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Tropheryma whipplei Endocarditis

Lara García-Álvarez and José Antonio Oteo

Abstract

Tropheryma whipplei mainly known as the causative agent of classical Whipple's disease, also produces acute, sub-acute and chronic localized forms of infection such as endocarditis. The development of molecular tools has allowed increasing the number of cases of endocarditis due to blood culture use to be negative in *T. whipplei* endocarditis and most of the cases are confirmed post-surgery when molecular analyses of heart valves are performed. Although, *T. whipplei* endocarditis is an uncommon condition with an atypical presentation it must be considered in the diagnosis of blood culture negative endocarditis and in patients with heart failure in which valve affectation is present. Other clinical features such as long lasting arthralgia can be present in a high percentage of the patients. It is important to know that few cases are diagnosed in the context of the classical Whipple's disease. The prognosis is very good when an appropriate surgical management and anti-microbial-specific treatment is given. This chapter describes the epidemiological, clinical characteristics, diagnosis and treatments for *T. whipplei* endocarditis.

Keywords: *Tropheryma whipplei*, *Tropheryma whipplei* endocarditis, endocarditis, blood culture negative endocarditis, infectious endocarditis

1. Introduction

Tropheryma whipplei, formerly *Tropheryma whipplei*, is an intracellular gram-positive Actinobacteria ubiquitous in the environment that is involved in a large variety of clinical forms [1, 2]. The initial name was proposed by Relman *et al.* in 1992, and comes from the Greek *trophe*, nourishment, and *eryma*, barrier, due to the malabsorption it causes, and from the surname of George Hoyt Whipple [3]. In 2001, the name of the bacterium was slightly modified to conform to the proper spelling of Dr. George H. Whipple's name [4].

Dr. Whipple was the first who reported, in 1907, a "hitherto undescribed disease" he named "intestinal lipodystrophy" in a 36-year-old man with malabsorption, weight loss, diarrhea, migratory polyarthritits, cough and mesenteric lymphadenopathy [5]. Now, we refer to this disease as Whipple's disease. Although this disease was first described at the beginning of the last century, the hypothesis of its bacterial origin goes back to the late 40's and was supported with use of periodic acid-Schiff (PAS) staining and the success of the first antibiotic treatment [6, 7]. Subsequently, the presence of the microorganism was confirmed by electron microscopy (rod-shaped organism), polymerase chain reaction (PCR) of the 16S rRNA and finally by culture [1, 3, 8–12]. The isolation and later sequencing of its genome made possible to define its antibiotic susceptibility [13–16].

Until recently, *T. whipplei* was known to be only the causative agent of Whipple's disease, now called by some authors "classical Whipple disease", a rare

chronic multisystemic infection [5]. Incidence of Whipple's disease was reported in approximately 1 per 1.000.000, although it remains unclear and epidemiological estimates varies among different studies [17–19]. Classical form of Whipple's disease usually involves the gastrointestinal tract, joints and central nervous system with malabsorption, diarrhea, abdominal pain and/or weight loss and arthralgia as prominent manifestations. Cardiac, ocular or other organs involvement has been also reported in patients with Whipple's disease [20–29]. The knowledge of the genome of *T. whipplei* has allowed developing specific and sensible tools that have let to involve this microorganism in a broad spectrum of clinical conditions [13, 14]. Therefore, *T. whipplei* can produce acute localized forms of infection such as pneumonia [30, 31], bacteremia [32], acute diarrhea [33, 34], uveitis [35, 36]; sub-acute forms such as adenitis [37] and chronic forms as uveitis [38], and, overall, endocarditis [39, 40].

T. whipplei has also been detected in asymptomatic carriers based, mainly, on stools and saliva analysis with very different prevalence among populations [41–52]. The carriage of *T. whipplei* varies considerably across studies and subjects. Many factors are involved in those differences such as the geographical region, exposure or the age of the studied subjects. The prevalence of asymptomatic carriers of *T. whipplei* in Africa and Asia is higher than in Europe and it is also higher in children than in adults [49–51, 53]. Actinobacteria are environmental microorganisms that can be found in freshwater, soil or seawater sediments, this fact could explain the high prevalence of *T. whipplei* in people expose to sewage and sewage plant workers [2, 41, 47, 54, 55]. People in contact with patients with Whipple's disease, as patients' relatives or carriers, or those with poor hygiene conditions such as homeless, also presents higher prevalences [56–59]. Differences between the targets used for the PCR and the samples used have been also observed and could explain these reported differences [52, 60]. Li *et al.* assessed that genomic variants of *T. whipplei* are associated with neither the organotropism of the bacteria nor the geographical residence of the individuals [61], however later studies show that different genotypes are more frequent in some populations [34, 56, 58, 62]. Therefore, despite Whipple's disease is rare, the high number of healthy carriers, the ubiquitous presence of the bacteria in the environment [41, 47, 57, 59] and the possibility of interhuman transmission [49, 56–59, 63, 64] make *T. whipplei* a common bacterium in humans.

2. Epidemiology

First implication of *T. whipplei* as causative agent of infective endocarditis was reported in Switzerland in 1997, in a patient with blood culture negative endocarditis (BCNE) using a broad-range PCR followed by sequencing [64]. Curiously, first stable cultivation of the bacterium of Whipple's disease was carried out in 2000, from the mitral valve of a patient with BCNE [1]. Since then, the number of cases has increased and to date *T. whipplei* endocarditis is one of the more frequent causes of BCNE in some areas [65, 66].

BCNE is a relative frequent condition among endocarditis representing 5–30% in big series [67–70]. The main reasons are the previous administration of antimicrobials and fastidiously culture microorganisms [67, 68, 71–75]. The application of molecular tools has allowed doing new approximations to the etiology of BCNE and new agents have been involved [69].

Sporadic cases of *T. whipplei* endocarditis have been reported from different countries, but there are few published series of *T. whipplei* endocarditis. France, Spain, Germany and Switzerland have the largest number of diagnosed cases

[39, 64, 65, 70]. This fact could be due to their larger experience in the knowledge and use of the molecular tools to heart valves [40]. The incidence of *T. whipplei* endocarditis among BCNE varies depending on the series. The incidence rate estimated varies between 2.6% and 7.1% depending on the country (France: 2.6% [76], Spain and Denmark: 3.5% [70, 77], Switzerland: 4.3% [78], Germany: 6.3% [65], Czech Republic: 7.1% [79]). However, it is difficult to know the true incidence of *T. whipplei* endocarditis since its study by molecular tools is not the rule in all hospitals. Thus, several parameters seem to affect the incidence of *T. whipplei* endocarditis such as the diagnostic tools available, the working group experience and the true incidence itself [39].

A total of 174 cases of *T. whipplei* endocarditis have been reported between 1999 and 2020 [21, 39, 65, 70, 78–117]. The vast majority of cases were men (>85% of the cases) and the average age was around 57 years (range: 33–81 years).

3. Clinical features

Comorbidities or other predisposing risk factors have been not uniformly reported in the literature [118]. Previous valvular affectation has been documented in 21% of the diagnosed cases, while prosthetic valve replacement previously to the event seems not an important condition (<5% of the available series). Alcohol abuse has been reported in very few cases, however alcohol intake (>60 g/d) was referred by the 23.5% of the patients in the Spanish series [70]. Previous cardiac condition or a cardiac event (i.e., coronary heart disease) has been observed in 50% of cases [66]. Data of historical immunosuppression forms (autoimmune disease or immunosuppressive therapies such as steroids or tumor necrosis factor inhibitors) have been reported in 21 cases (12%).

Classical Whipple's disease has been reported as concomitant with the diagnose of endocarditis in few cases (6%) [66, 70]. However, in lot of cases this data is not available and in some of them although, classical Whipple's Disease has not been diagnosed, it cannot be excluded.

The signs and symptoms *T. whipplei* endocarditis are not the typical ones. Fever has been only reported in 21% of the cases. Cardiac failure and arthralgia have been shown as the main presenting symptoms and have been described in 43% and 52% of patients, respectively. Cardiac failure is of special interest because it is the first manifestation in a high percentage of patients. Long lasting arthralgias presence as a prominent symptom varies depending on the series. While in the French series arthralgias were present in 75% of patients [39], in the Spanish one this condition was present in 53% [70]. These variations could be due to this symptom is sometimes weak and only detected after an exhaustive clinical research. Some authors suggest that, in those patients with sub-acute endocarditis and low-grade fever or not fever, if arthralgias are present, *T. whipplei* as causative agent should be suspected [39, 103]. Asthenia and malaise lasting more than six months were notified by the 41.2% of the patients in one series [70]. Other signs such as weight loss or gastrointestinal symptoms have been observed in 25% and 21% of the reported patients [118]. In addition, central nervous system manifestations (i.e., emboli) have been detected in 16% of patients.

The valve involved in patients with *T. whipplei* endocarditis has been predominantly the aortic (63%). Involvement of multiple valves (mainly aortic valve in combination with the mitral or tricuspid valve, and mitral-tricuspid affection) has been noticed in 23% of patients. Only mitral valve affectation has been observed in 20% of patients and tricuspid valve just in six of 174 patients (3%). Native valve was affected in the vast majority of cases.

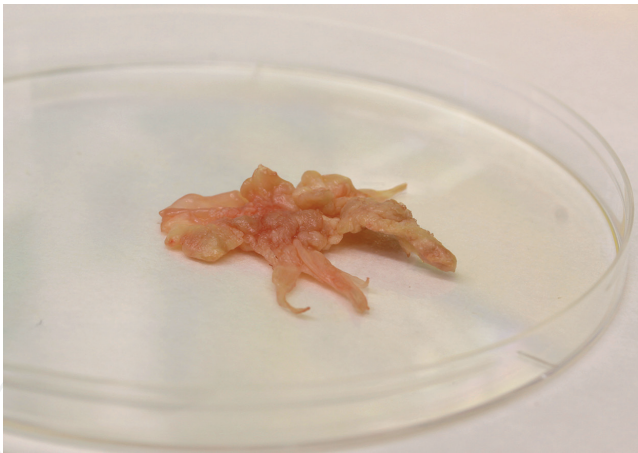


Figure 1.
*Valve vegetation specimen obtained after surgery from a patient with *T whipplei* endocarditis.*

		% (No.)
Patients (No.)	174	
Epidemiological data		
Medium Age (years)	57	
Male gender		85% (148)
Medical history		
Immunosuppression		12% (21)
Valvular abnormality		21.8% (38)
Affected valve		
Aortic		63% (110)
Mitral		20.7% (36)
Tricuspid		3.4% (6)
Multiple valves		22.9% (40)
Presenting symptoms		
Arthralgia		51.7% (90)
Heart failure		43% (75)
Weight loss		25.2% (44)
Fever		21.3% (37)
Central nervous system		16.1% (28)
Gastrointestinal symptoms		20,7% (36)
Laboratory abnormalities		
Anemia		39,1% (68)
Outcome		
Valve surgery		73.5% (128)
Death		17.8% (31)

Table 1.
*Main clinical epidemiological, clinical and outcome characteristics of patients with *T. whipplei* endocarditis reported in the literature. Updated from McGee et al. [118].*

Echocardiography features are one of the most valuable tools for suspecting infectious endocarditis. According to the literature, when these data were recorded, presence of vegetations was observed in more than the half of patients [66]. In our series, echocardiography was performed in all patients (both transthoracic and trans-esophageal in more than 80%) and allowed the diagnosis of infectious endocarditis in 70% of patients through the visualization of vegetations in the vast majority, or by indirect signs in a few [70]. Valve vegetation from a patient after cardiac valve surgery is shown in **Figure 1**. In the French series, echocardiography showed vegetations in 78% of the patients, but these data are not recorded in the German one [39, 65]. Data of vegetation appearance or size is rarely reported. Data of size vegetations when available, shown a minimum size of 5 mm and a maximum of 33 mm [118].

The main laboratory recording abnormalities at the time of the diagnosis have been anemia, which was detected in 40% of patients but this date can reach 88.2% in some series, and increasing of C-reactive protein in range from 2.3 to 137 mg/L [70]. In patients who had heart failure, B-type natriuretic peptide (BNPs) of up to 2536 ng/L has been also reported [118].

Main characteristics of patients are shown in **Table 1**.

4. Diagnosis

The suspicion and diagnosis of *T. whipplei* endocarditis is complicated. To date, 174 cases have been reported but, due to the difficulties for the identification of *T. whipplei*, the prevalence of the endocarditis it causes could be underestimated [119].

Diagnosis of *T. whipplei* endocarditis remains a challenge for several reasons. One of them is because this endocarditis does not exhibit the typical sings (no fever nor peripheral stigmata and low inflammatory response) and blood cultures used to be negative; therefore, modified Duke's criteria are ineffective for diagnosis before heart valve analysis [39]. In this sense, some series have shown that only 3.6% patients met criteria for endocarditis according to the modified Duke criteria and 60.7% met for possible endocarditis [39]. It is very difficult to perform a microbiological or histological diagnose without analyzing the surgical remove valve. Routine blood and tissue culture are not often useful for the diagnosis. Thus, the diagnosis is often made post-surgery and valve analysis requires specialized laboratories, moreover if culture of the bacteria is intended to carry out.

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%) [120], while specific qPCR for *T. whipplei* have showed higher sensitivities [48, 60]. 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. PCR yield in other specimen different from valves varies depending on the specimen type and should be interpreted with caution according to the clinical context [66, 118]. A positive PCR result from a non-sterile site such as stool or saliva samples has been used to diagnose classical Whipple's disease and to detect asymptomatic carriers, but is nor sensible nor specific for the diagnosis of *T. whipplei* endocarditis without clinical evidence of disease [42, 121, 122].

The role of serological tests in the diagnosis of Whipple's disease is unclear because healthy carrier patients may paradoxically have a higher immune response

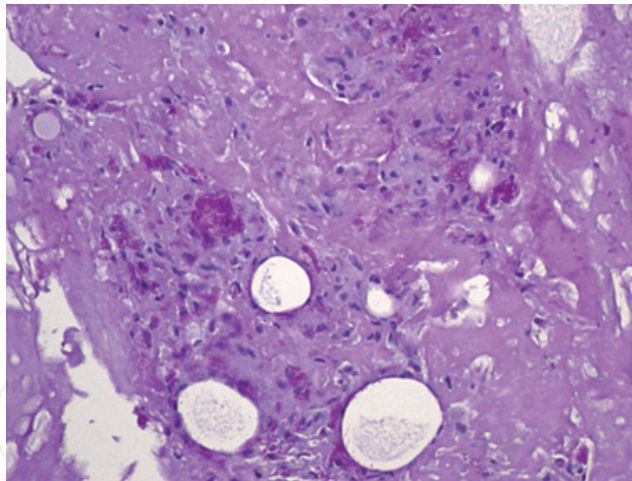


Figure 2.
PAS staining positive in valvular tissue and vegetation.

to *T. whipplei* compared with patients with active Whipple's disease [123]. Specific tools for an indirect diagnose for *T. whipplei* endocarditis are not available. This fact does not occur in other BCNE such as Q fever endocarditis or *Bartonella* spp. endocarditis. Curiously, a patient with Q fever and *T. whipplei* concomitant endocarditis has been described [124]. Valvular inflammatory infiltrates of *T. whipplei*-infected heart valves mainly consisted of foamy macrophages and lymphocytes. These macrophages have been observed in valvular tissue and in the vegetations on the surface of the heart valves. The dense and granular material that foamy histiocytes are filled with is strongly positive on PAS staining or immunopositive with a specific antibody against *T. whipplei* [39]. Thus, PAS staining and specific immunohistochemistry test (IHC) using specific antibodies against *T. whipplei* of cardiac valves could be useful for the diagnosis of *T. whipplei* endocarditis (**Figure 2**).

According to the literature, 156 patients have been diagnosed of definite *T. whipplei* endocarditis by direct examination of the valve, of which more than 70% had positive PCR, almost 40% reported PAS staining positive on valve tissue and around 50% showed positive IHC. Seven patients were diagnosed of possible endocarditis regarding to vegetations on valve imaging and classical Whipple's disease concomitant diagnosis. In these last cases, 85% had positive PCR on different specimen such as duodenal sample, stool, saliva or central nervous system samples and more than 50% had positive PAS staining in other tissue specimen [118].

In summary, definitive *T. whipplei* endocarditis could considered if positive results of PAS staining and/or specific IHC test using specific antibodies against *T. whipplei* and/or 2 positive results of PCR assays targeting 2 different sequences in a cardiac valve specimen are met [60]. It is important to notice that 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 [39, 103].

5. Treatment

The optimal treatment of IE caused by *T. whipplei* remains uncertain. Treatment options and duration are based on previous experience and expert opinion owing to the microorganism's nature, the lack of large series (because of the low incidence) in which follow-up is documented and because clinical trials have not been developed [74]. Recommendations are mainly based on the experience obtained from the treatment of classical Whipple's disease and other types of BCNE such as Q fever

endocarditis [125, 126]. Two weeks treatment with ceftriaxone, followed by 1 year of trimethoprim/sulfamethoxazole, has been the most recommended treatment for years [126]. However, *in vitro* studies have shown best results with the combination of doxycycline and hydroxychloroquine [127, 128].

According to the literature, treatments used in *T. whippiei* endocarditis include, in most cases, two weeks of parenteral high dose of ceftriaxone (others such as meropenem, penicillin G have been also used) followed by an oral treatment strategy of 12 months with sulfamethoxazole (160/800 mg BID) or, at least, 18 months of doxycycline (100 mg BID) plus hydroxychloroquine (600 mg/d), in a smaller proportion [125, 129, 130]. Available data indicate that the average treatment length (range) has been 17 months (12 months to indefinite) [118].

Last European guidelines published in 2015, recommend doxycycline (200 mg/24 h) plus hydroxychloroquine (200–600 mg/24 h) orally for at least 18 months (in the case of central nervous system involvement, sulfadiazine 1.5 g/6 h orally must be added to doxycycline). As alternative therapy, 2–4 weeks of ceftriaxone (2 g/24 h intravenously) or 2–4 weeks of penicillin G (2 million U/4 h) and streptomycin (1 g/24 h) intravenously can be used, followed by, at least, 1 year of oral trimethoprim/sulfamethoxazole (800 mg/12 h) [74]. It is likely that this recommendation was included after taking into consideration an *in vitro T. whippiei* resistant to trimethoprim, a case report of a patient with clinically acquired resistance to trimethoprim/sulfamethoxazole and the cases of *T. whippiei* endocarditis relapses after treatment with trimethoprim/sulfamethoxazole which were apparently cured after two years of doxycycline and hydroxychloroquine [109, 114, 131, 132]. Furthermore, some authors do not recommend the use of trimethoprim/sulfamethoxazole because the clinical, microbiological and genetic data analyses show that it is an antibiotic not efficient for the management of *T. whippiei* endocarditis [109]. In fact, three *T. whippiei* endocarditis relapses after treatment with trimethoprim/sulfamethoxazole have been published.

After the end of treatment, some authors recommend checking for the presence of *T. whippiei* in blood, saliva, and fecal samples every six months for two years and every year for the entire life of the patient [39]. If colonization is detected, they recommend treating again, but there is not still evidence for this procedure.

Follow-up data and long-term outcome of the treatments used in this condition have not been widely reported. These data are well documented in the Spanish series. Although in this series only the 35% of the patients received treatment according to guidelines, all the treatment lines used in this cohort in the management of *T. whippiei* endocarditis were effective and well tolerated and therapeutic failures or relapses were not detected either during the treatment or after it was finished [133]. Furthermore, no major complications were detected once the treatment was established or during the follow-up. Even though, follow-up of all patients continues in order to identify possible late relapses. It has been demonstrated that doxycycline plus hydroxychloroquine treatment of duration shorter than 18 months was not associated with either relapses or fatal outcomes. Moreover, data suggest that, with a very careful post-treatment monitoring, in patients who require the replacement of the infected valve and without classical manifestation of Whipple's disease, replacement of the affected valve and a shorter duration antimicrobial treatment might be sufficient [133].

Since *T. whippiei* is not present in the stool or saliva of patients with endocarditis caused by this microorganism and in the absence of other biological markers indicating the discontinuation of the antimicrobials, other tools are needed. In this regard, the role of PCR of urine should be explored both as a tool for monitoring patients post-treatment and the non-invasive diagnosis of *T. whippiei* endocarditis [134].

6. Conclusions

In the last years and with the development of molecular tools, new cases of *T. whipplei* endocarditis have been diagnosed. For this reason, although *T. whipplei* infective endocarditis is an infrequent condition has emerged as an important differential diagnosis for BCNE. Endocarditis due to *T. whipplei* is often slowly progressive, similar to that caused by *Coxiella burnetii* and *Bartonella* spp. and it could be diagnosed with specific procedures when BCNE 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 (including surgery). In our opinion, patients with unexplained valve destruction which requires cardiac surgery, an exhaustive clinical investigation must be performed and removed valves should be studied by molecular tools for to rule out an underlying infectious endocarditis.

Conflict of interest

The authors declare no conflict of interest.

Author details

Lara García-Álvarez and José Antonio Oteo*
San Pedro University Hospital - Center for Biomedical Research of La Rioja (CIBIR), Logroño, Spain

*Address all correspondence to: jaoteo@riojasalud.es

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