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MAJOR ARTICLE

Clinical Features and Outcomes of *Streptococcus anginosus* Group Infective Endocarditis: A Multicenter Matched Cohort Study

Francesc Escrihuela-Vidal,[1] Luis Eduardo López-Cortés,[2] Laura Escolà-Vergé,[3,4] Arístides De Alarcón González,[5] Guillermo Cuervo,[1,©] Antonio Sánchez-Porto,[6] Nuria Fernández-Hidalgo,[3,4] Rafael Luque,[5] Miguel Montejo,[7] José M. Miró,[8] Miguel Ángel Goenaga,[9] Patricia Muñoz,[10] Maricela Valerio,[10] Marco Ripa,[11] Dolores Sousa-Regueiro,[12] Mercé Gurguí,[13] María Carmen Fariñas-Alvarez,[14] Lourdes Mateu,[15] Elisa García Vázquez,[16] Juan Gálvez-Acebal,[2,a] and Jordi Carratalà[1]; for the Grupo de Apoyo al Manejo de la Endocarditis Infecciosa en España (GAMES) Cohort Investigators and the Barcelona Endocarditis Study Team (BEST)[b]

[1]Department of Infectious Diseases, Hospital Universitari de Bellvitge, Institut d´Investigació Biomèdica de Bellvitge, University of Barcelona, Barcelona, Spain, [2]Clinical Unit of Infectious Diseases and Microbiology, Hospital Universitario Virgen Macarena Institute of Biomedicine of Seville, Universidad de Sevilla, Sevilla, Spain, [3]Department of Infectious Diseases, Hospital Universitari Vall d´Hebron, Universitat Autònoma de Barcelona, Barcelona, Spain, [4]Spanish Network for Research in Infectious Diseases, Madrid, Spain, [5]Clinical Unit of Infectious Diseases, Microbiology and Preventive Medicine Infectious Diseases Research Group, Institute of Biomedicine of Seville, University of Seville/Centro Superior de Investigaciones Científicas (CSIC)/University Virgen del Rocío and Virgen Macarena, Sevilla, Spain, [6]Department of Infectious Diseases, Hospital Servicio Andaluz de Salud (SAS) Línea de la Concepción, Cádiz, Spain, [7]Unit of Infectious Diseases, Hospital Universitario de Cruces, Universidad del País Vasco, Bilbao, Spain, [8]Infectious Diseases Service, Hospital Clínic-Institut d'Investigacions Biomèdiques August Pi I Sunyer, University of Barcelona, Barcelona, Spain, [9]Department of Infectious Diseases, Hospital Universitario Donosti, San Sebastián, Spain, [10]Clinical Microbiology and Infectious Diseases Department, Hospital General Universitario Gregorio Marañón, Instituto de Investigación Sanitaria Gregorio Marañón, Centro de Investigación Biomédica en Red (CIBER) Enfermedades Respiratorias, Facultad de Medicina, Universidad Complutense de Madrid, Madrid, Spain, [11]Unit of Infectious and Tropical Diseases, Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) San Raffaele Scientific Institute, Milan, Italy, [12]Department of Infectious Diseases, Complejo Hospitalario Universitario A Coruña, A Coruña, Spain, [13]Department of Infectious Diseases, Hospital de la Santa Creu i Sant Pau, Universidad Autónoma de Barcelona, Barcelona, Spain, [14]Department of Infectious Diseases, Hospital Universitario Marqués de Valdecilla, Universidad de Cantabria, Santander, Spain, [15]Department of Infectious Diseases, Hospital Germans Trias i Pujol, Badalona, Spain, and [16]Department of Infectious Diseases and Internal Medicine, Instituto Murciano de Investigación Biosanitaria (IMIB), Hospital Clínico Universitario Virgen de la Arrixaca, Facultad de Medicina, Universidad de Murcia, Murcia, Spain

Background. Although *Streptococcus anginosus* group (SAG) endocarditis is considered a severe disease associated with abscess formation and embolic events, there is limited evidence to support this assumption.

Methods. We performed a retrospective analysis of prospectively collected data from consecutive patients with definite SAG endocarditis in 28 centers in Spain and Italy. A comparison between cases due to SAG endocarditis and viridans group streptococci (VGS) or *Streptococcus gallolyticus* group (SGG) was performed in a 1:2 matched analysis.

Results. Of 5336 consecutive cases of definite endocarditis, 72 (1.4%) were due to SAG and matched with 144 cases due to VGS/SGG. SAG endocarditis was community acquired in 64 (88.9%) cases and affected aortic native valve in 29 (40.3%). When comparing SAG and VGS/SGG endocarditis, no significant differences were found in septic shock (8.3% vs 3.5%, $P = .116$); valve disorder, including perforation (22.2% vs 18.1%, $P = .584$), pseudoaneurysm (16.7% vs 8.3%, $P = .108$), or prosthesis dehiscence (1.4% vs 6.3%, $P = .170$); paravalvular complications, including abscess (25% vs 18.8%, $P = .264$) and intracardiac fistula (5.6% vs 3.5%, $P = .485$); heart failure (34.7% vs 38.9%, $P = .655$); or embolic events (41.7% vs 32.6%, $P = .248$). Indications for surgery (70.8% vs 70.8%; $P = 1$) and mortality (13.9% vs 16.7%; $P = .741$) were similar between groups.

Conclusions. SAG endocarditis is an infrequent but serious condition that presents a prognosis similar to that of VGS/SGG.

Keywords. infective endocarditis; *Streptococcus anginosus*; viridans group streptococci; *Streptococcus gallolyticus*.

Infective endocarditis is one of the most life-threatening infections encountered in clinical practice and still represents a significant diagnostic and therapeutic challenge. About 40%–50% of patients with endocarditis require valve surgery at some point during the clinical course and mortality remains around 20%–25% in the first year after diagnosis [1].

In recent years, epidemiological changes in endocarditis have been documented in high-income countries, with an increasing rate of episodes caused by staphylococci and enterococci [2, 3]. Nevertheless, streptococci are still a major cause of endocarditis, mostly in developing countries [4]. Concerning streptococcal endocarditis, there is a clear predominance of cases due to viridans group streptococci (VGS), whereas β-hemolytic streptococci [5] and *Streptococcus anginosus* group (SAG)

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[a]Deceased 18 March 2020.

[b]Members of the GAMES and BEST study teams are listed in the Appendix at the end of this article.

Correspondence: Guillermo Cuervo, MD, PhD, Department of Infectious Diseases, Hospital Universitari de Bellvitge, Feixa Llarga s/n, 08907 L'Hospitalet de Llobregat, Barcelona, Spain (guillermo.cuervo@bellvitgehospital.cat).

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[1] are identified less often as causative agents. The species encompassing SAG (*Streptococcus anginosus*, *Streptococcus intermedius*, and *Streptococcus constellatus*) are known for their propensity to cause pyogenic infection and abscess formation in the head, neck, or abdomen. SAG can also cause bacteremia and, more rarely, endocarditis [6, 7].

Although endocarditis caused by SAG is thought to be associated with valve destruction, abscess formation, and embolic events [8], little information is available to support the assumption that it is more severe than other causes. We therefore aimed to characterize the main clinical features and outcomes of endocarditis caused by SAG and compared this with endocarditis and cases due to VGS or *Streptococcus gallolyticus* group (SGG) in a large cohort of patients with infective endocarditis.

METHODS

Patient Population and Data Collection

This was a large multicenter cohort study of consecutive adult patients with a definite diagnosis of endocarditis at 27 different Spanish hospitals (24 of them included within the Grupo de Apoyo al Manejo de la Endocarditis Infecciosa en España [GAMES] prospective cohort) and 1 Italian hospital. GAMES is a prospective registry into which multidisciplinary teams prospectively record all consecutive episodes of endocarditis since 2008 [9]. We therefore performed a retrospective analysis of prospectively collected data for the period 2008–2017, using a standardized case report form. Data included demographic and clinical variables, echocardiography findings, treatment, and outcomes, namely septic shock, valvular and paravalvular complications, heart failure, embolic events, indication for surgery, and mortality.

We analyzed all cases of definite endocarditis due to SAG and compared these with cases due to VGS or SGG using a 1:2 matched analysis. Matching was performed according to the type of valve (native or prosthetic), patient's sex, age (±5 years), year of diagnosis, and when feasible, hospital. Episodes of device-related infection (pacemaker and implantable defibrillators) and isolated right-side valve endocarditis were excluded.

Definitions

Definite infective endocarditis was defined according to the modified Duke criteria [10, 11]. Acquisition was categorized as community-acquired or non-community-acquired, with the latter including nosocomial-acquired and health care–associated infections [12]. All patients were followed up for up to 1 year and were considered cured in the absence of relapse or death. Relapse during follow-up was defined as positive blood cultures with the same microorganism. A new episode of endocarditis caused by a different microorganism was classified as a reinfection. Embolic events were defined as radiological findings consistent with ischemia of a major organ, either symptomatic or asymptomatic. Request for imaging tests was made at the discretion of the treating physicians. Acute kidney injury was defined as an abrupt decrease in kidney function with an increase of at least 1.5-fold in serum creatinine levels. Heart conduction disorders were defined as newly identified auriculoventricular blockage or heart bundle blockage. Septic shock was defined as hypotension persisting despite adequate fluid resuscitation [13, 14]. Indication for surgery was considered for heart failure due to valve regurgitation, intracardiac complications, or signs of uncontrolled infection, as listed in both the European and US guidelines [11, 15]. Overall mortality was defined as all-cause death during follow-up. Endocarditis-related mortality was defined as death during active antibiotic treatment at initial hospitalization or when occurring as a complication of valve surgery.

Microbiological Identification

Identification of microorganisms to the species level was performed according to standard methods in each participating center [16]. Before 2011, bacteria isolated from blood culture isolates were identified using conventional biochemical tests or by 16S polymerase chain reaction and sequencing in cases of inconclusive results. Since 2011, isolates have been identified using matrix-assisted laser desorption/ionization–time of flight in the majority of the participant hospitals. Viridans group streptococci included *Streptococcus mitis* group (*S mitis*, *S oralis*, *S sanguinis*, *S parasanguinis*, *S gordonii*), *Streptococcus mutans* group (*S mutans*), and *Streptococcus salivarius* group (*S salivarius*). *Streptococcus gallolyticus* group included 4 subspecies: *gallolyticus*, *pasteurianus*, *infantarius*, and *lutetiensis*. *Streptococcus anginosus* group included *S anginosus*, *S constellatus*, and *S intermedius*. Antibiotic susceptibility was evaluated according to the Clinical and Laboratory Standards Institute recommendations.

Statistical Analysis

Categorical variables are expressed as frequencies and percentages. Continuous variables are expressed as mean and standard deviation (SD). Qualitative variables were compared using χ^2 or Fisher exact tests, and quantitative variables were compared using the Student *t* test or Mann-Whitney *U* test, as appropriate. Statistical significance was set at $P < .05$, and all *P* values were 2-sided. Analyses were performed using IBM SPSS version 20 (IBM Corporation, Armonk, New York).

Ethical Considerations

This observational study was conducted in accordance with the Declaration of Helsinki and was approved by the regional ethics committee (Comité Ético de Investigación Clínica Regional de la Comunidad de Madrid, approval code 07/18). To protect personal privacy, identifying information in the electronic database was encrypted for each patient. Written informed consent was obtained from all patients reviewed in the GAMES cohort. Informed consent was waived by the

ethics committee in each of the Barcelona Endocarditis Study Team (BEST) participating hospitals because no intervention was involved and no patient-identifying information was included.

RESULTS

Clinical Characteristics and Outcomes of SAG Endocarditis

During the study period, 5336 episodes of definite endocarditis were recorded in the participating hospitals. Of these, 72 cases (1.4%) were due to SAG, and these cases were matched with 144 controls of patients with VGS or SGG endocarditis. Characteristics by infective agent are detailed in Tables 1 and 2. Most cases of SAG (76%) occurred in men, and the mean age was 67 years (SD, 16 years). Most cases were community-acquired (90%) and affected native valves (80.6%). The aortic valve was involved most often (40.3%), followed by the mitral valve (38.9%) and the aortic and mitral valves combined (19.4%).

New valve regurgitation developed in 20 (27.8%) patients, with severe mitral regurgitation being the most frequent. Notably, 15 patients (20.9%) suffered some form of intracranial hemorrhage and 14 (19.4%) suffered splenic emboli. Acute heart failure occurred in 34.7%, with 26.4% of cases having a New York Heart Classification III or IV. Acute kidney injury occurred in 20.8%, heart conduction disorders in 15.3%, and septic shock in 8.3%, but there were no cases of symptomatic osteoarticular involvement.

All patients received β-lactams as backbone antibiotic therapy, in 37 cases (51%) in synergic combination with gentamicin. The mean antibiotic treatment length was 34.5 days (SD, 12.6 days). Although more than two-thirds of cases had an indication for surgery, it was eventually not performed in 14% due to a poor prognosis and/or lack of patient consent. There was an elective indication in 33% of surgeries. Ultimately, 83% of cases were deemed to have been cured. Overall mortality occurred in 10 patients (14%), all cases considered endocarditis-related mortality due to peri- or postoperative complications, severe bleeding, multiorgan failure, and septic or cardiogenic shock.

Microbiology

The most frequently isolated microorganism in SAG endocarditis was *S anginosus* (n = 40 [55%]), followed by *S constellatus* (n = 15 [20%]) and *S intermedius* (n = 7 [10%]). In 10 (14%) cases, a SAG microorganism was isolated but not identified to the species level. Among the cases of VGS/SGG endocarditis, *S mitis* was the most commonly isolated microorganism (n = 40 [28%]), followed by *S oralis* (n = 22 [15%]), *S sanguinis* (n = 20 [14%]), and other species (Table 3). In 29 (20%) cases of VGS/

Table 1. Comparative Analysis of General Characteristics and Clinical Manifestations of Infective Endocarditis Caused by *Streptococcus anginosus* Group and Viridans Group Streptococci/*Streptococcus gallolyticus* Group

Characteristic	SAG Endocarditis (n = 72)	VGS or SGG Endocarditis (n = 144)	*P* Value
Male sex	55 (76.4)	106 (73.6)	.846
Mean age, y (SD)	67 (16)	68 (15)	.845
Chronic lung disease	12 (16.7)	23 (16)	1.000
Diabetes mellitus	16 (22.2)	22 (15.3)	.283
Chronic kidney disease	6 (8.3)	18 (12.5)	.491
Age-adjusted Charlson index, y, mean (SD)	3.8 (2.6)	3.7 (2.5)	.960
Acquisition			.834
Community-acquired	64 (88.9)	133 (92.4)	.552
Non-community-acquired	6 (8.4)	9 (6.3)	.776
Type of endocarditis			.951
Native	58 (80.6)	118 (81.9)	.951
Prosthetic	14 (19.4)	26 (18.1)	.951
Affected valve			.876
Aortic	29 (40.3)	60 (41.7)	.961
Mitral	28 (38.9)	52 (36.1)	.803
Mitral and aortic	14 (19.4)	26 (18.1)	.950
Embolic phenomena	30 (41.7)	47 (32.6)	.248
Central nervous system emboli	18 (25)	22 (15.3)	.122
Echocardiographic findings			
Perforation or valve rupture	16 (22.2)	26 (18.1)	.584
Pseudoaneurysm	12 (16.7)	12 (8.3)	.108
Abscess	18 (25)	27 (18.8)	.264
Intracardiac fistula	4 (5.6)	5 (3.5)	.485
Prosthesis dehiscence	1 (1.4)	9 (6.3)	.170

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: SAG, *Streptococcus anginosus* group; SD, standard deviation; SGG, *Streptococcus gallolyticus* group; VGS, viridans group streptococci.

Table 2. Comparative Analysis of Treatment and Outcomes of Infective Endocarditis Caused by *Streptococcus anginosus* Group and Viridans Group Streptococci/*Streptococcus gallolyticus* Group

Characteristic	SAG Endocarditis (n = 72)	VGS or SGG Endocarditis (n = 144)	*P* Value
Treatment duration, d, mean (SD)	34.5 (12.6)	33.8 (10.8)	.854
Combination treatment with gentamicin	37 (51)	82 (56.9)	.494
Complications			
Acute heart failure	25 (34.7)	56 (38.9)	.655
Persistent bacteremia	4 (5.6)	8 (5.6)	.602
Heart conduction disorder	11 (15.3)	18 (12.5)	.739
Acute kidney injury	15 (20.8)	44 (30.6)	.177
Septic shock	6 (8.3)	5 (3.5)	.116
Surgery			
Surgery indicated	51 (70.8)	102 (70.8)	1
Elective	24 (33.3)	47 (32.6)	1
Urgent	12 (16.7)	19 (13.2)	.618
Emergent	5 (6.9)	7 (4.9)	.749
Surgery indicated but not performed	10 (13.9)	29 (20.1)	.348
Prognosis[a]			
Definitely cured	60 (83.3)	114 (79.2)	.584
Overall mortality	10 (13.9)	24 (16.7)	.741
Endocarditis-related mortality	10 (13.9)	16 (11.1)	.711
Relapse	0	1 (0.7)	
Reinfection	0	2 (1.4)	

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: SAG, *Streptococcus anginosus* group; SD, standard deviation; SGG, *Streptococcus gallolyticus* group; VGS, viridans group streptococci.

[a]There were 2 and 3 losses to follow-up among SAG and VSG/SGG endocarditis, respectively.

SGG endocarditis, identification was not performed to the species level.

Comparative Analysis of SAG and VGS/SGG Endocarditis

Tables 1 and 2 show the comparison between SAG and VGS/SGG endocarditis. There were no statistically significant differences in either valve involvement (perforation: 22.2% vs 18.1%, $P = .584$; pseudoaneurysm: 16.7% vs 8.3%, $P = .108$; prosthesis dehiscence: 1.4% vs 6.3%, $P = .170$) or paravalvular complications (abscess: 25% vs 18.8%, $P = .264$; intracardiac fistula: 5.6% vs 3.5%, $P = .485$). Equally, no significant differences were detected between SAG and VGS/SGG endocarditis when comparing the rate of acute heart failure (34.7% vs 38.9%, $P = .655$), heart conduction disorders (15.3% vs 12.5%, $P = .739$), septic shock (8.3% vs 3.5%, $P = .116$), indication for surgery (70.8% vs 70.8%, $P = 1$), or overall mortality (13.9% vs 16.7%, $P = .741$). There was 1 case of relapse due to *S oralis*. No molecular typing was performed.

Table 3. Distribution of Viridans Group Streptococci or *Streptococcus gallolyticus* Group Isolates Causing Endocarditis, by Species

Species of Microorganism	Frequency (%)
Streptococcus mitis	40 (27.8)
Nonidentified *Streptococcus viridans* group	29 (20.1)
Streptococcus oralis	22 (15.3)
Streptococcus sanguinis	20 (13.9)
Streptococcus salivarius	12 (8.3)
Streptococcus mutans	9 (6.3)
Streptococcus gordonii	8 (5.6)
Streptococcus gallolyticus group	3 (2.1)
Streptococcus parasanguinis	1 (0.7)

DISCUSSION

In this largest study of SAG endocarditis to date, we found that SAG accounted for 1.4% of all definite cases of endocarditis in our cohort. This figure concurs with that reported in a previous study of 18 patients [17]. Also in accordance with previous observations, we found that *S. anginosus* was the most commonly identified causative species in SAG endocarditis [8, 18].

Controversy remains about the true virulence of SAG in infective endocarditis. Some sporadic case reports depict SAG endocarditis as an aggressive infection with frequent intracardiac complications, embolic events, and abscess formation [19–21]. In a retrospective study of 56 cases of endocarditis caused by β-hemolytic streptococci, 29 cases of SAG endocarditis had a less aggressive presentation and fewer extracardiac complications [1]. However, the conclusions in previous studies are limited by the limited by the small number of cases of endocarditis caused by SAG.

We observed no statistically significant differences when comparing SAG with VGS/SGG endocarditis regarding either local complications (valve perforation or abscess, pseudoaneurysm, prosthesis dehiscence, or intracardiac fistula) or systemic

complications (heart failure and septic shock). Similarly, we found no differences in the proportion of patients with surgical indications nor in mortality. These results are consistent with those of a previous study in which SAG endocarditis had a comparable prognosis to VGS/SGG endocarditis [17]. It could be hypothesized that prior observations reporting a higher virulence of SAG endocarditis may have been biased toward describing the most severe cases. It should be noted, however, that higher rates of pseudoaneurysms, intracardiac abscess, and central nervous system emboli were actually identified, although without achieving statistical significance. Anatomic damage and prognostic differences may ultimately be subtle and difficult to detect; thus, the non–statistically significant differences observed could reflect a type II statistical error due to the limited number of SAG endocarditis cases in our cohort.

Our study has some limitations that should be acknowledged. Due to its retrospective design, some information such as the formation of extracardiac abscesses was not available for comparison between groups. Moreover, the small number of cases with certain complications, such as prosthesis dehiscence or intracardiac fistula, diminishes the power of these analyses. On the other hand, the well-known difficulties for the accurate identification of streptococcal species and some changes in the microbiological tools used for this task throughout the study period should be recognized as another potential limitation. We believe, however, that the multicenter nature of this study and the contemporary period of data collection strengthen our results.

In conclusion, SAG endocarditis is an infrequent but serious condition that follows a similar clinical course to VGS/SGG endocarditis, regarding valvular complications and prognostic variables such as indication for surgery or endocarditis-related mortality.

Appendix

Members of the GAMES prospective registry. Hospital Costa del Sol (Marbella): Fernando Fernández Sánchez, Mariam Noureddine, Gabriel Rosas, Javier de la Torre Lima; Hospital Universitario de Cruces (Bilbao): Elena Bereciartua, Roberto Blanco, María Victoria Boado, Marta Campaña Lázaro, Alejandro Crespo, Laura Guio Carrión, Mikel Del Álamo Martínez de Lagos, Gorane Euba Ugarte, Josune Goikoetxea, Marta Ibarrola Hierro, José Ramón Iruretagoyena, Josu Irurzun Zuazabal, Leire López-Soria, Miguel Montejo, Javier Nieto, David Rodrigo, Regino Rodríguez, Yolanda Vitoria, Roberto Voces; Hospital Universitario Virgen de la Victoria (Málaga): Mª Victoria García López, Radka Ivanova Georgieva, Guillermo Ojeda, Isabel Rodríguez Bailón, Josefa Ruiz Morales; Hospital Universitario Donostia-Poliklínica Gipuzkoa-IIS Biodonostia (San Sebastián): Harkaitz Azkune Galparsoro, Elisa Berritu Boronat, Mª Jesús Bustinduy Odriozola, Cristina del Bosque Martín, Tomás Echeverría, Alberto Eizaguirre Yarza, Ana Fuentes, Miguel Ángel Goenaga, Muskilda Goyeneche del Río, Ángela Granda Bauza, José Antonio Iribarren, Xabier Kortajarena Urkola, José Ignacio Pérez-Moreiras López, Ainhoa Rengel Jiménez, Karlos Reviejo, Alberto Sáez Berbejillo, Elou Sánchez Haza, Rosa Sebastián Alda, Itziar Solla Ruiz, Irati Unamuno Ugartemendia, Diego Vicente Anza, Iñaki Villanueva Benito, Mar Zabalo Arrieta; Hospital General Universitario de Alicante (Alicante): Rafael Carrasco, Vicente Climent, Patricio Llamas, Esperanza Merino, Joaquín Plazas, Sergio Reus; Complejo Hospitalario Universitario A Coruña (A Coruña): Nemesio Álvarez, José María Bravo-Ferrer, Laura Castelo, José Cuenca, Pedro Llinares, Enrique Miguez Rey, María Rodríguez Mayo, Efrén Sánchez, Dolores Sousa Regueiro; Complejo Hospitalario Universitario de Huelva (Huelva): Francisco Javier Martínez; Hospital Universitario de Canarias, (Canarias): Mª del Mar Alonso, Beatriz Castro, Teresa Delgado Melian, Javier Fernández Sarabia, Dácil García Rosado, Julia González González, Juan Lacalzada, Lissete Lorenzo de la Peña, Alina Pérez Ramírez, Pablo Prada Arrondo, Fermín Rodríguez Moreno; Hospital Regional Universitario de Málaga (Málaga): Antonio Plata Ciezar, José Mª Reguera Iglesias; Hospital Universitario Central Asturias (Oviedo): Víctor Asensi Álvarez, Carlos Costas, Jesús de la Hera, Jonnathan Fernández Suárez, Lisardo Iglesias Fraile, Víctor León Arguero, José López Menéndez, Pilar Mencia Bajo, Carlos Morales, Alfonso Moreno Torrico, Carmen Palomo, Begoña Paya Martínez, Ángeles Rodríguez Esteban, Raquel Rodríguez García, Mauricio Telenti Asensio; Hospital Clínic-IDIBAPS, Universidad de Barcelona (Barcelona): Manuel Almela, Juan Ambrosioni, Manuel Azqueta, Mercè Brunet, Marta Bodro, Ramón Cartañá, Carlos Falces, Guillermina Fita, David Fuster, Cristina García de la Mària, Delia García-Pares, Marta Hernández-Meneses, Jaume Llopis Pérez, Francesc Marco, José M. Miró, Asunción Moreno, David Nicolás, Salvador Ninot, Eduardo Quintana, Carlos Paré, Daniel Pereda, Juan M. Pericás, José L. Pomar, José Ramírez, Irene Rovira, Elena Sandoval, Marta Sitges, Dolors Soy, Adrián Téllez, José M. Tolosana, Bárbara Vidal, Jordi Vila; Hospital General Universitario Gregorio Marañón (Madrid): Iván Adán, Juan Carlos Alonso, Ana Álvarez-Uría, Javier Bermejo, Emilio Bouza, Gregorio Cuerpo Caballero, Antonia Delgado Montero, Ana González Mansilla, Mª Eugenia García Leoni, Esther Gargallo, Víctor González Ramallo, Martha Kestler Hernández, Amaia Mari Hualde, Marina Machado, Mercedes Marín, Manuel Martínez-Sellés, Patricia Muñoz, María Olmedo, Álvaro Pedraz, Blanca Pinilla, Ángel Pinto, Cristina Rincón, Hugo Rodríguez-Abella, Maricela Valerio, Pilar Vázquez, Eduardo Verde Moreno; Hospital Universitario La Paz, (Madrid): Isabel Antorrena, Belén Loeches, Mar Moreno, Ulises Ramírez, Verónica Rial Bastón, María Romero, Sandra Rosillo; Hospital Universitario Marqués de Valdecilla (Santander): Jesús Agüero Balbín, Cristina Amado, Carlos Armiñanzas Castillo, Ana Arnaiz, Francisco Arnaiz de las Revillas, Manuel Cobo Belaustegui, María Carmen Fariñas, Concepción Fariñas-Álvarez, Marta Fernández Sampedro, Iván García, Claudia González Rico, Laura Gutierrez-Fernandez, Manuel Gutiérrez-Cuadra, José Gutiérrez Díez, Marcos Pajarón, José Antonio Parra, Ramón Teira, Jesús Zarauza; Hospital Universitario Puerta de Hierro (Madrid): Jorge Calderón Parra, Marta Cobo, Fernando Domínguez, Alberto Fortaleza, Pablo García Pavía, Jesús González, Ana Fernández Cruz, Elena Múñez, Antonio Ramos, Isabel Sánchez Romero; Hospital Universitario Ramón y Cajal, (Madrid): Tomasa Centella, José Manuel Hermida, José Luis Moya, Pilar Martín-Dávila, Enrique Navas, Enrique Oliva, Alejandro del Río, Jorge Rodríguez-Roda Stuart, Soledad Ruiz; Hospital Universitario Virgen de las Nieves (Granada): Carmen Hidalgo Tenorio; Hospital Universitario Virgen Macarena (Sevilla): Manuel Almendro Delia, Omar Araji, José Miguel Barquero, Román Calvo Jambrina, Marina de Cueto, Juan Gálvez Acebal, Irene Méndez, Isabel Morales, Luis Eduardo López-Cortés; Hospital Universitario Virgen del Rocío (Sevilla): Arístides de Alarcón, Emilio García, Juan Luis Haro, José Antonio Lepe, Francisco López, Rafael Luque; Hospital San Pedro (Logroño): Luis Javier Alonso, Pedro Azcárate, José Manuel Azcona Gutiérrez, José Ramón Blanco, Antonio Cabrera Villegas, Lara García-Álvarez, Concepción García García, José Antonio Oteo; Hospital de la Santa Creu i Sant Pau (Barcelona): Natividad de Benito, Mercé Gurguí, Cristina Pacho, Roser Pericas, Guillem Pons; Complejo Hospitalario Universitario de Santiago de Compostela (A Coruña): M. Álvarez, A. L. Fernández, Amparo Martínez, A. Prieto, Benito Regueiro, E. Tijeira, Marino Vega; Hospital Santiago Apóstol, (Vitoria): Andrés Canut Blasco, José Cordo Mollar, Juan Carlos Gainzarain Arana, Oscar García Uriarte, Alejandro Martín López, Zuriñe Ortiz de Zárate, José Antonio Urturi Matos; Hospital SAS Línea de la Concepción (Cádiz): Sánchez-Porto Antonio,

Úbeda Iglesias Alejandro; Hospital Clínico Universitario Virgen de la Arrixaca (Murcia): José Mª Arribas Leal, Elisa García Vázquez, Alicia Hernández Torres, Ana Blázquez, Gonzalo de la Morena Valenzuela; Hospital de Txagorritxu (Vitoria): Ángel Alonso, Javier Aramburu, Felicitas Elena Calvo, Anai Moreno Rodríguez, Paola Tarabini-Castellani; Hospital Virgen de la Salud (Toledo): Eva Heredero Gálvez, Carolina Maicas Bellido, José Largo Pau, Mª Antonia Sepúlveda, Pilar Toledano Sierra, Sadaf Zafar Iqbal-Mirza; Hospital Rafael Méndez (Lorca-Murcia):, Eva Cascales Alcolea, Ivan Keituqwa Yañez, Julián Navarro Martínez, Ana Peláez Ballesta; Hospital Universitario San Cecilio (Granada): Eduardo Moreno Escobar, Alejandro Peña Monje, Valme Sánchez Cabrera, David Vinuesa García; Hospital Son Llátzer (Palma de Mallorca): María Arrizabalaga Asenjo, Carmen Cifuentes Luna, Juana Núñez Morcillo, Mª Cruz Pérez Seco, Aroa Villoslada Gelabert; Hospital Universitario Miguel Servet (Zaragoza): Carmen Aured Guallar, Nuria Fernández Abad, Pilar García Mangas, Marta Matamala Adell, Mª Pilar Palacián Ruiz, Juan Carlos Porres; Hospital General Universitario Santa Lucía (Cartagena): Begoña Alcaraz Vidal, Nazaret Cobos Trigueros, María Jesús Del Amor Espín, José Antonio Giner Caro, Roberto Jiménez Sánchez, Amaya Jimeno Almazán, Alejandro Ortín Freire, Monserrat Viqueira González; Hospital Universitario Son Espases (Palma de Mallorca): Pere Pericás Ramis, Mª Ángels Ribas Blanco, Enrique Ruiz de Gopegui Bordes, Laura Vidal Bonet; Complejo Hospitalario Universitario de Albacete (Albacete): Mª Carmen Bellón Munera, Elena Escribano Garaizabal, Antonia Tercero Martínez, Juan Carlos Segura Luque; Hospital Universitario Terrassa: Cristina Badía, Lucía Boix Palop, Mariona Xercavins, Sónia Ibars. Hospital Universitario Dr. Negrín (Gran Canaria): Xerach Bosch, Eloy Gómez Nebreda, Ibalia Horcajada Herrera, Irene Menduiña Gallego, Imanol Pulido; Complejo Hospitalario Universitario Insular Materno Infantil (Las Palmas de Gran Canaria): Héctor Marrero Santiago, Isabel de Miguel Martínez, Elena Pisos Álamo. Hospital Universitario 12 de Octubre (Madrid): Eva Mª Aguilar Blanco, Mercedes Catalán González, María Angélica Corres Peiretti, Andrea Eixerés Esteve, Laura Domínguez Pérez, Santiago de Cossío Tejido, Francisco Galván Román, José Antonio García Robles, Francisco López Medrano, Mª Jesús López Gude, Mª Ángeles Orellana Miguel, Patrick Pilkington, Yolanda Revilla Ostalaza, Juan Ruiz Morales, Sebastián Ruiz Solís, Ana Sabín Collado, Marcos Sánchez Fernández, Javier Solera Rallo, Jorge Solís Martín. Hospital Universitari Bellvitge (Barcelona): Guillermo Cuervo, Francesc Escrihuela-Vidal, Jordi Carratalà, Inmaculada Grau, Sara Grillo, Carmen Ardanuy, Dámaris Berbel, Jose Carlos Sánchez Salado, Oriol Alegre, Alejandro Ruiz Majoral, Fabrizio Sbraga, Arnau Blasco, Laura Gracia Sánchez, Iván Sánchez-Rodríguez. Hospital Universitario Fundación Jiménez Díaz (Madrid): Beatriz Álvarez, Alfonso Cabello Úbeda, Ricardo Fernández Roblas, Miguel Ángel Navas Lobato, Ana María Pello. Hospital Basurto (Bilbao): Mireia de la Peña Triguero, Ruth Esther Figueroa Cerón, Lara Ruiz Gómez. Hospital del Mar (Barcelona): Mireia Ble, Juan Pablo Horcajada Gallego, Antonio José Ginel, Inmaculada López, Alexandra Mas, Antoni Mestres, Lluís Molina, Ramón Serrat, Núria Ribas, Francisca Sánchez, Ana Silverio, Marina Suárez, Luisa Sorlí, Lluís Recasens, Manuel Taurón.

Members of the Barcelona Endocarditis Study Team (BEST). Hospital Universitari de Bellvitge (L'Hospitalet de Llobregat): Guillermo Cuervo, Francesc Escrihuela-Vidal, Jordi Carratalà, Inmaculada Grau, Sara Grillo, Carmen Ardanuy, Dámaris Berbel, Jose Carlos Sánchez Salado, Oriol Alegre, Alejandro Ruiz Majoral, Fabrizio Sbraga, Arnau Blasco, Laura Gracia Sánchez, Iván Sánchez-Rodríguez. Hospital Universitari Vall d'Hebron (Barcelona): Benito Almirante, Laura Escolà-Vergé, Rubén Fernández, Nuria Fernández-Hidalgo, Maria Teresa Gonzàlez-Alujas, Olga Maisterra, Gerard Oristrell, María Nazarena Pizzi, Pau Rello, Remedios Ríos, Albert Roque, Antonia Sambola, Toni Soriano. Hospital de la Santa Creu i Sant Pau (Barcelona): Mercè Gurguí Ferrer, Antonio José Barros Membrilla, MªAlba Rivera Martinez. Hospital Can Trias i Pujol (Badalona): Lourdes Mateu Pruñonosa, Núria Vallejo, María Dolores Quesada, Elisabeth Berasategui, María Luisa Pedro-Botet, Cinta LLibre, Esteban Reynaga, Raquel Nuñez Aragón, Ainhoa Vivero, Luis Delgado, Christian Muñoz Guijosa, Nieves Sopena. Istituto Scientifico Universitario San Raffaele (Segrate-Milano): Marco Ripa, Paolo Scarpellini, Michele De Bonis, Eustachio Agricola, Silvia Carletti, Elena Busnardo.

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