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EDITORIAL

A double negative: culture-negative infective endocarditis

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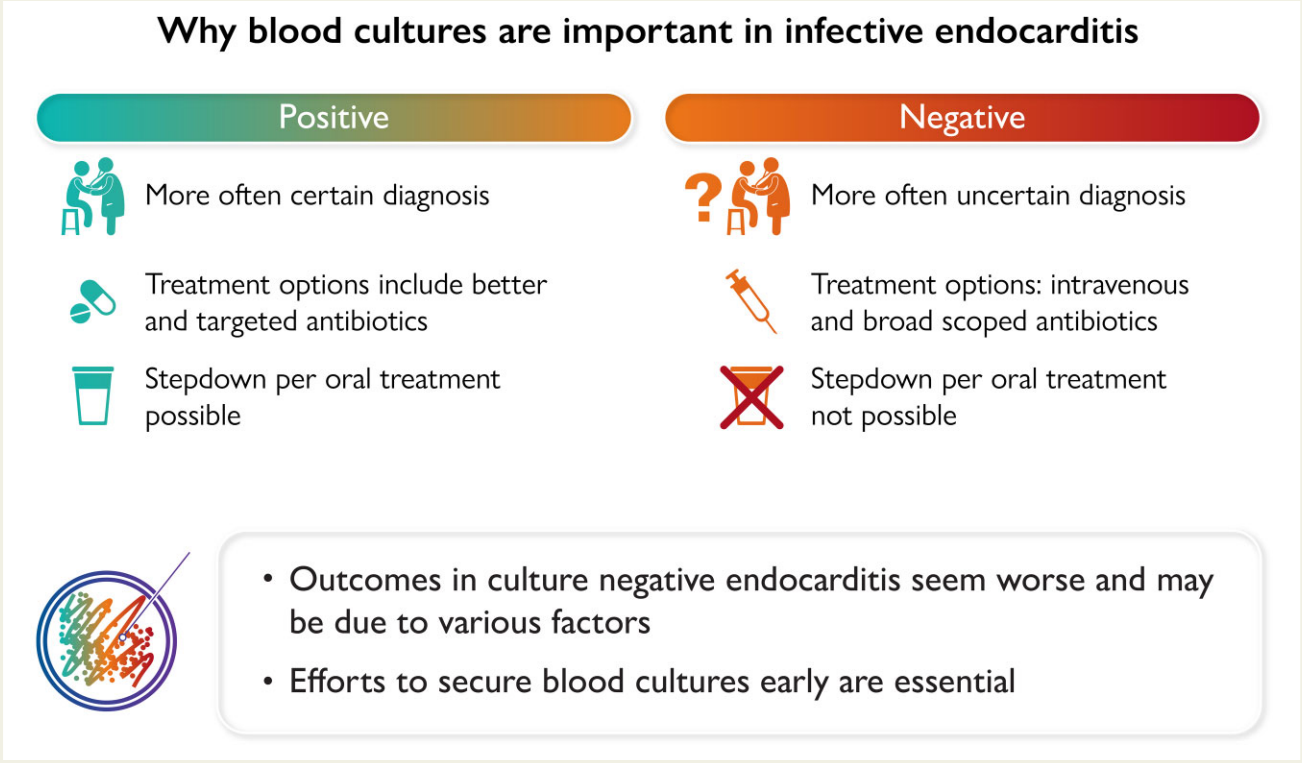
This editorial refers to 'Outcomes of culture-negative vs. culture-positive infective endocarditis: the ESC-EORP EURO-ENDO registry', by W.K.F. Kong *et al*., https://doi.org/10.1093/eurheartj/ehac307.

Graphical Abstract



Graphical abstract for positive and negative aspects of culture negative infective endocarditis vs culture positive endocarditis.

Diagnosis, risk, and treatment of infective endocarditis are all highly contingent on the underlying microorganism. Overall, infective endocarditis remains a clinical challenge, and patient outcomes have been similarly grim over the last decades.[1] We have not seen pivotal improvements in outcomes despite the fact that our diagnostics and treatment options are evolving.

Diagnosis of infective endocarditis is challenging and, by the Duke/ESC modified diagnostic criteria, blood cultures are essential.

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If cultures are not secured early (and preferably before antibiotic treatment is initiated), we might end up in a situation where we are not certain of the diagnosis, and are also challenged in terms of treatment. In cases where our clinical assessment has not determined a causative microorganism, we base our diagnosis on clinical signs (e.g. minor criteria such as fever, emboli, vasculitis, rheumatic factor, etc.) with the inherent risk of both over- and under-diagnosis. Diagnostic work-up also often becomes broader, including tests for rare conditions (e.g. mycobacteria, *Bartonella*, *Coxiella*, etc., as well systemic disease such as lupus erythematosus), which is clinically and financially illogical. Risk prediction in culture-negative endocarditis is also more difficult, and most prediction models in endocarditis are based on specific larger groups of common endocarditis-related microrganisms.[2,3]

Most difficult, however, is treatment of culture-negative infective endocarditis compared with culture-positive cases. With positive blood cultures we can narrow down our selection when choosing antibiotic treatment, and monotherapeutic antibiotic treatment may easily be initiated.[4] Issues with medical side effects and ecological antibiotic resistance become less than when we are forced to combine more and broader spectrum antibiotics (i.e. for culture-negative endocarditis). In addition, stepdown oral treatment of endocarditis will also be difficult and was not tested in the recent POET trial.[5,6] Hence, culture-negative endocarditis may in many instances mean 6 weeks of intravenous treatment, whereas culture-positive patients often require only 7–10 days of intravenous treatment and then may be discharged as early as 5 weeks before those patients with culture-negative endocarditis (given that these patients are stable and suitable for per oral step-down therapy). Surgical therapy may also be influenced by whether or not we have identified the microorganism although a surgical indication is determined more by valve destruction rather than by the oranism responsible.

In this issue of the *European Heart Journal*, Kong *et al.* compare patient characteristics, clinical practice patterns, and especially outcomes in those with culture-negative vs. culture-positive endocarditis.[7] The data source for the analysis was the collaborative endocarditis effort supported by the European Society of Cardiology (the ESC EORP EURO-ENDO registry).[8] This registry is a large effort including a little over 3 years of data (2016–2019) from 156 centres from 40 countries. Some large centres contributed with many patients and quite a lot of centres with few patients, resulting in a total of 3113 patients with endocarditis. For a disease such as infective endocarditis, this is an impressive and important data source and may compare with the older ICE (International Collaboration on Infective Endocarditis) registry.[9,10] In the present study, Kong *et al*. show that 16.8% of patients in ESC EORP EURO-ENDO were culture negative. Most noticeably, patient characteristics showed that patients with culture-negative endocarditis were younger on average and adult congenital heart disease was more prevalent. The proportion of patients with culture-negative vs. culture-positive endocarditis who underwent surgery was similar (44.5% vs. 48.8%), and 1-year mortality was higher in those with culture-negative vs. culture-positive endocarditis (adjusted hazard ratio 1.28, 95% confidence interval 1.04–1.56), but this association was modified by surgery and showed no difference among those who received surgery. The authors conclude that 'Additional efforts are required both to improve the aetiological diagnosis of IE and early identification of CNIE cases before progression to advanced disease that may exclude the possibility of surgery.' The authors should be commented for focusing on this important issue, and the ESC EORP EURO-ENDO registry data do provide novel and incremental knowledge. However, it is also important to acknowledge that the registry is built from data from mostly tertiary centres with voluntary participation. This is also seen by the high use of surgery and also from the relatively low median age of the patients. The results should be interpreted with this in mind, and the true epidemiology of endocarditis and culture-negative endocarditis is likely to be somewhat different from that shown here. In studies of granular and unselected national data, results generally show a different picture of the disease, with older and sicker patients with even worse outcomes.[11–13]

The study by Kong *et al*. provides new insight into the important subgroup that is culture-negative infective endocarditis. We do need to secure proper cultures at an early stage of the disease and aim to reduce the prevalence of culture-negative infections. By identifying a proper causative organism, we may potentially modify patients' risk and hopefully improve their outcomes. Future studies should examine new methods for proper diagnostics but also how treatment strategies (medical as well as surgical) should be best implemented in patients with culture-negative endocarditis. Hopefully, we can remove the double negative associated with this subgroup.

Conflict of interest: none declared.

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