Staphylococcus aureus septicemia in non-neutropenic adult patients hospitalized in internal medicine units

Gallucci F[1], Amato G[2], Esposito P[1], Belli CMC[2], Russo R[1], Uomo G[1]*

[1] Department of Internal Medicine, Cardarelli Hospital, Napoli, Italy
[2] Department of Clinical Pathology, Cardarelli Hospital, Napoli, Italy

Abstract

Purpose: ***Staphylococcus aureus*** **septicemia (*SAS*) is usually described in immunocompromised patients and during serious weakening diseases, associated with a neutropenic condition. Over the last recent years, clinic relevance of *SAS* has become more prominent owing to the progressive rise of methicillin-resistent strains in hospital-acquired infections and to its development in non-neutropenic patients.**

Material and methods: **The aim of our study was to evaluate the clinical features and outcome of non-neutropenic patients with positive blood culture for *Staphylococcus aureus* (*SA*) hospitalized in Internal Medicine Wards of our hospital during 1 year of observation. 24 patients with those characteristics were retrospectively recruited; five of them were then excluded from the analysis because of concomitant oncohematologic disease. The median age of the study group of patients (19 cases) was 56 years (range 18-87); 10 (52.6%) patients were male.**

Results: **Infection was hospital-acquired in 10 patients (52.6%). Predisposing factors were: central venous catheter (CVC) (47.4%), recent surgical intervention (21.0%), drug-addiction (15.8%). Main comorbidities were diabetes mellitus in 10 patients (52.6%), heart disease in 4 (21.0%), chronic renal failure in 3 (15.8%), cerebral vascular disease in 3 (15.8%). Fever >38°C was found in all patients at the moment of *SA* isolation in blood culture. *SA* isolated-strains were methicillin-resistant in 7 patients (36.8%). Complications of bacteremia were: pneumonia in 4, endocarditis in 3, vertebral osteomyelytis in 2, septic splenic embolization in 1 and endophtalmitis in 1 patient. The septicemia-attributable mortality was 36.8% (7 patients).**

Conclusions: ***SAS*** **in non-neutropenic patients observed in Internal Medicine Units are associated with significant morbidity and mortality, closer to that reported for neutropenic illnesses.**

Key words: *Staphylococcus aureus*, sepsis, nosocomial infections.

* CORRESPONDING AUTHOR:
Internal Medicine Department, Cardarelli Hospital
via Cardarelli 9, 80131 Napoli, Italy
Tel: +39 81 7472101; Fax: +39 81 7474042
e-mail: generoso.uomo@ospedalecardarelli.it (Generoso Uomo)

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Introduction

Staphylococcus aureus (*SA*) is one of the most common etiological agents of both endemic and epidemic infection acquired in hospitals and in community. Sustained morbidity and mortality are associated with *SA* infections. In fact, when this microorganism enters the blood, it represents one of the most lethal human pathogens also because it is often characterized by multidrug resistance [1]. Humans are a natural reservoir of *SA* that colonizes the nares, axillae, vagina, pharynx or damaged skin surfaces. Rates of staphylococcal colonization are high among patients with type 1 diabetes, intravenous drug users, patients undergoing hemodialysis, surgical patients and patients with the acquired immunodeficiency syndrome [2].

Infections are initiated when a breach of the skin or mucosal barrier allows staphylococci access to adjoining tissues or the bloodstream. Whether an infection is contained or spreads, it depends on a complex interplay between *SA* virulence determinants and host defense mechanism. Patients with qualitative or quantitative defects in leukocyte function are also at increased risk for staphylococcal disease. The risk of infection is increased by the presence of foreign material (devices and intravenous catheters) by means of several pathogenic factors. Staphylococcal bacteremia may be complicated by endocarditis, metastatic infection, or the sepsis syndrome [3-6].

Over the past last years, the frequency of *SA* bacteremia has increased dramatically. This increasing frequency, also in non-neutropenic patients, coupled with rising rate of antibiotic

resistance, has renewed interest in this serious, common infection [7].

The aim of our study was to evaluate the clinical and microbiological characteristic of *Staphylococcus aureus* septicemia (*SAS*) by means of an investigation in non-neutropenic patients hospitalized in the Internal Medicine wards of a regional referral hospital.

Patients and methods

We performed a retrospective study of all *SAS* in non–neutropenic patients, consecutively hospitalized into the five Internal Medicine wards of Cardarelli Hospital, Naples, Italy, a regional referral hospital with a total of 1100 beds. During the study period (January – December 2003) all patients with positive blood culture (confirmed in two samples) for *SA* were enrolled. We excluded patients less than 18 years old, those who had polymicrobic infection, those with a number of neutrophil cells $<2000/mm^3$ at the hospital admission and/or at blood cultural isolation and those who were affected by oncohematologic disease. Significant data derived from the patients' charts togheter with computer-assisted analysis of all microbiological 2003 data-base of our institution. A specific form elaborated for this study was utilized.

We evaluated the following data for each patient: age and sex, place of infection acquisition (community or hospital), predisposing factors (such as devices or intravenous catheters, pre-existent diseases), fever, white blood cells number at hospital admission and at the time of blood cultural isolation, site of infection, complications, antibiotic therapy and antibiotic resistance of isolated streams, duration of hospital stay, relapses and final outcome.

SAS was ascertained in case of positive blood culture (no less than two) in presence of signs and symptoms of septicemia. Borrowing the criteria of pneumonia classification [8], *SAS* was considered "community-acquired", if the first positive blood culture was found before 48 hours from hospital admission; it was classified "hospital-acquired" when the first positive blood culture was after 48 hours from the hospital admission and no clinical evidence of infection was present at admission.

Predisposing factors were considered all known conditions able to help *SA* to access to the bloodstream and to develop (central venous catheter – CVC, recent surgical intervention, drug-addiction). Metastatic infections and relapses were considered as *SAS* complications.

Recovery was considered the diseapparance of infection clinical signs during antibiotic therapy with negative blood cultures and without complications; relapses were defined the *SAS* recurrences during hospital stay with at least a week of delay after the end of antibiotic treatment. *SAS*-attributable mortality was considered the persistence of infection at the death time without other fortuituos causes of death. *SAS* non-attributable mortality was related to a pre-existent illness or to other causes without clinical evidence of infection at death time and without positive blood culture during the last week before death.

Table 1. **Main clinical characteristics of the study-group of patients**

Patients	19		
Age	56 years (range 18-87)		
Sex	9 F, 10 M	N°	%
Infection acquisition site	nosocomial	10	52.6
	community	6	31.6
	non evaluable	3	15.8
Predisposing factors	Central venous catheter	9	47.4
	Recent surgical intervention	4	21.0
	Toxicomania	3	15.8
	None	4	21.0
Comorbidities	Diabetes mellitus	10	52.6
	Heart disease	4	21.0
	Chronic renal failure	3	15.8
	Cerebral vascular disease	3	15.8
	None	2	10.5
Secondary complications	Pneumonia	4	21.0
	Endocarditis	3	15.7
	Vertebral osteomyelitis	2	10.5
	Septic splenic embolization	1	5.2
	Endophtalmitis	1	5.2
Methicillin resistance		7	36.8
Septicemia attributable mortality		7	36.8

Results

Twenty-four patients with above-mentioned inclusion criteria were enrolled; five of them were excluded from the final analysis either because of oncohematologic disease or because of incompleteness of chart's data. Nine patients were female (47.0%); 10 (53.0%) patients were male; the median age was 56 years (range 18-87) (*Tab. 1*). Predisposing factors were CVC in 9 pts (47.4%), recent surgical intervention in 4 (21.0%), drug-addiction in 3 (15.8%); in 4 cases (21.0%) there was no predisposing factor. The most frequent pre-existent illness were: diabetes in 10 patients (52.6), heart chronic disease in 4 (21.0%), chronic renal failure in 3 (15.8%), cerebral vascular disease in 3 (15.8%). No pre-existent disease was in 2 patients (10.5%).

The median value of neutrophil cells was $11600/mm^3$ (range 5100-27900). Fever (T>38°C) was observed in all patients at positive blood culture time. In 6 of them (31.5%), fever was already existent some days before hospital admission and the patients had already been treated with antibiotics at home.

Infection was hospital-acquired in 52.6% of cases (10 patients), appearing on average 5.7 days after hospital admission (five of them showed infection during treatment with cephalosporins). *SA* strains resulted methicillin-resistant in 36.8% (7 patients).

Relevant complications were pneumonia in 4 patients (21.0%), endocarditis in 3 (15.7%), vertebral osteomyelitis in 2 (10.5%), septic splenic embolization in 1 case (5.2%), endophtalmitis in 1 patient (5.2%). Patients who recovered from *SAS* had not relapses; the median of their hospital stay was 24.6 days (range 10-56). The septicemia attributable mortality was 36.8%

Table 2. **Antibiotic *in vitro* susceptibility in the 19 *SA* strains isolated**

Tetracycline	17 (89%)	Rifampicin	17 (89%)	Methicillin	11 (60%)
Teicoplanin	18 (95%)	Amikacin	16 (84%)	Azitromycin	10 (53%)
Cotrimoxazol	18 (95%)	Ofloxacin	12 (63%)	Clindamycin	9 (47%)
Vancomycin	18 (95%)	Imipenem	11 (58%)	Erythromycin	9 (47%)

(7 patients), occurred on average 20.6 days after hospitalization (range 4-31). *Tab. 2* shows the in vitro susceptibility of the 19 *SA* strains isolated.

Discussion

SAS are rather frequent both in community and in hospital [9]. According to the National Nosocomial Infection Surveillance System of the Centers for Disease Control and Prevention of Atlanta (CDC), 16 percent of hospital-acquired cases of bacteremia in the USA from 1990 to 1995 were due to *SA*, that represents the second most common agent after coagulase-negative staphylococci [1]. In fact, within USA's 5400 acute care hospitals, the three leading causes of nosocomial infections of the bloodstream are coagulase-negative staphylococci (80% of which involve strains resistant to methicillin), *SA* (30% methicillin-resistant) and the enterococci (20% vancomicin-resistant). The rough mortality rate associated with these infections are 21%, 25% and 32%, respectively [10].

Multidrug resistant strains of *SA* have been reported with increasing frequency worldwide, including isolates that are resistant to methicillin, lincosamides, macrolides, aminoglycosides, fluorquinolones or combinations of these antibiotics [2]. The emergence of *SA* strains with intermediate resistance to glycopeptides has aroused concern about the development of strains resistant to all available antibiotics. The CDC estimates that 34% of *SA* isolates from cases of nosocomial bacteremia in USA hospitals in 1995 were resistant to methicillin [11]. Infections with methicillin-resistant *SA* are more likely to originate in patients who are seriously ill, immunocompromised and in intensive care units, than are infections with methicillin-susceptible isolates. Colonized patients are the chief source of *SA* in hospitals (nasal carriage) also in intensive care units where isolation of methicillin-susceptible and methicillin-resistant strains are both frequent.

Because there is an increased use of antimicrobial agents in areas where isolates of methicillin-resistant *SA* are found, and because these isolates are resistant to multiple antimicrobial agents and not exclusively to beta-lactams, selective pressure may promote colonization with methicillin-resistant *SA* to a greater degree than colonization with methicillin-susceptible isolates [12]. Patients may already be colonized with *SA* when they enter the hospital. The rising incidence of "community-acquired" infections with *SA* suggest that the rate of colonization with methicillin-resistant *SA* among outpatients is increasing, particulary among those who live in extended-care facilities or have recently been discharged from hospitals. Patients may be colonized with methicillin-resistant *SA* at sites other than the nose, particulary chronic wounds and dermatitides. It is difficult to eradicate *SA* from these sites, and thay can be sources of reinfection. Report of von Eiff and co-workers [13] documented that in most cases, the infecting *SA* isolates from the blood came from the patients themselves, who carried the bacteria in their anterior nares. In addition, nasal carriage has been associated with an increased risk of patients after surgery, in patients receiving continuous ambulatory peritoneal dialysis and in patients receiving hemodialysis.

Although the contribution of resistance to the outcome of such infections is unclear, nosocomial infections of the bloodstream may represent the eighth leading cause of death in the United States, and the relentless rise of antibiotic resistance has markedly curtailed options for therapy [14].

The prevention of hospital-acquired infections due to *SA* is a major goal of hospital infection-control practitioners. Such prevention requires an understanding of the source of the organisms that may eventually find their way into the blood.

Some additional epidemiological considerations arise from our experience. As concerns predisposing factors, it seems appropriate to underline the role of minor surgical interventions in the days before infection onset, particularly in patients with comorbidities. Two patients with diabetes mellitus died a few days after simple toilet of foot cutaneous ulceration; another patient died after displacement of Kirschner's wires in ambulatory. Diabetes mellitus was the most representative comorbidity in our patients. Very high susceptibility to *SAS* in patients suffering from liver cirrhosis is reported [15]. By contrast, no cirrhotic patients were included in our group of patients; this may be very likely related to the occurrence of neutropenia in these patients (neutropenia was considered an exclusion criterion in our study design). We also noted the absence of predisposing factors in a high percentage of cases.

Several studies demonstrated a contribution of methicillin resistance to morbidity and mortality associated with bacteremia caused by *SA* [16-18]. In our group of patients, this was not verified: methicillin resistance, found in 36.8% of isolated *SA* strains was not associated with deleterious clinical outcome. The results of Harbarth and co-workers [19] agree with our data. These authors stated that methicillin resistance in patients with *SAS* had no significant impact on patients outcome as measured by in-hospital mortality after adjustment was made for major confounders as age, sex, lenght of stay from admission to the onset of bloodstream infection, number of comorbidities, severity of underlying illness. *In vitro*, susceptibility of the *SA* strains isolated in our group of patients is shown in *Tab. 2*. Different classes of antibiotics with different degrees of toxicity were listed, thus representing a quite wide range of therapeutic alternatives. As concerns the methicillin-sensitive *SA* strains, we found sensitivity for the beta-lactamine class in percentage ranging from 60% (ceftriaxone, cefazolin, amoxicillin plus clavulanic acid, cefipime) to 100% (piperacillin plus tazobactam).

Conclusions

SAS is an important and frequent disease that physician must often match in Internal Medicine Units. It affects also non-neutropenic patients with a high morbidity and mortality and frequently originates from community-acquired infections.

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