Staphylococcus aureus Bacteremia in Children

Changes During Eighteen Years

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Background: *Staphylococcus aureus* is a major cause of bacteremia in children and is associated with high morbidity. Complete data are lacking on the incidence, related risk factors and mortality associated with this infection.

Methods: Descriptive study including patients younger than 16 years admitted to a tertiary reference hospital, with blood cultures exclusively positive for *S. aureus*. Four study periods were established: period 1, 1995–1999; period 2, 2000–2002; period 3, 2006–2008 and period 4, 2010–2012.

Results: In total, 269 episodes of *S. aureus* bacteremia (SAB) occurred in 242 patients. Over the total time studied, the incidence increased from 1.3 to 3.3 cases per 1000 patients hospitalized (relative risk: 2.71; 95% confidence interval: 1.85–3.95) and mortality decreased from 18% to 6% ($P = 0.008$). There were no differences in the resistance patterns of *S. aureus* strains. The prevalence of methicillin-resistant *S. aureus* (MRSA) increased from 3% to 13% between periods 1 and 2 and decreased from 14% to 3% between periods 3 and 4 ($P = 0.011$). The 30-day cumulative mortality was 3.3%, and the SAB-related mortality was 1.5%. Nosocomial acquisition and age 12–16 years were factors independently related with death on multivariate analysis.

Conclusions: The incidence of SAB tripled during the years studied but remained stable in the last period. Antimicrobial resistances did not increase. Although a decrease in mortality was documented, approximately half the 30-day cumulative mortality was caused by SAB.

Key Words: Bacteremia, *Staphylococcus aureus*, microbial drug resistance, risk factors, mortality

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Staphylococcus aureus bacteremia (SAB) is often difficult to manage and is a cause of considerable morbidity and mortality.[1] Approximately 12,500 cases occur per year in the United Kingdom, and the related mortality is 30%.[2] In a study performed in 59 hospitals in the US, *S. aureus* was the most commonly isolated nosocomial microorganism, being detected in 23% of the 6697 blood cultures analyzed.[3] These data are similar to the results of a more recent study, in which *S. aureus* was the predominant microorganism isolated in nosocomial bacteremia (16.2%).[4]

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The incidence of SAB in pediatric patients has not been fully defined. Studies carried out in the pediatric population of Denmark in the period of 1971–2000[5] describe an increase in the incidence of this infection from 4.6 to 8.4 cases per 100,000 children younger than 16 years. Naidoo et al[6] reported a mean annual incidence of 3.28 cases per each 1000 children hospitalized in South Africa during the years 2007–2011.

The intrinsic virulence of *S. aureus* has led to mortality rates reaching 20% in adults living in developed countries.[7] In general, the mortality in children is much lower, as is shown by data from a meta-analysis conducted in 2013 that placed the associated mortality rate at 9%.[8] However, neonates are a special population in which mortality rates similar to those in adults have been cited, reaching up to 17% in neonatal intensive care units (ICUs) in the US.[9]

One reason for the rise in the incidence of SAB is the parallel increase in risk factors, such as the use of invasive techniques (eg, surgery, intravascular catheters), associated comorbidities and the growing number of immunocompromised patients. Furthermore, methicillin-resistant *S. aureus* (MRSA) rates higher than 25% have been recorded in 7 of the 30 European countries included in the European Antimicrobial Resistance Surveillance System.[10,11] The latest data on the prevalence of MRSA in Spain showed a progressive rise in resistance from 1986 to 2006, reaching 29% at that time.[12] The rate stabilized thereafter, and after 2011, decreased to below 25%. No similar studies are available in the pediatric population of Spain, although the prevalence of MRSA infection is considered to be much lower in children than in adults.

Because of its clinical relevance, *S. aureus* is one of the microorganisms under surveillance in Antimicrobial Stewardship Programs (ASPs),[13] designed to optimize antimicrobial use and the mechanisms to control such infections. To date, there are no reports describing the impact of these programs on the incidence of SAB in children.

The aims of this study were to evaluate the changes occurring in the incidence, antimicrobial resistance patterns and mortality associated with SAB in pediatric patients over a lengthy study period, during which time ASPs were implemented in our hospital to control these infections.

PATIENTS AND METHODS

Study Population

A descriptive study investigating SAB was conducted in Hospital Universitari Vall d´Hebron, Barcelona (Spain) from 1995 to 2012, with 4 data collection periods: period 1, 1995–1999; period 2, 2000–2002; period 3, 2006–2008 and period 4, 2010–2012. These intervals were time periods in which cross sectional studies were conducted within our Pediatric Infectious Disease Department for SAB surveillance as part of our pediatric antibiotic stewardship program. The same inclusion and exclusion criteria were maintained in these studies, and the data were ultimately analyzed together for this study. All patients younger than 16 years

who had one or more cultures exclusively positive for *S. aureus* were included. The data were collected through an extensive medical chart review.

Starting in 2005, a specific ASP was implemented for pediatric patients in our center, and in 2009, "Bacteremia Zero," a national program adapted from the Keystone ICU Project, was launched in the neonatal and pediatric ICUs.

Microbiology and Molecular Study

The blood culture methods used were the BACTEC 9240 system (Becton Dickinson, NJ) in periods 1 and 2 and the BacT/ALERT 3D instrument (bioMérieux, Marcy-l'Etoile, France) in periods 3 and 4. Microorganisms were directly identified in positive vials using Gram stain, and colonies isolated on blood-agar medium were identified by positive findings for the following tests: catalase, plasma coagulase, deoxyribonuclease and mannitol fermentation. Antimicrobial sensitivity was studied by a disc-diffusion technique (Kirby–Bauer) using Mueller-Hinton agar and Rosco discs (Neo-Sensitabs; Rosco Diagnostica, Denmark), as recommended by the Clinical and Laboratory Standards Institute (referred to as National Committee on Clinical Laboratory Standards in period 1). Starting in 2012, the vancomycin minimum inhibitory concentration (MIC) was routinely determined using the E-test, following the recommendations of Van Hal et al.[14]

Definitions

An episode of SAB was established based on exclusive isolation of *S. aureus* on at least 1 blood culture. Reinfection was defined as isolation of *S. aureus* on another culture at least 90 days after the initial episode.[15,16] The definitions of del Rio et al[17] were used to determine the place of acquisition: community, hospital or other healthcare centers.

Statistical Analysis

The mean and standard deviation or median and interquartile range were calculated for the continuous variables. Differences in percentages were assessed using the χ^2 or Fisher exact test, and differences between means using the Student *t* test. In all cases, *P* values ≤0.05 were considered statistically significant.

Cox proportional hazards regression was used for the multivariate survival analysis, and Poisson regression was applied to calculate incidence. Statistical analysis of the data was performed using SPSS V.18.0 (SPSS Inc., Chicago, IL) and Stata SE (version 13.1; Stata Corp, College Station, TX).

RESULTS

In the 4 study periods analyzed, 242 pediatric patients had 269 different episodes of SAB. A total of 104,314 pediatric patients were hospitalized during these periods, thus yielding an overall SAB incidence of 2.18 episodes [95% confidence interval (CI): 1.9–2.4] per 1000 patients hospitalized. In the last 6 years of the study, SAB accounted for 8.4% of all bacteremia cases occurring in children. Taking period 1 as the reference, the incidence rates doubled in period 2 [relative risk (RR): 1.90; 95% CI: 1.29–2.81] and tripled in period 3 (RR: 3.35; 95% CI: 2.30–4.90), whereas there was a small reduction in period 4 (RR: 2.71; 95% CI: 1.85–3.95) (Fig. 1). SAB incidence by year is presented in Figure 1.

Epidemiologic Characteristics and Risk Factors for SAB

The epidemiologic characteristics of the sample and risk factors associated with SAB are described in Table 1. There were 27 reinfections (7.58% of all episodes), and an upturn was seen in the last period. Almost half the total number of SAB cases (n = 114) occurred in infants younger than 1 year, and 26% (n = 71) of cases were documented in neonates. Overall, more than 60% (n = 164) of the infections recorded were hospital acquired, 29% (n = 76) were community acquired, and 10% (n=28) were related to other healthcare centers. In neonates and infants younger than 1 year, 76% (n = 86) of infections were hospital acquired, with significant differences relative to the remaining age groups (*P* = 0.001). The percentage of nosocomial infections gradually decreased during the 4 study periods, whereas that of community-acquired infection showed an upswing in the last period (Table 1).

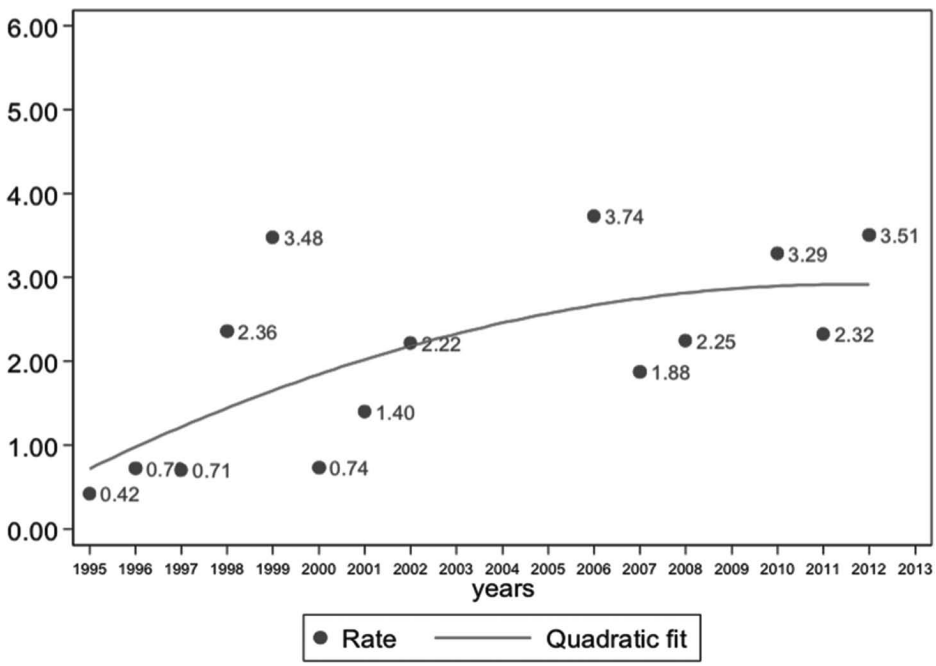

FIGURE 1. Annual incidence of *Staphylococcus aureus* bacteremia per 1000 patients admitted.

TABLE 1. Epidemiologic Characteristics and Risk Factors of SAB in Pediatric Patients During the 4 Study Periods

	Period 1, 1995–1999 (n = 79)	Period 2, 2000–2002 (n = 58)	Period 3, 2006–2008 (n = 66)	Period 4, 2010–2012 (n = 66)	*P*
Episodes/1000 patients hospitalized	1.3	2.6	3.7	3.3	NS
Total % bacteremia episodes	—	—	9.5	7.5	NS
Reinfections, % (n)	7.9 (10)	12 (7)	1.5 (1)	13.6 (9)	NS
Mean age, yr (range)	5.6 (0.01–16)	4.7 (0.1–15.7)	4.5 (0.01–15)	2.8 (0.01–16)	*0.04*
Neonate, % (n)	24 (17)	24 (17)	21 (15)	31 (22)	
1–12 mo	20 (10)	8 (4)	38 (19)	34 (17)	*0.004*
1–5 yr	27 (17)	33 (21)	14.5 (9)	25.5 (16)	
6–11 yr	51 (20)	10.5 (4)	23 (9)	15.5 (6)	
12–16 yr	31 (14)	27 (12)	31 (14)	11 (5)	
Male, % (n)	64 (51)	45 (26)	62 (41)	70 (46)	NS
Caucasian, % (n)	—	90 (52)	61 (40)	59 (39)	*<0.001*
Acquisition of SAB, % (n)					
Community acquired	28 (22)	33 (19)	20 (13)	33 (22)	NS
OHC	13 (10)	0	13 (9)	13 (9)	
Hospital acquired	60 (47)	66 (38)	67 (44)	53 (35)	
Risk factors % (n)	24 (19)	47 (27)	45.5 (30)	60.5 (40)	*0.001*
CVC	69 (55)	33 (19)	62 (41)	41 (27)	*0.001*
Parenteral nutrition	27 (21)	16 (9)	17 (11)	3 (2)	*0.002*
Previous ICU admission	34 (27)	12 (7)	54 (36)	35 (23)	*<0.001*
Prematurity	0	14 (8)	24 (16)	24 (16)	*<0.001*
Secondary IS	3 (2)	31 (19)	36 (22)	30 (18)	NS
Dialysis	0	0	31 (4)	69 (9)	NS

Italic values indicate significant *P* values.
NS indicates not significant; OHC, other healthcare centers; IS, immunosuppression.

Clinical Characteristics and Origin of Bacteremia

The primary origin of SAB in all periods was central venous catheter (CVC) infection (Fig. 2). Nonetheless, CVC-related SAB significantly decreased during the 2010–2012 period compared with previous years ($P = 0.001$), whereas a rise in SAB with no evident focal origin occurred in the last years ($P = 0.001$). There were 73 (27%) episodes of sepsis. A decrease was found between the 2006–2008 and 2010–2012 periods (n = 26, 39% and n = 14, 21%; $P = 0.02$), but an overall decrease was not observed when all 4 periods were evaluated together [1995–1999, 23% (n = 18) and 2000–2002, 26% (n = 15); $P = 0.07$].

Microbiologic Data

With regard to microbial resistance (Table 2), MRSA accounted for 8% (n = 21) of all the strains isolated. During the 2000–2002 and 2006–2008 periods, a 4-fold increase in MRSA isolation was documented (14% in both), which significantly decreased in the last period, reaching a percentage similar to the initial one [3% (n = 2), $P = 0.015$]. The antimicrobial sensitivity of *S. aureus* strains according to the setting of acquisition showed no significant differences, and reinfection by a MRSA strain occurred in only 1 patient. The vancomycin MIC was examined in 20 isolates, which showed a MIC of 1 mg/L in 5 (25%) strains, 1.5 mg/L in 14 (70%) and 2 mg/L in 1 (5%) Resistance to rifampin or glycopeptides was not detected.

Treatment, Evolution and Mortality

The empirical antibiotic treatment most often used was vancomycin (30.5%, n = 82), followed by amoxicillin–clavulanate (14.5%, n = 39) and cloxacillin (10%, n = 28). In neonates, empirical vancomycin was given in 31% of episodes (n = 28), whereas cloxacillin use was significantly lower than in the remaining age groups (7%, $P = 0.01$). However, implementation of vancomycin as initial, empirical antimicrobial treatment decreased from 47% (n = 31) in the 2006–2008 period to 33% (n = 22) in 2010–2012 ($P = 0.014$).

In 4 cases (3.2%), SAB was complicated by a second focus of infection (2 cases of pneumonia and 2 of infective endocarditis).

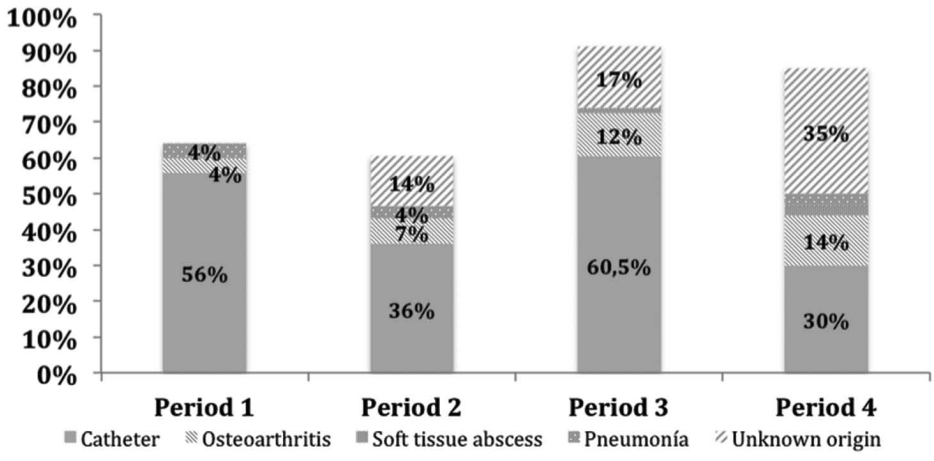

FIGURE 2. Primary origin of *Staphylococcus aureus* bacteremia.

TABLE 2. Changes in *Staphylococcus aureus* Resistance to Antimicrobials in Pediatric Bacteremia During the Study Periods

Antimicrobial, n (%)	Period 1 (1995–1999)	Period 2 (2000–2002)	Period 3 (2006–2008)	Period 4 (2010–2012)	*P*
Penicillin	NT	0 (100%)	4 (94%)	4 (94%)	NS
Ciprofloxacin	NT	6 (10%)	9 (14%)	2 (3%)	NS
Clindamycin	NT	7 (12%)	10 (15.2%)	10 (15.2%)	NS
Cloxacillin	2 (2.5%)	8 (14%)	9 (14%)	2 (3%)	*0.015*
Trimethoprim-sulfamethoxazole	NT	0	2 (3%)	0	NS
Erythromycin	NT	8 (13%)	14 (21%)	14 (21%)	NS
Gentamicin	5 (6.8%)	7 (12%)	4 (6%)	3 (4.5%)	NS
Rifampicin	0	0	0	0	0
Teicoplanin	0	0	0	0	0
Tobramycin	8 (13%)	12 (20.7%)	9 (14%)	7 (12%)	NS
Vancomycin	0	0	0	0	0

Italic values indicate significant *P* values.
NT indicates not tested; NS, not significant.

There were 37 (13.8%) deaths. Mortality significantly decreased in the last 2 periods: period 1, 18% (n = 14); period 2, 24% (n = 14); period 3, 8% (n = 5) and period 4, 6% (n = 4) ($P = 0.008$). In total, 40.5% (n = 15) of deaths occurred in infants younger than 1 year ($P = 0.04$), and 21% (n = 8) of them were neonates ($P = 0.47$). Three-quarters of neonatal deaths occurred in the first 2 periods (n = 6). The mortality rate in infants younger than 1 year was 12.4% and specifically in neonates, 11.3%. Children in the 12-to-16-year-old group had the highest mortality rate, recorded at 24.5%. Mortality in those with nosocomial infection was slightly higher than in the other 2 acquisition groups (15% hospital acquired, 14% acquired in other healthcare centers and 10.5% community acquired, $P = 0.62$). One third of deaths (n = 10) were directly caused by SAB, and most (8 of 10) occurred in the first 2 periods ($P = 0.214$). Estimated survival if patients remained hospitalized for 1 year would be 47% (Fig. 3). Thirty-day cumulative mortality was 3.3%, and SAB-related 30-day cumulative mortality was 1.5%. Significant risk factors for death on multivariate analysis were nosocomial acquisition and belonging to the oldest age group studied (12–16 years) (Table 3). Differential factors were sought in this age group to explain this last result. We found that children who died had a higher incidence of secondary immunodeficiencies than those who died in the other groups, but the difference was only marginally significant ($P = 0.053$). No other differences that might explain this finding were observed.

DISCUSSION

The results of this study illustrate the importance of having specific data on the epidemiology of SAB, the clinical features of affected patients and the microbiological characteristics of *S. aureus* in each hospital to enable effective prevention and proper management of these infections.

The estimated overall incidence we found was comparable with that of some other studies, such as the report by Kaech et al,[18] which described an incidence of 2.7 per 1000 patients hospitalized during a 5-year period. Studies carried out in Denmark (1981–2000),[19] Finland (1995–2001)[20] and Iceland (1995–2008)[21] have reported a significant increase in SAB along the study periods.

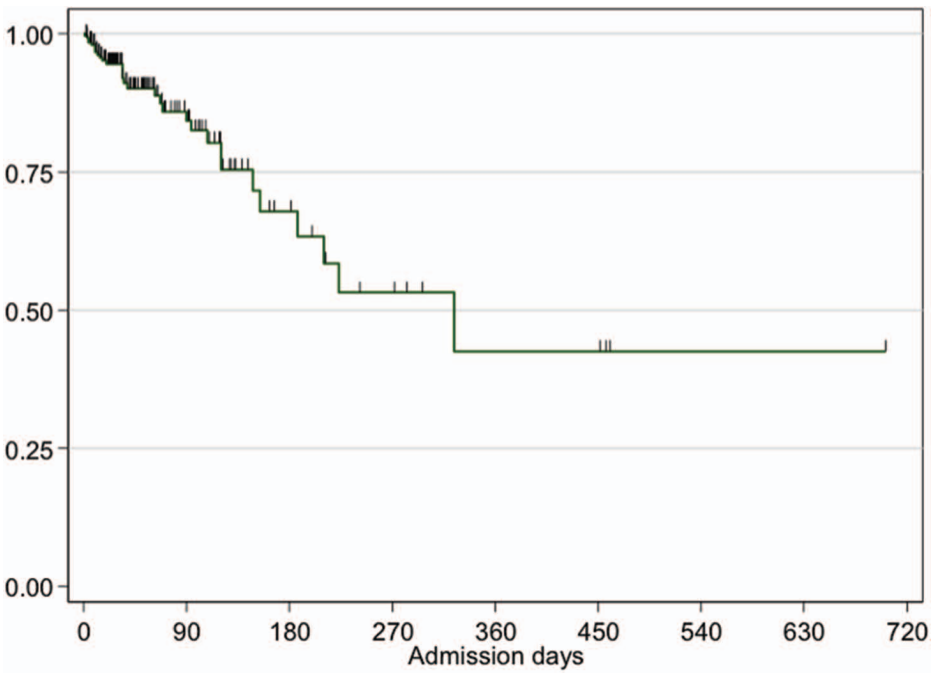

FIGURE 3. Kaplan–Meier survival curve after admission.

TABLE 3. Multivariate Survival Analysis Using COX Regression for the Entire Study Period (Follow-up Time: Days of Admission)

	Univariate Analysis		Multivariate Analysis	
Variables	Crude HR (95% CI)	*P*	Adjusted HR (95% CI)	*P*
Age (RC: <1 mo)				
1–11 mo	0.45 (0.12–1.67)	0.23	0.59 (0.21–1.67)	0.32
1–5 yr	0.76 (0.04–3.89)	0.78	0.33 (0.08–1.33)	0.12
6–11 yr	2.65 (0.76–6.51)	0.59	2.10 (0.73–6.01)	0.17
12–16 yr	3.34 (1.76–6.51)	0.04	4.34 (1.59–11.8)	0.004
Study period (RC: period 1)				
Period 2	1.37 (0.13–3.21)	0.15	1.27 (0.32–5.04)	0.74
Period 3	0.90 (0.13–1.01)	0.22	0.52 (0.92–22.36)	0.43
Period 4	0.32 (0.05–0.93)	*0.04*	0.69 (0.01–13.45)	0.05
Acquisition of infection (RC: community acquired)				
Hospital acquired	3.12 (1.92–5.67)	*0.02*	7.4 (1.93–29.1)	*0.01*
OHC	2.01 (0.59–7.26)	0.26	2.29 (0.74–7.06)	0.15
Prematurity	2.23 (1.07–2.77)	*0.01*	—	—
ICU admission	1.78 (1.05–2.98)	*0.04*	—	—
Catheter removal	0.22 (0.06–0.75)	*0.01*	—	—
MRSA	0.51 (0.25–1.07)	*0.07*		
Sepsis	2.56 (1.12–8.43)	*0.03*	2.61 (0.97–6.37)	0.06

Italic values indicate significant *P* values.
HR indicates hazard ratio; RC, reference category; OHC, other healthcare centers.

These findings differ from our results, which are more in accordance with those reported by Naidoo et al[6] in South Africa (2007–2011)—3.28 cases per 1000 patients younger than 13 years—likely because there was also an exclusively pediatric cohort.

The age group most commonly affected was infants younger than 1 year, as has been described in previous publications,[5,22] with 1 study citing a SAB rate 17-fold higher in these children.[5] Among our patients, neonates were highly represented, accounting for one quarter of the total incidence of SAB and one third of the nosocomial cases. In a recent meta-analysis, *S. aureus* bacteremia represented 3.7% of all cases of neonatal sepsis.[23] Considering these results and the fact that prematurity is on the rise in our cohort, it seems reasonable that programs advocating more meticulous management of the risk factors associated with SAB are needed in neonatal ICUs. If we can control such infections at this level, we may be able to achieve an overall decrease in the incidence of SAB.

The association of SAB with other potentially important risk factors, such as the use of CVCs, parenteral nutrition, and hospitalization in ICUs, showed a gradual decrease over time.

Nosocomial acquisition of SAB also decreased progressively in the 4 periods analyzed, in keeping with the situation in other European countries.[21] In part, this may be explained by a parallel reduction in CVC-related infections as the primary focus. This, in turn, may be attributable to improvements in preventive measures, such as implementation of the Antimicrobial Stewardship and Bacteremia Zero programs in our hospital.

With regard to antimicrobial resistance, a notably stable pattern was found in all the study periods, comparable with the trends in Spanish adults reported in the study of Cuevas et al.[12] Despite the mounting frequency of glycopeptide-resistant *S. aureus* infections reported in several studies,[24–28] we did not detect any strains with these characteristics; only one isolate had a vancomycin MIC of >1.5 mg/L, with potential clinical repercussions.

Whereas authors such as Khairulddin et al[29] and Burke et al[30] have reported an increase in MRSA strains over the last years, we found a significant reduction. This may be partly because of the decrease in isolates of nosocomial origin and an appropriate antibiotic policy. This latter factor is corroborated by the reduction in empirical vancomycin use documented in the last 3 years, which coincides with data reported in other studies.[12,31] Community-acquired MRSA has shown a rapid increase in many developed countries,[4,32,33] but in our cohort only 1 such case was detected.

SAB-related mortality in our series was 1.5%, a lower value than the 3.2% reported by Hill et al.[34] Our findings are more consistent with those of Frederiksen et al[5] who described a decrease in SAB mortality in children from 19.2% in 1971 to 2.5% in 2000.[5] In contrast, studies in the adult population show higher mortality rates,[35,36] such as the 25% reported by Laupland et al[36] in a study conducted in Canada, which concluded that mortality in children with SAB is lower than in adults. Most SAB-related deaths (80%) occurred in the first 2 periods studied. It is currently believed that age is the most consistent predictive factor of death.[7] In our study, almost half the deaths were in patients younger than 1 year of age and one quarter were in neonates. However, when SAB-related neonatal mortality was viewed in relation to the total of hospitalized infants younger than 1 month, the resulting mortality rate was lower than the values reported in recent studies.[8,9,23] The multivariate results confirmed this, as older age was an independent risk factor for mortality. One possible explanation for this finding may be the larger number of admissions in newborns relative to older children, which could have led to statistical overestimation of the death rate in the oldest group. In addition, this result may have been influenced by factors inherent to the population studied, as children in the oldest age group had a higher incidence of secondary immunodeficiency. Prospective studies are needed to confirm this current change in the mortality incidence.

This study has the limitations of a retrospective design in which follow-up of the patients was not possible, and long-term trends related to the variables studied could not be analyzed. Being a single-center study, the findings cannot be generalized to other parts of Spain. Nonetheless, it could serve as a point of departure for multicenter studies in this line, which are currently lacking in the pediatric setting. One advantage of this study is that the periods analyzed are long enough to ensure that the deaths and recurrences documented are not overestimated, and that the incidence and prevalence of MRSA infection are not underestimated.

In conclusion, the incidence of SAB tripled during the periods studied, and remained stable in the last period. The incidence

of recurrent infection did not increase and there was a reduction in SAB caused by MRSA strains, possibly related to the parallel decrease in nosocomial acquisition. Despite the drop in mortality rate, approximately half of the 30-day cumulative mortality was caused by SAB.

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