 days). The etiological agents in CVC-related bacteremia were *S. epidermidis* in 22 episodes (64%), *P. aeruginosa* in five (15%), *S. aureus* in three (9%), and *Corynebacterium jeikium* in one episode (3%). Three episodes were polymicrobial (9%).

Neutropenia occurred in 71 cases. Six patients were neutropenic for less than six days, the remaining 65 patients for more than six days (mean 14±7.7 days, with a range of 7-21).

Univariate analysis identified three risk factors which were significantly associated with bacteremia,

**Table 1. Etiological agents of bacteremia in patients with hematological malignancies (Group A) and HIV infection (Group C).**

| *Etiological agents* | *Group A n=125 (%)* | *Group C n=127 (%)* | *p* A vs C* |
|---|---|---|---|
| Staphylococcus epidermidis | 46 (36) | 14 (11) | <0.01 |
| Pseudomonas spp. | 12 (10) | 10 (8) | NS |
| *P. aeruginosa* | 6 (5) | 8 (6) | NS |
| *P. maltophilia* | 6 (5) | 2 (2) | NS |
| Escherichia coli | 12 (10) | 1 (1) | <0.01 |
| Staphylococcus aureus | 4 (3) | 38 (30) | <0.01 |
| Corynebacterium jeikium | 4 (3) | 4 (3) | NS |
| Streptococcus ß hemolyticus | 4 (3) | 2 (2) | NS |
| Propionibacterium spp.* | 4 (3) | 1 (1) | NS |
| Streptococcus pneumoniae | 3 (2) | 10 (8) | <0.05 |
| Enterobacter faecalis | 3 (2) | – | NS |
| Streptococcus viridans | 3 (2) | – | NS |
| Staphylococcus hominis | 2 (1) | – | NS |
| Staphylococcus hemolyticus | 2 (1) | – | NS |
| Micrococcus | 2 (1) | – | NS |
| NT-Salmonella | – | 19 (15) | <0.01 |
| Klebsiella pneumoniae | – | 9 (7) | <0.05 |
| Acinetobacter spp. | – | 6 (5) | <0.05 |
| Polymicrobial | 14 (11) | 15 (12) | NS |
| Other gram positive | 4 (2) | – | NS |
| Other gram negative | 6 (5) | – | NS |

*n = episodes number; NS = not significant; * = these species were not typed; $\chi^2$ test or Fisher's exact test (for small numbers).*

i.e. neutropenia for more than six days (OR=1.84; 95% CI=1.0-3.3; p = 0.03 vs. group B), absence of previous antibiotic prophylaxis (OR=1.94; 95% CI=1.0-3.6; p=0.03), and CVC usage (OR=2.03; 95% CI=1.2-4.0; p = 0.04) (see Table 2). Analysis of the relationship between the risk factors and the most frequent etiological agents of bacteremia is detailed in Table 3.

Multivariate analysis of bacteremia risk factors revealed that the use of CVC (OR=6.14; 95% CI=1.3-12.3; p = 0.01) and neutropenia for more than six days (OR=3.01; 95% CI=1.7-9.5; p = 0.03) independently predisposed for the development of bacteremia, while none of the other variables or interactions were statistically significant.

All patients received antibiotic therapy which was initially established according to the most likely etiological agent and later modified when the *in vitro* susceptibility of the isolate became known. The response to therapy was favorable in 107 episodes (86%; p=ns vs. group C), while 18 resulted in death (14%; p=ns). Mortality was higher in the episodes of polymicrobial bacteremia (5/10; 50%). Recurrences (most frequently caused by *S. epidermidis*) developed in ten patients (9%) and five of them died (50%).

**Table 2. Univariate analysis of bacteremia risk factors. Hematological patients with bacteremia (group A) compared with those without bacteremia (group B).**

| *Risk factors* | *Group A (n=106)#* | *Group B (n=106)* | *Odds ratio (95% CI)* | *p** |
|---|---|---|---|---|
| Sex (male) | 58 | 68 | 0.67 (0.3-1.2) | NS |
| Mean age (years) | 45±5 | 40±3 | - | NS |
| Absence of prophylaxis | 41 | 26 | 1.94 (1.0-3.6) | 0.03 |
| PMN cell count <0.5x10$^9$/L | 71 | 64 | 1.33 (0.7-2.4) | NS |
| < 6 days | 6 | 15 | 0.36 (0.1-1.0) | NS |
| > 6 days | 65 | 49 | 1.84 (1.0-3.3) | 0.03 |
| Central venous catheter | 34 | 20 | 2.03 (1.2-4.0) | 0.04 |
| Pulmonary infections | 48 | 55 | 0.76 (0.4-4.0) | NS |
| Enteric infections | 13 | 9 | 1.50 (0.5-4.0) | NS |
| Urinary infections | 10 | 7 | 1.47 (0.4-4.5) | NS |
| Mucocutaneous lesions | | | | |
| mucositis | 28 | 35 | 0.72 (0.3-1.3) | NS |
| gengivitis | 12 | 21 | 0.51 (0.2-1.1) | NS |
| perianal lesions | 4 | 2 | 2.03 (0.3-11.0) | NS |
| soft tissue infections | 5 | 2 | 2.57 (0.4-12.8) | NS |
| gastritis | 5 | 6 | 0.85 (0.2-3.1) | NS |
| esophagitis | 3 | 2 | 1.51 (0.2-9.1) | NS |

*# patients were considered at first episode; CI: confidence interval; n= number of patients; NS=not significant; *Quantitative variables: Student's test, differences in group proportion: $\chi^2$ test or Fisher's exact test (for small numbers).*

**Table 3. Analysis of bacteremia risk factors and the most common etiological agents isolated from patients with hematological malignancies.**

| *Etiological agents* | *Neutropenia** | | *Absence of prophylaxis* | | *CVC* | |
|---|---|---|---|---|---|---|
| | *n=71* | *p* | *n=41* | *p* | *n=34* | *p* |
| Gram-positive^ | 48 | NS | 24 | NS | 26 | NS |
| S. epidermidis | 35 | < 0.001 | 18 | NS | 22 | <0.001 |
| Gram-negative^ | 20 | NS | 17 | 0.01 | 5 | NS |
| Pseudomonas spp. | 11 | 0.03 | 7 | NS | 5 | NS° |
| E. coli | 7 | NS | 8 | 0.03 | 0 | ND |

**PMN <0.5x10$^9$/L for more than 6 days; CVC = central venous catheter; n = number of episodes; NS: not significant; ND: not done because of zero value; °p= 0.05; ^considered overall.*

The outcome of bacteremia was influenced by the presence of neutropenia for more than six days (p = 0.01) and by relapsed neoplasms (p = 0.04).

## *Discussion*

This retrospective study, which covers a period of six years (1990-1995), identified 125 episodes of bacteremia in 106 patients with hematological

malignancies. Our findings confirm the prevalence of gram-positive versus gram-negative bacteremia with special emphasis on the prevalence of coagulase-negative *Staphylococci* and the low frequency of *S. aureus* and *Streptococcus β-hemolyticus* bacteremia. At variance with other reports,[14-16] we observed only rare cases of bacteremia due to *Streptococcus viridans*. When hematological patients were compared with another model of immunocompromised subjects (i.e. HIV-infected patients), the rate of gram-positive bacteremia was the same in both groups, while the distribution of *Staphylococcus spp.* was different, *S. epidermidis* being prevalent in hematological patients, only. As regards the gram-negative agents, it is of note that no episode of *NT-Salmonella* bacteremia was observed in hematological patients unlike their HIV-infected counterparts in whom they represent the second leading etiological agents of bacteremia.

At univariate analysis we observed that persistent neutropenia, absence of antibiotic prophylaxis and the use of CVC were significantly associated with an increased risk of bacteremia in hematological neoplastic patients. In particular, neutropenia and CVC usage significantly correlated with the development of *S. epidermidis* bacteremia, while the absence of antibiotic prophylaxis increased the risk for gram-negative bacteremia. Based on the results of multivariate analysis we can affirm that neutropenia for more than six days and CVC usage were independent risk factors for the development of bacteremia. Prospective studies are, however, required to further confirm these associations in hematological patients with bacteremia.

The importance of neutropenia as a contributing factor to the development of bacteremia in hematological patients has been already stressed.[19-21] It is also well known that the frequency and severity of infection inversely correlate with the number of circulating neutrophils.[22] As regards this aspect, in our study a neutrophil count $< 0.5\times10^9$/L which lasted for more than six days was critical for the development of bacteremia.

Our findings indicate through univariate and multivariate analysis that CVC is an important source of bacteremia in a significant percentage of hematological patients, especially gram-positive bacteremia. This is due to the extended use of CVC in the clinical management of the patients with hematological malignancies. In fact, these subjects develop just as great a risk for CVC-related bacteremia, as other immunocompromised patients,[17] probably in relation to the length of time that the CVC stays in place. In particular, our study indicates a statistically significant correlation between the use of CVC and *S. epidermidis* bacteremia. Since *S. epidermidis* is usually found as a non-pathogenic commensal microorganism on the skin and the mucosa, it has been suggested that this microorganism may gain access to the vascular flow between the catheter and a soft tissue infection at the catheter exit site on the skin.[23] Another way in which *S. epidermidis* may penetrate into the organism is through the mucocutaneous lesions caused by various antineoplastic drugs such as cytarabine.[24] Once the microorganism has entered, the prolonged neutropenia with reduction of phagocytosis which usually follows chemotherapy, favors the development and the diffusion of the infection.

Another risk factor significantly associated with bacteremia at univariate analysis is the absence of antibiotic prophylaxis. It is well known that a selective decontamination of the alimentary tract with oral quinolones in neutropenic patients can significantly reduce the risk of gram-negative infections[11-13] without, however, affecting the incidence of gram-positive ones. Our findings confirm that antibiotic prophylaxis is important in preventing gram-negative bacteremia in hematological patients, although the true impact of this therapeutic approach in terms of prevention with respect to another form of prophylaxis could not be exactly quantified due to the retrospective nature of this study.

Our patients showed a low mortality rate compared to that observed in other reports[1-7] and one similar to HIV-infected patients. As expected, hematological patients with persistent neutropenia and relapsed disease had a poorer prognosis for bacteremia. This is probably due to the use of more aggressive salvage treatments in patients whose severe post-chemothreapy myelosuppression has worsened host defenses previously altered by the neoplastic disease.

In conclusion, patients with hematological malignancies show an increased risk for bacteremia that strictly correlates with the intensity and length of neutropenia and CVC usage. Our retrospective study further confirms that the epidemiology of bacteremia in neutropenic patients has recently changed from gram-negative to gram-positive microorganisms, in particular to coagulase-negative Staphylococci. Although we observed a low mortality rate for bacteremia, we stress that this clinical condition requires special attention from the physician, who must recognize and treat it promptly.



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