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Editorial

Infective endocarditis: New forms of the disease, new therapeutic options

Endocarditis infecciosa: nuevas formas de la enfermedad, nuevas opciones terapéuticas

Juan Gálvez-Acebal[a,b], Luis Eduardo López-Cortés[a,*]

[a] *Unidad Clínica de Enfermedades Infecciosas, Microbiología y Medicina Preventiva, Hospital Universitario Virgen Macarena/CSIC/Instituto de Biomedicina de Sevilla (IBiS), Seville, Spain*

[b] *Departamento de Medicina, Universidad de Sevilla, Seville, Spain*

Despite the undoubted advances made in recent years, infective endocarditis (IE) remains a disease of high morbidity and mortality that represents a major challenge for therapeutic decision making. The scientific evidence supporting these decisions continues to be insufficient. Most expert recommendations are based on grade B and C evidence,[1,2] with numerous observational studies and only 7 clinical trials published in recent decades.[3]

In addition to this, there have been significant epidemiological changes in recent years that affect the oldest and frailest patients, often with comorbidities, and with complicated subgroups, such as those with chronic liver and kidney diseases or malignancies. In many cases, the complexity is further complicated by the fact that infection is healthcare-associated and with a predominance of staphylococcal infections.[4]

Around a third of cases affect prosthetic valves, and another 10%, with an upward trend, involve implantable cardiac devices, such as permanent pacemakers and/or cardioverter-defibrillators.[5] Considerable advances in the correction of valvular lesions have been made in recent years with valve implants that do not require open heart surgery, especially in patients at high risk for surgery. This is the case of TAVI (transcatheter aortic valve implantation), one of whose complications is infective endocarditis. While the incidence of IE is low, according to a recent meta-analysis, and similar to that of surgical aortic valve replacement, both in the first 12 months post-implantation (0.86% vs 0.73%, OR 1.17, 95% CI 0.51–2.65, $p = 0.71$) and afterwards (1.3% vs 0.6%, OR 1.85, 95% CI 0.81–4.20, $p = 0.42$),[6] it is expected to increase in the coming years. Diagnosis can be challenging because of its atypical clinical manifestations and the difficulty of interpreting commonly used imaging techniques, such as echocardiograms. In most cases, it is not possible to carry out surgical treatment, since these are patients who were excluded from that particular option when TAVI was performed, thus increasing mortality, which is generally above 50%. The study by Rodríguez Vidigal et al.[7] published in this issue of *Enfermedades Infecciosas y Microbiología Clínica* (EIMC) is a good illustration of this new form of the disease, whose characteristics are, in the main, very similar to those described in other series, although an incidence of 5% is very high compared with what has been published up till now, and is highest in the first year post TAVI. This indicates that, in the majority of cases, the infection probably does not occur during the procedure, but in the months that follow implantation and related to bloodstream infections of diverse origin, including urinary catheters and intravascular catheters. The authors found that the risk factors for infection were the presence of malignancies and patients at very high risk for surgery according to the EuroSCORE scale, which is to be expected in this population, although it is difficult to perform an analysis of this kind with such a limited number of cases. The description of cases includes mention of a wide variety of circumstances associated with urological and abdominal problems, which explains the slight predominance of *Enterococcus faecalis* as the causative pathogen, and reminds us of the need for early diagnosis and adequate treatment of bloodstream infections in these patients.

Treatment of this disease continues in many cases to be medical and surgical treatment. With respect to antibiotics, there have been some modifications to the dose regimens used, many aimed at avoiding the use of aminoglycosides in order to prevent aminoglycoside-induced toxicity. In the case of *E. faecalis* endocarditis, the combination of ampicillin and ceftriaxone has shown similar efficacy to the conventional ampicillin and aminoglycoside combination, but with reduced nephrotoxicity and active in cases where there is high-level resistance to aminoglycosides, which has made it a preferred regimen, although there remain unanswered questions.[8] Likewise, combining aminoglycosides with a beta-lactam is discouraged for the treatment of endocarditis caused by methicillin-susceptible *Staphylococcus* spp., although it continues to be recommended in cases of prosthetic valve endocarditis caused by these microorganisms.[1,2] A recent observational study with a limited number of cases did not find differences in mortality when aminoglycosides were not used.[9] Likewise, a study

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* Corresponding author.
E-mail address: luiselopezcortes@gmail.com (L.E. López-Cortés).

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revealed that discontinuation of rifampin after surgical treatment for staphylococcal prosthetic valve endocarditis was not associated with increased mortality or an increased number of IE relapses,[10] which would favor tolerability and the prevention of oral anticoagulant drug interactions.

Antistaphylococcal penicillins continue to be used for treatment of endocarditis caused by methicillin-susceptible *Staphylococcus* spp., without there being a more effective alternative available at present. Cefazolin is considered a second-line option for allergic patients,[2] although it may be a better alternative in the future, given its efficacy and better toxicity profile, as well as being easy to use for home treatment.

Experience with new antimicrobials is as yet limited. Daptomycin is probably the most widely used, although we do not have sufficient evidence to demonstrate a clear superiority over traditional regimens, not even in combination with fosfomycin, beta-lactams or ceftaroline. There are observational data of dalbavancin, which showed promising results when used as continuation therapy following a first phase of intravenous therapy in hospital.[11] Once the patient has achieved stability, there are various alternatives available to reduce length of hospital stay without compromising efficacy, either by using devices to deliver intravenous antibiotics at home, even in patients previously considered at highest risk,[12] or by completing treatment with oral antibiotics, as was demonstrated in a recent clinical trial in patients with native and prosthetic valve endocarditis.[13]

Surgical treatment is a key component of treatment of disease management and in recent years, more than 50% of cases have been operated on. Nevertheless, in about 25% of cases, there are indications that it is not possible to perform surgery because of the severity of the patient's condition or comorbidities.[14] The use of different surgical risk indices to aid in decision making remains both controversial and not always applicable to all populations.[15] Current indications continue to be acute heart failure secondary to valvular dysfunction, persistent infection despite adequate antimicrobial treatment, and prevention of embolic events.[1,2] Patients frequently have more than one indication for surgery and it is difficult to specify the impact of each one on a given patient. The only clinical trial that has been performed in this context demonstrated a reduction in mortality, relapses, and new embolic events in patients with left-sided IE and large vegetations >10 mm who underwent early surgery within the 48 h after randomization versus those who continued with conventional treatment (3% vs 28%; HR 0.08 (95%CI 0.01–0.65) $p = 0.02$). Nonetheless, it is difficult to generalize from these results because the population included in the study were younger patients with low surgical risk and the causative pathogens were predominantly streptococci.[15] Deciding on the optimal timing of surgery is another challenging decision. A recent systematic review and meta-analysis including 21 studies, most of them observational, demonstrated that early surgery was associated with lower mortality, although the term "early" was defined in varying ways in the included studies. A sub analysis of patients who underwent surgery within the first 7 days showed similar results for in-hospital mortality OR 0.61; 95% CI 0.16–0.54; $p = 0.001$).[16] The long-term results of surgical treatment have been studied less, hence the interest of the study by Varela Barca et al.[17] in this issue of EIMC. Despite the inherent limitations of retrospective observational studies, the authors found an in-hospital mortality of 26%, associated with the severity of the condition and the existence of complications; around a half of patients underwent emergency surgery. Nonetheless, long-term mortality (1, 2 and 5 years) was not higher (30.3%) and was determined by indirect causes independent of the initial condition of the patient, which supports the opinion of performing surgery early provided that there are no contraindications. On the other hand, the various indicators of surgical risk analyzed (EuroSCORE, PALUSE, STS-IE, Costa, De Feo-Cotrufo) did not prove useful for predicting long-term mortality.

In cases of endocarditis related to implantable cardiac electronic devices, it is essential to completely remove the device as early as possible, using different extraction techniques.

Is it possible to improve the prognosis for this disease? There are few options associated with host-specific factors, such as age, baseline disease, or the pathogens involved, especially the most virulent such as *S. aureus*, so that extreme preventive measures should be taken, especially in high-risk patients. Early diagnosis of both the disease and complications can, on the other hand, help improve certain aspects of the prognosis by maintaining a high level of clinical suspicion that goes beyond the typical clinical manifestations, especially in patients with different types of indwelling prosthetic valves, including TAVI, or bacteremia caused by microorganisms such as *S. aureus*, coagulase-negative staphylococci or *Enterococcus* spp. The two key elements of diagnosis continue to be taking adequate blood cultures and early echocardiography. Nevertheless, in certain cases, such as patients with intravascular prosthetic material, it will sometimes be necessary to use newer imaging techniques, in particular ^{18}F-FDG PET/CT angiography,[18] because of its greater sensitivity and ability to detect intracardiac and extracardiac complications. It is also necessary to identify patients at higher risk of complications and to detect them as early as possible. In this context, immediate thrombectomy represents a significant advance in the management of the neurological complications of embolic events.[19] Appropriate empirical and definitive antibiotic therapy should be instituted, selecting the best drug, duration of treatment and dosage regimen for the individual case. The indication for and optimal timing of surgery is another key consideration. In many cases, this decision should be based on the characteristics of individual patients. The development of new, less invasive surgical techniques offers opportunities for carrying out surgical treatment in patients who are at greater surgical risk. All this should be carried out by multidisciplinary teams in centers with appropriate diagnostic and therapeutic capacity, which implies proper coordination between those centers that do not have resources and their reference centers.[20] Although endocarditis has always been a disease in which experience and clinical expertise have been decisive for its management, its current complexity requires a multidisciplinary approach and the development of new studies with the best available methodologies and clinical trials that can help dispel current uncertainties.

Conflicts of interest

LELC has been a speaker for Merck, Sharp and Dohme, Pfizer, and Angelini, has received funding from Novartis for research activities, and has served as trainer for Merck, Sharp and Dohme. JGA has no conflicts of interests to declare.

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