



Left-sided infective endocarditis caused by *Streptococcus agalactiae*: rare and serious

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Received: 5 August 2018 / Accepted: 6 November 2018 / Published online: 14 November 2018
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Abstract

A comparative study of the behaviour of left-sided infective endocarditis (left-sided IE) due to *Streptococcus agalactiae* (GBS) with left-sided IE caused by *Staphylococcus aureus* (SA). A prospective, multicentre cohort study in eight public hospitals in Spain, from January 1984 to December 2015; comparative analysis and factors associated with mortality. In total, there were 1754 episodes of left-sided IE; 41 (2.3%) caused by GBS vs. 344 (19.6%) due to SA, definitive IE 39 vs. 324 cases, males, 25 vs. 213, respectively. There were no differences in age or comorbidity, and healthcare-associated acquirement was 10% vs. 43%, p 0.001. Transthoracic echocardiogram (TTE) was performed in 95% vs. 96.8% and a transesophageal echocardiogram (TEE) in 61% vs. 56%. Vegetations were detected in 80% and measured > 1 cm in a similar proportion. It affected native valves in 85.4% vs. 82.6% and late prosthetic valve in 14.6% vs. 9.6%. The course was acute in both groups. There were more skin manifestations in SA left-sided IE, 7.3% vs. 32%, p 0.001. Both groups had similar complications, but in SA, there was more renal failure, 24% vs. 45%, p 0.010. Surgical risk and operated patients were similar. Mortality was proportionally higher in the SA group, without significance 29% vs. 43% (150), p 0.09. Heart failure, septic shock and neurological deterioration conditioned mortality: HR 1.96, 1.69 and 1.37 (CI 95% 1.40–2.73; 1.19–2.39 and 0.99–1.88 respectively) and to a lesser degree SA as aetiology agent and age. Left-sided IE caused by GBS is similar in severity to left-sided IE caused by SA.

Keywords Left-sided infective endocarditis · *Streptococcus agalactiae* · *Staphylococcus aureus*

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Introduction

Infective endocarditis (IE) caused by group B *Streptococcus* (*Streptococcus agalactiae*, GBS) is rare. A review of the literature shows few series of patients with this disease [1–8] and publications of isolated clinical cases are common [9, 10]. *Streptococcus agalactiae* IE frequently affects patients with debilitating diseases, is found mainly in native valves and is acquired to a great degree in community. It is characterised by a rapid clinical worsening and severe valve destruction, and high mortality has been reported [1–8]. In a previous study on our cohort of IE, collected between 1984 and 2008, we show that endocarditis in the left valves (left-sided IE) due to GBS is more serious than that caused by other species of *Streptococcus*, as it has multiple complications and increased mortality (27 vs 290 cases were compared) [11]. Sendi et al. (2012), in a letter to the editor, analysed the role of the aminoglycosides combination in the IE caused by GBS during a 13-year period from 1995 to 2007 and found similar data in their patients. They also consider that there are similarities in gravity between IE caused by GBS and IE caused by SA [12]. In this work, we evaluate if these similarities in the clinical presentation exist in our cohort.

Aim

Our principal aim is to analyse the clinical course of left-sided IE caused by GBS with respect to left-sided IE caused by *Staphylococcus aureus* (SA) in our cohort, as the latter is a microorganism that is well known for its aggressiveness and is normally associated with mortality in IE [13].

As *Streptococcus agalactiae* IE is acquired mainly in the community, our secondary aim was to analyse and compare the community-acquired cases.

Methodology

Scope of the study This is a multicentre prospective cohort study that includes all IE cases from January 1984 to December 2015 in eight public hospitals in Andalusia (Southern Spain), of which six have a Cardiac Surgery Department and are centres of reference in this field. All data were collected by the principal investigators in each centre, who were the physicians who cared for the patients. Data collection was carried out using a common database. It included epidemiological aspects, previous diseases, clinical presentation, complications, medical treatment used, need for surgery and whether it was performed, post-surgical complications and the clinical outcome with data related to in-hospital mortality. Only the first episode of every patient was included. The following complications have been analysed: heart failure, septic shock, central nervous manifestations, renal failure,

large blood vessel embolisms, visceral abscesses, septic arthritis, spondylitis and perivalvular complications. A sub-analysis of community-acquired cases has been done.

Definitions

Infective endocarditis was diagnosed when the modified Duke criteria were met [14]. Microbiological diagnosis was made by blood, by valve cultures and, exceptionally, by molecular techniques [15]. Transthoracic (TTE) and transesophageal echocardiography (TEE) were performed on patients with clinical or microbiological suspicion of IE, according to international recommendations. The same protocol was implemented for the diagnosis of valve dysfunction and intracardiac complications: abscess, vegetation, pseudoaneurysm and fistulae [16].

We considered healthcare-associated infective endocarditis (HAIE) as either episode manifesting (onset of signs and symptoms) > 48 h after admission to hospital or acquired in association with a significant invasive procedure performed in the 6 months before diagnosis in the following situations: (i) during a stay and/or manipulation in a hospital setting (nosocomial HAIE) or (ii) in patients with extensive out-of-hospital contact with healthcare interventions (non-nosocomial HAIE) [17, 18]. Since the aetiology and clinical course of nosocomial and non-nosocomial healthcare-associated IE are similar, we considered them together for the analysis (HAIE).

Comorbidity data, measured by the Charlson Index [19], were collected at admission.

Heart failure (HF) was diagnosed according to the Framingham criteria [20] and was considered severe when the patient required inotropic drugs. Septic shock was defined according to international clinical practice guidelines [21].

Renal failure (RF) was defined as an absolute increase of serum creatinine level of 0.3 mg/dl or an increase of more than 150% from baseline in patients without a history of kidney disease [22] or as a decrease in the glomerular filtration rate of 25% in patients with chronic kidney disease. Nephrotoxic treatment was considered when it included one or more drugs with a potential deleterious effect on the renal function administered for more than 7 days.

Impairment of the central nervous system (CNS) was considered in case of encephalopathy, meningitis, embolism or cerebral haemorrhage confirmed by neuroimaging, cerebrospinal fluid analysis or autopsy.

Septic shock was defined following the criteria of the international clinical practice guidelines according to the moment of the patient inclusion in the database [21].

Indication for cardiac surgery during hospitalisation was initially determined by the principal investigator in each centre in accordance with concomitant international guidelines, but the final decision was made in agreement with the centre's

cardiologists and cardiac surgeons. Surgical risk was estimated using the logistic EuroSCORE I model and was calculated for all patients for whom cardiac surgery was indicated [23]. For operated patients, the value was calculated on the day of intervention. For non-operated patients, it was calculated on the day in which the indication was determined.

Cardiac surgery was considered to have been delayed when the intervention was indicated but performed after more than 48 h in case of severe heart failure or after 7 days in case of progression despite the administration of an appropriate treatment.

For mortality, only early mortality was considered for analysis in this study and was defined as a death that occurred during hospitalisation regardless of cause (crude mortality) or within 1 month of discharge.

Statistical analysis Only cases which affected the mitral valve, aortic valve or either of those two along with the tricuspid valve were included in the analysis. IE localised exclusively in the right valves and IE which affected a pacemaker or other electrical cardiac stimulation systems were excluded.

Two types of bivariate analysis were performed: one between the different demographic and clinical variables of IE comparing GBS against SA and the other with variables related to mortality in both groups (SA and GBS). Lastly, we performed a multivariate analysis in which we introduced a variable related to the mortality associated with each bacterium. SA is the category with the highest mortality when compared with all variables that were shown to be significant in the bivariate analysis of both the SA and GBS groups. For the bivariate analysis, the chi-square test or Fisher's exact test was performed for quantitative variables according to the observed frequencies. Categorical variables were analysed using Mann-Whitney's *U* test. Then, multivariate analysis was performed using the Cox regression. To perform these analyses, we used the variables found to be significant by bivariate analysis, as well as those considered clinically relevant. Models were selected in a step-by-step descending procedure according to the likelihood ratio test. The entry and exit criteria for regression testing were 0.05 and 0.1 respectively. The HR and its 95% confidence interval were calculated. Statistical analyses assumed a bilateral alpha error of 0.05.

Results

In the period between January 1984 and December 2015, we collected 1927 episodes of IE, of which 1754 were left-sided IE. SA was the cause in 344 patients (19.6%), of which 32 (9%) were resistant to methicillin (MRSA). In that same period, we collected 41 episodes of left-sided IE caused by GBS (2.3%). In the comparative analysis of GBS vs. SA, there were 39 (95%) vs. 324 (94%) definitive left-sided IE; males 25

(61%) vs. 213 (62%), and the median age (IQR) was 65 (50.5–71.5) vs. 61 (48–73). Comorbidity according to Charlson Index, median (IQR), was 2 (0–3.75) vs. 1 (0–3). GBS left-sided IE was acquired predominantly in the community whereas SA left-sided IE had healthcare-associated acquirement (HAIE), 4 (10%) vs. 147 (43%), *p* 0.001. In the SA group, there were more manipulations prior to the episode, 9 (22%) vs. 200 (58%), *p* 0.001 and vascular manipulations predominated 0 vs. 139 (55%), *p* 0.001.

A transthoracic echocardiogram (TTE) was performed in 39 (95%) vs. 333 (96.8%) and transesophageal echocardiogram (TEE) in 25 (61%) vs. 193 (56%). Endocarditis was diagnosed by echocardiography, in all cases in which it was performed, in GBS left-sided IE, 39 (95%) vs. 317 (92%) cases in the SA group. Vegetations were found in 34 (83%) vs. 274 (80%) patients. Their size was able to be determined in 29 cases vs. 232; they measured greater than 1 cm in 19 (65.5%) vs. 127 (54.7%) patients. The localisation of left-sided IE was in the mitral valve in 23 (56%) vs. 194 (56.4%) patients, was in the aortic valve in 9 (22%) vs. 104 (30%) patients and was plurivalvular in 9 (22%) vs. 42 (12%) patients, without significant differences between the two bacteria. GBS infected native valves and prosthetic valves that were more than 1 year old without any differences to SA, 35 (85.4%) vs. 284 (82.6%) and 6 (14.6%) vs. 33 (9.6%) respectively. In contrast to SA, GBS did not lead to early prosthetic valve endocarditis, 0 vs. 20 (5.8%).

Both groups had an acute course with symptoms lasting less than a week, 24 (58.5%) vs. 247 (71.8%) patients, *p* 0.102. Fever was the usual initial symptom, 38 (92.7%) vs. 331 (96.5%). Equal proportions of patients had dyspnoea at the start of the episode or a worsening of prior dyspnoea, 21 (51%) vs. 170 (49.4%). Patients with SA had significantly more skin manifestations of IE, 3 (7.3%) vs. 113 (32%), *p* 0.001, whether they were petechiae, 1 (2.4%) vs. 81 (23.5%), *p* 0.001; Janeway lesions, 0 vs. 52 (15%), *p* 0.003; Osler's nodes, 1 (2.4%) vs. 62 (18%), *p* 0.007; or subungual splinter haemorrhages, 0 vs. 43 (12.5%), *p* 0.008. There were no differences in ophthalmic symptoms, 3 (7.3%) vs. 32 (9.3%), nor in the appearance of a new murmur or the worsening of an existing one, 22 (55%) vs. 204 (61%).

Both groups developed systemic complications in the same manner. Heart failure occurred in 20 (48.8%) vs. 170 (49%) patients, without significant differences and occurred in both groups during the first week of hospitalisation, with a median of days (IQR) from admission of 7 (6–14) vs. 7 (7–14), *p* 0.404. Proportionally, there were more cases of septic shock in the SA group, without significant differences, 6 (14%) vs. 93 (27%). The same pattern was observed in CNS impairment, 17 (41%) vs. 160 (46%), which occurred as a consequence of ischemic stroke, 9 (22%) vs. 62 (18%) or, to a lesser extent, haemorrhagic stroke, 1 (2.4%) vs. 11 (3.4%) and with embolic episodes in other vessels (excluding CNS), 4 (9.8%)

Table 1 Descriptive and bivariate analysis of GBS vs. SA

Variables	GBS left-sided IE N = 41	SA left-sided IE N = 344	Bivariate GBS vs. SA N = 385		
	n (%)	n (%)	p	OR	CI 95%
Left-sided definitive IE	39 (95.1)	324 (94.5)	1.000		
Male gender	25 (61)	213 (62)	1.000		
Median years of age (IQR)	65 (50.5–71.5)	61 (48–73)	0.545		
Charlson Index	2 (0–3.75)	1 (0–3)	0.519		
Acquisition (HAIE)	4 (10)	147 (43)	0.001	6.902	2.407–19.793
Prior manipulations	9 (22)	200 (58)	0.001	4.027	1.966–8.250
Vascular manipulations	0	139 (55%)	0.001		
GBS left-sided IE SA left-sided IE					
TT echocardiography	39 (95)	333 (96.8)	0.638		
TE echocardiography	25 (61)	193 (56)	0.619		
Vegetations	34 (83)	274 (80)	0.836		
Vegetations > 1 cm	19 (65.5)	127 (54.7)	0.324		
Localisation left-sided IE					
Mitral valve	23 (56)	194 (56.4)	1.000		
Aortic valve	9 (22)	104 (30.2)	0.363		
Plurivalvular	9 (22)	42 (12.2)	0.090		
Unknown	0	4			
Type of left-sided IE					
Native IE	35 (85.4)	284 (82.6)	0.827		
Early prosthetic IE	0	20 (5.8)	0.148		
Late prosthetic IE	6 (14.6)	33 (9.6)	0.283		
Native and early prosthetic IE	0	2 (0.6)	1.000		
Native and late prosthetic IE	0	5 (1.5)	1.000		
Acute course (< 1 week)	24 (58.5)	247 (71.8)	0.102		
Skin manifestations	3 (7.3)	113 (32)	0.001		
Complications					
Heart failure	20 (48.8)	170 (49.4)	1.000		
Septic shock	6 (14.6)	93 (27)	0.092		
Central nervous system (CNS)	17 (41.5)	160 (46.5)	0.620		
CVA ischemic stroke	9 (22)	62 (18)	0.526		
CVA haemorrhagic stroke	1 (2.4)	11 (3.4)	1.000		
Renal failure	10 (24.4)	156 (45.5)	0.010		
Large blood vessel embolisms	4 (9.8)	30 (8.8)	0.773	2.586	1.229–5.441
Visceral abscesses	0	0			
Septic arthritis	2 (4.9)	29 (8.4)	0.557		
Spondylitis	0	15 (4.4)	0.385		
Perivalvular complications	14 (34)	113 (33)	0.863		
Days of antibiotic treatment, median (IQR)	28.5 (21–36)	30 (15–42)	0.833		
Surgical indication	22 (53.7)	213 (62)	0.311		
Median logarithmic EuroSCORE I score (IQR)	17.7 (6–34.8)	20.8 (10–41.8)	0.139		
Surgery during hospitalisation	15 (36.5)	98 (28.5)	0.281		
Without surgical delay	12 (80)	93 (95)	0.853		
Left-sided IE relapse	0	4 (1.2)	1.000		
In-hospital mortality	12 (29.3)	150 (43.6)	0.094		

Table 2 Variables associated with mortality in GBS and SA. Bivariate analysis (living vs. deceased)

Variables	GBS left-sided IE (<i>N</i> = 41) exitus = 12				SA left-sided IE (<i>N</i> = 344) exitus = 150			
	<i>n</i> (%)	<i>p</i>	OR	CI 95%	<i>n</i> (%)	<i>p</i>	OR	CI 95%
Male gender	9 (75%)	0.305			94 (62.7)	0.824		
Median years of age (IQR)	65 (50–71.5)	0.785			61 (48–73)	0.003		1.840–9.237
Charlson Index	2 (0–3.75)	0.173			1 (0.3)	0.176		
HAIE	2 (16.7)	0.567			72 (48)	0.099		
Early prosthetic IE	0				13 (8.7)	0.182		
Complications								
Heart failure	10 (83.3)	0.006	9.500	1.735–52.021	100 (66.7)	0.001	3.543	2.263–5.548
Septic shock	3 (25%)	0.334			63 (42)	0.001	3.959	2.385–6.570
Central nervous system (CNS)	8 (66.7)	0.045	4.444	1.958–18.667	82 (54.7)	0.009	1.793	1.166–2.759
Renal failure	6 (50%)	0.040	6.250	1.330–29.371	86 (57.7)	0.001	2.418	1.561–3.746
Large blood vessel embolisms	2 (16.7)	0.567			10 (6.7)	0.254	1.561	0.991–2.459
Perivalvular complications	6 (50)	0.278			57 (38.8)	0.063		
Surgery during hospitalisation	5 (41.7)	0.730	1.357	0.342–5.939	41 (27.3)	0.719	0.904	0.563–1.452

vs. 30 (8.8%). The number of visceral metastatic abscesses, septic arthritis and spondylitis was also similar between both groups. There were differences in the development of renal failure; it was more frequent in the SA group, 10 (24%) vs. 156 (45%), *p* 0.010. Only 1 patient in the GBS group had renal embolism whereas there were 6 in the SA group. There were no cases of glomerulonephritis associated with GBS vs. 7 (2.5%) cases in the SA group. The median serum creatinine level (IQR) upon admission for GBS left-sided IE was 0.9 (0.73–1.17) vs. 1 (0.8–1.5) for SA. The median blood creatinine level (IQR) during the course of the disease and prior to surgery was 1.2 (0.9–1.9) vs. 2.1 (1.2–3.6), *p* 0.001. All patients received antibiotic treatment for a median number of days that did not differ significantly between both groups (28.5 days for GBS and 30 for SA). We know the regimens used in 352 patients out of a total of 385 patients. In the GBS group, we do not know the antibiotic treatment used in 2 patients (5% loss), and in the SA group, we do not know the treatment used in 31 patients (9% loss). GBS patients received

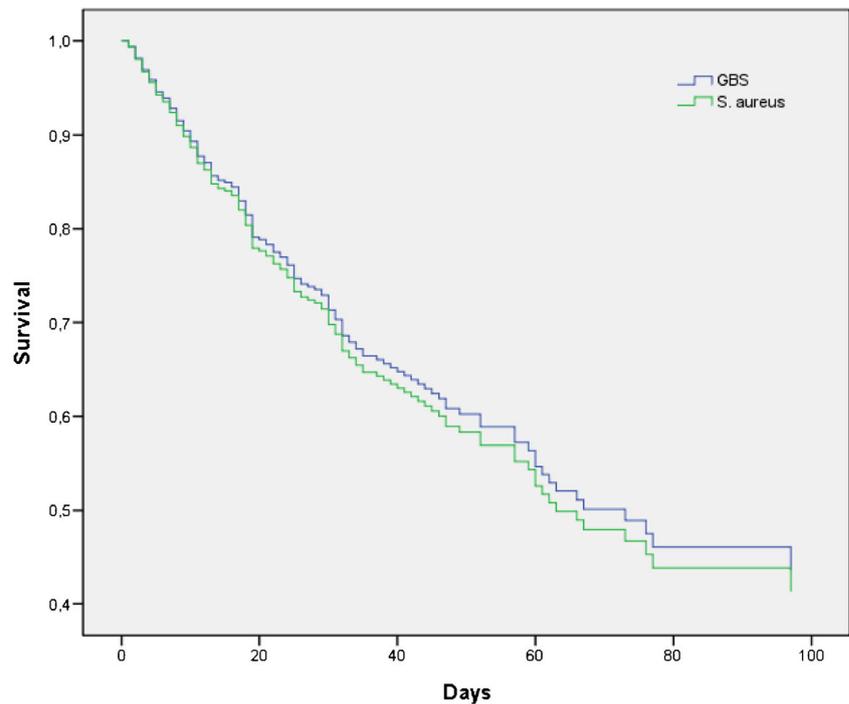
significantly more β -lactam antibiotics, 38 (97.4%) vs. 255 (81.5%), *p* 0.010—usually penicillin, ampicillin or ceftriaxone—and significantly more aminoglycosides, 26 (66.7%) vs. 122 (39%), *p* 0.002, usually gentamicin. Glycopeptides, usually vancomycin, were used in 2 (5%) vs. 29 (9.3%), *p* 0.554, and a glycopeptide + aminoglycoside combination was used in 1 (2.6%) vs. 34 (10.9%) in the SA group, *p* 0.152. Other pharmaceuticals used in the SA group were, in order of frequency, daptomycin, rifampicin, linezolid, quinolones and, exceptionally, fosfomycin combined with imipenem or daptomycin. The number of patients who had perivalvular complications was 14 (34%) vs. 113 (33%) and surgery was indicated for 22 (53.7%) vs. 213 (62%). The surgical risk (median and IQR) was 17.7 (6–34.8) vs. 20.8 (10–41.8). The number of patients who underwent surgery during hospitalisation was 15 (36%) vs. 98 (28.5%) and surgery was not delayed in 12 (80%) vs. 93 (95%), *p* 0.853. The in-hospital mortality rate was proportionally greater for SA, 12 (29%) vs. 150 (43%) without statistical differences. There were 4 (1%) relapses in the SA group and none in the GBS group (Table 1). In the bivariate analysis of factors related to mortality, heart failure, development of renal failure and CNS impairment determined mortality in both groups. In the SA left-sided IE group, septic shock also determined mortality. In the multivariate analysis, heart failure, septic shock and CNS impairment determined mortality (HR 1.96, CI 95% 1.40–2.73; 1.69, CI 95% 1.19–2.39 and 1.37, CI 95% 0.99–1.88 respectively) and, to a lesser extent, the aetiology of IE caused by SA as well as age (HR 1.06, CI 95% 0.58–1.93 and 1.01, CI 95% 1.00–1.002, respectively) (Tables 2 and 3; Fig. 1).

In the GBS IE group, 7 patients were not operated on despite having some surgical indications vs. 115 in the SA group

Table 3 Cox regression of variables associated with mortality in SA left-sided IE versus GBS left-sided IE

Variables	HR	CI 95%	<i>p</i>
Median years of age (IQR)	1.01	1.00–1.02	0.057
SA (<i>S. aureus</i>)	1.06	0.58–1.93	0.838
Complications			
Heart failure	1.96	1.40–2.73	< 0.001
Septic shock	1.69	1.19–2.39	0.003
Central nervous system (CNS)	1.37	0.99–1.88	0.055
Renal failure	1.38	0.99–1.92	0.053

Fig. 1 Function of survival of all patients. Comparing GBS and SA (*S. aureus*) variables



and 4 died (57%) vs. 74 (64%) (Table 4). These patients were older, all developed heart failure during the course of the disease, half had perivalvular complications and the surgical risk score was somewhat higher. In cases of SA left-sided IE patients with surgical criteria who did not undergo surgery, comorbidity was higher and there were more cases of renal failure and septic shock (Table 4).

The sub-analysis of community-acquired cases demonstrated that patients with GBS left-sided IE were significantly older, 37 (90%) vs. 197 (57.2%), with a median age of 65 vs. 55 years, p 0.009, and they had a median number of comorbidities of 2 vs. 0.60, p 0.002. The most frequent comorbidity

was diabetes mellitus in GBS left-sided IE patients, 13 (35%) vs. 37 (18.8%), p 0.047. There were no differences in other comorbidities (chronic renal failure, chronic pulmonary conditions, chronic liver disease, active neoplasia, prior transplant) or in regard to gender, with 23 male patients (62.2%) vs. 126 (64%). Thirty-one (83.8%) vs. 176 (89%) cases were native valve IE and 6 (16.2%) vs. 23 (11.7%) cases were late prosthetic valve IE. There were no differences in valvular localisation: 16 (43.2%) vs. 68 (34.7%) were aortic, 28 (75.7%) vs. 135 (69%) were mitral and 0 vs. 17 (8.6%) were also localised in the tricuspid valve in addition to the other valves. GBS only affected left valves, 7 (19%) vs. 25 (12.7%)

Table 4 Living patients and deceased patients with surgical indications not operated on

Variables	Living patients		deceased patients	
	GBS left-sided IE $N = 7$ n (%)	SA left-sided IE $N = 115$ n (%)	GBS left-sided IE $N = 4$ n (%)	SA left-sided IE $N = 74$ n (%)
Years of age (IQR)	72 (65–79)	64 (49–75)	74.5 (66.7–86)	68 (50–76)
Charlson Index (IQR)	0 (0–2)	2 (1–4)	1 (2–4)	2.9 (1–4)
Complications				
Heart failure	5 (71.4)	76 (66)	4 (100)	61 (82)
CNS	3 (43)	57 (49)	2 (50)	41 (55)
Renal failure	1 (14.3)	57 (50)	1 (25)	47 (64.4)
Septic shock	2 (28.6)	42 (36.5)	1 (25)	36 (48.6)
Periprosthetic leak	2 (28.6)	39 (34)	2 (50)	25 (34)
Log. EuroSCORE I (IQR)	35.30 (7.5–65.4)	28.7 (15–54)	50 (34.6–79.2)	41.3 (25–58.3)
Not operated on and deceased	4 (57)	74 (64)		

Table 5 Comparative analysis between community-acquired SBG left-sided IE and community-acquired SA left-sided IE

Variables	GBS left-sided IE	SA left-sided IE	Bivariate GBS vs. SA		
	<i>N</i> = 37	<i>N</i> = 197	<i>N</i> = 234		
	<i>n</i> (%)	<i>n</i> (%)	<i>p</i>	OR	CI 95%
Defined left-sided IE	35 (94.6)	189 (95.9)	0.661		
Male sex	23 (62)	126 (64)	0.854		
Median years of age (IQR)	65 (52–71.5)	55 (37–68)	0.009		
Charlson Index	2 (0–3.75)	0.60 (0–2)	0.002		
Diabetes mellitus	13 (35)	37 (18.8)	0.047	2.342	1.091–5.028
Chronic kidney failure	2 (5.4)	4 (9.1)			
Valvular heart disease prior to left-sided IE	17 (51.5)	94 (49.7)	1.000		
Vascular manipulations	0	37 (32.5)	0.033	1.48	1.304–1.681
Skin manipulations	3 (17.6)	24 (21.1)	1.000		
IVDU	0	17 (18.1)	0.003		
GBS left-sided IE					
SA left-sided IE					
TT echocardiography	36 (97)	131 (97)	1.000		
TE echocardiography	22 (59–5)	107 (54.3)	0.594		
Echo	35 (94.6)	184 (93.4)	1.000		
Vegetations	33 (89)	161 (81.7)	0.345		
Vegetations > 1 cm	19 (68)	80 (57)	0.400		
Localisation of left-sided IE					
Mitral valve	28 (75.7)	135 (69)	0.443		
Aortic valve	16 (43.2)	68 (34.7)	0.353		
Plurivalvular	7 (19)	25 (12.7)	0.304		
Tricuspid	0	17 (8.6)	0.082		
Type of left-sided IE					
Native IE	31 (83.8)	176 (89)	0.397		
Early prosthetic IE	0	1	1.000		
Late prosthetic IE	6 (16.2)	23 (11.7)	0.422		
Acute course (< 1 week)	23 (62.2)	138 (70)	0.341		
Skin manifestation left-sided IE	3 (8.1)	81 (41)	0.001		
Septic arthritis	2 (5.4)	24 (12.2)	0.390		
Spondylitis	0	11 (5.6)	0.221		
Ocular complications	3 (8.1)	27 (13.7)	0.433		
Complications					
Heart failure	18 (48.6)	97 (49.2)	1.000		
Septic shock	5 (13.5)	50 (25.4)	0.142		
Central nervous system (CNS)	17 (45.9)	105 (53.3)	0.475		
CVA ischemic stroke	9 (24.3)	39 (19.8)	0.512		
CVA haemorrhagic stroke	1 (2.7)	3 (1.6)	0.515		
Renal failure	9 (9.7)	84 (42.6)	0.044	2.052	1.015–4.148
Max. pre-surg. creatinine levels	1.2 (0.95–1.95)	1.9 (1.10–3.05)	0.033		
Large blood vessel embolisms	4 (10.8)	24 (12.2)	1.000		
Visceral abscesses	5 (2.5)	0	1.000		
Septic arthritis	24 (19.4)	2 (8.7)	0.371		
Spondylitis	11 (8.8)	0	0.215		
Perivalvular complications	12 (32.4)	69 (35.2)	0.852		
Days of antibiotic treatment, median (IQR)	28 (14–30)	28 (12–42)	0.331		
Surgical indication	19 (51.4)	115 (58.4)	0.471		
Logarithmic EuroSCORE	18.33	18.58	0.731		
I % median/(IQR)	(8.11–37.40)	(7.80–37.35)			
Surgery during hospitalisation	13 (35)	59 (30)	0.563		
Without surgical delay	10 (27)	57 (29)	1.000		
Left-sided IE relapse	0	2			
In-hospital mortality	10 (27)	78 (39.6)	0.195		

cases, and SA affected left valves and the tricuspid valve (17 of 25). Half of the patients in each group knew they had a prior valvular disease; the distribution was similar among rheumatic, myxoid, degenerative or congenital valvular heart disease between both groups. In the SA group, there were proportionally more vascular manipulations, 0 vs. 37 (32.5%), in large

part due to intravenous drug use. There were no differences in terms of other manipulations that could be a cause of left-sided IE. In both groups, the course of the disease was acute, 23 (62.2%) vs. 138 (70%), and fever was continuous, 34 (92%) vs. 190 (96.4%). In this community-acquired subgroup, skin manifestations of IE in any of its presentations (petechiae,

Table 6 Variables associated with mortality in GBS left-sided and community-acquired SA left-sided IE. Bivariate analysis (living vs. deceased in each group)

Variables	GBS left-sided IE <i>N</i> = 37 exitus = 10				SA left-sided IE <i>N</i> = 197 exitus = 78			
	<i>n</i> (%)	<i>p</i>	OR	CI 95%	<i>n</i> (%)	<i>p</i>	OR	CI 95%
Male gender	7 (70%)	0.710			55 (70.5)	0.132		
Median years of age (IQR)	65 (52–71.5)	0.243			55 (37–68)	0.063		
Charlson Index	2 (0–2)	0.023			0.6 (0–2)	0.182		
Early prosthetic IE	0				0			
Complications								
Heart failure (HF)	8 (80)	0.029	9.500	1.735–52.021	54 (69.2)	0.001	3.977	2.163–7.313
Septic shock	3 (30)	0.110			32 (41)	0.001	3.959	1.988–7.663
Central nervous system (CNS)	8 (80)	0.023	8.000	1.399–45.756	48 (61.5)	0.080		
Renal failure (RF)	5 (50)	0.041	5.750	1.124–29.411	39 (50)	0.106		
Large blood vessel embolisms	2 (20)	0.291			8 (10.3)	0.657		
Perivalvular complications	4 (40)	0.696			31 (40.3)	0.284		
Surgery during hospitalisation	3 (30)	1.000	0.729	0.153–3.474	23 (29.5)	0.964	0.516	0.563–1.800

Janeway lesions, Osler's nodes, subungual splinter haemorrhages) were more frequent in the SA left-sided IE group. In the community-acquired IE group, there was only 1 case of early prosthetic endocarditis and it was due to SA. A TTE and TEE were performed equally in both groups and vegetations were detected in similar percentages of patients. There were no differences in regard to complications, with the exception of renal failure, which was significantly more frequent in SA (p 0.044). It should be noted that only 5 cases of community-acquired left-sided IE were caused by methicillin-resistant SA, and therefore the cases treated with vancomycin were not highly represented in this subgroup. There were no other differences in variables related with antibiotic or surgical treatment. In the comparative analysis, in-hospital mortality was lower in the GBS group than that in the SA group patients, without statistically significant differences (Table 5). In the bivariate analysis of factors associated with mortality, comorbidity, heart failure, renal failure and CNS impairment determined mortality in GBS cases whereas in the SA group,

heart failure and septic shock were the principal factors (Table 6). In the multivariate analysis, only heart failure and septic shock determined mortality (HR 2.52, CI 95% 1.61–3.95 and 1.68, CI 95% 1.03–2.73, respectively) and, to a lesser extent, comorbidity (HR 1.01, CI 95% 0.9–1.13) and aetiology due to SA (HR 1.14, CI 95% 1.58–2.25). (Table 7 and Fig. 2).

Discussion

Under our knowledge, this is the first study which the objective is to compare the clinical course of left-sided IE caused by GBS with respect to left-sided IE caused by SA.

In our cohort, GBS left-sided IE is much less frequent than SA left-sided IE and represented less than 3% of all IE cases throughout the years and with a similar incidence as previously commented in other publications [6].

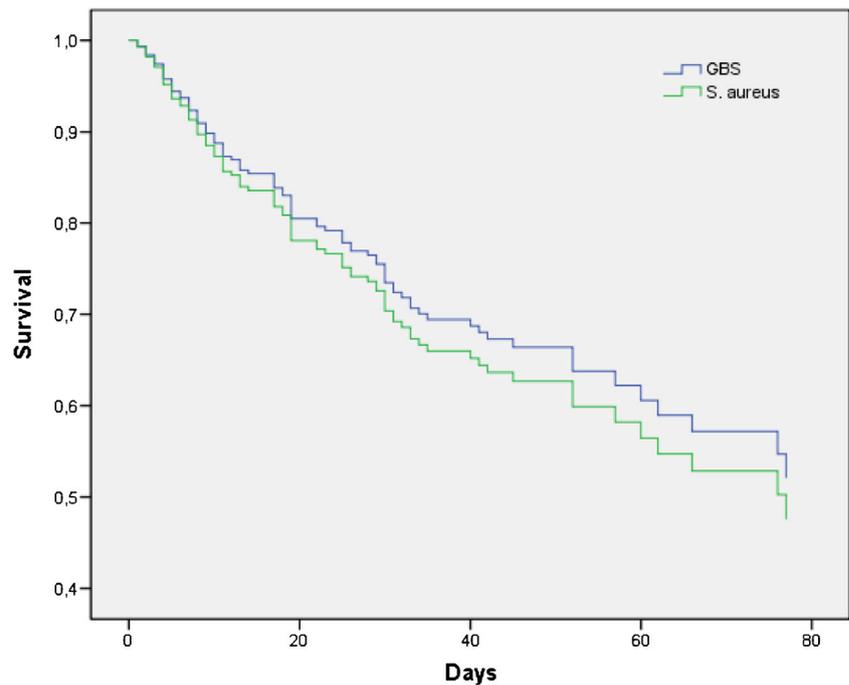
In our cohort, GBS left-sided IE behaves similarly to SA left-sided IE, in accordance with the opinion of Sendi et al. [12]. They affect the same sex and age group, they have similar associated comorbidities and acute course of a week or less of symptoms with fever being the usual form of presentation, and serious complications develop. However, in this study, we found some differences between them:

- (1) The form of acquiring the infection: community acquisition predominates in GBS whereas HAIE predominates in SA, mainly in relation to vascular manipulation.
- (2) GBS left-sided IE, in contrast to SA, does not cause early prosthetic valve endocarditis.

Table 7 Cox regression of variables associated with mortality in GBS left-sided and community-acquired SA left-sided IE

	HR	CI 95%	<i>p</i>
Charlson Index	1.01	0.90–1.13	0.873
SA (<i>S. aureus</i>)	1.14	0.58–2.25	0.705
Complications			
Heart failure (HF)	2.52	1.61–3.95	< 0.001
Septic shock	1.68	1.03–2.73	0.038
Central nervous system (CNS)	1.32	0.82–2.10	0.251
Renal failure (RF)	1.16	0.74–1.81	0.526

Fig. 2 Function of survival of community-acquired left-sided IE. Comparing GBS and SA (*S. aureus*) variables



- (3) In contrast to SA left-sided IE, GBS does not tend to cause the typical skin lesions associated with IE.
- (4) Upon analysing complications, there were no differences with the exception of the development of renal failure, which was greater in the SA group. The patients included in each group had similar creatinine levels upon admission, but the SA group developed greater renal deterioration over the course of the disease. Both groups received gentamicin among other potentially nephrotoxic drugs. It was used significantly more in the GBS group, though it did not determine kidney failure in the patients. In the SA group, gentamicin and vancomycin were used either alone or in combination in 52% of the patients. In addition, there were cases of glomerulonephritis and renal embolisms; these were unusual in GBS left-sided IE and, as such, it could be considered that the combination of nephrotoxic drugs [24, 25], glomerular disease [26, 27] and, to a lesser extent, renal embolism could have contributed to the renal deterioration observed in the SA left-sided IE group. Regarding the SA group, our results match with a recent study that includes more than 200 contemporary episodes of *S. aureus* IE. Nearly 50% of SA infective endocarditis developed acute impairment of renal function [28].

On the other hand, in both groups, perivalvular complications and need for surgery were also similar, as was theoretical perioperative risk. Overall in-hospital mortality was very high in the SA group and was lower in the GBS group, without statistical differences. It was higher in patients who were rejected for surgery (18% of GBS patients

and 33.5% of SA patients did not undergo surgery, despite that had surgical criteria). In these cases, surgery was not recommended either by the clinician responsible for the patient or by the surgeon, due to medical severity and/or an elevated risk of perioperative death (which amounted to 50% in the GBS group and was somewhat lower in the SA group). GBS left-sided IE patients with surgical criteria who were not operated died due to heart failure. Half also developed neurological complications or perivalvular lesions. Apart from that, those in the SA group mainly died of heart failure, renal failure or septic shock, in the order of frequency.

The comparative analysis of the community-acquired cases, the majority cases of GBS left-sided IE and 57% of SA cases, demonstrated that patients with GBS left-sided IE had significantly more age and comorbidity, frequently diabetes mellitus. The GBS did not affect early prosthetic valves. There were also significantly more cutaneous manifestations of IE and more renal failure in SA left-sided IE, without significant differences in other local or systemic complications.

In terms of mortality, in the bivariate analysis of the factors related, there were some differences between the two groups, without differences in the multivariate analysis.

Age, septic shock, heart failure, renal failure and neurological deterioration conditioned mortality in the SA group. In cases with GBS left-sided IE, heart failure, renal failure and neurological deterioration were associated with mortality.

In the communitarian group, the neurological deterioration in the SA left-sided IE had less impact on the mortality that GBS left-sided IE, and in this last group, there were a greater

number of comorbidities among the deceased. These differences lose significance in the multivariate analysis using Cox's regression.

In conclusion, *Streptococcus agalactiae* left-sided IE, although not frequent, is very important because it has an aggressive and similar behaviour as *Staphylococcus aureus* left-sided IE. Both present with acute fever, but GBS left-sided IE is not accompanied by skin lesions. It usually develops serious complications and a heart surgery is frequently required during the admission. Despite its easy medical treatment and the performance of early surgery, it has high mortality.

We believe that when there is clinical suspicion or confirmation by transthoracic echocardiography of *Streptococcus agalactiae* left-sided IE, as in the case of SA left-sided IE, it is advisable to optimise medical treatment and perform transesophageal echocardiography in order to establish quickly the best time for surgery and reduce associated mortality.

Strengths and weaknesses

The study's strength is that it was carried out on a homogeneous cohort of patients with a clinical management protocol in accordance with the recommendations of treatment guidelines throughout the period studied. Given the low frequency of GBS left-sided IE, we had to include all the cases throughout the 31 years of existence of our database, a long period, and this was the study's main limitation. For this reason and also due to the heterogeneity of the treatment times of the drugs administered in both groups, it was not possible to determine the relationship between drug use and the development of complications beyond what was mentioned regarding the development of renal failure.

Compliance with ethical standards

All procedures followed were in accordance with the ethical standards. Informed consent was obtained from all patients for being included in the study.

Conflict of interest The authors declare that they have no conflict of interest.

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