Update on blood culture-negative endocarditis

Les endocardites à hémocultures négatives : mise au point

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Abstract

Blood culture-negative endocarditis is often severe, and difficult to diagnose. The rate of non-documented infective endocarditis has decreased with the advent of molecular biology – improved performance for the diagnosis of bacterial endocarditis with blood cultures sterilized by previous antibacterial treatment – and cardiac surgery – access to the main infected focus, the endocardium, for half of the patients. Blood culture-negative endocarditis are classified in 3 main categories: (i) bacterial endocarditis with blood cultures sterilized by previous antibacterial treatment (usually due to usual endocarditis-causing bacteria, i.e. streptococci, more rarely staphylococci, or enterococci); (ii) endocarditis related to fastidious microorganisms (e.g. HACEK bacteria; defective streptococci – Gemella, Granulicatella, and Abiotrophia sp. – Propionibacterium acnes, Candida sp.): in these cases, prolonged incubation will allow identifying the causative pathogen in a few days; (iii) and the “true” blood culture-negative endocarditis, due to intra-cellular bacteria that cannot be routinely cultured in blood with currently available techniques: in France, these are most frequently Bartonella sp., Coxiella burnetii (both easily diagnosed by ad hoc serological tests), and Tropheryma whippeli (usually diagnosed by PCR on excised cardiac valve tissue). Non-infective endocarditis is rare, mostly limited to marantic endocarditis, and the rare endocarditis related to systemic diseases (lupus, Behçet).

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Keywords: Endocarditis; HACEK; Bartonella sp.; Coxiella burnetii; Candida sp.; Tropheryma whippeli; Lupus; Behçet; Marantic endocarditis

Résumé

Les endocardites à hémocultures négatives sont des pathologies souvent graves et de diagnostic difficile. La proportion d’endocardites infectieuses qui restent non documentées a diminué grâce au développement de la biologie moléculaire – meilleures performances pour le diagnostic des endocardites décapitées par une antibiothérapie préalable – et de la chirurgie cardiaque – accès au foyer infectieux principal, l’endocarde, pour la moitié des patients. On classe les endocardites infectieuses à hémocultures négatives en 3 grandes catégories : (i) les endocardites décapitées par une antibiothérapie préalable (causées en règle par des bactéries classiques : streptocoques, plus rarement staphylocoques ou entérocoques) ; (ii) les endocardites liées à des pathogènes de croissance fastidieuse (bactéries du groupe HACEK ; streptocoques déficients – Gemella, Granulicatella, et Abiotrophia sp. – Propionibacterium acnes, Candida sp.) : dans ces cas, la prolongation d’incubation des hémocultures suffira le plus souvent à apporter le diagnostic en quelques jours ; (iii) enfin, les « vraies » endocardites infectieuses à hémocultures négatives, liées à des bactéries intracellulaires non cultivables en routine dans le sang avec les technologies actuelles : en France, il s’agit de Bartonella sp., Coxiella burnetii (de diagnostic simple, par sérologies) et Tropheryma whippeli, dont le diagnostic est en général obtenu par PCR sur du tissu

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1. Introduction

Blood culture-negative endocarditis is a severe disease, difficult to diagnose for which medical knowledge has greatly improved over the past 2 decades [1]:

- the increasingly frequent use of valve replacement surgery allows access to the primary site of infection in acute endocarditis for almost half of the patients [2];
- the development of microbiological techniques (molecular biology, MALDI-TOF) allows better identification of pathogens when conventional microbiological cultures fail [3,4];
- multiple observational studies have helped clarify the distribution of the main etiologies of blood culture-negative endocarditis [2,5–10].

This review brings an update on the management of blood culture-negative endocarditis, by developing diagnostic strategies and empirical treatment according to the recommendations of expert societies [11–13].

2. Epidemiology

2.1. A low incidence of blood culture-negative infective endocarditis in France

The authors of the population-based study conducted in France in 2008, covering approximately one third of the country’s population, estimated the incidence of infective endocarditis (IE) at 33.8 cases per million inhabitants/year. Four hundred and ninety-seven cases of definitive IE, according to the modified Duke criteria were included in this study. Four hundred and fifty-one (90.7%) were documented by blood culture and 26 (5.2%) could not be documented; 20 (4.1%) were documented by PCR on valve tissue and/or blood (n = 8); by culture of valve tissue (n = 5), intracardiac leads (pacemaker, defibrillator; n = 3), joint fluid (n = 2), serology (n = 1); or by PCR on valve tissue and serology (n = 1) [2]. The rate of blood culture-negative infective endocarditis was similar (9%) to the one reported in the previous French survey conducted in 1999 [5], as well as the rate of non-documented endocarditis (5%). This was probably the most accurate estimation of the epidemiology of blood culture-negative endocarditis in France, since these population-based studies included all the cases diagnosed in the participating departments, thus avoiding the selection bias of series originating from reference centers [6,14]. However, since cases were included in these studies according to modified Duke criteria (Table 1), thus favoring blood cultures [15], the rate of blood culture-negative IE was probably underestimated.

Conversely, in some countries, when antibiotic therapy is initiated in most cases before blood is sampled for cultures, blood culture-negative endocarditis is predominant. The authors of a study conducted in Khon Kaen, in northeastern Thailand in 2010–2012, reported that 72 (54.5%) of 132 consecutive cases of endocarditis (modified Duke criteria [15]) could not be documented despite the frequent use of cardiac surgery in this population.

<table>
<thead>
<tr>
<th>Blood culture-negative infective endocarditis</th>
<th>Table 1</th>
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### Modified Duke criteria for the diagnosis of infective endocarditis [15], Critères modifiés de Duke pour le diagnostic d’endocardite infectieuse [15].

<table>
<thead>
<tr>
<th>Major criteria</th>
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<tbody>
<tr>
<td>Positive blood culture</td>
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<tr>
<td>Typical microorganism for infective endocarditis from 2 separate blood cultures</td>
</tr>
<tr>
<td>Oral streptococci (non groupable, alpha-hemolytic streptococci, S. viridans), group D Streptococci (previously S. bovis, new nomenclature, S. galloaiticus), HACEK group bacteria*</td>
</tr>
<tr>
<td>Community acquired Staphylococcus aureus or enterococci, in the absence of a primary infectious focus</td>
</tr>
<tr>
<td>Microorganisms compatible with a diagnosis of infective endocarditis, but that can be observed in many other cases, will be considered as major criteria only if they were identified in:</td>
</tr>
<tr>
<td>At least 2 blood cultures sampled more than 12 hours apart, or</td>
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<tr>
<td>3 blood cultures (out of 3 sampled) or most blood cultures (out of at least 4 sampled blood cultures), during ≥ 1 hour</td>
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### Endocardial lesions involvement

<table>
<thead>
<tr>
<th>Echography</th>
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<tbody>
<tr>
<td>Oscillating intracardiac mass, on valve or supporting structures, or</td>
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<tr>
<td>in the path of regurgitant jets, or on implanted material, in the absence of an alternative anatomic explanation</td>
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<tr>
<td>Myocardial abscess</td>
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<tr>
<td>New partial dehiscence of prosthetic valve</td>
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<tr>
<td>New valvular regurgitation (increase or change in pre-existing murmur is not sufficient)</td>
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<table>
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<th>Minor criteria</th>
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<tr>
<td>Predispoding heart condition (cardiac disease at risk or intravenous drug use)</td>
</tr>
<tr>
<td>Fever ≥ 38 °C</td>
</tr>
<tr>
<td>Vascular phenomena: major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage</td>
</tr>
<tr>
<td>Immunologic phenomena: glomerulonephritis, Osler’s nodes, Roth spots, rheumatoid factor</td>
</tr>
<tr>
<td>Microbiological criteria : positive blood culture not meeting major criterion or serologic evidence of active infection with organism consistent with infective endocarditis</td>
</tr>
<tr>
<td>Ultrasonographic criteria: abnormality compatible with a diagnosis of IE, but not acknowledged as major criteria</td>
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</table>

* HACEK: Haemophilus sp., Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens, Kingella kingae.
reference center (75% of cases), and the support of the Research Unit on Emerging Infectious and Tropical Diseases in Marseille for diagnostic tests. The rate of endocarditis diagnosed by blood culture in this study was only 22% (29/132) [16].

2.2. Main etiologies of blood culture-negative IE

Much progress has been made in understanding the main causes of blood culture-negative endocarditis over the past 2 decades, thanks to more frequent availability of valve tissue (increased use of cardiac surgery in the acute phase of endocarditis), improved diagnostic techniques, including in case of previous antibiotic therapy, and systematic studies on blood culture-negative endocarditis in Algeria [8], in France [7,10,14], and in the United Kingdom [9]. Table 2 is a list of the most frequent infectious causes identified in blood culture-negative endocarditis, with 3 main observations:

- the heterogeneity of diagnostic investigations effectiveness (20% to 80% of non-documented cases, depending on the series);
- the crucial role of Q fever, and to a lesser extent, of bartonellosis;
- the significant role of the 2 main causes of IE (Staphylococcus and Streptococcus sp.), that should therefore not be overlooked as a cause of blood culture-negative endocarditis; this is usually the case in patients having received antibiotics before blood culture is performed.

3. Diagnostic approach

3.1. Patient history, clinical examination

The etiological diagnosis of blood culture-negative endocarditis benefits from a rigorous clinical approach, including interviews with the patient, his physician, and his family to screen for a potential zoonosis (Bartonella sp. [17], Q fever [18,19]), and collect data on any extra-cardiac symptoms suggestive of specific infectious causes of endocarditis (e.g., joint, digestive, and/or neurological involvements during Whipple’s disease [20–22]) or non-infective endocarditis (Behçet’s disease [23], lupus [24], marantic endocarditis [25]).

Risk factors for fungal endocarditis should also be investigated, as it may present as blood culture-negative endocarditis. Endocarditis due to Candida sp. should be considered in the presence of risk factor(s) from the following list: intravenous drug users, parenteral nutrition, multiple complex digestive surgeries, active cancer, and prolonged broad-spectrum antibiotic treatment. The microbiological diagnosis may be obtained by repeating blood cultures with a prolonged incubation and/or serum antigen assays (galactomannan, mannan/anti-mannan, and β-glucan-1,3-d) [26,27]. Nevertheless, the incidence of fungal endocarditis seems to be decreasing in countries where single-use injection devices are available to drug users, as in France: only 6 cases of fungal endocarditis, all Candida sp., were documented among the 497 cases of endocarditis included in the 2008 survey (1.2) [2].

A complete clinical examination should be performed to detect any accessible infectious focus, which in a patient with suspected endocarditis could lead to an early microbiological diagnosis, sometimes more efficient than blood cultures. This is particularly true for musculoskeletal locations, peripheral emboli, and cutaneous lesions. In case of recurrent blood culture-negative endocarditis in a patient with bioprosthetic heart valve, it will be necessary to check whether it is a porcine bioprosthesis or not, since rare cases of allergy to porcine proteins have been reported in this context [28,29]. The main causes of blood culture-negative endocarditis are listed in Table 3 to guide the diagnostic management for these patients.
Table 3
Main causes of blood culture-negative endocarditis.

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Characteristics</th>
<th>Treatment</th>
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<tbody>
<tr>
<td><strong>Infective endocarditis with blood cultures sterilized by previous antibacterial treatment</strong></td>
<td></td>
<td></td>
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<tr>
<td>Staphylococci (35%)</td>
<td>Idem endocarditis with positive blood cultures</td>
<td>Amoxicillin-clavulanic acid + gentamicin in case of native valve or non-recent valve prosthesis (&gt; 1 year)</td>
</tr>
<tr>
<td>Streptococci (35%)</td>
<td></td>
<td>Vancomycin + gentamicin in case of recent valve prosthesis &lt; 1 year</td>
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<tr>
<td>Enterococci (10%)</td>
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<tr>
<td><strong>Endocarditis caused by fastidious pathogens</strong></td>
<td></td>
<td></td>
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<tr>
<td>HACEK group bacteriaa</td>
<td>Dental portal of entry</td>
<td>Ceftriaxone + gentamicin, or</td>
</tr>
<tr>
<td>Deficient streptococcib</td>
<td>Prolonged, pauci-symptomatic native valve</td>
<td>Amoxicillin + gentamicin</td>
</tr>
<tr>
<td>Candida sp.</td>
<td>Predispensing factors (intravenous drug use, prolonged central venous catheter, cancer)</td>
<td>Echinocandin or liposomal amphotericin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>B ± 5 fluoro-cytosine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Valve surgery when possible (or switch to lifelong fluconazole, recommended because of the risk of relapse &gt; 30%)</td>
</tr>
<tr>
<td><strong>True infective blood culture-negative endocarditis</strong></td>
<td></td>
<td></td>
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<tr>
<td>Coxiella burnetii (Q fever)</td>
<td>Zoonosis (ovine, caprine, bovine, etc.).</td>
<td>Doxycycline + hydroxychloroquine</td>
</tr>
<tr>
<td></td>
<td>Serological diagnosis ± valve PCR</td>
<td>Monitoring of plasma concentrations</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Duration ≥ 18 months (until antibodies phase I IgG &lt; 800, IgM/IgA &lt; 50)</td>
</tr>
<tr>
<td><strong>Bartonella sp.</strong></td>
<td>Contact with cats for B. henselae (agent of cat scratch disease)</td>
<td>Amoxicillin or ceftriaxone or doxycycline for 6 weeks</td>
</tr>
<tr>
<td></td>
<td>Precautious for B. Quintana (agent of Well’s disease).</td>
<td>Combination with gentamicin during the first 2 to 4 weeks</td>
</tr>
<tr>
<td></td>
<td>Serological diagnosis ± valve PCR</td>
<td></td>
</tr>
<tr>
<td><strong>Tropheryma whippeli</strong></td>
<td>Male patient, 60 years of age, extra-cardiac signs, Prolonged course, PCI diagnosis on valve or duodenal biopsy</td>
<td>Loading treatment with penicillin G + streptomycin for 2 weeks (discussed); relay with: - doxycycline + hydroxychloroquine with monitoring of plasma concentrations (at least 18 months) - or trimethoprim-sulfamethoxazole (at least 12 months) Monitoring of PCR negativation</td>
</tr>
<tr>
<td><strong>Non-infective endocarditis</strong></td>
<td></td>
<td></td>
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<tr>
<td>Behçet’s disease with endocarditis</td>
<td>Young male patient</td>
<td>Immunosuppressive or immunomodulating treatment</td>
</tr>
<tr>
<td></td>
<td>Aortic insufficiency</td>
<td>Curative anticoagulation</td>
</tr>
<tr>
<td>Lupus erythematosus endocarditis (Libman-Sacks)</td>
<td>Thickening/fibrosis of the mitral valve, immunologic manifestations (Osler nodes), antiphospholipid antibody syndrome</td>
<td>Immunosuppressive or immunomodulating treatment</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Curative anticoagulation</td>
</tr>
<tr>
<td>Marantic endocarditis</td>
<td>Multi-metastatic breast, lung, prostate, or colon cancer</td>
<td>Treatment of the neoplasm</td>
</tr>
<tr>
<td></td>
<td>Multiple small vegetables (3 mm), left heart</td>
<td>Curative anticoagulation</td>
</tr>
<tr>
<td>Allergic endocarditis on porcine bioprosthesis</td>
<td>Allergy to porcine proteins</td>
<td>Replacement by a non-porcine bioprosthesis</td>
</tr>
</tbody>
</table>

<sup>a</sup> Haemophilus sp., Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corroden, Kingella kingae.

<sup>b</sup> Abiotrophia sp., Granulicatella sp., Gemella sp.

### 3.2. Blood cultures

There has been a marked simplification of practice for blood cultures over the past 2 decades:

- the use of specific blood culture bottles for fastidious microorganisms is not recommended anymore;
- no systematic re-seeding is recommended during culture;
- the indications for an extended incubation of vials apply only when cultures remain sterile after 48 to 72 hours.

This simplification of practices, as recommended in the 2009 European guidelines [11], is due to the following observations:

- the performance of automated systems, used routinely in 2014, allows isolating most pathogens that can grow (including Candida sp., deficient streptococci, HACEK group bacteria) [30], as long as the seeded volumes comply with the manufacturer’s recommendations (ideally 10 mL per vial) [31];
- extending culture beyond 5 days is not contributive with these systems, even for HACEK group bacteria: indeed, an evaluation of the BacT/Alert system showed that 458 (98.7%) of the 464 pairs of blood cultures having identified a clinically relevant microorganism had become positive during the first 5 days [32];
- the evaluation of a complex protocol with a systematic seeding of blood cultures on multiple culture media and for
extended periods showed a very low efficiency of these additional measures: in 215 investigated patients presenting with suspected endocarditis, a potential pathogen not identified by usual cultures (Bactec® automated system, incubated for 5 days) was detected in only 3 cases; these were 2 strains of Mycobacterium avium complex in patients with AIDS, and a case of legionellosis [33]. Likewise, a survey of 11 American hospitals, practicing systematic prolonged culture in case of blood culture-negative endocarditis cultures, showed that with a cumulative experience of more than 80 years and hundreds of thousands of seeded vials, extended cultures had led to a diagnosis in 4 cases only: i.e. Histoplasma capsulatum, Streptococcus viridans, Propionibacterium acnes, and Cardiobacterium hominis (JM Miller, ClinMicroNet 1999, unpublished data);

- the main pathogens causing endocarditis in France are: staphylococci (35% of cases), streptococci (35%), and enterococci (10%) [2,5]. These pathogens are usually identified within 48 hours. In fact, and given the very low added value of incubation beyond day 5 [32], the European guidelines recommend that clinicians require prolonged incubation of vials only in the rare cases of cultures remaining negative at 48 to 72 h (Fig. 1), and if the diagnosis of IE remains plausible [11].

3.3. Serology

The list of serological tests to be performed in case of blood culture-negative endocarditis used to include: Legionella pneumophila, Mycoplasma hominis, Chlamydia pneumoniae, Brucella sp., Coxiella burnetii, and Bartonella sp. This list has been considerably shortened for the following reasons:

- two major series showed that only Bartonella sp. and C. burnetii serological tests are contributive: 348 cases of suspected blood culture-negative endocarditis were investigated between 1983 and 2001, the diagnosis was documented by serological tests in 268 cases (77%), including 266 cases of C. burnetii (n = 167) or Bartonella sp. (n = 99) [10]. The same team reported a second series of 745 patients presenting with suspected blood culture-negative endocarditis having received a panel of serological tests between 2001 and 2009. They documented the predominance of Q fever and bartonellosis: 354 of the 356 cases documented by serological tests were positive for C. burnetii (n = 274) or Bartonella sp. (n = 80) [14]. In other words, if only Bartonella sp. and C. burnetii serological tests had been used, only 4 out of 624 diagnoses obtained by serological tests would have been missed (Table 1);
- a review of endocarditis caused by fastidious pathogens shows that Mycoplasma sp. endocarditis is very rare (<10 reliable observations published to date, mostly due to M. hominis), as well as Legionella sp. endocarditis [4]. Moreover, most cases of endocarditis supposedly due to Chlamydia pneumoniae are probably cross-reactions with a Bartonella sp. serological test (there are no documented cases of Chlamydia pneumoniae sp. with identification performed on valve tissue);
- finally, brucellosis has been considered as eradicated in France since 2005, although an indigenous case was diagnosed in 2012 [34]. However, this diagnosis must always be considered in endemic regions, particularly in Mediterranean countries, and in patients coming back from these countries.

In 2014, the only routinely recommended serological tests in case of negative blood cultures are tests for Q fever and bartonellosis (cf. Pilly 2014, and recommendations of the British Society of Antimicrobial Chemotherapy [13]). Brucellosis serological tests can be added in case of risk factors (living in endemic areas, occupational exposure, consumption of nonpasteurized dairy products). Serological tests for Mycoplasma sp. and Legionella sp. are still recommended in the 2009 European guidelines [11].
3.4. Tests on valve tissue from patients having undergone surgery

The more frequent use of valve replacement in the acute phase of infective endocarditis (1 patient out of 2 in France [2]), and the advent of molecular biology techniques have revolutionized the diagnosis of blood culture-negative endocarditis: PCR systems based on universal bacterial 16S ribosomal RNA have demonstrated excellent sensitivity and specificity [3,35], as well as PCR targeting bacteria specifically responsible for endocarditis with negative blood culture: Bartonella sp., C. burnetii [36], and Tropheryma whippelii [21].

Moreover, the microscopic examination of valves after Gram staining, and cultures on appropriate media provide important information not only for the identification of the pathogen involved when the data was not available preoperatively [37], but also information on its viability at the time of valve replacement, which will impact the duration of post-replacement treatment [11,13]. Conversely, the histological analysis of valves did not demonstrate any added value in routine [37], although some rare diagnoses may benefit from a detailed analysis of the valve tissue, as in the original description of porcine bioprosthesis endocarditis mediated by allergy to porcine proteins [29].

4. Treatments

4.1. Empirical treatment

Pathogens usually responsible for endocarditis (staphylococci, streptococci, and enterococci) are also often found in the diagnostic workup of blood culture-negative endocarditis, especially with valves from patients having undergone surgery. The European guidelines, endorsed by the French Cardiology Society (SFC) and the French infectious diseases society (SPIIF), recommend the empirical treatment of undocumented endocarditis with amoxicillin-clavulanic acid + gentamicin in a community setting or vancomycin + gentamicin + rifampicin in patients carrying a valve prosthesis implanted during the previous year [11,13].

4.2. Antibiotic treatment of most frequent blood culture-negative IE

This is an area with a very limited level of evidence given the relative rarity of blood culture-negative endocarditis and the weakness of available pre-clinical data (few or no experimental models, no validation of the various sensitivity tests proposed in vitro).


- the treatment of T. whippelii endocarditis has long relied on cotrimoxazole for 1 year, with or without initial treatment with penicillin G + streptomycin for 2 weeks [11,20]. The authors of more recent publications recommend doxycycline + hydroxychloroquine for 12 to 18 months, with monitoring of plasma levels of these 2 agents (objective: achieving plasma concentrations of 0.8 to 1.2 mg/L for hydroxychloroquine, and <5 mg/L for doxycycline), and of negativity of samples initially positive for T. whippelii [21];
- the treatment of Bartonella sp. endocarditis is a beta-lactam antibiotic (amoxicillin or ceftriaxone) or doxycycline for 6 weeks in combination with gentamicin for the first 2 to 4 weeks [11–13];
- the treatment of C. burnetii endocarditis, is doxycycline + hydroxychloroquine until a phase I antibody rate <800 is reached for IgG, and <50 for IgM and IgA [11–13];
- the treatment of HACEK group endocarditis for Americans is a monotherapy with ceftriaxone for 4 weeks, whatever the outcome of susceptibility testing, given the difficulty to demonstrate the secretion of beta-lactamase by these fastidious bacteria [12]. Amoxicillin or ampicillin can be used in combination with gentamicin for 4 weeks, for Europeans [11], if no beta-lactamase is identified in vitro.

4.3. Surgical treatment of blood culture-negative IE

There is no specific recommendation for surgical treatment of endocarditis with positive blood cultures: cardiac surgery indications rely on the same criteria that apply for any type of endocarditis (heart failure, non controlled infection, risk of embolism [11]). However, an additional argument for the surgical treatment of blood culture-negative endocarditis is the ability to harvest valve tissue, which often finally allows microbiological documentation.

5. Non-infective endocarditis

5.1. Systemic diseases

Two inflammatory diseases can exceptionally cause endocarditis [38]:

- systemic lupus erythematosus, in which valve abnormalities are common (15–75% of autopsy series, depending on the severity of the disease), but rarely progress to a clinical stage of Libman-Sacks endocarditis [24]. The patients are usually young individuals with a very severe lupus poorly controlled by treatments. Immunological manifestations (Osler nodes) and embolism (stroke, often in combination with an antiphospholipid syndrome) may be observed. Valve lesions are mainly found in the left heart (mitral valve more often than aortic valve), with an echocardiographic aspect that can guide the diagnosis: the mitral valve is thickened or fibrotic. The progress in the treatment of lupus in developed countries has made Libman-Sacks endocarditis an exceptional disease [24];
- endocardium involvement is also very rare in Behçet’s disease, observed in 14 of 807 patients (1.7%) managed in the Paris Pitié-Salpêtrière Hospital between 1990 and 2010 [23]. It is a disease of young (mean age at Behçet endocarditis
diagnosis, 29.7 ± 9.9 years) male patients (85% of cases), with a predominantly aortic involvement (9/14). Endocardium involvement in Behçet’s disease is a poor prognostic factor. The treatment, as for Libman-Sacks endocarditis, is targeted on the systemic disease (immunosuppressants, immunomodulators) with lifelong curative anticoagulation [23].

5.2. Marantic endocarditis

Marantic endocarditis is observed in 1.2% of patients with active cancer at autopsy [39]. The initial lesion is usually breast, lung, prostate, or colon cancer. The echocardiographic aspect is typical with an almost exclusive involvement of left heart valves that are covered with multiple small vegetation-like lesions (3 mm). The major risk of embolism justifies routine anticoagulation. The differential diagnosis with an infectious cause of blood culture-negative endocarditis is difficult, and the prognosis is poor [25].

6. Conclusion

Blood culture-negative endocarditis is a potentially serious disease and difficult to diagnose. Tremendous progress has been made over the past 2 decades in understanding the main etiologies of blood culture-negative endocarditis, thanks to a more frequent access to valve tissue, the development of new diagnostic microbiological techniques, and high quality epidemiological studies.

Disclosure of interest

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