

Tropheryma Whipplei Endocarditis. An Epidemiological, Clinical and Treatment Review

García-Álvarez L, Sanz MM and Oteo JA*

Infectious Diseases Department, Hospital San Pedro-Center for Biomedical Research of La Rioja (CIBIR), Logroño (La Rioja), Spain

Abstract

T. whipplei, the causative agent of classic Whipple's disease, also produces acute, sub-acute and chronic localized forms of infection such as endocarditis. Blood culture of patients with *T. whipplei* endocarditis used to be negative and most of the cases are confirmed when molecular analyses of the heart valves, surgically obtained, are performed. The development of molecular tools has allowed increasing the number of cases of endocarditis due to this microorganism. This review describes the epidemiological and clinical characteristics, diagnosis, and treatments used in the 84 cases of *T. whipplei* endocarditis, to our knowledge, reported on the medical literature.

Keywords: *Tropheryma Whipplei*; Endocarditis; Blood Culture Negative Endocarditis

***Corresponding Author:** Oteo JA, Infectious Diseases Department, Hospital San Pedro-Center for Biomedical Research of La Rioja (CIBIR), Logroño (La Rioja), Spain; E-mail: jaoteo@riojasalud.es

Introduction

Tropheryma whipplei, formerly *Tropheryma whippelii* [1], is an intracellular gram-positive actinobacteria, ubiquitous in the environment, involved in a large clinical spectrum [2, 3]. The hypothesis of its bacterial origin was supported with use of PAS staining [4] and the success of the first antibiotic treatment

[5]. This bacterial origin was subsequently confirmed by electron microscopy, Polymerase Chain Reaction (PCR) of the 16S rRNA and finally by culture [1, 2, 6-10]. Until recently, *T. whipplei* was known to be only the causative agent of Whipple's disease, a chronic multisystemic infection first described in 1907 [11]. Typical manifestations of the classical form of Whipple's disease affect the gastrointestinal tract, joints, central nervous system and in some cases other organs, as eyes [12]. The knowledge of the genome of *T. whipplei* has allowed develop specific and sensible tools that have let to involve this microorganism in a broad spectrum of clinical conditions [13, 14]. So, *T. whipplei* can produce acute localized forms of infection such as pneumonia [15, 16], bacteremia [17], acute diarrhea [18, 19], uveitis [20, 21]; sub-acute forms such as adenitis [22] and chronic forms as uveitis [23], and, overall, endocarditis [24, 25]. *T. whipplei* has also been detected in asymptomatic carriers based, mainly, on stools and saliva analysis with very different prevalence among populations [26-36].

Blood culture negative endocarditis is a relative frequent condition among endocarditis (approximately, 5-30%) and the main cause if antimicrobials have been previously administrated [37-45]. Nevertheless, with the application of molecular tools we can do a new approximation to the etiology, and new agents have been involved.

First implication of *T. whipplei* as causative agent of infective endocarditis was reported from Switzerland in 1997 in a patient with negative cultures using a broad-range PCR of part of the 16S rRNA gene followed by sequencing [46]. Curiously,

first stable cultivation of the bacterium of Whipple's disease was carried out in 2000, from the mitral valve of a patient with blood culture negative endocarditis [2]. Since then the number of cases has increased and to date *T. whipplei* endocarditis is one of the more frequent causes of blood negative culture in some areas [47].

The aim of this review is to describe the epidemiological and clinical characteristics, diagnosis, and treatments used in the cases reported on the medical literature of *T. whipplei* endocarditis. We have made a searching in the PubMed database (<http://www.ncbi.nlm.nih.gov/pubmed>) with no time limit, using the terms "Whipple's disease and endocarditis", "*Tropheryma whipplei* endocarditis" and "blood culture negative endocarditis".

Epidemiology

Since the last great review of *T. whipplei* endocarditis published by Fenollar et al. in November 2013 [24], in which 77 cases were described, to our knowledge, seven more cases have been found in our research [48-52]. So, a total of 84 patients with *T. whipplei* endocarditis diagnosis have been described in the literature [24, 46-78]. The vast majority of cases were men, 73 (86.9%), 7 were female (8.3%) and in the four remaining, gender is not available. Mean age ($\pm$ SD) was 60.01 ($\pm$ 10.3) years. Most of the patients were from Europe 75 (89.3%), 8 from America (9.5%) (4 from USA and 4 from Canada), and one from Africa (1.2%). Among all the European patients, 32 were from France (42.7%), 17 from Germany (22.7%), 12 from Switzerland (16%), 5 from Spain (6.7%), 4 from UK (5.3%), 2 from Denmark (2.7%), 2 from the Czech Republic (2.7%) and 1 from Netherlands (1.33%) [24, 48-52]. The above data show differences in the incidence of cases among countries. France, Germany and Switzerland have the largest number of diagnosed cases. This fact could be due to their larger experience in the knowledge and use of the molecular tools to heart valves [24, 25, 46]. By other hand we do not know the true incidence of *T. whipplei* endocarditis since the practice of studying by molecular tools is not the rule in all hospitals. Nevertheless several parameters seem to affect the incidence of *T. whipplei*

endocarditis: the diagnostic tools available, working group experience and the true incidence itself [24].

Clinical Features

The signs and symptoms of endocarditis in *T. whipplei* infection are not the typical ones. Fever was only present in 24 of the total (28.6%). The presence of heart murmur is not available in most of the cases although previous valvular involvement was present in 22 patients (26.2%). Prosthetic valve replacement previously to the event seems not an important condition since has been only reported in 4 patients of the available series. Nevertheless, at least a previous cardiac condition or a cardiac event (ie: coronary heart disease) was present in 50% of cases. Alcohol abuse has been reported in some cases (at least in 4 of the patients). Most of cases do not report any data of historical immunosuppressive therapies. Only 10 of the patients, 7 previously reported by Fenollar *et al.* [24], had history of immunosuppressive therapy (3 of them were tumor necrosis factor inhibitors).

Cardiac failure was the main presenting symptom and it has been described in 47 of the 84 patients (55.9%). An embolic peripheral phenomenon was presented in the 9.75% of cases. Arthralgia was observed in 38 of 84 patients (45.2%). This last is of special interest. Long lasting arthralgias presence as a prominent symptom varies depending on the series. While in the France series [24], arthralgias are present in 21/28 patients (75%), in the remainder arthralgias are scarcely reported (30.9%). Due to these data and taking into account that this symptom is, sometimes, weak and only detected after an exhaustive clinical research, authors suggest that, in those patients with subacute endocarditis and low-grade fever or not fever, if arthralgias are present *T. whipplei* as causative agent should be suspected [24, 56].

The valve involved was predominantly the aortic, 52/84 (61.9%), followed by the mitral valve, 14/84 (16.7%). Mitro-aortic valve involvement was observed in 13 of the patients (15.5%). Only one case of tricuspid valve, one of mitro-tricuspid affection and one of aortic-tricuspid affection were observed (in two cases, this data is not available) [24, 48-51,

79]. Vegetations were observed in more than the half of patients (64.3%). These data are lower than those published before [24, 79], however, in 17 of 84 patients (20.2%) data of vegetations were not available. We cannot give data about the vegetations size since this data is not recorded.

Only in 4 (4.7%) of the cases a classic Whipple's disease was a concomitant with the endocarditis diagnose. However, in lot of cases this data is not available and in some of them although, classic Whipple's disease has not been diagnose, it can not be excluded.

Although the relationship observed between higher frequency of some HLA alleles and patients diagnosed of classic Whipple's disease [80, 81], no data regarding this topic were shown in any of the cases collected for this review.

Diagnosis

Although the suspicion and diagnosis of *T. whipplei* endocarditis is complicated, more than 80 cases have been reported in the literature since 1997. However, due to the difficulties for the identification of *T. whipplei*, the prevalence of endocarditis caused by this bacterium could be underestimated [82].

Blood culture of patients with *T. whipplei* endocarditis used to be negative. Blood culture negative endocarditis is estimated to account between 2.5 and 30% of all endocarditis cases reported [24]. However, the percentage represented by *T. whipplei* in them has not been defined. Some blood culture negative endocarditis series showed a rate of *T. whipplei* as causative agent around for 0.6-2.6% of all the studied cases [59, 82]. A study of 348 patients diagnosed of blood culture-negative infective endocarditis, in 2005, allowed identify that *Coxiella burnetii* and *Bartonella* spp. were the most prevalent pathogens in the blood culture negative endocarditis while *T. whipplei* was implicated in only two cases [82]. In other big series, of a total of 740 patients with blood culture-negative endocarditis suspicion, *T. whipplei* was identified in the 2.6% of the cases [59]. Geissdörfer *et al.* [47] found a frequency of 6% *T. whipplei* positive valves among all patients with detection of bacteria on explanted valves while *Bartonella* spp., *Coxiella*

burnetii, and bacteria of the HACEK group, were identified in only three (1.2%), two (0.8%), and two (0.8%) cases, respectively. Thus there seems to be a regional difference in the appearance of *T. whipplei* as agent of endocarditis that needs to be discussed.

Current Duke Criteria for the diagnosis of endocarditis is not useful in *T. whipplei* endocarditis [79]. Among the 28 patients reported by Fenollar *et al.* [24] only 3.6% met criteria for endocarditis according to the modified Duke criteria, and 60.7% met for possible endocarditis. It is very difficult to perform a microbiological or histological diagnose without analyzing the surgical remove valve. Since the prevalence of asymptomatic carriers of *T. whipplei* is very high [27, 28, 30, 35] in some populations and the same for the prevalence of antibodies we have not sensible and specific tools for an indirect diagnose as occurs with Q fever endocarditis or *Bartonella* spp. endocarditis. According to the 84 cases reported on the literature, all the cases, which had available data regarding removed cardiac valves analysis, showed positive PCR results (78/84). One of the patients, in which valve surgery was not carried out, *T. whipplei* was confirmed by positive PCR in EDTA blood samples [51]. PAS staining of cardiac valves is recorded in 48 patients; only four of them (8.3%) showed a negative PAS result. Only 29 of the patients had IHC analyses of the valves performed. All of them belong to the France and German series [24, 47] and all showed a positive IHC result. Therefore, some authors suggest adding new major criteria in the Duke classification for the diagnosis (performance of repeat PCR for *T. whipplei* on blood samples or PCR analysis of removed cardiac valve) taking into account that data have to be interpreted according to the clinical context and performing standardized assays [24, 47, 83, 84].

Although stools and saliva samples have been used to diagnose classic Whipple's disease and to detect asymptomatic carriers, these samples are not useful for the diagnosis of endocarditis due to *T. whipplei*. Criteria to make a correct diagnostic to assess a definitive infective endocarditis caused by *T. whipplei* were defined by Fenollar *et al* in 2008 [85]. This paper established definitive *T. whipplei* endocarditis if positive

results of Periodic Acid-Schiff (PAS) staining and/or specific Immuno Histo Chemistry Test (IHC) using specific antibodies against *T. whipplei* and 2 positive results of PCR assays targeting 2 different sequences in a cardiac valve specimen were met [85].

Different targets are used for the PCR analyses. PCR based on the 16S rRNA amplification and subsequent sequencing has been widely used, however some authors alert that this broad-spectrum PCR could have a limited sensitivity (value sensitivity 60%, specificity 100%) [86], while specific qPCR for *T. whipplei* have showed higher sensitivities [29, 85].

Diagnosis of *T. whipplei* endocarditis in our laboratory is carried out with molecular tools on heart valve tissue and/or blood samples. The first line screening in our laboratory is based on the 16S rRNA PCR amplification, in the case this PCR and subsequent sequencing amplifies *T. whipplei*, specific qPCR are performed. We test three different qPCR targets, two based on a noncoding sequence repeated 7 times in the genome of the bacterium (85), and another one that amplifies *rpoB* gene [87]. To ensure no contamination we realize samples on duplicate and we use always positive and negative controls. At least two of the qPCR had to be positive and their sequences have to show higher identity with the bacterium studied.

Treatment

Treatment for *T. whipplei* endocarditis is still unclear and standard treatment has not been agreed [24, 47]. Current management is based on the experience acquired of the treatment of classic Whipple's disease and in the treatment of Q fever endocarditis [88, 89]. Most treatments used in *T. whipplei* endocarditis include 2 weeks of parenteral high-dose of meropenem, penicillin G or ceftriaxone followed by a oral treatment strategy of 12 months with trimethoprim-sulfamethoxazole (160/800 mg BID) or at least 18 months of doxycycline (100 mg BID) plus hydroxychloroquine (600 mg per day) [47, 88, 89]. Treatment of 2 weeks with ceftriaxone followed by one year or shorter with trimethoprim-sulfamethoxazole seems the most recommended line [90]. However, in vitro studies have shown best results with the

combination of doxycycline and hydroxychloroquine [12, 91]. Therefore, best treatment for *T. whipplei* endocarditis is nowadays a controversial issue.

According to all cases of *T. whipplei* endocarditis where treatment data are available (63/84), all but 2 received antimicrobial treatment (96.8%). However, different antimicrobials have been used. Trimethoprim-sulfamethoxazole treatment was the antibiotic most often used (40/63: 63.5%). Of these 40 patients, 21 of them (52.5%) had previously received penicillin G or ceftriaxone during at least 2 weeks. Fourteen patients received doxycycline plus hydroxychloroquine. Follow up was good in the 86.4% of 59 patients in which these data are available. Follow up was lost in 2 of the cases and 6 died.

Three *T. whipplei* endocarditis relapses after treatment with trimethoprim/ sulfamethoxazole have been also published [92, 93]. *T. whipplei* resistance to trimethoprim/ sulfamethoxazole has been previously reported [91]. Two of the patients had been previously diagnosed of classic Whipple's disease and correctly treated with trimethoprim/ sulfamethoxazol [93]. One of them developed *T. whipplei* endocarditis 4 years after the cessation of antibiotics, the second one six months after the initiations of this regime (this last patient had been also treated with intravenous ceftriaxone for two weeks). During the endocarditis episode both patients were treated with doxycycline and hydroxychloroquine, the first one also with trimethoprim/ sulfamethoxazole but he was lost of follow up. The second one after 2 years of doxycycline and hydroxychloroquine, lifelong doxycycline was included and he is apparently cured [93]. The other case was a patient diagnosed of *T. whipplei* aortic native valve endocarditis who relapsed despite surgery and treatment with trimethoprim/ sulfamethoxazole and previously ceftriaxone [92]. The patient was cure after 18 months of oral doxycycline- hydroxychloroquine [92].

Other considerations and Conclusions

In the last years and with the development of molecular tools, new cases of *T. whipplei* endocarditis have been diagnosed. For this reason, *T. whipplei* has emerged as an important differential diagnosis for blood culture-negative endocarditis

[47]. Infectious endocarditis caused due to *T. whipplei* is often slowly progressive, similar to that caused by *C. burnetii* and *Bartonella* spp. [89]. Endocarditis in the course of classical WD occurs frequently and not necessarily necessitates valve explantation. However, these cases often are not reported in the literature as *T. whipplei* endocarditis.

To diagnose *T. whipplei* endocarditis the patient has to present compatible clinical manifestations and complementary proofs, positive PAS staining and/or IHC from the affected tissue, and/or at least two PCR positive with different targets from heart valves. PCR positive from stools and saliva samples or positive PAS of intestinal tissues are not a criteria for the diagnosis.

Drawing conclusion about the disease course is difficult, however and due to the presence of arthralgias and low-grade fever of long duration in a high proportion of the cases, it seems to be a subacute process.

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