Staphylococcus aureus bacteremia in patients with hematologic malignancies: a retrospective case-control study

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Background and Objectives. *Staphylococcus aureus* bacteremia (SAB) continues to be a major problem related to both community and nosocomially acquired infection. Nevertheless few data are presently available in literature about this infection in patients with hematologic malignancies.

Design and Methods. The purpose of this retrospective study was to report further data on the clinical characteristics and outcome of patients with SAB. All episodes of SAB occurring between January 1997 and June 2001 were identified and defined by analysis of the patients' clinical records.

Results. The nosocomial mortality rate was only 3.5% and no patient developed secondary complications. Comparison between neutropenic hematologic patients with SAB and neutropenic hematologic patients with Gram-negative bacteremia (GNB) revealed an higher mortality in the latter group (p=0.03); furthermore, severe sepsis and septic shock were more frequent in patients with GNB (p<0.001). Comparison between neutropenic patients with hematologic malignancies and non-neutropenic ones with other underlying diseases revealed significantly higher morbidity and mortality rates in the latter group. Non neutropenic patients seemed to be more susceptible to both early complications, such as severe sepsis or septic shock (p=0.002) and to later ones, such as endocarditis and metastatic abscesses (p=0.02).

Interpretation and Conclusions. Our results seem to suggest that SAB in patients with hematologic malignancies is often a low inoculum infection associated with negligible morbidity and mortality rates, especially when adequate antistaphylococcal therapy is administered promptly.

Key words: *Staphylococcus aureus* bacteremia, hematologic malignancies, inflammatory response.

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Staphylococcus aureus has been found to be the most prevalent cause of skin and soft tissue infections, bloodstream infections, and pneumonia in Europe and most regions of the world.[1] *Staphylococcus aureus* bacteremia (SAB) continues to be a major problem related to both community and nosocomially acquired infection.[2-3] In the hospital setting, both methicillin-resistant *S. aureus* (MRSA) and methicillin-susceptible *S. aureus* (MSSA) are common causes of bacteremia and usually related to invasive infections in patients with various debilitating diseases. In addition, once *S. aureus* invades the bloodstream it has a peculiar propensity to produce metastatic infections such as endocarditis, osteomyelitis, septic arthritis or abscesses in virtually every organ.[4-9]

Over the past three decades many authors have studied the clinical features and outcome of various populations of patients with SAB.[2,4-13] Nevertheless, few studies have focused attention on hematologic patients[14-17] and in particular on those who would appear to be at such a high risk of infection as neutropenic ones.

The purpose of this study was to report further data on the clinical characteristics and outcome of patients with hematologic diseases and SAB and compare these cases with those of SAB in other categories of patients or cases of Gram-negative bacteremia (GNB) in hematologic patients.

Design and Methods

Subjects and setting

The Policlinico Umberto I is a 1500-bed tertiary care facility affiliated to the University La Sapienza of Rome. The hospital has five Departments of Internal Medicine (approximately 300 beds) and a 55-bed hematology unit: the latter is housed separately from the rest of the hospital.

The majority of patients admitted to the hematology unit have acute leukemia, lymphoma, or other hematologic malignancies. They receive inpatient and outpatient care, which is provided by a non-rotating cohort of medical, nursing and paramedical personnel. Patients undergoing induction chemotherapy are placed in single-bedded rooms and given oral prophylaxis: oral quinolones (norfloxacin 400 mg bid or ciprofloxacin 500 mg bid)[18] for adults and oral trimethoprim/cotrimoxazole (150 mg/m^2 of trimethoprim + 750 mg/ m^2 of cotrimoxazole daily in two divided doses)[19] for children,

when their granulocyte counts are less than 1000/mm^3. Bone marrow recipients are placed in single-bedded rooms, and reverse isolation procedures are performed to prevent infection. Surveillance cultures of oropharyngeal and rectal swabs, urine specimens, and stools are performed weekly. A transthoracic echocardiography (TTE) examination is performed on all patients upon their admission to evaluate and monitor cardiotoxicity of cytostatic therapy. If fever and granulocytopenia occur, all patients are thoroughly evaluated for a potential infectious etiology, and empiric systemic antibiotics are started within 4-8 hours. Usual empiric regimens with intravenous antibiotics are the following: ceftriaxone (2 g every 24 hours) + amikacin (20 mg/kg every 24 hours, maximum 1.5 g),[20-22] piperacillin (4 g every 6-8 hours) + amikacin, piperacillin/tazobactam (4.5 g every 8 hours) +/- amikacin;[23-24] in cases of proven or presumed Gram-positive infection unresponsive to initial empiric antibiotics after 72 hours, intravenous teicoplanin (7 to 10 mg/kg every 24 hours) or vancomycin (1 g every 12 hours) are subsequently added.[23-25]

Using the archives of the two Microbiology Laboratories affiliated to the 5 Internal Medicine Departments, 2 Neurology divisions, 1 Dermatology division and to the Hematology unit we identified all cases of *S. aureus* isolation from blood cultures between 1 January 1997 and 30 June 2001. In addition, using the archives of the Microbiology laboratory affiliated to the Hematology unit we identified cases of Gram-negative bacteremia (GNB) during the same period. All these cases were divided into three groups: cases of SAB in patients with hematologic malignancies hospitalized in the Hematology unit, cases of GNB in patients with hematologic malignancies hospitalized in the Hematology unit and cases of SAB in non-neutropenic non-hematologic patients hospitalized in the 5 Departments of Internal Medicine, 2 Neurology divisions and 1 Dermatology division. All cases with one or more positive blood cultures were initially included in this study, but only those meeting SAB or GNB case definition criteria were evaluated in the retrospective analysis. Cases with definite risk conditions for infective endocarditis,[26] were also excluded from the study.

To this end two case-control studies were planned: (i) SAB and GNB cases in neutropenic patients with hematologic malignancies; (ii) SAB cases in neutropenic hematologic patients and SAB cases in non-neutropenic, non-hematologic patients. In both these studies, cases were matched on the basis of the two following criteria: patients of similar age (age difference not exceeding 5± years) and similar date of onset of bacteremia (time interval within a 12 month-period). Data on sex, age, underlying disease, administration of steroids, cytotoxic chemotherapy, presence of an indwelling central venous catheter (CVC), oral prophylactic antibiotics, prior or concomitant therapeutic antibiotics, focus of sepsis, neutropenia, duration of neutropenia, profound neutropenia, persistent profound neutropenia, complications during hospitalization, severity of illness at the onset of bacteremia (assessed by a grading system),[27] severity of underlying disease assessed using Mc Cabe and Jackson criteria,[28] degree of the systemic inflammatory response[29] and outcome were all extracted from the patients' clinical records with the use of a data collection form specifically designed for this study.

Definitions

A patient was considered to have true SAB if: (i) two or more separate positive blood cultures for *S. aureus* were obtained within 24-h, or if (ii) one single positive blood culture was obtained in association with clinical evidence of infection (fever, leukocytosis, and localizing signs and symptoms).[2,5] A patient was considered to have GNB when signs or symptoms of systemic infection were observed concurrently with bacteremia, or when an organism was isolated from blood and also from a clinically evident local infection. Bacteremia was considered to be community-acquired if the first positive blood culture specimen was obtained within the first 72 h of admission or if there was clinical and culture evidence of bacterial infection at the time of admission. Bacteremia was considered to be nosocomial if the first positive blood culture specimen was obtained ≥ 72 h after admission and there was no clinical evidence of infection on admission. A localized focus of staphylococcal infection was considered to be the source of SAB if signs and symptoms of infection preceded the bacteremia. SAB or GNB were considered to be related to the intravascular catheter if there was inflammation at the site of catheter insertion, purulent drainage — positive on culture — from the insertion site, or a semiquantitative culture of the catheter tip without another identified source of infection. SAB or GNB were categorized as mucocutaneous-tissue related if the patient had a mucocutaneous culture positive for the abovementioned bacteria or clinical evidence of mucocutaneous tissue infection without another identified source of infection. Pneumonia was considered the source of bacteremia if a new or progressive infiltrate was noted on a chest radiograph within 24 hours of the first positive blood culture result, if bacteria were cultured from sputum on the same day or within 3 days before the blood culture positivity and there was no other source of infection. SAB or GNB were categorized as having unknown focus if physical examination, radiological studies, cultures and surgical exploration did not reveal a portal of entry.

A patient was considered neutropenic if the total granulocyte count was <1000/mm^3, severely neutropenic if the total granulocyte count was <100/mm^3, and as having persistent profound neutropenia when, in those episodes of bacteremia in which the granulocyte count was < 100/mm,^{3} the count did not return to a level >500/mm^3 after 2 weeks. The duration of neutropenia was calculated from the time when the granulocyte count decreased to 1000/mm^3 until it returned to a level >1000/mm^3. Severity of illness was assessed by a grading system (Illness score) that evaluated mental status (disoriented, 1; stupor, 2; coma, 4 points), fever (≥ 37.6°C and < 40°C, 1; ≥ 40°C, 2 points), hypotension (drop in systolic pressure > 20 mmHg or diastolic pressure > 10 mmHg or administration of intravenous pressor agents, 2 points), mechanical ventilation, 2 points and cardiac arrest, 4 points.[27] Severity of illness was graded on the basis of clinical data available at the time positive blood cultures were obtained. Severe sepsis was defined as sepsis associated with organ dysfunction, hypoperfusion, or hypotension.[28] Septic shock was defined as sepsis associated with hypotension, despite adequate fluid resuscitation, along with the presence of perfusion abnormalities as listed for severe sepsis.[29] A metastatic infection was defined as infective endocarditis (IE) or an infection at a distant site in a patient with another known portal. IE was defined using the Duke criteria.[30-31] Polymicrobial bacteremia was defined as the isolation of more than one organism from a single blood culture. Breakthrough bacteremia was defined as an episode of bacteremia occurring at least 48 hours after the start of systemic antibiotic therapy. For each episode, the duration of bacteremia was defined as the number of consecutive days with at least one positive blood culture. Empiric antibiotic treatment was defined as therapy administered for at least 48 hours prior to the availability of the results of *in vitro* susceptibility results. Antimicrobial treatment was defined adequate if the organism was susceptible to ≥ 1 antibiotics prescribed for each case.

Microbiological studies

All clinical isolates were identified according to standard methods;[32] in particular identification of Gram-positive cocci as *S. aureus* was obtained by growth in mannitol-salt agar and by the coagulase test and confirmed by a semiautomatic method (Sceptor, Becton-Dickinson, Milan-Italy). Susceptibility to oxacillin and other antibiotics was tested by both the agar diffusion (Kirby-Bauer) and microdiluition methods, according to NCCLS criteria.[33]

Outcome

The following outcomes were considered: cure (resolution of clinical signs of infection during therapy with negative blood cultures and no complications), relapse (recurrent bacteremia during hospitalization with at least one week or two weeks follow-up observation after antibiotic discontinuance), attributable mortality (bacteremia-related deaths because of clinical evidence of infection at the time of death without an alternative cause of death, or autopsy evidence of tissue infection) and overall mortality (bacteremia-related deaths plus deaths due to underlying disease or another cause without evidence of infection at the time of death and no positive blood cultures during the week preceding death).

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 χ^2 test. Fisher's exact test was used when a cell value was expected to be less than 5.

Results

SAB in patients with hematologic malignancies

From January 1997 to June 2001 we identified 168 cases of *S. aureus* out of 1944 blood culture isolates from patients with hematologic malignancies (8.6%). The annual frequency of *S. aureus* blood isolation remained constant during the period of the study. After a preliminary analysis, 83 cases were excluded from the study because of polymicrobial bacteremia (n=10), death occurring before positive blood culture results were known (n=5), patients' discharge before positive blood culture results for *S. aureus* were known (n=9), or criteria defining true SAB not met (n=59).

The remaining 85 patients were included in the retrospective analysis (Table 1). At the onset of SAB the median illness score was 1.4 (range 0 to 8) and most patients were febrile (90.5%), neutropenic (67%), under cytotoxic (70.5%) and/or steroid (80%) treatment, and had a CVC in place (60%). Twenty-six (30.5%) of these 85 patients remained profoundly and persistently neutropenic during the SAB episode. All patients underwent a transthoracic echocardiography at admission and no high risk conditions for infective endocarditis[26] were documented. According to our definition, SAB was nosocomially acquired in 66 cases (77.6%) with a mean duration of hospitalization prior to SAB of 15.3 days (range 0-100). The offending *S. aureus* was found to be methicillin-resistant in 22 cases (25.8%). Quinolones or co-trimoxazole prophylax-

Table 1. Demographic data, response and outcome of hematologic patients with *Staphylococcus aureus* bacteremia.

Number of patients	85
Median age (range)	42.3 (7-76)
Male sex	51 (60%)
Underlying disease	
Acute myeloid leukemia	36
Non-Hodgkin's lymphoma	15
Multiple myeloma	12
Acute lymphoid leukemia	9
Chronic myeloid leukemia	8
Other hematologic malignancies	5
Severe sepsis or septic shock	3 (3.5%)
Mean days to adequate treatment	1.55 (0-9)
Duration of fever (days)	4.02 (0-24)
Duration of bacteremia (days)	1.63 (1-6)
Metastatic infections	0
Breakthrough bacteremia	11 (12.9%)
Relapse rate	8 (9.4%)
Duration of antibiotic therapy (days)	10 (1-22)
Overall mortality	11 (12.9%)
Attributable mortality	3 (3.5%)

Table 2. Comparison between neutropenic hematologic patients with SAB and GNB.

	S.aureus	*Gram-negative bacilli*	*p value*
Number of patients	57	57	
Profound-persistent neutropenia	26 (45.6%)	39 (68.4%)	0.01
Illness score (median)	1.46 (0-5)	3.45 (1-11)	<0.001
Severe sepsis or septic shock	3 (5.2%)	27 (47.3%)	<0.001
Unidentifiable primary focus	41 (71.9%)	31 (54.3%)	0.052
Mean days to adequate treatment	1.83 (0-8)	0.56 (0-4)	<0.01
Duration of fever (days)	5.5 (0-22)	5.08 (0-20)	
Duration of bacteremia (days)	1.62 (1-6)	1.66 (1-6)	
Metastatic infections	0	0	
Breakthrough bacteremia	9 (15.7%)	9 (15.7%)	
Relapse rate	4 (7%)	2 (3.5%)	
Duration of antibiotic therapy (days)	10.2 (1-22)	10.5 (3-36)	
Overall mortality	7 (12.2%)	14 (24.5%)	0.09
Attributable mortality	3 (5.2%)	10 (17.5%)	0.03

is was given to 48 patients (56%). SAB was related to intravascular devices in 7 cases (8.2%) and to mucocutaneous tissue infection in 10 cases (17.8%). In the remaining 68 cases (80%) no identifiable primary site of infection was found. All patients were initially treated with the following empiric antibiotics: ceftriaxone+ amikacin in 86% of cases, piperacillin+/- tazobactam+amikacin in 10.3% or ceftriaxone in 3.7% of cases. A glycopeptide (usually teicoplanin) was subsequently added in 63% of cases.

No patient developed metastatic infections. The rate of SAB relapse was 8.9% (8 cases). The overall mortality rate was 12.9% (11 patients), SAB-related mortality was 3.5% (3 patients, all presenting with severe sepsis or septic shock). Response and outcome are summarized in Table 1.

Case-control study between hematologic neutropenic patients with SAB and hematologic neutropenic patients with GNB

During the study period 57 neutropenic hematologic patients with SAB could be compared with 57 neutropenic hematologic patients who developed GNB in the case control analysis. The agents causing the Gram-negative bacteremia were: *Escherichia coli* (n=34, 59.6%), *Klebsiella spp.* (n=8, 14%), *Enterobacter spp.* (n=7, 12.2%), *Pseudomonas aeruginosa* (n=6, 10.5%), *Stenotrophomonas maltophilia* (n=1, 1.7%), and *Serratia marcescens* (n=1, 1.7%). No statistically significant differences were found between the study groups concerning median age, male sex, nosocomial acquisition, mean duration of hospitalization prior to bacteremia, presence of fever, administration of steroids, cytotoxic treatment, or presence of CVC. The underlying hematologic malignancies were also similarly distributed between study groups with the exception of multiple myeloma that was significantly more represented in patients with SAB (10 vs 2, p=0.01). As shown in Table 2 profound-persistent neutropenia (p=0.01) was more commonly encountered in GNB patients than in SAB ones. Despite SAB patients having received adequate antibiotic treatment later than patients with GNB (p< 0.01) no major differences were found in the study groups regarding mean duration of fever, mean duration of bacteremia, mean duration of antibiotic therapy or relapse rate. Three patients (5.2%) with SAB developed severe sepsis or septic shock as a complication caused by bacteremia, whereas twenty-seven (47.3%) with GNB did so (p< 0.001).

The identifiable focus of SAB was an intravascular device in 6 cases (10.5%) and a mucocutaneous infection in 10 cases (17.5%); in the remaining 41 cases (71.9%) the primary focus of bacteremia remained unknown. The primary foci of GNB were:

Table 3. Case-control study between neutropenic, hematologic patients and non-neutropenic non-hematologic patients with SAB.

	Neutropenic pts	*Non-neutropenic pts*	*p value*
Number of patients	36	36	
Mucositis	14 (38.8%)	0	<0.001
Mean illness score	1.28 (0-9)	2.8 (1-12)	<0.001
Severe sepsis or septic shock	1	10(27.7%)	0.002
Mean days of hospitalization*	27.2 (4-59)	44.5 (6-103)	0.004
Days to adequate treatment	1.18 (0-4)	1.96 (0-7)	0.02
Duration of fever	4.1 (1-14)	6.3 (0-31)	0.052
Duration of antibiotic therapy	9.3 (3-22)	19.6 (3-63)	0.009
Duration of bacteremia	1.33 (1-6	1.95 (1-7)	0.03
Relapse rate	4 (11.1%)	2 (5.5%)	
Metastatic infections	0	5 (13.8%)	0.02
Overall mortality	4 (11.1%)	13 (36.1%)	0.01
Attributable mortality	1 (2.7%)	9 (25%)	0.006

**Excluding patients who died during hospitalization.*

mucocutaneous (16 episodes, 7%), pneumonia (4 episodes, 7%), urinary tract (5 episodes, 8.7%), and an intravascular device (1 episode, 1.7%); no identifiable primary site of infection was found in the remaining 31 (54.3%) episodes. Patients with GNB had a significantly higher mortality rate attributable to the bacteremia (p=0.03) and more prolonged hospitalization (p=0.01) than did SAB patients.

The same significant differences were confirmed from analyzing the subgroups of patients with profound-persistent neutropenia (*data not shown*).

Case-control study between hematologic neutropenic patients and non-neutropenic non-hematologic patients with SAB

During the period of study we identified 80 cases of *S. aureus* isolation from blood cultures in patients hospitalized in the 5 Departments of Internal Medicine, 2 Neurology divisions and 1 Dermatology division. Out of these, 56 episodes met case definition criteria for SAB and were included in the further analysis. Eventually, 36 SAB episodes in non-hematologic, non-neutropenic patients were considered for the case control analysis with 36 SAB episodes in hematologic, neutropenic ones as required by the protocol of the study. The majority of the non-neutropenic patients had more than one of the following underlying diseases: hypertension (36.1%), diabetes (25%), cirrhosis (25%), malignancy (25%), chronic renal failure (16.6%), ischemic heart disease (16.6%), collagen disease (8.3%), chronic obstructive pulmonary disease (8.3%).

No significant differences regarding median age (55.2 vs 51.2), male sex, nosocomial acquisition (83.3% vs 77.7%), methicillin-resistance (33.3% vs 30.5%), presence of an intravascular device (72.2% vs 55.5%), risk conditions for endocarditis, or mean duration of hospitalization prior to SAB (15.9 vs 16.2 days) were detected in the two groups. In contrast, as shown in Table 3, non-neutropenic patients had a higher illness score at the onset of SAB (p< 0.001), more frequent presentation with severe sepsis or septic shock (p= 0.002), more prolonged duration of bacteremia (p= 0.03), antibiotic therapy (p= 0.009), and hospitalization (p= 0.004). Non-neutropenic patients developed metastatic infections of their SAB (3 IE, 1 osteomyelitis and 1 distant abscess) whereas no patient among the neutropenic ones did (p= 0.02). Overall mortality and attributable mortality rates were both significantly higher among non-neutropenic patients (p= 0.01 and p= 0.006, respectively).

Since earlier institution of adequate antistaphylococcal therapy in neutropenic patients as compared to in non-neutropenic ones (p= 0.02) may have affected the abovementioned differences in morbidity and mortality, we also analyzed subgroups of patients who initiated *in vitro* active antibiotic therapy on the same day from the clinical onset of SAB. As listed in Table 4, 22 neutropenic patients could be matched with 22 non-neutropenic ones who received adequate antibiotics on the same day from the clinical onset of SAB (range 0-3 days): severe sepsis or septic shock were significantly more frequent in the latter group. Analogously, the duration of bacteremia was significantly more prolonged in non-neutropenic patients than in neutropenic ones.

Discussion

This retrospective evaluation of a large group of hematologic patients with SAB resulted in several provocative findings. The attributable mortality rate of the series of patients with SAB (3.5%) was surprisingly good and no patient developed secondary complications. These findings are in contrast with some previous studies evaluating SAB that found higher related morbidity-mortality rates.[15-17] Several factors may explain this discrepancy. Firstly, previous studies examined series of patients who had been hospitalized more than 10 years ago. Thus the low mortality observed in the present study may be explained by improvements achieved during the last two decades in antistaphylococcal therapy and in supportive care of patients with hematologic malignancies.[34-35] In corroboration of this hypothesis, Skov *et al.*,[16] in a ret-

Table 4. Analysis of subgroups of patients who initiated *in vitro* active antibiotics on the same day from clinical onset of SAB.

	Neutropenic	*Non-neutropenic*	*p value*
Number of patients	22	22	
Median age	49.0 (24-75)	52.3 (24-72)	
Male sex	15 (68.1%)	10 (45.4%)	
Mean hospitalization prior SAB	14.6 (0-50)	16.1 (0-72)	
Mean duration of hospitalization*	26.1 (8-59)	42.2 (11-103)	0.02
MRSA	9 (40.9%)	4 (18.1%)	
Mucositis	7 (31.8%)	0	0.004
Illness score	1.4 (0-5)	2.4 (1-10)	0.051
Severe sepsis or septic shock	0	6 (27.2%)	0.01
Days to adequate therapy (range)	(0-3)	(0-3)	
Duration of fever	4.5 (1-10)	6.0 (1-15)	
Duration of bacteremia	1.2 (1-3)	2.2 (1-8)	0.04
Duration of antibiotic therapy	9.3 (3-20)	20.4 (7-60)	0.003
Metastatic infections	0	4 (18.1%)	0.05
Relapse rate	3 (13.6%)	3 (13.6%)	
Overall mortality	3 (13.6)	8 (36.3%)	0.08
Attributable mortality	1 (4.5%)	5 (22.7%)	0.08

**Excluding patients who died during hospitalization.*

rospective study, observed a decreasing mortality rate from 53% during the period 1977-1984 to 37% in the period 1984 to 1990. It is possible that an analysis of the annual mortality rates might have provided similar findings also in other studies.[15,17] On the other hand, our findings agree with those of a previous study of Sotman and co-workers[14] evaluating SAB in patients with acute leukemia: not only were endocarditis and secondary foci of staphylococcal infection not seen but the SAB-related mortality rate was also judged to be surprisingly low (17%). Along the same line, it is probable that most of our patients did not show any clinical evidence of the source of their SAB because of their inability to mount an adequate inflammatory response during neutropenia. The similar profile, clinical presentation and inpatient care of the patients probably explain the concordance between our study and that of Sotman *et al.*[14] As expected, comparison between patients with SAB and GNB revealed a higher mortality rate in the latter group (p=0.004). Severe sepsis and septic shock were associated with a poor prognosis. In fact 14 of 37 GNB patients (38%) who developed these early complications died as a direct result of their infection whereas 6 out of 48 (12.5%) who did not develop these complications did so (p= 0.006). Analogously, the majority of SAB patients (9 in the non-neutropenic group and 1 in the neutropenic group) who developed severe sepsis or septic shock eventually died. In the presence of septic shock microbially-derived mediators and other cell wall components initiate an uncontrolled network of host-derived pro-inflammatory mediators, which ultimately lead to cardiovascular failure and death.[36-37] In Gram-negative sepsis, endotoxins (LPS) play a key role in the pathogenesis of septic shock; LPS act directly on endothelial cells[38-39] and the levels of endotoxemia correlate with more extreme physiologic variables.[40] In contrast, although cell wall components, such as lipoteichoic acid (LTA) and peptidoglycan (PepG),[41] seem to be involved in the inflammatory response to Gram-positive sepsis, they are not able to determine systemic effects.[42] Gram-positive organisms, in fact, require a highly orchestrated host response, with intracellular killing by neutrophils and macrophages.[43] Thus, in the cases of SAB, the inflammatory response may be negatively influenced by neutropenia. Moreover, *in vitro* experiments show that prolonged survival of *S. aureus* inside neutrophils may be a mechanism by which this microrganism persists in certain infections.[44] In this context it is suggestive to observe that both in our study and in that by Sotman *et al.*[14] the majoriy of patients who had no increase in granulocyte count nevertheless had a resolution of their *S. aureus* infection. Thus, the host-pathogen relationship in the presence of SAB seems to be paradoxically more favorable to the neutropenic host in relation to this latter's inability to induce a highly regulated inflammatory response. This hypothesis is corroborated in the present study by the higher morbidity and mortality rates from SAB observed in non-neutropenic patients than in neutropenic ones. Non-neutropenic patients not only seemed to be more susceptible to early complications (such as severe sepsis or septic shock) but also to later ones such as endocarditis and metastatic abscesses (p=0.02). Previous studies also showed very low rates of endocarditis in SAB patients with hematologic malignancies, with rates ranging from 0 to 0.5%.[14-17]

Several factors may explain these observations. Many patients had thrombocytopenia at the time of bacteremia. This may prevent the formation of vegetations which are necessary for bacterial growth and for protecting the organism from host defences and antibiotics. However it is also possible that, in instances of neutropenia, even few *S. aureus* cells are able to gain access to the bloodstream through altered mucosal and skin barriers. Under these circumstances of *altered bacterial clearance* it is possible that blood cultures readily demonstrate even cases of very *low inoculum* staphylococcal bacteremia. Indead, as shown in Table 2, our febrile neutropenic patients received *in vitro* active antibi-

otics significantly earlier than did non-neutropenic ones (p=0.02), a fact that may have prevented metastatic complications of their SAB.[9-10] However it was remarkable to observe that the duration of bacteremia, the duration of hospitalization, the duration of antibiotic therapy and the presentation with severe sepsis or septic shock remained significantly associated with SAB episodes in the non-neutropenic patients even when the analysis was conducted only on the subgroups of patients who received adequate antistaphylococcal therapy on the same day from the clinical onset of SAB.

This study has several limitations. First, the study was retrospective, a design which can make identification of the source of SAB difficult at times. Second, echocardiography was performed only in a few cases within 5-7 days of diagnosis of SAB. Transesophageal echocardiography is recommended because it can detect a significant number of cases of IE not identified by clinical examination or transthoracic echocardiography.[45-48] Therefore, it is possible that the rate of endocarditis was underestimated in this study. However, it should also be underlined that all cases of bacteremia are regularly and carefully surveilled in our Hematologic unit. All patients receive inpatient and outpatient care provided by a non-rotating cohort of medical, nursing, and paramedical personnel. Thus most cases of fever acquired after discharge are thoroughly evaluated in the day-hospital facility of our department or at home.[49-50] Thus, it can be assumed that only very few cases of endocarditis, if any, went undiagnosed in this study.

In conclusion SAB in hospitalized patients with hematologic malignancies, particularly during neutropenia, seems to be a low inoculum bloodstream infection associated with negligible morbidity and mortality expecially if adequate antistaphylococcal therapy is promptly administered. Further studies with prospective analysis of larger populations of patients are needed to clarify the clinical significance of SAB in patients with hematologic malignancies.

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Pre-publication Report & Outcomes of Peer Review

Contributions

MV conceived and designed the study and participated in writing the manuscript; MF, FT and PC collected all data from patients' clinical records. MF also participated in writing the manuscript. AM participated in the analysis and interpretation of data. PS and PM monitored the work and critically revised the final version of the manuscript. All authors approved the final, submitted version.

Disclosures

Conflict of interest: none.

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Manuscript processing

This manuscript was peer-reviewed by two external referees and by Professor Mario Cazzola, Editor-in-Chief. The final decision to accept this paper for publication was taken jointly by Professor Cazzola and the Editors. Manuscript received April 18, 2003; accepted June 26, 2003.

In the following paragraphs, Professor Cazzola summarizes the peer-review process and its outcomes.

What is already known on this topic

Staphylococcus aureus bacteremia continues to be a major problem related to both community and nosocomially acquired infection.

What this study adds

In patients with hematologic malignancies *Staphylococcus aureus* bacteremia is often a low inoculum infection associated with negligible morbidity and mortality rates.