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# Culture Negative Endocarditis: Advances in Diagnosis and Treatment

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## Abstract

Culture-negative endocarditis (CNE) is a challenging clinical entity, both diagnostically and therapeutically. In this chapter, the changed epidemiology and microbiology of CNE are reviewed with cases highlighting typical pathogens in patients pre-treated with antibiotics, less common fastidious pathogens such as bacteria of the HACEK group, nutritionally deficient bacteria, *Legionella* spp. and Mycobacteria, “quintessential” CNE pathogens such as *Bartonella* spp., *Coxiella burnetti* and *Tropheryma whipplei*, as well as fungal CNE. Contemporary diagnostic methods are reviewed including polymerase chain reaction-based pathogen 16s RNA amplification coupled with electrospray ionization mass spectrometry (PCR/ESI-MS). Finally, treatment options per the recently updated 2015 American Heart Association and European Society for Cardiology guideline are presented.

**Keywords:** culture-negative endocarditis, *Bartonella* spp., *Coxiella burnetti* and *Tropheryma whipplei*, PCR/ESI-MS

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## 1. Introduction

Culture-negative endocarditis (CNE) is one of the most challenging infectious diseases clinical syndromes both diagnostically and therapeutically. The prevalence of CNE varies widely in various modern series: it is estimated that on average, in 20% (range 5–71%) of echocardiographically evident endocarditis, both native and prosthetic valve, blood cultures do not yield a specific pathogen [1–7]. The morbidity but not necessarily mortality associated with CNE is higher than in instances where a specific pathogen is found, primarily due to the increased burden of diagnostic testing, delays in administration of antibiotics and the

extended use of broad spectrum anti-microbial agents [8]. This chapter will review the epidemiology and likely microbiology of CNE, as well as enhanced diagnostic methods and treatment recommendations.

A useful definition of CNE has been put forth by Tattévin et al. [9] wherein one can think of this entity as (1) true bacterial endocarditis with blood cultures sterilized by previous receipt of antimicrobials; (2) CNE caused by fastidious or unusual organisms such as the bacteria known as the “HACEK” group, nutritionally deficient *Streptococci*, *Pasturella* spp., *Helicobacter* spp., Mycobacteria and fungal organisms and (3) “true” CNE involving intracellular organisms that are detectable via serology or polymerase chain reaction (PCR) of valvular tissue, e.g. *Bartonella quintana*, *Coxiella burnetti* and *Tropheryma whippelii*. In addition, there are non-infectious causes of endocarditis, e.g. mural thrombus that will not be covered in this chapter.

## 2. Epidemiology of CNE

The epidemiology of infective endocarditis, and hence CNE, has changed over the last five decades [5, 10]. Patients are generally older and male, with greater numbers of hospital associated cases, and with indwelling devices such as catheters, pacemakers and prosthetic valves. Accordingly the numbers of cases of infective endocarditis with *Staphylococcus aureus*, coagulase-negative *Staphylococci* and *Enterococci* have increased. With the advent of novel diagnostic methods (PCR-based testing), the prevalence of CNE may have decreased to 14.2% [5] in the last decade, but other reviews indicate otherwise [10]. Specific aspects of the patient's medical history may provide “epidemiological clues” (Table 6 in Ref. [1]) to the microbiological cause. Military personnel have some higher risk of CNE due to *C. burnetti* for example [11].

## 3. Microbiology of CNE

The microbiology of CNE is varied and depends on host and environmental factors that predispose to one type of pathogen versus another [1]. As per the classification of Tattévin et al. [9], the microbiologic discussion will follow this paradigm.

### 3.1. CNE due to pre-treatment of typical bacterial endocarditis

According to one of the largest surveys of infective endocarditis recently performed, in the last decade, 29.7% of IE were due to *S. aureus*, 17.6% were due to oral *Streptococci*, 10% were due to coagulase-negative *Staphylococci* and 10% were due to *Enterococci*. Approximately, 16% of IE cases were thus due to Gram-negative bacteria, fungi and mycobacteria that could be cultured from blood. Because the presentation of infective endocarditis can be non-specific and is often associated with clinical sepsis, patients receive empiric broad spectrum anti-bacterials before sufficient numbers of blood cultures can be obtained. In one contemporary survey, antibiotics were used before blood cultures 74% of the time, with many patients

coming from outside hospitals before a diagnosis of endocarditis was established [4]. The distribution of bacterial etiologies in these cases should represent what is seen generally when blood cultures are obtained prior to initiation of antibiotics. PCR of valve tissue in the cases where pretreatment occurred showed a predominance of *Streptococcus oralis* (54%), *Streptococcus aureus* (7.7%) and *Streptococcus gallolyticus* (formerly known as *Streptococcus bovis*) 5.1%. This likely reflects the ability of these organisms to attach to endovascular epithelium and be detectable by PCR methods.

### 3.2. CNE due to fastidious micro-organisms

#### 3.2.1. HACEK group

Much of the early literature regarding CNE focused on infections with so-called “fastidious” organisms that were traditionally difficult to grow in blood culture, due to specific nutritional requirements of these organisms. These included a number of oral Gram-negative bacteria (*Haemophilus* species, *Aggregatibacter* species, *Cardiobacterium hominis*, *Eikenella corrodens* and *Kingella* species) that came to be known by the acronym “HACEK” (reviewed in [12]). Automated blood culture methodology involved the use of media that lacked particular nutrients like hemin, and extended incubation of 3 weeks was recommended in order to isolate HACEK group and other fastidious Gram negatives (ref). However, as early as 1993, it was evident that extended incubation was no longer necessary in order to isolate these bacteria [13, 14]. Standard 5–7 day incubation was sufficient to recover an organism in most instances.

HACEK organisms are rarely the cause of infective endocarditis, and because of the improved ability to isolate these organisms from standard blood culture specimens, even more rarely the cause of CNE. In a recent series, four out of 77 patients with HACEK IE had negative blood cultures [15]. Of these, three had previously received antibiotics. Diagnosis was made by culture of devices, and in one patient, by PCR of valvular tissue. *Cardiobacterium valvarum* has been described as an unusual *Cardiobacterium* spp. associated with endocarditis, in this case, an infected aortic graft in a middle-aged man with gingivitis and a sub-acute bacterial endocarditis presentation. In this case, the organism grew in blood culture but could not be identified by routine microbiological examination. 16S rRNA analysis revealed the species.

Pediatric populations, especially young children between the ages of 6 months and four years, appear to be particularly vulnerable to infections with *Kingella kingae* [16]. *K. kingae* is present in the oropharynx and respiratory tract of young children and can be transmitted person-to-person with resulting outbreaks of infection. *K. kingae* has a variety of colonization and virulence factors such as pili that allows the organism to anchor itself to human mucosal epithelium, polysaccharide capsule that decreases opsonization by complement, the ability to produce exopolysaccharide and biofilm that is an important factor in the formation of endovascular vegetations and RTX toxin, a potent cytotoxin that targets macrophages and respiratory epithelium [17]. Fortunately, bacteremia and endocarditis are relatively rare syndromes associated with this organism [16], causing 7.1–7.8% of pediatric endocarditis cases [18, 19]. The presentation can be dramatic as illustrated in a child with mycotic aneurysm of the aorta and cerebral infarcts [20].

### 3.2.2. Non HACEK group organisms

Other fastidious bacteria causing CNE include *Pasturella multocida* and other *Pasturella* spp. which constitute part of the normal oral flora of dogs and cats in particular [21]. While bite wounds are obviously a portal of entry for *Pasturella* spp., in immunocompromised patients, more superficial contact especially with cat fur, minor cat scratches and cat saliva can lead to bacteremia and subsequent endocarditis [22]. Culture-negative endocarditis caused by *Abiotrophia defectiva* and *Granulicatella* spp.—so-called nutritionally deficient *Streptococci* [23]—can also be associated with infected intracranial aneurysms and may be difficult to isolate in routine blood cultures [24]. Special consideration for length of therapy must be given and is covered below. *Clostridia* and other anaerobic organisms [25] may be difficult to recover in routine blood cultures if specimens are not handled appropriately. These organisms are likely a rare cause of CNE, but true prevalence is unknown. *Gemella* spp. have been described rarely as a cause of CNE [9, 21] including *Gemella burgeri* tricuspid valve endocarditis [26] and *Gemella hemolysans* prosthetic valve endocarditis identified by PCR of prosthetic valve material and requiring implantation of a total artificial heart as a bridge to transplantation [27]. *Brucella mellitensis* is another unusual pathogen associated with culture-negative endocarditis [2], especially in regions of the world where consumption of unpasteurized milk (cow, goat and sheep) occurs. In one series of six patients subsequently found to have *Brucella* endocarditis, only two patients had blood cultures that revealed the diagnosis [28]. Several different *Legionella* spp. have been reported as causes of culture-negative endocarditis, both in native valves and prosthetic valves. These include cases of *Legionella pneumophila* in an immunocompromised patient with pneumonitis, a positive BAL fluid *Legionella* antigen, and subsequent BAL fluid and blood isolation of the organism when subcultured onto buffered charcoal yeast extract agar (BCYE agar) [29]. Another CNE case with *L. pneumophila* was identified when the patient presented with septic arthritis and the organism was identified from synovial fluid by 16s rDNA PCR and was subsequently found to have a new murmur and a mitral vegetation [30]. Mycobacteria are another rare cause of CNE, especially in association with porcine bioprosthetic valves [31]. This study from a reference laboratory conducted between 2010 and 2013 found PCR evidence of Mycobacterial infection in six out of 370 valve samples submitted from patients with suspected CN [31] with five cases of *Mycobacterium chelonae* and one case of *M. lentiflavum*\*\*\*. While typically associated with immunodeficiency states, mycobacterial infections have also been reported in immunocompetent hosts as in the case of a patient with disseminated *M. chelonae* infection and resulting pacemaker CNE [32]. Special stains and cultures for acid fast bacilli should be considered in patients with device-related CNE [33]. Finally there are also rare reports with unusual causes of endovascular infections such as CNE in an immunocompromised patient on high dose corticosteroids [34] and infected aortic aneurysm in an immunocompetent patient [35] with *Helicobacter cinaedi*.

### 3.3. CNE due to *Bartonella* spp., *C. burnetti* and *T. whipplei*

This section deals with CNE attributable to organisms that are not typically identified with blood cultures but are responsible for a significant portion of cases of culture-negative infective endocarditis [36].



*Bartonella* endocarditis has been described as the “quintessential culture-negative endocarditis” [37]. *Bartonella* species were first described as a cause of infectious endocarditis in 1993 (reviewed in [38]). A recent study in Brazil estimated that 19.6% of CNE cases were due to *Bartonella* spp. [36]. There are currently 23 different species of *Bartonella* reported; the most common etiology of CNE, however, is the result of louse transmitted *B. quintana* especially in homeless persons, or infection with *Bartonella henselae* transmitted by contact with young cats. *B. henselae* is more often associated with immunocompromised hosts and prosthetic valve endocarditis [39–41]. Diagnosis of *Bartonella* CNE is typically made via serologies and/or PCR of valvular material. Further modifications to the modified Duke diagnostic criteria for endocarditis have been proposed to incorporate positive PCR, Western blot or serum IgG titer  $\geq 800$  as major criteria [38]. Unusual clinical presentations with severe renal impairment have been described with *Bartonella* CNE where there is a delay in diagnosis including anti-neutrophil cytoplasmic antibody (ANCA) positive necrotizing glomerulonephritis [42], C3 predominant glomerulonephritis [39] and proliferative glomerulonephritis (GN) with erythroblastopenia [43]. One case of *B. henselae* tricuspid valve CNE was diagnosed after the patient presented with chronic pulmonary emboli [44]. In this patient, the source was felt to be a tick bite rather than exposure to cats.

*C. burnetti* is a rickettsial like organism associated with true CNE [9, 21]. In Brazil, it was estimated that the prevalence of *C. burnetti* as a cause of CNE was 7.9% [36] by PCR and serologic methods. In France, in the 1990s, annual incidence was estimated at 1 per million or <5% of all cases of endocarditis [45]. Acquisition in humans is usually through exposure to parturient animals such as sheep [21]. Presentation can be quite severe especially in immunocompromised persons, pregnant women and in persons with prosthetic valves or native valvular heart disease [46]. A new genotype, MST 54 [47] was recently described in a child with CNE secondary to congenital heart disease from an area endemic for *C. burnetti*.

*T. whipplei* is an *Actinomycete* bacterium found in the stool and environment [48]. Stool carriage in uninfected humans can be detected in the range of 4–31%. An infectious cause of lipodystrophia intestinalis, later known as Whipple's disease, was first proposed by George Whipple in 1907 based on the presence of lipid laden foamy macrophages in the lamina propria of the small intestine. Clinical manifestations are protean, but generally patients present with diarrhea, weight loss, fever and malabsorption. *T. whipplei* is a known cause of CNE, and its true prevalence may be underestimated. When associated with arthralgia in middle-age men, it is almost pathognomonic for *T. whipplei* as the etiologic agent [49, 50]. While the organism can be cultured in fibroblasts [48], diagnosis of CNE typically requires PCR analysis of valvular tissue [51].

### 3.4. CNE due to fungal pathogens

Invasive mold infections are another cause of CNE, due to the difficulty in isolating these organisms from routine blood cultures. They are an important cause especially of early culture-negative prosthetic valve endocarditis [52] but can cause late prosthetic valve, pacemaker associated as well as native valve endocarditis. Among cases in the recent literature, infections with *Aspergillus* spp. [53–55], *Histoplasma capsulatum* [56–58] and *Trichosporin* spp. [59,

60] are the most widely reported. Commercial tests that detect fungal wall antigens such as galactomannan [2, 61, 62] and  $\beta$ -1,3-D-glucan [62] can show good sensitivity and specificity in diagnosis of fungal CNE. Jinno et al. [56] reported negative urine *Histoplasma* antigen results in their patient with *H. capsulatum* CNE, with diagnosis based on valvular pathology and tissue culture.

## 4. Diagnostic methods

Our understanding of the etiology of CNE and our ability to offer more targeted treatment to patients with CNE have been dramatically affected by the large number of novel diagnostic tests now available to add to our investigative armamentarium. The following discussion will focus on methods that allow diagnosis without removal of infected valves or cardiac devices (prosthetic valves, endovascular grafts, pacemaker and defibrillator leads, ventricular assist devices, etc.) versus methods that require removal of tissue or a device for diagnostic and therapeutic reasons.

### 4.1. Non-invasive methods

Imaging using positron emission tomography (PET) scanning has been utilized to diagnose a case of *T. whipplei* endocarditis [63]. The infected prosthetic valve was subsequently removed providing material for PCR-based methods to confirm the diagnosis, but the impetus to remove the valve came from the PET scan. Four-dimensional cardiac MRI was used to better define valvular damage and diagnose aortic valve endocarditis in a case of *C. burnetii* CNE in a patient with exposure to domesticated buffalos and positive serologies [64]. PCR combined with electrospray ionization mass spectrometry (PCR/ESI-MS) methods have been applied to detect pathogens in blood cultures in patients already receiving antibiotics and made a diagnosis in 41 out of 410 cases, although not specifically in persons with CNE [65]. Broad range PCR on blood culture specimens has also been utilized [2]. Serum galactomannan and  $\beta$ -1,3-D-glucan have already been mentioned as serum diagnostic tests for fungal CNE [2, 61, 62].

### 4.2. Invasive methods

Methodologies to increase numbers of planktonic organisms that can be cultured from devices have been devised, using sonication of the devices [66, 67]. Metagenomic analysis of the results of next generation sequencing has been used to diagnose *A. defectiva* CNE [68]. A universal PCR/sequencing test has been applied to diagnose CNE on blood and valvular tissue [69]. Immunofluorescent antibody detection, Western blot analysis and real time-PCR of 16S RNA have been used to diagnose CNE due to *Bartonella* spp. [38]. PCR/ESI-MS has been utilized on valve tissue to diagnose CNE [70, 71].

## 5. Treatment of CNE

There are some distinct differences in the management of infective endocarditis according to the United States [1] versus European guidelines [72] updated in 2015. These are reviewed in Tattevin et al. [73]. However, in regard to treatment of the following etiologic agents of CNE, there is good agreement in general.

### 5.1. Empiric therapy for CNE

For patients with acute clinical presentations of native valve endocarditis, according to the US guidelines, empiric coverage for *S. aureus*,  $\beta$ -hemolytic *Streptococci* and aerobic Gram-negative bacilli is provided. Such regimens should include vancomycin and cefepime at the beginning. For patients with a subacute presentation of native valve endocarditis, additional empirical coverage of viridans *Streptococci*, HACEK and *Enterococci* is added. Vancomycin and ampicillin-sulbactam is a suggested regimen. If blood cultures eventually become positive for a typical pathogen, empiric treatment can be tailored accordingly. For patients with early (<1 year) culture-negative prosthetic valve endocarditis, empiric coverage for *Staphylococci*, *Streptococci*, *Enterococci* and Gram-negative bacilli is appropriate. Vancomycin, rifampin, gentamicin and cefepime are offered as options. For late prosthetic valve endocarditis, antibiotic therapy to cover viridans *Streptococci*, *Staphylococci* and *Enterococci* such as vancomycin and ceftriaxone is suggested. Empiric antibiotics can be narrowed based on specific pathogens that are subsequently identified. Surgical source control and removal of infected devices are required more often with the pathogens associated with CNE.

### 5.2. *A. defectiva*, *Granulicatella* spp.

As summarized in the European guidelines, these nutritionally deficient bacteria produce endocarditis with a protracted course which is associated with large vegetations ( $\geq 10$  mm), higher rates of complications and valve replacement (around 50%), possibly due to delayed diagnosis and treatment. Antibiotic recommendations include penicillin G, ceftriaxone or vancomycin for 6 weeks, combined with an aminoglycoside for at least the first 2 weeks.

## 6. HACEK

Per the US and European guidelines, microbiologic susceptibility testing might be difficult to perform on HACEK microorganisms, and they should be considered ampicillin resistant secondary to  $\beta$ -lactamase production. Penicillin and ampicillin should not be used for the treatment of patients with endocarditis. Ceftriaxone should be used unless the patient has a severe  $\beta$ -lactam allergy. The duration of therapy for HACEK native valve endocarditis is 4 weeks; for prosthetic valve infections, duration of therapy is 6 weeks or longer. Gentamicin is not recommended in the US guidelines because of its nephrotoxicity risks but is an option in the European guidelines. A fluoroquinolone (ciprofloxacin, levofloxacin, or moxifloxacin) can be used in patients with a  $\beta$ -lactam allergy. Ampicillin-sulbactam is also a treatment option.



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<i>Bartonella</i> spp.	Doxycycline 100 mg/12 h orally for 4 weeks plus gentamicin (3 mg/24 h) i.v. for 2 weeks
<i>Brucella</i> spp.	Doxycycline (200 mg/24 h) plus cotrimoxazole (960 mg/12 h) plus rifampin (300–600/24 h) for ≥3–6 months orally
<i>Coxiella burnetii</i>	Doxycycline (200 mg/24 h) plus hydroxychloroquine (200–600 mg/24 h) orally (>18 months of treatment)
<i>Legionella</i> spp.	Levofloxacin (500 mg/12 h) i.v. or orally for ≥6 weeks or clarithromycin (500 mg/12 h) i.v. for 2 weeks, then orally for 4 weeks plus rifampin (300–1200 mg/24 h)
<i>T. whipplei</i>	Doxycycline (200 mg/24 h) plus hydroxychloroquine (200–600 mg/24 h)c orally for ≥18 months

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Treatment of the following unusual pathogens in CNE is best summarized in the European guidelines and in Broqui et al. [21].

## 7. Fungal CNE

Per the European guidelines, for *Aspergillus* infections, voriconazole is the drug of choice, and some experts recommend the addition of an echinocandin or amphotericin B. Surgery is generally required, and prolonged suppressive therapy is recommended. For *H. capsulatum*, surgical management followed by 6 weeks of amphotericin B and additional suppressive oral itraconazole is recommended. Most agents have poor activity against other mold species like *Trichosporon* spp. The mainstay of therapy is surgical.

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