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General review

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 burnetti* (both easily diagnosed by ad hoc serological tests), and *Tropheryma whipplei* (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).

Keywords: Endocarditis; HACEK; *Bartonella* sp.; *Coxiella burnetti*; *Candida* sp.; *Tropheryma whipplei*; 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 burnetti* (de diagnostic simple, par sérologies) et *Tropheryma whipplei*, dont le diagnostic est en général obtenu par PCR sur du tissu

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valvulaire. Les endocardites non infectieuses, rares, sont essentiellement les endocardites marastiques et les rares localisations endocardiques de maladies systémiques (lupus, Behçet).

Mots clés : Endocardites ; HACEK ; *Bartonella* sp. ; *Coxiella burnetti* ; *Candida* sp. ; *Tropheryma whipplei* ; Lupus ; Behçet ; Endocardite marastique

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

Table 1
Modified Duke criteria for the diagnosis of infective endocarditis [15].
Critères modifiés de Duke pour le diagnostic d'endocardite infectieuse [15].

Major criteria
Positive blood culture
Typical microorganism for infective endocarditis from 2 separate blood cultures
Oral streptococci (non groupable, alpha-hemolytic streptococci, *S. viridans*), group D Streptococci (previously *S. bovis*, new nomenclature, *S. gallolyticus)*, HACEK group bacteria[a]
Community acquired *Staphylococcus aureus* or enterococci, in the absence of a primary infectious focus
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:
At least 2 blood cultures sampled more than 12 hours apart, or
3 blood cultures (out of 3 sampled) or most blood cultures (out of at least 4 sampled blood cultures), during ≥ 1 hour
Endocardial lesions involvement
Echography
Oscillating intracardiac mass, on valve or supporting structures, or in the path of regurgitant jets, or on implanted material, in the absence of an alternative anatomic explanation
Myocardial abscess
New partial dehiscence of prosthetic valve
New valvular regurgitation (increase or change in pre-existing murmur is not sufficient)
Minor criteria
Predisposing heart condition (cardiac disease at risk or intravenous drug use)
Fever ≥ 38 °C
Vascular phenomena: major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage
Immunologic phenomena: glomerulonephritis, Osler's nodes, Roth spots, rheumatoid factor
Microbiological criteria : positive blood culture not meeting major criterion or serologic evidence of active infection with organism consistent with infective endocarditis
Ultrasonographic criteria: abnormality compatible with a diagnosis of IE, but not acknowledged as major criteria

[a] HACEK: *Haemophilus* sp., *Actinobacillus actinomycetemcommitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, *Kingella kingae*.