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REVIEW TOPIC OF THE WEEK

Critical Questions About Left-Sided Infective Endocarditis

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ABSTRACT

Research in different topics in cardiovascular medicine is evolving rapidly. However, this is not the case for endocarditis, despite its being the cardiovascular disease with the highest mortality and, at the same time, the entity with relatively less scientific evidence supporting its treatment. Many problems are delaying research: it is an uncommon disease, few multicenter registries are ongoing, financing for research in this topic is lacking, randomization is costly, difficult, and considered unethical by some, and conclusions coming from propensity score analysis are taken as if they came from randomized trials. In this review, we put forward the main issues in need of evidence and propose a different approach to advance the understanding of left-sided infective endocarditis. We summarize the limited evidence available, the questions that are pending, and how we should proceed to answer them. (J Am Coll Cardiol 2015;66:1068–76)

In 1885, Sir William Osler wrote in his third Gustonian lecture on infective endocarditis (IE) that "few diseases present greater difficulties in the way of diagnosis, difficulties which in many cases are practically insurmountable" (1). We bet that he did not expect his words to be applicable more than 150 years later. Several reasons can be exposed to account for this apparent lack of advance in research. We underscore 2. First, IE is infrequent, kaleidoscopic, and unpredictable. Clinical manifestations involve almost all body systems, and the diagnosis remains elusive in many cases. Second, research has been incorrectly oriented, retrospective, and solely based on registries, and evidence is lacking. In this regard, not a single level A recommendation is given in the most recent guidelines (2). More than 2 decades ago, it was stated that "there is still as much art as science in the care of patients with endocarditis" (3). It is our duty to tip the balance in favor of science.

Despite undisputable improvements in its management, no other cardiovascular disease bears poorer short-term outcome than left-sided infective endocarditis (LSIE). Mortality is in the range of 20% to 30%. Two steps can be considered crucial in the fight against LSIE: 1) the inclusion of antibiotics, which decreased mortality dramatically in a disease that until then was considered fatal; and 2) the introduction of surgery in its early management. Despite the design of new more powerful antibiotics and advances in surgical methods, mortality has remained steady for the last few decades.

We will review the main issues in need of evidence and propose a different approach to advance the understanding of LSIE. We will summarize the limited evidence available, what questions are pending, and how we should proceed to answer them. **Table 1** summarizes what is known and what is unsettled in the different topics in the following sections. We hope this review will spur the minds of basic and clinical researchers in endocarditis for the sake of our future patients.

Given the different epidemiological and clinical profile and outcome of "right-sided" IE (4) we will focus on LSIE.

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MANAGEMENT OF NEUROLOGICAL COMPLICATIONS IN ENDOCARDITIS IS FAR FROM CLEAR

Management of neurological complications has to be improved. When neurological complications are present, mortality rises up to 50%, clinical management is difficult, and cardiopulmonary bypass may be deleterious; nonetheless, neurological complications are frequently present when surgery is indicated for other reasons, and even the appearance of them may be a surgical indication.

Neurological complications appear in 20% to 40% of patients with LSIE; one-half of them correspond to ischemic stroke, 20% to cerebral hemorrhage, and 30% to other complications (transient ischemic attack, meningitis, infectious aneurysm, brain abscess). Their best predictor is delayed initiation of antibiotic therapy (5); thus, the best preventive measure is to initiate an appropriate antibiotic treatment as soon as IE is suspected, always after blood cultures have been obtained.

Whether neurological complications predict poor outcome is an unsolved issue, and studies based on a dichotomous classification offer different results (6,7). The key point of this question may be in recognizing that there are gray areas. Poor outcomes associated with relevant neurological complications (complicated [8], moderate-severe [9], or clinical [10]) as compared with irrelevant (uncomplicated [8], small [9], or subclinical [10]) have been demonstrated.

The detection of asymptomatic cerebral lesions by means of radiological techniques may improve diagnosis (11). However, their use cannot be generalized unless it is demonstrated that new unexpected findings by these techniques effectively improve diagnosis, change management, and mainly improve prognosis.

The decision to send patients with neurological complications to surgery is challenging, but can be summarized in 2 short questions (2). 1) Does the patient have an indication for surgery? 2) Does the patient have a prohibitive surgical risk? If the answers are yes and no, surgery should be strongly considered.

UNCONTROLLED INFECTION IS ARBITRARILY DEFINED

Frequently, antibiotic treatment is not sufficient to eradicate the infection in LSIE. This situation leads to an uncontrolled infection, also known as "failure of medical therapy," which increases the risk of death (12). Uncontrolled infection is, after heart failure, the most frequent indication for surgery (13), and surgery in these patients results in a worse prognosis than when surgery is performed for other reasons (14). Uncontrolled infection encompasses persisting infection, which is defined as fever and persistent positive blood cultures after 7 to 10 days of appropriate antibiotic treatment; infection due to resistant microorganisms; and locally uncontrolled infection (abscess, false aneurysm, fistula, and enlarging vegetation) (2). In our opinion, this time-dependent definition is arbitrary and vague. The cut-off point is based not on the available evidence but on clinical observations and expert opinions. This period of a lack of response to antibiotic treatment, although appropriate in other clinical scenarios, is probably too long in IE, because the patients' clinical condition deteriorates quickly and makes surgery more risky. It is paramount to anticipate this situation by identifying the patients who are at risk of developing uncontrolled infection on the basis of clinical, echocardiographic, and microbiological variables obtained within the early stages of the disease. These patients could benefit from an early aggressive approach.

There is only 1 study focused on this topic (15). We observed that the persistence of positive blood cultures 48 to 72 h after the initiation of antibiotic treatment identified patients with poor outcome, and we support this simple strategy to identify patients with a high probability of developing uncontrolled infection. Nonetheless, this finding should be validated in larger prospective series. The subsequent step would be to test whether early surgery improves the prognosis of those patients whose blood cultures remain positive. In addition, other markers related to a low probability of cure with antibiotics should be investigated.

BEYOND NEGATIVE BLOOD CULTURES

Blood culture-negative IE is diagnosed when 3 or more blood cultures collected over 48 h remain negative despite prolonged incubation (>1 week). Negative blood cultures can be found in different clinical scenarios: 1) IE with blood cultures sterilized by previous antibacterial treatment; 2) IE related to fastidious microorganisms; and 3) IE due to intracellular bacteria that cannot be routinely cultured in blood. Negative blood cultures have been associated with a delayed diagnosis and treatment and a worse clinical outcome. However, most recent series find neither a delay in the diagnosis and treatment nor an increase in complications or mortality (16). This could be partly explained by the advance in the diagnostic

ABBREVIATIONS AND ACRONYMS

FDG = fluorodeoxyglucose

IE = infective endocarditis

LSIE = left-sided infective endocarditis

PET-CT = positron emission tomography–computed tomography