Tropheryma whipplei endocarditis in Spain
Case reports of 17 prospective cases

Lara García-Álvarez (BSc)a, María Mercedes Sanz (MD, PhD)b, Mercedes Marin (MD, PhD)c, MªCarmen Farinías (MD, PhD)d, Miguel Montejo (MD)d, Josune Goikoetxea (MD)d, Raquel Rodríguez García (MD)d, Aristides de Alarcón (MD)d, Manuel Almela (MD)d, Núria Fernández-Hidalgo (MD, PhD), María del Mar Alonso Socas (MD)d, Miguel Ángel Goenaga (MD),

*Members of Spanish Collaboration on Endocarditis-Grupo de Apoyo al Manejo de la Endocarditis Infecciosa en España Group: Hospital Costa del Sol (Marbella): Fernando Fernández Sánchez, Mª del Mar Alonso, Beatriz Castro, Dácil García Marrero, Mª del Carmen Durán, Mª Antonia García-Álvarez, María Rodríguez Mayo, Efren Sánchez, Dolores Sousa Requena; Complejo Hospitalario de Especialidades (A Coruña): Mª Eugenia García Leoni, Marcela González del Vecio, Víctor González Ramallo, Martha Kortajarena Urkola, Carlos Requena, Jesús A. Oteo, María del Carmen Palomino, José Luis Rodríguez Baño; Hospital Universitario Virgen del Rocío (Sevilla): Manuel Almela, Juan Ambrosioni, Yesilda Amorano, Francisco Javier Martínez, Emilio García, Juan Luis Haro, José Antonio Parra, Ramón Teira, Jesús Zarazua; Hospital Universitario Puerta de Hierro (Madrid): Pablo García Pava, Jesús González, Beatriz Ordóñez, Antonio Ramos, Elena Rodríguez González; Hospital Universitario Ramón y Cajal (Madrid): Tomasa Centella, José Manuel Herrieta, José Luis Moya, Pilar Martín-Dávila, Enrique Navas, Enrique Oliva, Ángel Rodríguez Baño; Hospital Universitario Virgen Macarena (Sevilla): Antonio de Castro, María Carmen de Cueto, Pastora Calleja, Juan Gálvez Azcárate, Jesús Rodríguez Baño; Hospital Universitario Virgen del Rocío (Sevilla): Aristides de Alarcón, Emilio García, Juan Luis Haro, José Antonio Lepe, Francisco López, Rafael Luque; Hospital San Pedro (Logroño): Luis Javier Alonso, Pedro Azcarate, José Manuel Azcóna Gutiérrez, José Ramón Blanco, Lara García-Arzáte, José Antonio Oteo, Mercedes Sanz; Hospital de la Santa Creu i Sant Pau (Barcelona): Natali Martín, Mercè Gurguí, Cristina Pacho, Roser Pericas, Guillem Pons; Complejo Hospitalario Universitario de Santiago de Compostela (A Coruña): A. Prieto, Benito Rodríguez, T. Tena, Maria Vázquez; Hospital San Juan de Dios (Barcelona): Ana Benito, Mercè Brunet, Ramón Cartañá, Carlos Falces, Guillermina Fita, D. Fuster, Cristina García de la Maria, José M. Gafet, Juanne Llopis Pérez, Christian Manzardo, Francesc Marco, José M. Miró, Asunción Moreno, Salvador Ninot, Eduard Quintana, Carlos Parés, Daniel Pereda, Juan Manuel Pericas, José L. Pumar, José Ramírez, Irene Rojo, Marta Sitges, Dolores Soy, Adrián Téllez, Bárbara Vidal, Jordi Vila; Hospital General Universitari Gregorio Marañón (Madrid): Javier Benitez; Emilio Bousa, Gregorio Cueva, Victoria de Geusa, Alla Escora, Ana Fernández Cruz, Mª Eugenia García Leoni, Marcela González del Vecio, Victor González Ramallo, Martha Kortajarena Urkola, Mercedes Marin, Manuel Martínez-Sedés, Mª Cruz Pérez Seco.

Correspondence: José A. Oteo, Departamento de Enfermedades Infecciosas, Hospital San Pedro-CIBIR, C/Piquerias 98-7a NE, 26006 Logroño (La Rioja), Spain (email: jaoteo@riojasalud.es)
Abstract

Tropheryma whipplei endocarditis is an uncommon condition with very few series and <90 cases reported in the literature. The aim of the study was to analyze the epidemiological, clinical, and outcome characteristics of 17 cases of T. whipplei endocarditis recruited in our country from a multicentric cohort from 25 Spanish hospitals from the Spanish Collaboration on Endocarditis—Grupo de Apoyo al Manejo de la Endocarditis Infecciosa en España (GAMES).

From a total of 3165 cases included in the cohort, 14.2% were diagnosed of blood culture negative endocarditis (BCNE) and 3.5% of these had T. whipplei endocarditis. This condition was more frequent in men. The average age was 60.3 years. Previous cardiac condition was present in 35.5% of the cases. The main clinical manifestation was cardiac failure (76.5%) while fever was only present in the 35.3%. Echocardiography showed vegetations in 64.7% of patients. Surgery was performed in all but 1 cases and it allowed the diagnosis when molecular assays were performed. A broad range rRNA 16S polymerase chain reaction was used for first instance in all laboratories and different specific targets for T. whipplei were employed for confirmation. A concomitant Whipple disease was diagnosed in 11.9% of patients. All patients received specific antimicrobial treatment for at least 1 year, with no relapse and complete recovery.

T. whipplei endocarditis is an uncommon condition with an atypical presentation that must be considered in the diagnosis of BCNE. The prognosis is very good when an appropriate surgical management and antimicrobial-specific treatment is given.

Abbreviations: BCNE = blood culture negative endocarditis, BID = “bis in die” (twice a day), CSF = cerebrospinal fluid, GAMES = grupo de apoyo al manejo de la endocarditis infecciosa en España, IE = infectious endocarditis, IHC = immunohistochemistry, PAS = periodic acid-Schiff, SXT = trimethoprim-sulfamethoxazole, TOE = transthoracic echocardiography, TTE = transthoracic echocardiography, WD = Whipple disease.

Keywords: blood culture negative endocarditis, infectious endocarditis, T. whipplei endocarditis, Tropheryma whipplei

1. Introduction

Blood culture negative endocarditis (BCNE) is a relative frequent condition among patients affected by infectious endocarditis (IE) representing 5% to 30% in great series.[11-13] The main reasons for this condition are the previous administration of antimicrobials and fastidiously culture microorganism. Anyway, in the past decades, the application of certain tools as automated blood cultures, molecular assays, immunohistochemistry (IHC), and serology has improved the diagnosis of this condition and has involved new agents.[4] These facts have been incorporated in new guidelines.[3,6]

Tropheryma whipplei, formerly Tropheryma whippeli, is an intracellular gram-positive Actinobacteria ubiquitous in the environment that is involved in a large variety of clinical forms.[7,8] First implication of T. whipplei as causative agent of infective endocarditis was reported from Switzerland in 1997, in a patient with BCNE using a broad-range polymerase chain reaction (PCR) followed by sequencing.[9] First stable cultivation of the bacterium of Whipple disease (WD) was carried out in 2000, from the mitral valve of a patient with BCNE.[7] The knowledge of the genome of T. whipplei has permitted the development of specific and sensible tools for diagnosis and have involved this microorganism in a broad spectrum of clinical conditions.[10,11]

Sporadic cases of T. whipplei endocarditis have been reported from different countries,[12] but there are few published series of T. whipplei endocarditis.[13,14] In this article, we describe the epidemiological, clinical, and outcome characteristics of 17 cases of T. whipplei endocarditis diagnosed in several hospitals from Spain. Some cases have been previously reported.[13,16]
3. Results

3.1. Epidemiological data

A total of 3,165 cases of IE were recorded in the GAMES Cohort between 2008 and 2014. From the total, 451 (14.2%) were diagnosed of BCNE and 16 (3.5%) of these had IE by *T. whipplei*. One case was added from a hospital not included in the GAMES group. Main epidemiological, clinical, and outcome characteristics are shown in Table 1.

The mean age of *T. whipplei* endocarditis was 60.3 years (48–79 years) and most of cases were men, 14 (82.4%). Twelve patients (70.6%) were from the North of Spain, 1 from the Center (5.9%), 3 from the South (17.6%), and 1 (5.9%) from the Canary Islands.

3.2. Clinical features

According to the medical history, 6 patients had associated pathological cardiac conditions (35.3%): 4 had aortic insufficiency, 1 atrial fibrillation with mitral insufficiency, and 1 chronic pericarditis. One patient suffered a previous IE and carried a prosthetic valve. Of 17 patients, 5 had hypertension (29.4%), 4 patients (23.5%) suffered a cerebrovascular disease, and 2 patients (11.7%) chronic lung disease. Immunosuppressive therapy had been given only to 1 of the 17 patients (5.9%). One patient was HIV-positive (no AIDS) (5.9%). One had diabetes mellitus (5.9%) and 1 suffered of chronic renal insufficiency. Another 1 presented hypothyroidism and had been operated for knee osteoarthritis. Alcohol intake (>60 g/d) was referred by the 23.5% of the patients.

Cardiac failure was the main presenting form of *T. whipplei* endocarditis described in our patients. It was present in 13 of the 17 patients (76.5%). Another patient developed cardiac failure during the course of the illness. Chronic arthralgia was related in 9 of 17 patients (53%). Asthenia and malaise lasting more than 6 months were reported in 7 patients (41.2%). Fever was only recorded in 6 patients (35.3%). Only 2 patients presented classical WD (11.8%). One of them was diagnosed during the endocarditis process and the other, 1 month before.

Echocardiography was performed for all 17 patients: trans-thoracic echocardiography for 14 patients (82.4%) and trans-esophageal echocardiography for the same number. Echocardiography showed vegetations in 11 patients (64.7%). The valve involved was the aortic in 16 cases (94.1%), although 6 of them (37.5%) also presented mitral valve involvement. In 1 of the patients, the unique valve involved was the mitral. Native valve was affected in 16 patients (94.1%) while prosthetic valve was affected only in 1 case (5.9%). The size of the vegetations was larger than 80 cases have been reported in the literature since 1997.[12] Here we report 17 patients affected by *T. whipplei* endocarditis from a prospective cohort in Spain. This series joined to the French and German ones is the largest series of *T. whipplei* endocarditis described in our patients. It was present in 13 of the 17 patients (76.5%). Another patient developed cardiac failure during the course of the illness. Chronic arthralgia was related in 9 of 17 patients (53%). Asthenia and malaise lasting more than 6 months were reported in 7 patients (41.2%). Fever was only recorded in 6 patients (35.3%). Only 2 patients presented classical WD (11.8%). One of them was diagnosed during the endocarditis process and the other, 1 month before.

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The main laboratory recording abnormalities at the time of the diagnosis were anemia which was detected in 88.2% of the patients (hemoglobin level average of 11 g/dL with a range between 9.7 and 12.4 g/dL) and an increasing of C-reactive protein with an average level of 51.8 mg/L (range: 2.3–136.7 mg/L). The glomerular filtration rate average was 66 ml/min (range: 26–98).

Surgery was performed in 16 patients (94.1%) and gave the definitive diagnosis of IE in 16/17 patients (94.1%) since none of the patients met the criteria for IE according to the Duke’s university. The reasons of surgery were heart failure in 9 patients (56.3%) and severe regurgitation in 7 (43.8%). The other patient was diagnosed because of valve cardiac involvement in the context of classical WD.

3.3. Microbiological diagnosis

Culture of the valves was negative in all the cases. PAS staining was performed in valves from 6 patients (35.3%) with a positive result in 5 of them (83.3%). PCR against *T. whipplei* were positive in all studied valves with at least 2 different targets. An rDNA 16S PCR was used for first instance in all laboratories. Then, different targets were employed for confirmation (Table 2). PCRs were also positive in the intestinal biopsy in the 2 patients with classical WD and in the pericardial fluid of the patient with chronic pericarditis. In 1 of the patients affected by classical WD, a positive PCR in an adenopathy was also obtained. The patient in which cardiac valve surgery was not performed had a positive PCR in samples from small bowel, cerebrospinal fluid (CSF), and synovial fluid.

3.4. Treatment and outcome

Eleven patients (64.7%) started treatment with ceftriaxone (2 g IV at least for 2 weeks as initial therapy followed of different antimicrobials. Twelve patients (70.6%) received trimethoprim-sulfamethoxazole (SXT) 160/800 mg “bis in die” (BID) at least during 1 year (3 only SXT without another antimicrobial; 1 used gentamicin during the 1st week and other hydroxychloroquine). In 5 patients (29.4%), the elected antimicrobial drug was doxycycline 100 mg BID plus hydroxychloroquine 600 mg/d (1 of them first started with SXT and continued with doxycycline plus hydroxychloroquine). Details of the combinations are shown in Table 1. All regimens were administered during at least 1 year (average of treatment: 15.8 months).

The course during the treatment was satisfactory in all but 1 patient who suffered a new IE caused by an *Enterococcus faecalis*. None of the patients died during the IE process or during the follow-up after the end of treatment (Table 1). The follow-up after finishing the treatment has been from 2 to 65 months, with an average of 28.8 months.

4. Discussion

Although the suspicion and diagnosis of *T. whipplei* endocarditis can be difficult, more than 80 cases have been reported in the literature since 1997.[12] Here we report 17 patients affected by *T. whipplei* endocarditis from a prospective cohort in Spain. This series joined to the French and German ones is the largest series of patients with *T. whipplei* endocarditis.[13,14] Diagnosis of *T. whipplei* endocarditis remains a challenge due to this endocarditis does not exhibit the typical sings and blood cultures used to be negative. According to BCNE series, the rate of *T. whipplei* as causative agent of this condition is around the 0.6% to 2.6% of all the studied cases.[12,14] These data are consistent with those presented in this article. Nevertheless, the prevalence of *T. whipplei* endocarditis could be underestimated due to the difficulties that involve the identification of *T. whipplei*. We do not know if the data shown in this article show the true incidence of *T. whipplei* endocarditis in our country, as it could happen in other countries, but we know that is a good approximation since the molecular study of removed valves is the rule in all hospitals of the GAMES cohort when IE is suspected. As in other studies, males (82.4%) are more frequently affected than females. The age of presentation (60.3 years) is also
## Table 1
Main epidemiological, clinical, and outcome characteristics of the 17 patients with *T. whipplei* endocarditis.

| Patient No. | 1     | 2     | 3     | 4     | 5     | 6     | 7     | 8     | 9     | 10    | 11    | 12    | 13    | 14    | 15    | 16    | 17    |
|------------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
| Age, y     | 57    | 62    | 64    | 62    | 56    | 62    | 71    | 48    | 79    | 59    | 62    | 49    | 54    | 52    | 70    | 68    | 50    |
| Gender     | F     | M     | M     | M     | M     | M     | M     | M     | F     | M     | M     | M     | M     | M     | M     | F     | M     |
| Geographical area | Madrid | Basque | Basque | Basque | Basque | La | La | Canary | Andalucía | Andalucía | Andalucía | Catalonia | Catalonia | Catalonia | Asturias | Asturias |
| Cardiac history | N     | AVI  | PIE  | PV   | AF   | MVI  | CP   | N     | N     | AVI  | N     | N     | N     | N     | N     | N     | N     |
| Alcohol intake | N     | N     | N     | N     | N     | N     | N     | N     | N     | N     | N     | N     | N     | N     | N     | N     | N     |
| Other historical conditions | IS    | DM  | CVA  | CVA  | HT   | CLD  | HT   | CLD  | HT   | CHI  | CVA  | N     | N     | N     | N     | HP    | N     | CVA  |
| Cardiac failure | Y     | Y     | Y     | Y     | Y     | Y     | Y     | Y     | Y     | Y     | Y     | Y     | Y     | Y     | Y     | Y     | Y     |
| Arthritis-malaise | N     | N     | N     | N     | N     | N     | Y     | N     | N     | N     | N     | N     | N     | N     | Y     | Y     | N     |
| Fever        | N     | Y     | N     | N     | N     | N     | N     | N     | Y     | N     | Y     | N     | N     | Y     | Y     | Y     | Y     |
| Arterialgia-malaise | Y     | N     | Y     | Y     | Y     | N     | Y     | N     | Y     | N     | Y     | N     | Y     | Y     | Y     | Y     | Y     |
| Affected valve/s | AV    | AV + MV | AV + MV | AV + MV | AV + MV | AV + MV | AV + MV | AV + MV | AV + MV | AV + MV | AV + MV | AV + MV | AV + MV | AV + MV |
| Vegetations  | Y     | N     | Y     | N     | Y     | N     | Y     | N     | Y     | N     | Y     | N     | Y     | Y     | Y     | Y     | Y     |
| Classical WD | N     | N     | N     | N     | N     | N     | N     | N     | N     | N     | N     | N     | N     | N     | N     | N     | N     |
| Antibiotic duration, mo | 18 mo | 12 mo | 12 mo | 12 mo | 12 mo | 12 mo | 12 mo | 15 mo | 12 mo | 24 mo | 12 mo | 12 mo | 12 mo | 24 mo | 12 mo | 12 mo | 40 mo |
| Surgery      | Y     | Y     | Y     | Y     | Y     | Y     | Y     | Y     | Y     | Y     | Y     | Y     | Y     | Y     | Y     | Y     | Y     |
| Cardiac valve analysis/PCR/PAS | PCR+ | PCR+ | PCR+ | PCR+ | PCR+ | PCR+ | PCR+ | PCR+ | PCR+ | PCR+ | PCR+ | PCR+ | PCR+ | PCR+ | PCR+ | PCR+ | PCR+ |
| Other analysis | PCR+ liquid pericardial | N     | N     | N     | N     | N     | N     | N     | N     | N     | N     | N     | N     | N     | N     | N     | N     |
| Outcome      | TF/NR | TF/NR | TF/NR | TF/NR | TF/NR | TF/NR | TF/NR | TF/NR | TF/NR | TF/NR | TF/NR | TF/NR | TF/NR | TF/NR | TF/NR | TF/NR | TF/NR |

Table 2

<table>
<thead>
<tr>
<th>Application</th>
<th>Target Primer name</th>
<th>Primer sequence (5'-3')</th>
<th>Reference</th>
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<tr>
<td>Conventional PCR rRNA 16S</td>
<td>fD1, rP2</td>
<td>AGAGTTTGATCCTGGCTCAG; ACGGCTACCTTGTTACGACTT</td>
<td>[19]</td>
</tr>
<tr>
<td>Conventional PCR rRNA 16S specific for T. whipplei</td>
<td>W3FE, W2RB</td>
<td>GGAATTCCAGAGATACGCCCCCCGCAA; CGGGATCCCATTCGCTCCACCTTGCGA</td>
<td>[20]</td>
</tr>
<tr>
<td>SYBER green PCR rRNA 16S</td>
<td>PSL, P13P</td>
<td>AGGATTAGATACCCTGGTAGTCCA; AGGCCCGGGAACGTATTCAC</td>
<td>[21]</td>
</tr>
<tr>
<td>SYBER green PCR Repeated sequence</td>
<td>TW27F, TW182R</td>
<td>TGTTTTGTACTGCTTGTAACAGG; TCCTGCTCTATCCCTCCTATCAT</td>
<td>[18]</td>
</tr>
<tr>
<td>SYBER green PCR Repeated sequence</td>
<td>TW13F, TW163R</td>
<td>TGAGTGATGGTAGTCTGAGAGATATGT; TCCATAACAAAGACAACAACCAATC</td>
<td>[18]</td>
</tr>
<tr>
<td>SYBER green PCR rpoB</td>
<td>TwrpoB-F, TwsrpoB-R</td>
<td>CTCGGTGTTGATGTTGATCCAA; GCACCGCAACCTCGGAGAAA</td>
<td>[22]</td>
</tr>
<tr>
<td>Taqman PCR Repeated sequence</td>
<td>TW27F, TW182R, Probe 27F-182R</td>
<td>TGTTTTGTACTGCTTGTAACAGGATCT; TCCTGCTCTATCCCTCCTATCATC; 6-FAM-AGAGATACATTTGTGTTAGTTGTTACA-TAMRA</td>
<td>[18]</td>
</tr>
<tr>
<td>Taqman PCR Repeated sequence</td>
<td>TW13F, TW163R, Probe 13F-163R</td>
<td>TGAGTGATGGTAGTCTGAGAGATATGT; TCCATAACAAAGACAACAACCAATC; 6-FAM-AGAAGAAGATGTTACGGGTTG-TAMRA</td>
<td>[18]</td>
</tr>
</tbody>
</table>

PCR = polymerase chain reaction.

Q fever endocarditis.[29,30] Most treatments used in the experience acquired in the treatment of classical WD and in classic WD concomitant with endocarditis[12] and we have the reviewed literature, only 4 (4.7%) of the cases reported a described cases.[12] depending on the series, showing values from 31% to 75% of the 5.9%. The presence of arthralgia as a prominent symptom varies fever was present only in 35% of patients and embolic events in 5.9%. The presence of arthralgia as a prominent symptom varies depending on the series, showing values from 31% to 75% of the described cases.[12–14] In our series, it has been 47% although in many cases we have looked for it when the diagnosis was made. This symptom is, sometimes, weak and only detected after an exhaustive clinical questioning. So, in patients with subacute endocarditis with negative blood cultures and low-grade fever (or not fever), if arthralgias are present, T. whipplei as causative agent should be suspected.[14,26]

Echocardiography features are 1 of the most valuable tools for suspecting IE. In our series, echocardiography allowed the diagnosis of IE in 70.6%: visualization of vegetations in 11 and indirect signs in 1. In a previous report, we analyzed all the published cases in which these data were recorded and vegetations were seen in 64.3% of cases.[12] In the French series,[14] echocardiography showed vegetations in 78.6% of the patients, but these data are not recorded in the German one.[13] In the reviewed literature, only 4 (4.7%) of the cases reported a classic WD concomitant with endocarditis[12] and we have noticed it for 2 (11.8%) of cases. One of them was diagnosed during the IE process. In any case, to perform an echocardiogram should be made to these patients since endocarditis in the context of classic WD is more frequent than in other diseases and than in general population.

The histological study by PAS staining is considered a good tool for demonstrating WD. In our series, this technique was made in 6 patients and 5 of them demonstrate the PAS positive inclusions (sensitivity of 83.3%). Data of literature recorded PAS staining in 48 patients with similar results.[12]

Diagnosis of T. whipplei endocarditis in our series has been carried out with molecular tools on heart valve tissue. Different targets have been used for molecular analyses. PCR based on the 16S rRNA amplification and subsequent sequencing has been widely used and has been the first-line screening in our series. However, some authors alert that this broad-spectrum PCR could have a limited sensitivity (value sensitivity 60%, specificity 100%).[27] while specific qPCR for T. whipplei have showed higher sensitivities.[14,28] So, if 16S rRNA PCR has been negative, specific targets should be used in highly suspected cases of T. whipplei. At least 2 of the PCRs must be positive and their sequences have to show higher identity with the bacterium studied.

Current management of T. whipplei endocarditis is based from the experience acquired in the treatment of classical WD and in Q fever endocarditis.[29,30] Most treatments used in T. whipplei endocarditis include 2 weeks of parenteral high dose of meropenem, penicillin G or ceftriaxone followed by an oral
treatment strategy of 12 months with SXT (160/800 mg BID) or, at least, 18 months of doxycycline (100 mg BID) plus hydroxychloroquine (600 mg/d)10,29,30. Treatment of 2 weeks with ceftriaxone followed by 1 year with SXT has been the most recommended line,31 although in the recently published European guidelines32–34 for the management of infective endocarditis recommends doxycycline (100 mg BID) plus hydroxychloroquine (200–600 mg/24 h) orally for ≥18 months. This fact could be in relationship with the resistance observed in vitro of T. whippelii to trimethoprim35 and the reported case of a patient with clinically acquired resistance to SXT.33 In our series, most of patients have been treated with ceftriaxone for 2 weeks followed by SXT or with doxycycline plus hydroxychloroquine with good outcomes. Other combinations have been also employed with satisfactory results and none of our patients died during the IE process and neither had a relapse in the follow-up.

After the end of treatment, some authors34,36 recommend the checking for the presence of T. whippelii in blood, saliva, and fecal samples every 6 months for 2 years and every year for the entire life of the patient. If colonization is detected, they recommend treating again, but there is not still evidence for this procedure.

In summary, T. whippelii IE is an infrequent condition that could be diagnosed with specific procedures (mostly molecular tests and thereafter PAS coloration) when culture negative IE undergo cardiac surgery. An early and appropriate diagnosis is required since this condition has a very good course and prognosis when the appropriate treatment is started. In our series, all patients who have finished the treatment have had good outcome and tolerance to the antimicrobial regimens used. Furthermore, we believe that in patients with unexplained valve disease and outcome and tolerance to the antimicrobial regimen used. In our series, most patients who have been treated with ceftriaxone for 2 weeks followed by SXT or with doxycycline plus hydroxychloroquine with good outcomes. Other combinations have been also employed with satisfactory results and none of our patients died during the IE process and neither had a relapse in the follow-up.

References