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Species and biotypes of *Streptococcus bovis* causing infective endocarditis

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ABSTRACT

Introduction: *Streptococcus bovis/equinus* complex (SBEC) is a major cause of infective endocarditis (IE), although its incidence varies greatly depending on the geographical area. The characteristics of IE caused by *Streptococcus gallolyticus* susp. *gallolyticus* are well known; there are hardly any descriptions of IE caused by other species or biotypes.
Methods: Retrospective cohort study, from 1990 to 2019, of all SBEC IE in adults in three Spanish hospitals, Lugo (LH), Barcelona (BH) and Ferrol (FH) where the population is mainly rural, urban and mixed, respectively. The incidence of IE was analyzed in 3 areas. Clinical characteristics of IE (277 cases, 258 biotyped) were compared according to SBEC species and biotypes.
Results: There are significant differences between the incidence of SBEC IE in HL ($27.9/10^6$) vs. HF and HB (8.8 and 7,1, respectively, $p < 0.001$). We found significant differences (SbI vs. SbII) in mean age (68.5 vs. 73 years; $p < 0.01$), duration of symptoms before diagnosis (46.9 ± 46.5 vs. 30.4 ± 40.9 days; $p < 0.01$), presence of comorbidities: 39.1% (78) vs. 54.2% (32; $p < 0.04$), predisposing heart illness:62.3% (124) vs. 81.3% (48; $p < 0.006$), particularly, prosthetic or intravascular devices IE: 24.6% (49) vs. 52.4% (31; $p < 0.001$), bivalve involvement:23.6% (47) vs. 11.8% (7; $p < 0.05$) and heart failure: 24.6% (49) vs. 38.9% (23; $p < 0.03$). There were no significant differences in embolic events, need for surgery or mortality. The association with CRC was high in both groups: 77.7% vs. 66.6%.
Conclusions: IE due to SBEC has geographical variations in incidence and different clinical characteristics among biotypes. The association with CRC was high.

Especies y biotipos de *Streptococcus bovis* causantes de endocarditis infecciosa

Palabras clave:
Streptococcus bovis
Endocarditis infecciosa
Biotipos
Especies
Cáncer colorrectal

RESUMEN

Introducción: El complejo *Streptococcus bovis/equinus* (SBEC) es una de las principales causas de endocarditis infecciosa (EI), aunque su incidencia es muy variable según la zona geográfica. Las características de EI causada por *Streptococcus gallolyticus* subsp. *gallolyticus* son bien conocidas; apenas hay descripciones de EI causada por otras especies o biotipos.
Métodos: Estudio de cohorte retrospectivo, desde 1990 hasta 2019, de todas las EI por SBEC en adultos en 3 hospitales españoles, Lugo (LH), Barcelona (BH) y Ferrol (FH) donde la población es mayoritariamente rural, urbana y mixta, respectivamente. Se analizó la incidencia de EI en 3 áreas. Se compararon las características clínicas de EI (277 casos, 258 biotipados) según las especies y biotipos de SBEC.

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Resultados: Existen diferencias significativas entre la incidencia de EI por SBEC en HL (27,9/10^6) vs. HF y HB (8,8 y 7,1, respectivamente, p < 0,001). Encontramos diferencias significativas (SbI vs. SbII) en edad media (68,5 vs. 73 años; p < 0,01), duración de los síntomas antes del diagnóstico (46,9 ± 46,5 vs. 30,4 ± 40,9 días; p < 0,01); comorbilidades: 39,1 (78) vs. 54,2% (32; p < 0,04); enfermedad cardíaca predisponente: 62,3 (124) vs. 81,3% (48; p < 0,006), en particular, EI protésica o sobre dispositivos intravasculares: 24,6 (49) vs. 52,4% (31; p < 0,001); afectación bivalva: 23,6 (47) vs. 11,8% (7; p < 0,05) e insuficiencia cardiaca: 24,6 (49) vs. 38,9% (23; p < 0,03). No hubo diferencias significativas en cuanto a eventos embólicos, necesidad de cirugía o mortalidad. La asociación con el CCR fue alta en ambos grupos: 77,7 vs. 66,6%.
Conclusiones: La EI por SBEC tiene variaciones geográficas en la incidencia y diferentes características clínicas entre los biotipos. La asociación con el CCR fue elevada.

Introduction

Streptococcus bovis/equinus complex (SBEC) is a group of bacteria involving 7 species which colonize the gastrointestinal tract of animals, mainly birds and ruminants, and they can be transmitted to humans.[1] The species causing human infections are: *S. gallolyticus* subsp. *gallolyticus* (former *S. bovis* biotype I), *S. infantarius* (former *S. bovis* biotype II/1, with two subspecies: *S. infantarius* subsp. *coli* (or *S. lutetiensis*) and *S. infantarius* subsp. *infantarius*) and *S. gallolyticus* subsp. *pasteurianus* (former *S. bovis* biotype II/2). The other 3 species: *S. equinus*, *S. alactolyticus* and *S. gallolyticus* subsp. *macedonicus* have rarely been implicated in human infections.[1,2]

SBEC causes different types of infection being bacteremia the most prevalent.[3–13] A variable proportion of bacteremic cases have been associated with infectious endocarditis (IE) and colorectal cancer (CRC), depending mainly on the prevalence of *S. gallolyticus* subsp. *gallolyticus* (SGG), which is the species with strongest association to both entities.[3,12–14]

SBEC is the fifth leading cause of IE in the world,[15] although its frequency varies among countries and geographic areas.[12,17] Its prevalence is higher in Europe than in the USA, being a very frequent cause of IE in some areas of southern Europe.[17]

The clinical profile has been reported,[16–19] but the lack of identification of species or biotypes of SBEC causing IE is of concern. For this reason, the information available is basically referred to biotype I,[16,18,19] with only anecdotal case on IE caused by *S. gallolyticus* subsp. *pasteurianus* (SGP) or *S. infantarius* (SI).[20,21]

The objectives of our study were: (1) to analyze a series of patients with *S. bovis* IE, the incidence over time and their clinical/epidemiological characteristics in 3 different geographic areas, and (2) to carry out a comparative study between IE caused by SGG (former *S. bovis* biotype I) and the other species of SBEC, most of which were formerly included in *S. bovis* biotype II.

Methods

This is a retrospective observational IE study pulled out from a prospective protocol of all patients with bacteremia in adult patients who were admitted to three hospitals in Spain from 1/1990 to 12/2019. Hospital Universitario de Lugo (HL) and Hospital Universitario de Ferrol (HF), both located in Galicia county in the northwest of Spain, and Hospital Universitario de Bellvitge (HB) located in Barcelona, Catalonian county in the northeast of Spain. The Hospital Lugo (HL) is a teaching hospital with 690-beds serving an area of approximately 230,000 inhabitants, which is mainly a cattle production area. The Hospital Ferrol (HF) is a teaching hospital with 350-beds serving an area of approximately 200.000 inhabitants, which is mostly a fishing area; both institutions have no cardiac surgery or organ transplantation programs. The Hospital Bellvitge (HB) is a 900-bed university hospital, which serves an overall population of about one million people in an urban area, and it has an active program of organ transplantation and cardiac surgery. All three institutions have a prospective surveillance protocol of all patients with bacteremia since 1990s. In a previous study we described all cases of bacteremia caused by SBEC in our institutions.[13]

Study design

From 1990, in our institutions (HL, HF and HB) we have prospectively studied all patients with bacteremia. In a daily basis the Microbiology laboratory identify those cases with positive blood cultures and an Infectious Disease physician visited the patients. The microbiology and clinical data were included in a computerized database in each institution using the same protocol. From these databases we selected the cases with SBEC EI. In patients who had more than one episode of IE only the first episode was included in the present study.

Definitions and outcome

Definitive and probable IE were diagnosed applying modified Duke's criteria, and retrospectively before the year 2000.[22] Transthoracic echocardiography was used in all patients with IE and transesophageal ultrasound was also used where the previous test was not conclusive.

Intravascular devices were defined as a permanent pacemaker and/or cardioverter-defibrillator.

Embolic events were defined as emboli in various parts of the body, such as the brain, lung, coronary artery, spleen, intestine, kidney, and large artery of the extremities. Symptomatic and asymptomatic cases were included, but we have not systematically performed imaging tests in the asymptomatic patient to detect emboli.

We tried to submit to colonoscopy to most patients with SBEC IE. The colon was examined up to the cecum by colonoscopic evaluation during the episode of IE in most cases, but in some others, colon examination had been performed earlier when the diagnosis of colorectal cancer (CRC) was made. All visible polyps were removed and sent to the Pathology Department for histological examination. CRC included both adenoma and carcinoma; advanced adenoma was defined as an adenoma with a diameter of ≥1 cm, or tubulovillous (25–75% of villous component) or villous (>75%) histology, or high-grade dysplasia. Carcinoma in situ was classified as adenoma with high-grade dysplasia, and the criterion for invasive cancer was the presence of malignant cells beyond the muscularis mucosa.

Microbiological studies

Blood cultures were performed according to standard criteria applied to all participating Microbiology laboratories of the three hospitals. Species identification was performed by the API 20 Strep

Table 1
Incidence of *Streptococcus bovis* EI in three geographic areas in Spain.

	Area 1: Lugo	Area 2: Ferrol	Area 3: Barcelona
Periods	No. of cases (cases/10^6 person-years)		
1990–2004*	16.5	6.1	4
2004–2019**	27.9	8.8	7.1

* p value Area 1 vs 2: $p = 0.05$; Area 1 vs 3 $p = 0.03$.
** p value Area 1 vs 2: $p = 0.003$; Area 1 vs 3 $p < 0.001$.

system (BioMérieux, Marcy-l'Etoile, France), and with Vitek 2 system using the gram-positive (GP) identification card (bioMérieux, Marcy l'Etoile, France). In recent years, Matrix-assisted laser desorption ionization -time of flight mass spectrometry (MALDI-TOF MS) has been implemented as a first step for diagnosis. Additional confirmatory tests were performed by conventional methods.[23] Analysis of the complete rRNA gene sequence[6] and the polymorphism of manganese-dependent superoxide dismutase gene (sodA) according to the indications of Poyart[24] were used for molecular identification. The sequences obtained were compared with those of the corresponding genes available in GenBank by using Blast sequence software (http://www.ncbi.nlm.nih.gov/).

Statistical analysis

Statistical analysis was carried out with the PASW-20. Categorical variables were expressed as proportions with binomial 95% confidence intervals and compared using two-sided Chi-square test or Fisher exact tests. Continuous variables were analyzed with Student's t test when normally distributed; otherwise, they were analyzed using the Mann–Whitney *U* test. To determine the increase in the incidence, we considered two periods: 1990–2004 and 2005–2019. Variations in incidence rates among the three areas were determined by comparing incidence rate ratios with 95% confidence intervals using Poisson regression. The alpha level was set at .05 for all statistical tests. Denominators for the incidence rates calculation were extracted from the official census.[25]

Conflict of interest

The authors declare that they have no conflict of interest - Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Results

Epidemiological aspects

During the study period, we detected 277 cases of IE caused by SBEC. They accounted for 14.1% of the total IE (277/1952); this proportion ranged between 26.2% (134/511) in HL (1st cause of IE), 13.1% (41/312) in HF (3rd cause of IE) and 9.0% of all IE (102/1129) in HB (5th cause of IE). In addition, the incidence (1990–2004 vs. 2005–2019) ranged between 16.5 and 27.9 per million inhabitants/year in Lugo (HL); 6.1 and 8.8 in Ferrol (HF), and 4.0 and 7.1, respectively, in Barcelona (HB) (Table 1).

The incidence rate ratio was higher in Lugo in the 1990–2004 period than in Ferrol (RR 2.67; 95%CI: 1.04–6.81, $p = 0.05$) and in Barcelona (RR 4; 95%CI: 1.29–16.44, $p = 0.01$), it was also higher in the 2005–2019 period: vs. Ferrol (RR 3.11; 95%CI: 1.47–6.59, $p = 0.003$), and vs. (Barcelona RR 4; 95%CI: 1.75–9.16, $p < 0.001$). Comparing 2005–2019 and 1990–2004 periods, the incidence of endocarditis increased in all three geographical areas, mostly in Lugo without being a significant increase (RR 1.75; 95%CI: 0.95–3.23, $p = 0.09$).

Etiology

In 258 of the 277 (93.1%) IE cases the species or biotypes of SBEC could be determined. 199 IE caused by SbI (SGG) and 59 caused by SbII (*S. gallolyticus* subsp. *pasteurianus* 33, *S. infantarius* 17, *S. equinus* 2 and biotype II 7) were identified.

Although in the 3 medical centers SGG was the predominant species among IE caused by SBEC, there were important differences in their proportions. Thus in the HL and HF the SGG/SGP ratio was 11 times (HL: 117/10; HF: 34/3), in the HB this ratio was 2.4 times (48/20). This is because while in the two Galician hospitals (HL and HF) SGG was the predominant species in bacteremia cases, in the HB, SGP was the main species.

During the same period, 292 bacteremia cases of SbI and 429 of SbII were detected. The association with IE was greater for SbI: 68.1% (199/292) than for SbII: 13.7% (59/429; $p < 0.001$). On the other hand, we analyzed the association of species and subspecies of SBEG with IE. According to other reports, in our series the association of SGG with IE was greater than that occurred with SGP and SI; this association was similar for SGP and SI: 18.1% vs. 14.0%, respectively (Table 3). However there was a great difference between the two subspecies of SI: *S. lutetiensis* and *S. infantarius* subsp. *infantarius*, while for the first subspecies only 7 of 96 bacteremia cases were associated with IES (7.2%), for the second this association was 60% (6/10).

Clinical characteristics

We compared the demographic and epidemiological/clinical characteristics between biotype I (199 cases) and biotype II (59 cases). There was a predominance of elderly men in both groups, but patients with Sb II IE were older, had more comorbidities, predisposing heart illness, particularly, prosthetic valves or intravascular devices.

IE had a subacute evolution, with significant differences in the duration of symptoms, being longer in the SbI group (46.9 (± 46.5) vs. 30.4 (± 40.9) days). Patients with IE due to SbII had less bivalvular involvement than those with IE due to SbI. Heart failure was more common in patients with SbII IE. Embolic events or discitis were high in both groups, but without statistical significance. Colonoscopy was performed in 77.1% of patients, with high rates of colorectal neoplasia in both groups, but without statistical significant differences. Likewise, there were no differences in the need for valve replacement or mortality between the two groups (Table 2).

Discussion

Our study agrees with previous data on important regional differences in incidence and predominant species of SBEC causing IE.[15,17,18] Although the reasons are not well known, a higher incidence of bacteremia and IE caused by SBEC has been described in rural areas.[13] Thus, in a French study[16] several differences were found in the incidence of SBEC IE between a rural region (Marne) and an exclusively urban region (Ille de France), (23.9 vs. 11.4 cases/million person-years, respectively). It was similar to those found in our study when comparing a predominantly rural area (HL) and an exclusively urban area (HB): 27.9 vs. 7.1/10^6. This incidence in the HL area is even higher than in any region of France, which is the country with the highest reported incidence of IE due to Sb.[17] Recently, a case of IE with possible zoonotic transmission has been reported[26] and there is evidence of increased intestinal colonization by SGG in people in contact with animals or manure.[27] Likewise, in Galicia (where the HL and HF are located), a higher

Table 2
Comparative between *S. bovis* biotype I and II infective endocarditis with regard to demographic characteristics, clinical features and outcome.

	S.bovis I *N* = 199	*S. bovis* II *N* = 59	*p value*
Percent of total endocarditis	10.1% (199/1952)	3.0% (59/1952)	<0.001
Percent of total SBEC bacteremias	68.1% (199/292)	13.7% (59/**429**[a])	<0.001
Age, mean (±SD, years)	68.5 (±11.7)	73.0 (±12.5)	0.01
Male sex	156 (78.3%)	40 (78.6%)	0.09
Predisposing heart disease	124 (62.3%)	48 (81.3%)	0.006
Prosthetic valve	42 (21.1%)	25 (42.3%)	0.001
Degenerative valve disease	60 (30.1%)	11 (18.6%)	0.08
Intravascular devices	7 (3.5%)	6(10.1%)	0.04
Others	15 (7.5%)	6 (10.1%)	0.5
Comorbidities	78 (39.1%)	32 (54.2%).	0.04
Diabetes mellitus	41 (20.6%)	19 (32.2%)	0.06
Liver cirrhosis	17 (8.5%)	8 (13.5%)	0.2
Intravenous drug use	1(0.5%)	1 (1.7%)	0.3
Non-colorectal neoplasm	24 (12.0%)	3 (5.0%)	0.1
End stage renal failure	17 (8.5%)	11 (18.6%)	0.02
Immunosuppressive condition	11 (5.5%)	6 (10.1%)	0.2
Age adjusted Charlson	5 ± 2.03	6.9 ± 1.46	0.03
Colorectal neoplasm[b]	122/157 (77.7%)	28/42 (66.6%)	0.14
Adenomas	95 (47.7%)[c]	23 (38.9%)[d]	0.5
Carcinomas	27 (17.9%)	5 (11.9%)	0.4
Colonoscopy	157 (78.9%)	42 (71.2%)	0.2
Symptoms duration in days, mean (±SD)	46.9 (± 46.5)	30.4 (± 40.9)	0.01
Fever	166 (83.4%)	43 (72.8%)	0.06
Number of positive blood cultures, mean (±SD)	4.1 (±1.8)	3.3 (± 1.6)	0.002
Affected valve			
Mitral alone	52 (26.1%)	15 (25.4%)	0.9
Aortic alone	78 (39.1%)	31 (52.5%)	0.06
Aortic and mitral	47 (23.6%)	7 (11.8%)	0.05
Tricuspid	2 (1.0%)	0	0.9
Intravascular devices	7 (3.5%)	6 (10.1%)	0.04
Others	2 (2.5%)	0	0.9
Vegetations	137 (68.8%)	30 (50.8%)	0.01
Heart failure	49 (24.6%)	23 (38.9%)	0.03
Embolisms	70 (35.1%)	16 (27.1%)	0.2
Vertebral osteomyelitis	22 (11.1%)	8 (13.5%)	0.6
Septic arthritis	15 (7.5%)	5 (8.4%)	0.8
Duke criteria			
Definite	155 (77.8%)	40 (67.7%)	0.11
Possible	44 (22.2%)	19 (32.3%)	0.11
Cardiac surgery during hospitalization	21 (10.5%)	4 (6.7%)	0.3
In-hospital mortality	25 (12.5%)	9 (15.2%)	0.5

[a] 121 *S. infantarius,* 182 *S. pasteurianus,* 126 SbII.
[b] Patients undergoing colonoscopy.
[c] 53 were advanced adenomas.
[d] 15 were advanced adenomas.

Table 3
Literature review. Reported cases of endocarditis among bacteremia cases caused by *Streptococcus bovis-equinus* complex.

First author/country (Ref.)	*S. gallolyticus* subsp. *gallolyticus* Endocarditis/Bacteremia	*S. infantarius* Endocarditis/Bacteremia	*S. gallolyticus* subsp. *pasteurianus* Endocarditis/Bacteremia
Ruoff/USA (3)	16/17	1/10	2/7
Claridge/USA (4)	1/1	1/2	3/10
Tripodi/Italy (5)	18/20	0/1	4/4
Beck/Germany (6)	9/21	4/14	0/11
Gómez-Garcés/Spain (7)	10/15	2/5	2/24
Romero/Spain (8)	1/14	0/7	6/24
Vaska/Australia (9)	6/10	0/1	1/5
Lazarovitch/Israel (10)	6/14	0/5	3/13
Sheng/Taiwan (11)	16/31	0/15	17/126
Marmolin/Denmark (12)	10/19	3/19	4/12
Total (% endocarditis)	93/162 (57.4%)	11/79 (13.9%)	42/236 (7.7%)
Our series/Spain	199/292 (68.1%)	17/121 (14.0%)	33/182 (18.1%)

incidence of cases of bacteremia caused by SBEC has been found in areas with a high density of cattle.[28] It should noted that this region is the largest producer of cattle and milk in Spain, and France is one of the largest producers of cattle in Europe.[28]

Our data also confirm that SGG has a greater association with IE than the other species, being most of SBEC IE cases due to SGG (3–12, Table 3). However, it should be noted that in those areas where *S. gallolyticus pasteurianus* is the predominant species causing bacteremia, the proportion of IE caused by this species can be significantly increased, as occurred in one of the centers participating in our study (HB) as well as in other institutions.[4,8] We have also detected a high association of *S. infantarius* subsp. *infantarius* with IE, as have been suggested in a previous study,[21] although more data are needed to confirm these results.

To our knowledge, there are no previous studies comparing the characteristics of IE caused by different species of SBEC. In our series, patients with IE caused by microorganisms included in the former Sb II are even older than patients with IE caused by Sb I, had more comorbidities and predisposing heart illness. The older age could partially explain why the former have a higher percentage of heart failure. However, despite being older and having a higher frequency of heart failure, and more comorbidities, they do not need a higher rate of valve replacement surgery or had greater mortality.

The presence of pre-existing valve disease is not a main characteristic of IE caused by SGG in some reports.[16]

Its ability to adhere to collagen in the colon and heart valves may explain its high association with CRC and IE, even on healthy valves. Although less known, the other Sb species do not have this ability to adhere to healthy valves. This could explain the high percentage of IE associated with prosthetic devices that we found in cases of IE caused by SGP and SI, which could illustrate a lower pathogenicity of these species compared to SGG.

Another relevant finding in our study was the high percentage of CRC found in IE caused by SGP and SI. Over the last years, the need to perform a colonoscopy in those patients with bacteremia or IE caused by SGG has been clearly established, because of the high frequency of occult neoplasms.[3,14] However, in the case of Sb II bacteremia, its indication is controversial.[29] A small preliminary study suggested the need to perform colonoscopy in these cases of IE caused by Sb II, due to the high frequency of neoplasms.[13] Our study confirms these previous findings, although more studies are needed to confirm these results. In this line, recent studies have shown that SGG is found in a high percentage of tumor tissues in cancer patients (74%) but not *S. pasteurianus* (11%), the former being implicated in the development of colorectal cancer.[30] However, a later study showed that not all SGG strains promoted the development of colorectal cancer.[31] On the other hand, a study conducted in Africa showed that colorectal colonization by *S. infantarius* subsp. *infantarius* was associated with colorectal cancer.[32]

Strengths and weaknesses of our study. The present study includes a high number of patients with IE and a high percentage with a colon examination. Our series come from 3 centers, two of them without cardiac surgery, which eliminates referral bias, and describes the clinical characteristics of IE caused by Sb species other than SGG. Although it incorporates the new SBEC taxonomy, an important limitation of the study is that a molecular study was not carried out in all isolates. Although most species can be reasonably distinguished by conventional methods, certain species and subspecies such as *S. equinus* and those of the *S. infantarius* group require molecular methods for their proper identification.[1,2,21] In recent years, MALDI-TOF MS has emerged as a fast and cost-effective methodology for identification of microorganisms but the high similarity in mass spectral patterns of some strains of the SBEC may hinder the differentiation at species/subspecies level.[33] New studies are needed with greater number of patients and identification at molecular level to better define differences among species and subspecies of the former Sb biotype II causing IE.

Conflicts of interest

The authors declare that they have no competing interests.

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