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Review

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Complex pathogens in infective endocarditis

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Abstract

Infective endocarditis (IE) is a complex disease whose prognosis depends on the causative microorganism, among other factors. The latter can be difficult to identify and/or treat. In this narrative review, we identify knowledge gaps in the diagnosis and antimicrobial treatment of IE, and attempt to shed light on current questions. Specifically, we: (1) analyze the factors that may hinder the microbiological diagnosis of blood culture-negative IE, as well as the role of new imaging techniques, such as ^{18}F-fluorodeoxyglucose ([^{18}F]FDG PET/CT), in the diagnostic capacity of this disease, understanding their advantages and assuming their limitations; (2) discuss the therapeutic approach to various difficult-to-treat microorganisms. In particular, we focus on the treatment of staphylococcal IE since, at present, staphylococci are the most frequent cause of IE in developed countries and staphylococcal IE is one of those with the highest short- and long-term mortality. We critically evaluate the current evidence on combination therapy and address the occurrence of serious side effects, an aspect that is often overlooked owing to the severity of the infection; and (3) emphasize the need for home antimicrobial treatment of patients with IE, as these are fragile people who benefit from an early return to their environment. This poses undoubted logistical challenges

and requires robust evidence to ensure the best short- and long-term outcomes.

Keywords: Endocarditis, diagnosis, treatment, blood culture-negative infective endocarditis, outpatient, PET/CT, difficult to treat

INTRODUCTION

Infective endocarditis (IE) is a rare and severe disease. One hundred thirty-seven years after Sir William Osler published the Gulstonian Lectures[1-3], this infection is still a diagnostic and therapeutic challenge.

Regardless of the geographical area and economic context, current crude in-hospital mortality remains above 20%[1-6], higher than that of aortic dissection[7]. However, the prognosis varies enormously depending on several factors, among which are: baseline situation of the patient[8]; etiology[9-11]; diagnosis, treatment or transfer delay[12]; performance of surgery when indicated[8]; and expertise of the treating medical team[12,13]. Thus, the causative microorganism should not be considered an isolated variable but put in context in the complex scenario of IE.

What makes a microorganism difficult? The Cambridge dictionary defines difficult as: (1) needing skill or effort; and (2) not friendly, easy to deal with, or behaving well. Hard, complicated, complex and tricky are synonyms[14]. Regarding the topic of this article, some bacteria causing IE can be difficult to identify and/or treat. To this, we must add the practical absence of clinical trials and the multiple and not very well controllable biases of the many publications in the field.

From personal experience and opinion, we address some of those difficulties, identify knowledge gaps, and suggest some strategies to improve the overall management of IE caused by microorganisms that are difficult to identify or treat. In particular, we focus on three areas: (1) factors hindering the microbiological diagnosis of blood culture-negative IE, as well as the role of new imaging techniques, such as PET/CT, in the diagnostic capacity of this infection; (2) the therapeutic approach to various difficult-to-treat microorganisms, especially staphylococci, in which case we analyze the evidence for and against the use of antibiotic combinations; and (3) the current knowledge supporting home antimicrobial treatment of IE patients. Data were obtained from articles published in English and indexed in PubMed until June 2022, but a systematic review was not performed. We also searched the reference lists of retrieved papers.

INFECTIVE ENDOCARDITIS DIFFICULT TO DIAGNOSE BY CONVENTIONAL METHODOLOGY

Microbiology methodology

Blood culture-negative IE

Blood culture-negative IE is a broad concept that goes beyond IE of unknown aetiology. Blood cultures may be negative due to several factors: administration of antibiotics prior to blood drawn (frequent in *viridans* group streptococci) or insufficient blood collection; infection caused by intracellular microorganisms (e.g., *Coxiella burnetii* or *Bartonella* spp.) or by non-culturable or difficult to culture bacteria (e.g., *Abiotrophia defectiva*, HACEK group or *Tropheryma whipplei*). When IE is suspected and blood cultures are negative, it is necessary to make an additional effort to rule out or confirm the presumptive diagnosis[15]. The different causes of BCNIE mentioned above should be considered when interpreting the enormous differences in the series from the literature.

Recent general series report that the percentage of IE with negative cultures ranges from 8% to 52%[16-20]. This percentage varies greatly depending on the characteristics of the series, which are highly influenced, among other variables, by patient inclusion criteria and geographic area [Table 1].

In any case, IE with negative blood cultures poses a diagnostic and therapeutic challenge. Is it IE? If it is, how do I treat it? Finally, what is the acceptable percentage of IE with negative blood cultures?

The diagnostic algorithm for blood culture-negative IE proposed by the European Society of Cardiology[21] is extremely complex and is not entirely applicable to all centers. For example, *C. burnetii* is relatively frequent in the Mediterranean basin, but not in South Africa, where *Bartonella* spp. predominate[22]. Therefore, in our opinion, algorithms should be adapted to the local epidemiology and resources of each geographical region. Where possible, some molecular biological techniques, such as 16S or 18S ribosomal sequence identification in tissue, can provide a definitive diagnosis in patients who have received previous antibiotic treatment as well as confirm doubtful diagnoses (e.g., patients with two out of eight positive blood cultures for *Staphylococcus*).

Theoretically, the delay or absence of a microbiological diagnosis hinders the choice of appropriate antibiotic treatment. However, it does not seem to be detrimental to the prognosis[16-18,20]. Thus, in our experience, despite the 2015 ESC guidelines recommendation, in cases of clinically stable patients with subacute infections, it is not usually necessary to start an empirical antibiotic before the results of blood cultures are known. Additionally, in cases of acute infections in septic patients, it is doubtful that aminoglycosides provide more than nephrotoxicity and rifampicin would not be indicated initially[21]. Careful evaluation of each individual episode, as well as standardization of antibiotic treatment in these cases, can help to make the right decision.

To minimize the percentage of IE in which an etiological diagnosis is not reached, we must: (1) ensure that blood cultures (at least three sets from different vein punctures) are taken before starting antibiotic treatment in the population at risk; (2) inform the laboratory of the suspected diagnosis (this can accelerate the subsequent report of the results and ensure that blood cultures positive for coagulase-negative staphylococci are not treated as contaminants in people with prosthetic valves or devices); and (3) apply the diagnostic algorithm most appropriate to the epidemiological context, which should include specific serologies and molecular biology studies in tissue if the patient finally undergoes any kind of surgery.

Regarding the choice of empirical antimicrobial therapy, several factors should be taken into account, including age, comorbidities, predisposing factors (e.g., prosthetic valves or devices), healthcare or community acquisition of the infection, and acute or subacute presentation.

Imaging techniques

Impact of the type of microorganism and antimicrobial treatment on new imaging techniques

The introduction of positron emission computed tomography with ^{18}F-fluorodeoxyglucose ([^{18}F]FDG PET/CT) has significantly improved the diagnostic yield of IE and cardiac implantable electronic device (CIED) infections, by reclassification of most cases of *possible* infection into a more conclusive diagnosis (*definite* or *rejected*)[23-26]. Hence, PET/CT findings have been incorporated into the latest guidelines for the diagnosis of IE and CIED infections[21,27,28]. However, this diagnostic performance is not directly extensible to the heterogeneity of scenarios that constitute IE. While PET/CT has shown good diagnostic accuracy for prosthetic valve IE (PVE) and generator-pocket infection of cardiac devices (86% and 93% sensitivity, 84% and 98% specificity, respectively), the diagnostic accuracy is lower for native valve

Table 1. Recent series (≥ 2,010) reporting clinical characteristics and prognosis of IE with negative blood cultures

Study, year of publication	Geographical area and sample size	Period of study	Design	Definite BCNIE (% total BCNIE)	BCNIE (% total IE)	Other etiology work-up (apart from blood cultures)	In-hospital mortality
Ferrera *et al.*, 2012[16]	Spain (3 centers) *n* = 749 (left-sided)	1996-2011	Prospective	75%	106 (14%)	Serologies (*Brucella*, *Legionella*, *Coxiella*, *Mycoplasma*, *Chlamydia*, *Bartonella*) Histological study of valves	26% definite BCNIE 31% definite BCPIE*
Lamas *et al.*, 2016[17]	Brazil (1 center) *n* = 131 (left- and right-sided, all of them undergoing cardiac surgery)	2006-2014	Prospective	100%	53 (40%)	Specific PCR for *C. burnetii*, *Bartonella* spp., *T. whipplei*, *S. aureus*, *S. oralis*, *S. gallolyticus*, *Enterococcus* spp., *E. coli* and fungi in excised valves Histological study of valves	17% definite BCNIE 25% definite BCPIE*
Diez-Villanueva *et al.*, 2016[18]	Spain (26 centers) *n* = 2,000 (left- and right-sided)	2008-2012	Prospective	82% overall 86% known aetiology 45% unknown aetiology	290 (15%) overall 7% known aetiology	PCR in excised valves Serology (not specified)	27% overall 27% known aetiology 33% unknown aetiology*
Firiana *et al.*, 2020[19]	Indonesia (1 center) *n* = 283 (left- and right-sided)	2013-2018	Retrospective	56%	162 (57%)	PCR in tissue Serology (not specified)	14% BCNIE
Suardi *et al.*, 2021[20]	Spain (8 centers in Southern Spain) *n* = 1,001 (left- and right-sided)**	2008-2018	Prospective	100%	83 (8%)	16S gene PCR in excised valves Serologies (*C. burnetii*, *Bartonella* spp., *Mycoplasma* spp., *Brucella* spp., *Legionella* spp.)	31% definite BCNIE 26% definite BCPIE*

BCPIE: Blood culture-positive IE; BCNIE: blood culture-negative IE; *No statistically significant difference between groups; **Overlap with Diez-Villanueva P series.

IE (NVE) and lead infection of CIED (31% and 65% sensitivity, 98% and 88% specificity, respectively)[29,30]. But beyond these known limitations, there are still several diagnostic challenges for this technique, even in the appropriate indications currently recommended by guidelines. The sensitivity of PET/CT may decrease when performed sometime after the start of antibiotic therapy, especially in highly sensitive microorganisms, as appropriate antibiotic treatment will lead to decreased inflammation over time [Figure 1]. Although the risk of a false-negative scan probably increases with the duration of treatment, suggesting that PET/CT should be performed as soon as possible when IE is suspected, the precise time at which sensitivity may be compromised is unknown[31].

Performing cardiospecific PET/CT scans, especially if they include a cardiac CT, will contribute significantly to the correct interpretation of images. Moreover, knowledge about the morphometabolic features that allow differentiating reactive inflammation from infection is important to avoid possible misdiagnoses, especially in the recent post-implantation period of a cardiac prosthesis. Although the use of follow-up PET/CT scans is not a formal clinical indication, it can help monitor the response to medical treatment in patients with IE and high surgical risk, supporting clinical decisions in this group of complex patients.

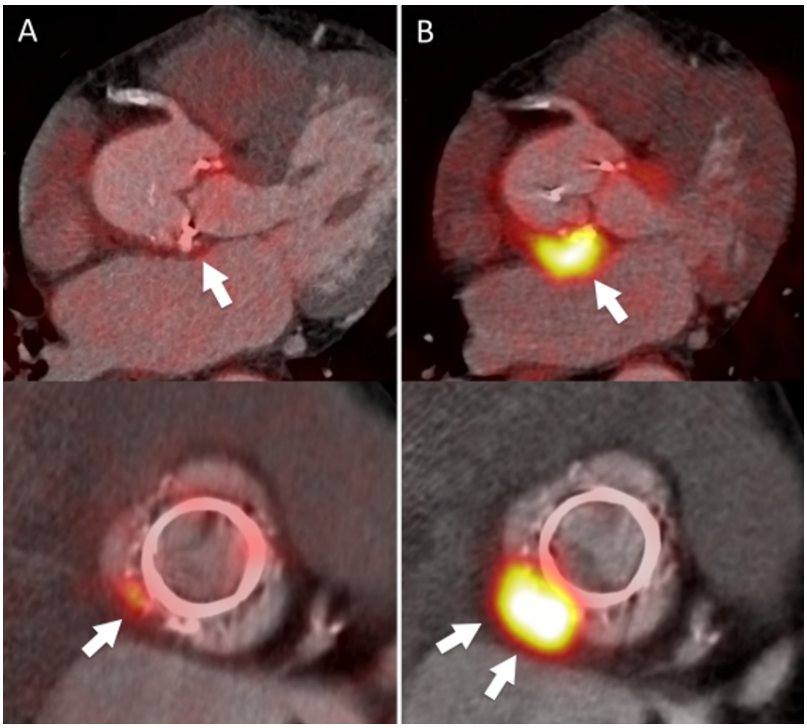

Figure 1. A 65-year-old man with a bioprosthetic aortic valve replacement presented with a 2-month history of fever and severe asthenia, for which he had received several courses of antibiotic treatment. Initial blood cultures were negative, and echocardiography was also negative for vegetations. Since high clinical suspicion persisted, he underwent [^{18}F]FDG PET/CT that did not show conclusive findings of IE beyond a very slight periprosthetic FDG uptake (A, arrows). He completed 6 weeks of empirical antibiotics and remained under close follow-up. Two months later, he was readmitted due to recurrent fever and blood cultures were positive for *E. faecalis*. Echocardiography showed slight thickening of the valve leaflets. A new PET/CT confirmed PVE (intense focal hypermetabolic periprosthetic soft tissue lesion compatible with a periprosthetic abscess (B, arrows). PET/CT under prolonged antibiotic treatment can lead to a false negative result and may not allow ruling out the diagnosis of infection with certainty. [^{18}F]FDG PET/CT: ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography. PVE: prosthetic valve IE.

Another important issue is not foreseen in the current guidelines and diagnostic algorithms: it has been assumed that IE will manifest in the same way on a PET/CT scan, irrespective of the responsible microorganism. Some pathogens may cause an aggressive infection with great inflammatory response and tissue destruction (i.e., *Staphylococcus aureus, Enterococcus faecalis*), leading to intense metabolic activity detectable by PET/CT (intense FDG uptake) and a higher probability of perivalvular extension and anatomic lesions depicted by CT, whereas other microorganisms like *Cutibacterium acnes* cause low-grade, less destructive infections with a more insidious course and lower morphometabolic evidence [Figure 2]. Moreover, IE may be secondary to atypical bacteria (i.e., *C. burnetti, Mycobacterium chimaera*) or other uncommon non-bacterial pathogens, like fungal infections. Differences in the pathogenesis of the infection may determine the type and proportion of cells involved in the inflammatory response. The diagnostic yield of PET/CT for each specific microorganism is unknown, and we can face situations where blood cultures are positive and PET/CT is negative, and conversely, a positive PET/CT scan in cases with no microbiological demonstration.

To overcome the limitations derived from using the same nonspecific tracer (FDG) for detecting infection, hope has been placed on the development of new radiotracers, which can focus on detecting: (a) general aspects of the infectious process, such as hypervascularization and hypermetabolism; (b) infection-related targets (specific antibodies, antibiotics, antimicrobial peptides, radiolabeled bacteriophages and antifungal drugs); (c) bacterial metabolic activities, such as thymidine kinase activity, folic acid synthesis pathway and

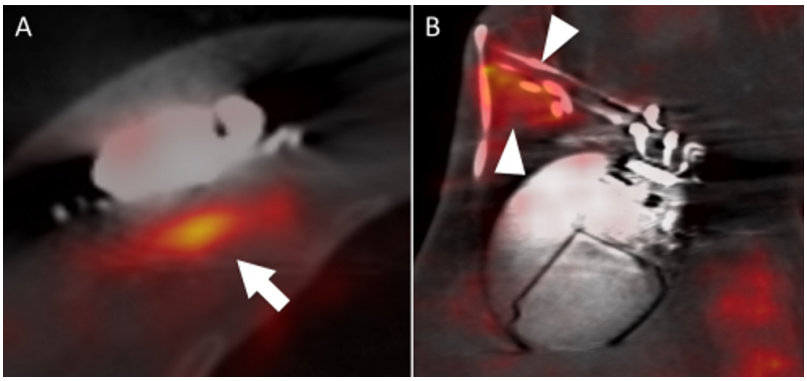

Figure 2. Two cases of low-grade cardiac device infection due to *C. acnes*.Mild and focal FDG uptake on the rear of the generator/pocket of the device (A, arrow) and along the extravascular segment of the leads (B, arrowheads). There were no significant associated soft tissue changes. Both patients complained of intense local pain without clear signs of inflammation at physical examination. [^{18}F]FDG PET/CT should be carefully evaluated to detect these low-grade infections since findings are subtle and may be unnoticed. The diagnosis was confirmed in both cases by cultures of the removed devices. FDG: fluorodeoxyglucose; [^{18}F]FDG PET/CT: ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography.

carbohydrate metabolism; and (d) bacterial membrane and extracellular structures (biofilm)[32,33]. Limitations of bacteria-specific radiotracers include the fact that the number of bacteria present in a low-grade infection may be too low to be detected by current PET/CT systems.

INFECTIVE ENDOCARDITIS "DIFFICULT TO TREAT"

"Difficult to treat" microorganisms

Staphylococci: Since the beginning of the 21st century, staphylococci has represented the leading cause of IE in large series from developed countries[9,34,35]. However, unlike streptococci and enterococci, there is no agreement on what is the best antimicrobial regimen in this group of patients[36]. While the guidelines have been superseded, the practical absence of randomized studies and the limitations of observational studies means that yet we cannot make solid progress in establishing a safe and effective standard of care in terms of antimicrobial therapy.

Migrating to a multidimensional approach

The classical approach of staphylococcal IE antimicrobial treatment orders episodes according to whether the causative strain is susceptible or resistant to methicillin and whether the infection affects native or prosthetic valves[21]. However, IE is, by definition, a heterogeneous disease, and the real picture is much more complex. Multiple factors must be considered in the equation: the species of *Staphylococcus*, the clonal complex and virulence factors, the age and comorbidities of the patient, the extent of the infection, the possibility of acting surgically on the foci of infection (including valve surgery), the toxicity of the drugs and even the end point of evaluation, which can be persistent bacteremia, short-term mortality, recurrence or even functional status. In addition, the severity of the infection means that these patients are highly manipulated and can suffer different nosocomial infections while under antibiotic treatment. Therefore, it is common for a patient with staphylococcal IE to receive several antibiotic treatment regimens during hospitalization.

The importance of the species and other microbiological factors

S. aureus and coagulase-negative staphylococci (CNE) IE are not the same disease. The former is invariably an acute infection, with a median number of days from symptom onset to blood cultures of 3 days and

primarily affecting native valves[10]. The second is often a subacute infection that settles on prosthetic valves or implantable devices in two-thirds of cases[37]. Despite these differences and the lack of large studies on CNE IE, it has been assumed that the treatment must be the same in both cases.

Furthermore, not all strains are the same. Some retrospective studies suggested that a vancomycin minimum inhibitory concentration ≥ 1.5 μg/mL was associated with a poor prognosis in methicillin-susceptible *S. aureus* bacteremia, even if treated with beta-lactams[38,39]. However, in a prospective study of 213 consecutive definitive *S. aureus* IE episodes, vancomycin MIC was not related to any of the endpoints studied, including persistent bacteremia and mortality. Interestingly, in the same study, variations in clinical presentation were observed according to different clonal complexes (CC). Specifically, CC15 was more frequent in patients with early mortality (≤ 2 days after initiation of antibiotic treatment) and CC30 was associated with persistent bacteremia > 5 days of targeted antibiotic but, conversely, was associated with lower in-hospital mortality[10]. Unfortunately, this information is not routinely available, and even if it were, at the present time, we do not know whether this should imply a different antibiotic approach.

Does the end justify the means?

In-hospital mortality of staphylococcal IE exceeds 30% and is higher in prosthetic valve IE and if caused by methicillin-resistant *S. aureus* (MRSA)[10,37]. In the specific case of *S. aureus* IE, it usually affects frail people in close contact with the healthcare system, with high baseline percentages of diabetes (34%) and renal failure (27%), and who will develop some degree of worsening renal function in 50%, as well as heart failure in 31%[10].

This context of extreme severity of infection has justified the use of different aggressive antibiotic combination therapies, without clear proven benefits and with varying degrees of associated toxicity. This should lead us to reflect on the lost opportunities. Although IE is a rare disease, there are numerous study groups and national and international collaborations that could provide answers to the therapeutic challenges. Unfortunately, patient registries generally do not adequately reflect antibiotic treatment and clinical trials, as we will see below, have not been definitive due to limited sample size.

What do combination treatments offer?

The principle of the use of antibiotic combinations in the treatment of staphylococcal IE is the search for synergy. Classically, gentamicin and rifampicin have been added to the main antibiotic treatment, the latter in infections on prosthetic valves. Currently, gentamicin is no longer recommended in infections on native valves and there is some evidence against its use in infections on prosthetic valves, since it does not improve survival and, on the contrary, increases the risk of renal failure[40]. In the case of rifampicin, a multicenter, randomized, double-blind, placebo-controlled trial did not find the benefit of adding this antibiotic to a standard regimen in adults with *S. aureus* bacteremia[41]. Additionally, two retrospective studies suggest that it is not useful in IE on prosthetic valves because it does not improve survival or reduce the risk of recurrence, and makes patient management more difficult due to intolerance and interactions with other drugs[42,43].

More recently, other antibiotic combinations have been explored. In a randomized controlled trial, adding daptomycin to the standard of care in methicillin-susceptible *S. aureus* bloodstream infections did not demonstrate to shorten the duration of bacteremia or reduce 90-day mortality[44]. In addition, daptomycin and fosfomycin have been compared with daptomycin monotherapy in patients with MRSA bacteremia and IE in a randomized study[45]. Although the combined treatment group presented less persistent bacteremia, overall, there were no differences in terms of clinical failure and mortality. However, patients who received fosfomycin presented more adverse effects requiring withdrawal of antibiotic treatment. In this study,

fosfomycin was administered at a dose of 2 g/6 h, which represents a considerable salt intake, an important limitation in patients at risk of or with heart failure. Another limitation of the study is that the number of patients with IE was very small (9 in each branch).

Another recently published randomized study compared the efficacy and safety of administering vancomycin or daptomycin in monotherapy or in combination for 7 days with a beta-lactam (cloxacillin or cefazolin) for the treatment of MRSA bacteremia. Again, there were no differences in terms of mortality or recurrences, but the presence of adverse effects was higher in the combination treatment group, in particular, a higher risk of renal failure. Here again, the number of IE included was small[46].

Some experience with ceftaroline alone or in combination with daptomycin, vancomycin, or rifampicin for the treatment of staphylococcal IE has also been reported with comparable results to previous observational studies[47,48]. However, more evidence is needed to properly assess the potential of this promising antibiotic combination. Finally, a randomized study was designed to compare the effectiveness of vancomycin *vs.* the combination of imipenem plus fosfomycin for the treatment of MRSA IE. Unfortunately, the study was terminated with very few patients due to the lack of recruitment[49].

The burden of side effects

Apart from the lack of evidence supporting the use of combined treatments, we must take into account that the different drugs are not free of side effects. This is especially in the case of staphylococcal IE, where patients receive long courses of at least 6 weeks. We have already seen how gentamicin and rifampin can be more sources of concern rather than solutions, and that the fosfomycin salt load is a very limiting factor in the treatment of a disease in which one-third of patients will develop heart failure.

Until recently, cloxacillin was considered the standard treatment for methicillin-susceptible staphylococcal IE. Recently, experience has accumulated in favor of cefazolin since, with equal effectiveness, it has fewer side effects, especially less risk of interstitial nephritis[50]. Going further, increasing evidence suggests that penicillin G may be at least as effective as and less toxic than cloxacillin in treating susceptible *S. aureus* bloodstream infections[51,52]. Daptomycin has emerged as the main treatment for IE caused by methicillin-resistant strains. However, in up to 15% of cases, it can cause eosinophilic syndromes, the most serious being pneumonitis[53]. Finally, high doses of ceftaroline can cause leukopenia after the first two weeks of treatment[54].

In conclusion, no combination of antibiotics can be categorically recommended for the treatment of staphylococcal IE at the present time, as the current scientific evidence does not strongly support this option and the risk of serious side effects is high.

Candida spp.

Fungi represent one of the most feared etiologies in IE. Fortunately, this very rare disease represents less than 2.5% of all IE episodes[9,55], with *Candida* spp. being by far the most common cause of fungal IE. This difficult-to-treat microorganism is mostly responsible for nosocomial acquired IE, especially in patients with prosthetic material, in people who inject drugs, or in immunosuppressed patients[56-58].

Last ESC, IDSA, and ESCMID guidelines[21,59,60] recommend valve surgery for all patients with *Candida* spp. IE. However, in the largest series of *Candida* spp. IE mortality was similar in patients who received combination surgical and antifungal therapy *vs.* antifungal therapy alone[57,58,61]. These results need to be taken with caution, as the sample size of these studies is small and clinical scenarios can be very diverse. For

instance, the case of an immunocompromised patient with prosthetic valve IE is different from that of a person who injects a drug and with a native valve IE.

Regarding the best antifungal treatment, international guidelines recommend liposomal amphotericin B (or other lipid formulations) with or without flucytosine or an echinocandin at high doses, followed by step-down therapy to oral azoles and long-term suppressive treatment sometimes for life, especially for patients who cannot undergo valve replacement (recommendation with a low grade of evidence)[21,59,60]. Apart from the potential toxicity, there is no strong evidence regarding the possible benefit of combining two antifungals in the intensive phase and probably an active antifungal against biofilm is enough. A systematic literature review of 140 *Candida* spp. IE (including 29 cases from the Italian Study of Endocarditis) found that an effective anti-biofilm antifungal regimen (defined as the administration of echinocandin or amphotericin B) was associated with increased survival as compared with azoles[62]. Another multicenter observational study found no difference in clinical cure rates between amphotericin B and echinocandins[58]. Therefore, in the case of frail patients with *Candida* spp. IE, echinocandins appear to be the more attractive option due to fewer side effects and high antibiofilm activity. The optimal duration of antifungal treatment remains to be established, especially in patients who do not undergo surgery.

The special case of M. chimaera

M. chimaera is a nontuberculous mycobacterium causing IE and disseminated infection following cardiopulmonary bypass because of exposure to contaminated heater-cooler devices[63]. Most cases are subacute, often manifest as a systemic disease (up to 50% mimicking sarcoidosis), although cases of acute and catastrophic presentation after cardiac surgery have been described[64]. The definitive diagnosis is established with a positive culture for *M. chimaera*. However, despite being an intravascular infection, the yield of blood cultures for mycobacteria is low and often requires sampling of valves or other tissues.

Although the wild-type strain is common to all cases and has a known sensitivity, the optimal treatment of this entity is unknown. In addition, the proposed regimens are complex and potentially nephro- and ototoxic as they contain aminoglycosides for an undetermined time (first-line therapy includes azithromycin, rifampicin (or rifabutin), ethambutol and amikacin)[63]. Even so, therapeutic success is not guaranteed without complete replacement of the infected prosthetic material and the long-term prognosis in the small published series is poor, with a mortality rate over 50% one year after diagnosis[65]. Fortunately, no new cases of *M. chimaera* IE have been described in patients operated on beyond 2015, so we can consider the outbreak over.

"Difficult to treat" at home

IE is a very debilitating disease, especially in the elderly[66], and requires prolonged antimicrobial therapy. In stable patients, once the initial phase of medical treatment (including surgery, if necessary) has been overcome, early discharge facilitates functional rehabilitation. However, home administration of antibiotics faces some difficulties.

Although outpatient parenteral antimicrobial therapy (OPAT) has demonstrated undeniable benefits in terms of patient's quality of life and economic savings for the health system[67], in the specific case of IE, the guidelines are conservative, considering discharge home only before 2 weeks, in streptococcal IE on native valves[21,68,69]. Fortunately, a recently published study provided evidence for more lax criteria allowing earlier discharge home[70]. However, for enterococcal IE, the rate of patients treated at home was significantly lower than those treated in the hospital (9.3% *vs.* 15.7%, $P < 0.001$), since not all units have the capabilities to administer any antibiotic regimen. There is recent clinical experience with the administration of ampicillin

plus ceftriaxone on an outpatient basis with good results[71]; however, while both drugs may soon be co-administered via continuous infusion[72], so far, it requires two electronic pumps, which is sometimes challenging in this group of elderly and frail patients[11]. In non-HLAR *E. faecalis* IE, another option would be using the ampicillin plus gentamicin combination for 2 weeks[73,74], completing the rest of the treatment with ampicillin in monotherapy. Alternatively, a more convenient treatment for *E. faecalis* IE in OPAT would be teicoplanin. Teicoplanin is a long half-life glycopeptide that can be administered as a single daily dose, bolus rather than perfusion, has fewer side effects, and is not associated with renal failure[75]. Apart from some evidence in the treatment of experimental enterococcal IE[76-79], two recent retrospective cohort studies have been published with good results[80,81]. Finally, an even more convenient antibiotic for enterococcal IE patients would be dalbavancin, which can be administered every 7-14 days. However, clinical experience is scarce in this scenario and allows no recommendations at this moment.

Long duration of antimicrobial therapy is another limitation in IE. Again, in the case of *E. faecalis*, the length of antibiotic treatment with ampicillin plus ceftriaxone was established at 6 weeks since the initial studies[82,83]. Although it is possible that this treatment could be shortened to 4 weeks in some uncomplicated cases, so far, there is not enough solid evidence to make a clear recommendation in this regard[84,85].

In this sense, an early switch to oral treatment in IE facilitating hospital discharge could be the key. In the POET trial, enterococcal etiology represented around 24% of the patients included and the proposed oral therapy contained two different antibiotics with important toxicities, such as linezolid or rifampicin, especially relevant in the case of frail and aged patients with enterococcal IE[86]. The French multicenter randomized trial RODEO 2 will provide more evidence if an oral switch to a simpler antibiotic regimen with amoxicillin at high doses is also effective[87].

In the case of staphylococci IE, a promising alternative to facilitate outpatient parenteral antibiotic treatment is dalbavancin. There is positive observational evidence regarding its effectiveness when used as a sequential treatment with clinical cure rates higher than 90%[88,89] and the high plasma levels obtained when administered every week or two weeks are reassuring. Oral treatment is also gaining more evidence. As in the case of enterococcal IE, the antibiotic regimens used in the POET trial also have some toxicities, although adverse effects rates were similar between patients in the oral group compared to the IV group. We believe that this option, especially in the case of "difficult to treat" microorganisms, such as staphylococci, needs close monitoring and follow-up to ensure early detection of intolerances that can lead to malabsorption or treatment discontinuation and to ensure treatment compliance.

THE ROLE OF SURGERY

Despite recent advances in antimicrobial therapy, IE remains a surgical disease in more than 50% of cases[35] and difficult-to-treat microorganisms are themselves an urgent/elective indication for surgery[21]. Cardiac surgery in IE aims to cure the infection and restore the anatomy and thus cardiac function.

Timing of surgery is a very difficult decision. Early surgery is desirable to eliminate the primary source of infection. However, if performed too early, there is a risk of intraoperative vasoplegia due to sepsis or relapse after antibiotics are completed. But if performed too late, there is a risk of embolism, paravalvular spread of infection (increased technical complexity) and worsening of the patient's condition.

In the absence of evidence to support clear recommendations on the timing of surgery that apply to all patients, it is necessary to individualize this decision according to the patient's characteristics and in a consensus with all professionals involved in the management.

CONCLUSION

To summarize, in IE, certain microorganisms can be difficult to identify and/or difficult to treat. The algorithm for the microbiological diagnosis of blood culture-negative IE should be easy and adapted to the characteristics of the patients and the epidemiological context of each center. New imaging techniques, such as PET/CT, have significantly improved the diagnostic yield of IE, and may represent the key to diagnosing IE with negative blood cultures, where imaging remains the only major criterion. However, the performance of PET/CT may be affected when patients previously received prolonged antibiotic treatment or the infection is caused by microorganisms of low virulence. Regarding specific antibiotic treatment, there is no solid evidence to justify the use of combinations of antimicrobials in the case of staphylococcal IE and, on the contrary, they can lead to the appearance of serious adverse effects. Finally, early discharge home is desirable and necessary in this group of fragile individuals, and we must guarantee the quality of life of the patients who survive.

DECLARATIONS

Authors' contribution

Conceived and designed the manuscript: Escolà-Vergé L, Roque A, Pizzi MN, González-López JJ, Almirante B, Fernández-Hidalgo N

Availability of data and materials

Not applicable.

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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