



## Epidemiological study of secondary bloodstream infections: The forgotten issue

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### ABSTRACT

**Objective:** Secondary bacteraemia infections (SBI) are poorly studied. We analyse the epidemiology of nosocomial SBI, potential risk factors and mortality of affected patients.

**Methods:** Prospective study of patients with bacteraemia from 2009 to 2014 in a tertiary hospital. For each SBI was recorded: primary source of infection, aetiological agent, demographic data, intrinsic and extrinsic risk factors and mortality during the episode.

**Results:** 429/1918 episodes of Nosocomial Bacteraemia (NB) (22%) were SBI (average Incidence Density: 0.41% days of admission). Onco-hematological services had the highest Incidence Density of SBI. Surgical Site Infection-SBI (SSI-BSI) was the most frequent SBI (27%), followed by Urinary Tract Infection-SBI (UTI-BSI) (24%). Gram-negative bacteria were the most prevalent microorganism (61.1%). The median interval between SBI episodes to discharge was  $37 \pm 59$  days. Mortality rate was 29%. These patients had many intrinsic and extrinsic risk factors such as urinary catheterization (68%), CVC (69%), Arterial hypertension (48%) and hospitalization in the six previous months (45%).

Mean age was significantly higher in patients with UTI-BSI and SSI-BSI. Average stay from admission to the development of bacteraemia was statistically lower in patients with Intra-abdominal Infection bacteraemia (IAB-BSI). Patient with SSI-BSI had oncologic processes and had undergone for more Mechanical ventilation than UTI-SSBI and Respiratory Tract Infections Bacteraemia (RTI-BSI). The use of CVC was significantly higher in RTI-BSI.

**Conclusions:** SBI accounts for almost a quarter of all NB. Patients has multiple comorbidities, increases hospital stay and mortality. It would be necessary to establish measures to rapidly diagnose and treat the primary infection, in order to prevent the onset of SBI.

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### Introduction

Nosocomial bacteraemias (NB) are not the most prevalent infections at hospitals, but they are usually the most serious ones, increasing the length of hospital stay, causing a greater rise in healthcare cost and entailing a higher mortality risk [1]. Most NB are caused by the insertion of medical devices such as Central venous catheterization or, in many cases, do not have a definite origin (Primary Bacteraemia – PBI –), although the majority of the latter have been associated with catheter insertion [2]. Therefore, a large num-

ber of publications that refer to risk factors, measures of control and prevention of PBI and bacteraemia associated to central line devices [3] can be found in the literature. Specific programmes of direct intervention have also been developed to reduce Central Line Associated Bloodstream Infection (CLABSI), starting in 2006 with the introduction of specific measures' packages proposed by Pronovost in the United States [4] and subsequently imitated in the rest of the world [5], as well as in Spain [6] and a reduction of up to 46% in the incidence rates of this type of infection has been obtained [7].

Basically, a secondary bacteraemia infections (SBI) is a bacteraemia that concurs with an infection in another primary location. This type of bacteraemia represents the lowest percentage of total NB, but also has serious consequences of high morbidity and mortality, increased hospital stay and associated costs; and most of

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them could be prevented before their onset by treating the infection early in origin.

In scientific literature few articles can be found describing the epidemiology of SBI, since some only focus on certain types of localization [9] and others are part of the overall epidemiology of bacteraemia described in certain types of services [10,11], pathologies [12] or age groups [13,14].

The aim of our study is to analyse the SBI that take place in a tertiary hospital, reference hospital for the population it serves. In a temporal evolution over a six-year period, we analysed the source infection and aetiological agent of SBI, as well as describing the potential risk factors, the evolution of the patients affected and the groups of bacteraemias that presented higher mortality.

## Methods

### Setting and patients

This study was carried out at the University Hospital of the Canary Islands (HUC, by its initials in Spanish) in Tenerife (Spain), a 660-bed tertiary care hospital that provides a medical and surgery ICU and has a kidney transplant Unit.

This is a retrospective study of all hospitalized patients with clinically significant bacteraemias from 1 January 2009 to 31 December 2014. Firstly, the positive blood cultures are reported to the Infection Control Team, who are in charge of studying the epidemiological and clinical data of episodes and classify the bacteraemias as community-acquired or healthcare-associated bacteraemias, as well as Primary Bloodstream Infections (PBI), Central Line-Associated Bloodstream Infections (CLABSI) and Secondary Bloodstream Infections (SBI), according to CDC criteria [15] and its National Healthcare Safety Network (NHSN) annual update.

We excluded bacteraemias diagnosed in patients coming from Home Hospitalization, either from patients hospitalized in the Emergency Room, or who had been treated in External Consultations. Outpatients device carriers (home-based parenteral nutrition, chemotherapy) with a hospital stay of less than 48 h at the time of detection of the positive blood culture were also excluded, as well as patients in the dialysis programme.

The study was approved by the HUC Institutional Review Board.

### Definitions

Those bacteraemias classified as nosocomial infections were categorized as PBI, CLABSI and SBI according to CDC [15,16] criteria and NSHN annual update.

SBI were also classified according to the location of the associated infectious process: Surgical Site Infection (SSI), Urinary Tract Infection (UTI), Lower Respiratory Tract Infection (LRI), Intra-abdominal Infection (IAB), Skin/Soft Tissue Infection (SST) and "Other". For a better data comprehension we have unified the infections of the Lower Respiratory System and Pneumonia in "Respiratory Tract Infections".

### Epidemiological and clinical data

We defined Cumulative Incidence (CI) as number of new cases per year patients admitted and Incidence Density (ID) as number of new cases per 1000 days of admission. Relative frequency of different types of bacteremia are analysed in the study period.

For each case of SBI, the following information was recorded: primary source of infection leading to SBI, aetiological agent, demographic data (sex, age, ward of admission, hospital length of stay from admission to SBI, hospital length of stay from SBI to discharge, death or discharge), intrinsic risk factors (Neoplasia, Liver failure, Renal failure, Pre-entry pressure ulcer, Arterial hypertension,

**Table 1**  
Types and frequency of "Other SBI" over total SBI.

Other primary infection	N (%)
Retrograde Endoscopic Cholangiopancreatography (ERCP)	14 (3)
Percutaneous transhepatic cholangiogram (PTHC)	8 (2)
Osteoarticular infection	6 (1)
Endocarditis	4 (1)
Genital-urinary infection	4 (1)
Nervous system infection	2 (0.5)
Nephrostomy	2 (0.5)
Other devices/prosthesis	2 (0.5)
Phlebitis	2 (0.5)
Biliary drainage	1 (0.2)
Echoendoscopy	1 (0.2)

Diabetes mellitus, Dyslipidemia, Immunosuppression or treatment with corticosteroids/chemotherapy/radiotherapy, previous hospitalization episode in the preceding 6 months, Charlson severity index) and extrinsic factors (Bladder catheter, Mechanical ventilation, Central venous catheter and surgery during admission [in non-SSI bacteraemia]).

### Data analysis

The sample size available for the type of bacteraemia in this study (n=45–112) confers, in the worst case, a power of 90% in the detection of differences of at least 35% between nominal variables and 15 points between scales. All comparisons between bacteraemia types and bilateral hypothesis were tested at 5% alpha statistical significance level. Numerical variables were summarized as mean (SD) if it was normally distributed and median (P<sub>5</sub>–P<sub>95</sub>) if non-normally distributed, and nominal variables were described with relative frequencies of their categories. The verification of normality was performed by exploring variable histogram and results of the Kolmogorov–Smirnov normality test. Variables were compared between types of bacteraemia with the One-way ANOVA with Bonferroni post hoc tests, Kruskal–Wallis H test with post hoc U of Mann–Whitney U post hoc tests or Pearson chi<sup>2</sup> test, depending on type and distribution of these variables. The evolution of relative frequency, Cumulative Incidence and annual Incidence Density of the different types of bacteraemia during the study period was estimated by the direction of its temporal progression through linear trend analysis.

Statistical significance was defined as bilateral p < 0.05. Analyses were performed using IBM SPSS™ 21.0 for Windows NT Professional operating system.

## Results

During the 6 years of the study, a total of 1918 episodes of NB were detected. Of them, 429 (22%) were SBI. Relative frequency of PBI, CLABSI and SBI in relation to the total NB is shown in Fig. 1. CLABSI shows a decreasing annual trend (2%, p = 0.035) in the years under study.

SBI represented an average Cumulative Incidence (CI) of 0.29 × 100/year patients admitted and an average Incidence Density (ID) of 0.41 × 1000 days of admission.

SSI-SBI were the most common type of SBI (n = 112. 27%), followed by UTI-SBI (n = 102. 24%), LRI-SBI (n = 95. 23%), IAB-SBI (n = 45. 11%) and SST-SBI (n = 33. 8%). Finally, a wide variety of processes have been included in "Other SBI" (n = 42. 7%), which are shown in Table 1.

The mean age of SBI patients was 60 ± 22 years and 56% were males. The median interval between admission to hospital and identification of the SBI process was 27 ± 37 days (3–116 days) and the median interval between SBI episode and discharge was

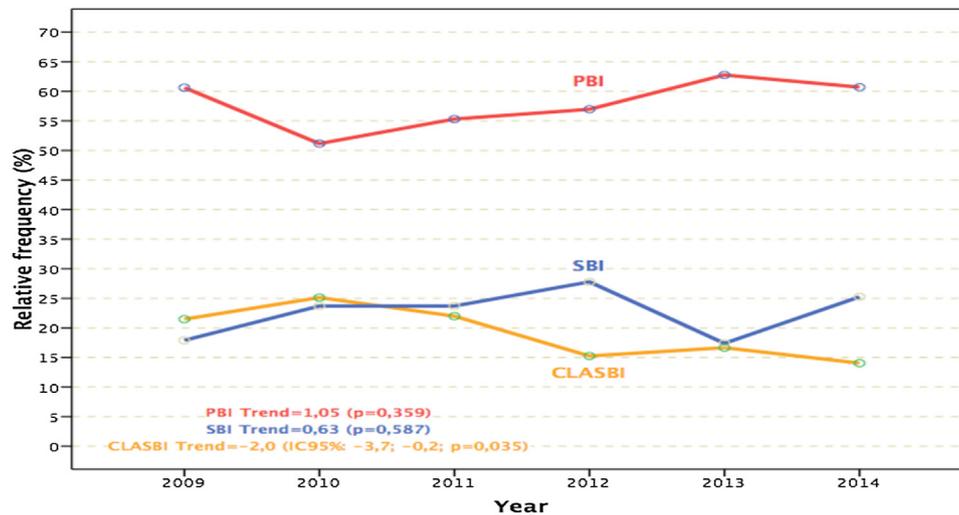


Fig. 1. Relative frequency (%) of PBI, SBI and CLASBI from total of bloodstream infection in 2009–2014 period at the University Hospital of the Canary Islands, Spain.

Table 2

Patient demographics and clinical characteristics according to the type of secondary bloodstream infection.

	UTI (n = 102)	SSI (n = 112)	LRT (n = 95)	SST (n = 33)	IAB (n = 45)	OTHER (n = 42)	p-Value
Age <sup>a</sup>	62 ± 22 <sup>d</sup>	64 ± 22 <sup>e</sup>	59 ± 22	53 ± 22	50 ± 22 <sup>d,e</sup>	58 ± 22	0.005
Sex <sup>b</sup> (men)	55 (54)	75 (67)	75 (79)	23 (69)	36 (80)	23 (55)	0.163
Length stay admission-bacteraemia (days) <sup>f</sup>	19(4–94) <sup>f</sup>	18 (5–80)	20 (5–98) <sup>g,h</sup>	22 (6–64)	15 (3–89) <sup>h</sup>	13 (4–80) <sup>f,g</sup>	0.046
Length stay bacteraemia-discharge (days) <sup>f</sup>	22 (4–145)	20 (3–163)	24 (2–102)	15 (1–299)	16 (1–102)	17 (1–189)	0.277
Exitus <sup>b</sup> (n,%)	19 (19) <sup>i</sup>	29 (26) <sup>j</sup>	51 (54) <sup>j,k,l,m</sup>	11 (33) <sup>l</sup>	6 (13) <sup>k,n</sup>	5 (12) <sup>m,n</sup>	<0.001
I. Charlson <sup>e</sup>	4 (0–7)	4 (0–8)	3 (0–8)	3 (0–7)	3 (0–7)	4 (0–8)	0.329

<sup>a</sup> Mean(SD) compared by One way ANOVA test and Bonferroni post hoc tests.

<sup>b</sup> Frequency(%) compared by means chi<sup>2</sup> Pearson test.

<sup>c</sup> Median(P<sub>5</sub>–P<sub>95</sub>) compared by Kruskal–Wallis H and with Mann–Whitney U post hoc tests.

<sup>d</sup> p = 0.022.

<sup>e</sup> p = 0.005.

<sup>f</sup> p = 0.04.

<sup>g</sup> p = 0.009.

<sup>h</sup> p = 0.014.

<sup>i</sup> p < 0.001.

<sup>j</sup> p < 0.001.

<sup>k</sup> p < 0.001.

<sup>l</sup> p = 0.004.

<sup>m</sup> p < 0.001.

<sup>n</sup> p = 0.025, the rest of differences does not reach statistical significance.

37 ± 59 days (2–495 days). The mortality rate among patients with SBI was 29% (123/429). Demographics and clinical characteristics of patients according to the type of SBI are shown in Table 2.

Table 3 shows SBI rates for services in the period under study. In medical and onco-haematology services UTI-SBI was the most common type of infection (37% and 32%, respectively). In the surgical services the most frequent type was SSI-SBI (53%). In contrast, on ICU ward the most frequent group was LTR-SBI (54%).

A total of 513 pathogens were isolated out of 429 episodes of nosocomial SBI. polymicrobial SBI was detected in 73 (17%) episodes. Gram negative microorganisms accounted for 61.1%, with a predominance of Enterobacteria (43% of the total) compared to Not Fermenting Gram Negative Bacteria (NFGNB) (20.1% of the total), followed by 30% of Gram positive bacteria and 6% of yeast (Table 4). 9.16% of the microorganisms were classified as multidrug-resistant according to a total 3% (14) MRSA, 0.2% (1) VRE (Vancomycin-Resistant *Enterococcus faecium*), 4% (18) BLEE (Extended Spectrum Betalactamase), 1% (4) CPE (carbapenem-producing Enterobacteriaceae), 0.2% (1) BLEE + CPE, 1% (4) carbapenem-resistant *Acinetobacter baumannii* and 0.97% (5) multidrug-resistant *Pseudomonas aeruginosa*.

Gram negative bacteria were most frequently the cause of SBI in all categories, except in SST-SBI, in which Gram positive cocci were predominant (Table 4).

The incidence of intrinsic and extrinsic risk factors associated with all SBI, as well as those SBI due to the most frequent source infections (SSI, UTI and LRI) are shown in Table 5.

## Discussion

Nosocomial SBI are poorly studied and there are no reports analysing them as a whole in hospital centres. In our six-year study, nosocomial SBI series have meant 22.4% of the total bacteraemias with clinical significance, which is not an insignificant figure.

These numbers are similar to those found in the Prevalence Study of Healthcare-Related Infections in European acute-care hospitals reported by European Center for Disease Prevention and Control (E-CDC) during 2011–2012, in which they obtained 29% SBI of the total bacteraemias [17]. However, in the last report of the Spanish study on the prevalence of nosocomial infections in acute hospitals (EPINE) [18] this percentage rose to 35%.

In the Nosocomial Infection Surveillance study in Spanish Intensive Care Units (ENVIN-HELICS) [19] reported in 2015, SBI

**Table 3**  
Medical Service and Type of infection causing SBI.

Microorganism	N (%)	Type of infection (N)					
		SSI	UTI	RTI	SST	IAB	OTHER
Gram positive Cocci	159 (30)	43(30)	24 (21)	27 (25)	24 (53)	20 (36)	21 (44)
<i>S. aureus</i>	29	5	2	8	8	1	5
CNS <sup>a</sup>	32	14	4	2	3	5	4
<i>Enterococcus</i>	89	23	18	12	11	14	11
<i>Streptococcus</i>	9	1	0	5	2	0	1
Gram negative rod	323 (61)	83 (57)	83 (73)	81 (73)	19 (42)	35 (62)	22 (46)
Enterobacterales	221 (43)	59	62	46	10	26	18
NFGNB <sup>b</sup>	102 (20)	24	21	35	9	9	4
Yeast	29 (6)	14 (10)	6 (5)	4 (2)	2 (5)	0	3 (6)
Others	8	4 (3)	1 (1)	0(0)	0 (0)	1 (2)	2 (4)

<sup>a</sup> CNS: Coagulase Negative Staphylococcus.

<sup>b</sup> NFGNB: Not Fermenting Gram Negative Bacteria.

**Table 4**  
Distribution of microorganisms producing SBI and according to the type of SBI.

	UTI (N,%)	SSI (N,%)	LRI (N,%)	SST (N,%)	IAB (N,%)	Others (N,%)	ID (%)
Medical services	42 (37)	19 (17)	15 (13)	10 (9)	14 (12)	14 (12)	0.23
Surgical services	27 (19)	75 (53)	11 (8)	6 (4)	8 (6)	14 (10)	0.27
Onco- hematology services	15 (32)	0 (0)	11 (24)	5 (4)	10 (21)	6 (12)	0.47
ICU	14 (15)	13 (14)	49 (54)	7 (8)	4 (4)	4 (4)	0.19
Paediatric ICU	2 (7)	2 (7)	8 (28)	5 (18)	8 (28)	3 (11)	0.02
Paediatric services	2 (25)	3 (38)	1 (13)	0	1 (13)	1 (13)	0.16

**Table 5**  
Univariate analysis results of potential risk factors for SBI acquisition.

Potential risk factors for SBI acquisition	SBI according to source infection				p-Value
	Total (n = 429)	Surgical site (n = 112)	Urinary tract (n = 102)	Respiratory tract (n = 95)	
Neoplasia	157 (37)	53 (46) <sup>a,b</sup>	32 (31) <sup>a</sup>	26 (27) <sup>b</sup>	<b>0.006</b>
Renal failure	115 (27)	33 (28)	32 (31)	17 (17)	0.069
Liver failure	62 (14)	18 (16)	12 (12)	10 (10)	0.451
Pressure ulcer	73 (17)	18 (16)	16 (15)	20 (21)	0.543
Hypertension	205 (48)	63 (54)	58 (56)	42 (43)	0.134
Diabetes mellitus	168 (39)	50 (43)	36 (35)	37 (38)	0.370
Dyslipidemia	127 (30)	32 (28)	36 (35)	25 (26)	0.354
Immunosuppression	127 (30)	32 (28)	32 (31)	25 (26)	0.734
Bladder catheter	293 (68)	90 (77)	76 (74)	67 (69)	0.254
Mechanical ventilation	222 (52)	73 (63) <sup>c</sup>	45 (44) <sup>c,d</sup>	60 (62) <sup>d</sup>	<b>0.003</b>
Central venous catheter	297 (69)	81 (70) <sup>e</sup>	62 (60) <sup>f</sup>	81 (84) <sup>e,f</sup>	<b>0.001</b>
Previous hospitalization (6 months)	192 (45)	56 (48)	43 (42)	38 (39)	0.305
Surgery during admission	264 (61)	96 (82) <sup>g,h</sup>	50 (50) <sup>g</sup>	45 (46) <sup>h</sup>	<b>&lt;0.001</b>
Charlson Index	4 (0–8)	4 (0–8)	4 (0–7)	3 (0–8)	0.365

Bold value p < 0.05.

<sup>a</sup> p = 0.017.

<sup>b</sup> p = 0.003.

<sup>c</sup> p = 0.002.

<sup>d</sup> p = 0.007.

<sup>e</sup> p = 0.024.

<sup>f</sup> p < 0.001.

<sup>g</sup> p < 0.001.

<sup>h</sup> p < 0.001; the rest of differences does not reach statistical significance.

accounted for 45% of the total bacteraemias and the CLABSI rate (including PBI) was 3 episodes per 1000 days of CVC, that is linked to the decrease-rates of bacteraemia related to invasive devices at which “Bacteraemia Zero” (BZ) campaigns have aimed. These campaigns included standardized intervention for the prevention of bacteraemia related to the insertion and management of catheters based on the best scientific knowledge: hand hygiene, use of Chlorhexidine and total barriers measures during catheter insertion, subclavian vein of choice, hygienic management of catheters and withdrawal if the catheter is not necessary. And on the other

hand, the implementation of the Comprehensive Security Program in ICU. The Integral Safety Plan in the ICU facilitates the improvement of the safety culture. It is based on the recognition that the professionals who are in the first line of attention are those who have the greatest knowledge about the risks of quality and safety in their Units. This plan facilitates that the professionals of each Unit of attention can work with the management teams and in that way they can jointly reduce some of the risks that derive from the patient attention. In our hospital, this programme was implemented in Adult Intensive Care Units in 2010 and, despite the fact that we have analysed the bacteraemia of the entire hospital, we

can observe the repercussion that the BZ programme has had on the constant decrease of CLABSI throughout the study period (Fig. 1).

We have found the higher frequency of SBI in those secondary to SSI infections, followed closely by those secondary to UTI and LRTI. These three types, in different order of frequency, are the most prevalent in different series: Javaloyas et al. [20] in a 10-year study at a Spanish hospital found that the most frequent SBI were UTI, followed by those secondary to LRTI; Endimiani et al. [21] found that UTI and CLABSI were the most common causes of SBI. In the EPINE study [18] SBI-UTI was the most prevalent (32%), followed by secondary to SSI (19%) and LRTI (17%) Obviously, this variation in data is related to the number of surgical interventions performed in the hospitals, and to the manipulation on the urinary and respiratory tract, through the use of Bladder catheters and invasive devices for ventilation. However, it is remarkable that in our study, as well as in EPINE, almost 10% of SBI are due to a huge variety of invasive procedures, such as Retrograde Endoscopic Cholangiopancreatography and Percutaneous transhepatic cholangiogram, which could also be avoided by appropriate handling in these procedures.

When comparing patient characteristics in the SBI different groups there were no differences between sexes regarding length of stay (bacteraemia-discharge), the average of the latter until discharge or death being very long (37 days). However, mean age was significantly higher in patients with SBI due to UTI and SSI, compared to secondary to IAB. Patients in our study had a very prolonged average stay from admission to the development of bacteraemia, the median being statistically lower in the group of patients with bacteraemia secondary to IAB.

Onco-hematological services had the highest Incidence Density of BSI, followed by surgical and medical services, being minority in paediatric and adult ICUs. Of course, bacteraemia secondary to UTI predominated in medical and onco-hematological services, in surgical services SBI were due to SSI and bacteraemia secondary to LRTI predominated in intensive care units. ICU admission is associated with a risk of presentation of NB, which is calculated up to 7 times higher than that presented by patients admitted to other areas of the hospital [22]. However, in the present study we observed how this type of bacteraemia is no longer in ICU.

The aetiology of primary and associated CVC bacteraemias is usually caused by GPC; in the European Prevalence Study, these bacteria accounted for 47% of all microorganisms [17]. In our series there is a clear predominance of GNB, especially at the expense of Enterobacteria, which is explained by the origin of the primary infection. It is worrying that almost 10% of these infections were caused by a multidrug-resistant bacterium, as is the case with other infections both at the hospital and within the community, a problem met by campaigns and programmes that have started to combat them [23].

It can be observed that, in general, these patients had many intrinsic and extrinsic risk factors, such as urinary catheterization (68%), Central venous catheter (69%), Arterial hypertension (48%) and hospitalization in the six previous months (45%). We have compared the three most frequent groups of SBI (SSI, UTI and RTI), obviously finding that patients suffering from SBI-SSI had oncologic processes and had been operated more frequently than the other two groups of patients, but had also undergone more Mechanical ventilation. The extrinsic risk factor Central venous catheter was significantly higher in those bacteraemias secondary to RTI.

Our study has some limitations. Firstly, not in every case of infection symptoms and signs clinical samples are collected in other locations besides blood culture; so, the definitions and results could be skewed, namely PBI results are oversized. Surveillance and diagnosis of SBI is not easy. When assessing a positive blood culture, you should be sure that there is no other infection in another primary site that has resulted in a secondary bacteraemia, and this depends

on the clinicians having applied for microbiological cultures or performed complementary tests for diagnosis. Otherwise, bacteraemia could erroneously be classified as PBI, and sometimes be mistakenly associated with the use of CLABSI. In fact, it is assumed that those PBI of patients with CVC have their origin in the catheter [8]; but in daily practice a significant percentage of PBI are diagnosed in patients who do not have a CVC, so it can be assumed that there may not have been a correct collection of samples or other diagnostic methods that help to know the origin of the bacteraemia.

Secondly, it is a single centre study, which limits its external validity, and to better understand the epidemiology of SBI in tertiary-level hospitals it would be necessary to carry out a multi-centre study.

Taking into account these limitations and in view of our results we can conclude that SBI accounts for almost a quarter of all NB. It occurs in patients with multiple comorbidities and increases hospital stay and patient mortality, so it would be necessary to establish the necessary measures to rapidly diagnose and treat the primary infection, in order to prevent the onset of SBI.

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