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Editorial

Current status of infectious endocarditis: New populations at risk, new diagnostic and therapeutic challenges[☆]



Estado actual de la endocarditis infecciosa: nuevas poblaciones de riesgo, nuevos retos diagnósticos y terapéuticos

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Infective endocarditis (IE) is a serious, rare infection that is becoming increasingly widespread. For nearly a decade, the medical community has been aware that a high percentage of IE cases are health care-related.¹ However, instead of reducing the incidence rate with preventive actions, new forms of endovascular infections have appeared, such as IE associated with transcatheter aortic valve implantation (TAVI). In view of the growing complexity of today's medical interventions and the increasing frailty of patients, clinicians must always be on the alert for the risk of infection.

In this issue of Infectious Diseases and Clinical Microbiology, the study from Mesa del Castillo-Payá et al. compares the clinical and evolutionary characteristics of patients with IE with and without a diagnosis of concomitant neoplasia.² Although this is a retrospective, single-centre study, the results are similar to those of another recently published, prospective, multicentre study with the same objective.³ Compared with the rest of the series, the incidence of *Staphylococcus aureus* infection and health care-related IE (particularly associated with the use of vascular catheters) was higher among neoplastic patients. This group were also less likely to receive surgery and presented a higher in-hospital mortality rate. Oncology patients are doubly at risk for IE for 2 reasons: they frequently undergo invasive therapies and the neoplastic disease itself can act as a portal of entry for infection. This is why it is so important to reiterate the need to systematically search for the focus of infection in all cases of IE. This will not only prevent recurrence of the disease but can also help diagnose a potentially curable neoplasia, as shown by the recently described association between enterococcal IE and colorectal adenomas.⁴ Bearing in mind the significant increase in recent decades in the average age of patients presenting *Enterococcus spp.* infection, which is the third most common cause of IE, it is important to consider this association.

In the study in question, fewer cancer patients underwent valve surgery.² Unfortunately, the authors did not stratify surgery and mortality according to the degree of extension of the neoplasia or the functional status of the patient, both of which could contribute to therapeutic decision-making. Be that as it may, the heterogeneity of IE patients evidently calls for individualised decisions.

TAVI patients represent a new population at risk of endocarditis. This population is, generally speaking, elderly (median of 80 years) with a high incidence of enterococcal and staphylococcal infections.⁵ The evidence available to date suggests that the incidence of IE in TAVI patients could be similar to that in individuals with conventional prosthetic valves. However, long-term follow-up of this population is needed to confirm this hypothesis and identify the differential characteristics of these patients and of the materials used in the valves, since some types of valve have been associated with a higher incidence of IE.

The first outbreak of prosthetic endocarditis due to *Mycobacterium chimaera* infection was reported in 2015.⁶ This mycobacterium colonises the heater-cooler units used during extracorporeal circulation and becomes aerosolised in the operating theatre. This enables it to enter the surgical field, producing endocarditis and/or disseminated infections that can mimic or even be diagnosed as sarcoidosis, with a reported mortality of 50%. Although colonisation of these heating-cooling units has been shown to be widespread in all countries, the incidence of this infection is fortunately low, so experts believe that several circumstances must occur at the same time to cause infection in patients. The preventive measures taken so far have consisted in replacing the colonised heating-cooling units and performing regular microbiological controls. However, IE has a latency period of up to 5 years, so the appearance of new episodes cannot be ruled out.

The increased survival of patients with congenital heart disease has also increased the risk of IE in this patient group to the extent that it now far exceeds that of the general population.⁷ The two microorganisms most frequently involved in IE in this group of patients are oral streptococci of the *viridans* group (young patients who frequently present periodontal disease) and coagulase-negative staphylococci (associated with the presence of prosthetic material).⁸ Improved dental health, therefore, should be

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a priority in this group of patients, particularly before considering any type of reconstructive surgery. However, it is currently proving as difficult to reduce the incidence of IE in high-risk populations as it is in general patients. Therefore, every effort must be made to improve early diagnosis in the foregoing known risk groups. These patients are usually in close contact with specialised units, so it should be simple to teach them to identify the warning signs and get in contact immediately if needed.

A high percentage of patients with IE present some type of symptomatic peripheral embolism⁹ and those involving the central nervous system can have the greatest impact on prognosis in IE patients. These embolisms cause a high degree of morbidity and mortality and can delay valve repair surgery (if indicated) due to the risk of cerebral bleeding in patients with ischaemic lesions or the increased risk of intracranial haemorrhage associated with the need to use extracorporeal circulation to perform this operation.¹⁰ Similarly, because of the risk of bleeding, fibrinolysis is contraindicated in patients with ischaemic stroke caused by embolisms secondary to the detachment of clots. Mechanical thrombectomy, therefore, in centres with extensive experience in this technique, could improve survival and functional prognosis in these patients.¹¹

The anatomical complexity of patients at risk of IE, whether due to the presence of prosthetic material (intracardiac devices, valves, tubes and patches) or to anatomical variations in the case of uncorrected congenital heart defects, impairs the diagnostic sensitivity of ultrasound findings, which are currently one of the 2 major criteria for IE.¹² Other imaging tests, such as PET-CT (particularly PET/angio-CT) have recently been shown to improve the diagnostic capacity of traditional Duke criteria in patients with prosthetic material under various circumstances, thus minimising the number of possible endocarditis diagnoses.^{13,14} The ability to rule out or confirm infection at an early stage has a clear clinical benefit for the patient and an economic advantage for the health system. This technique can also detect secondary septic embolisms (considered a minor criterion of IE) and neoplasias (often at the incipient stage), which may be the portal of entry of IE. Nevertheless, although the European Society of Cardiology considers PET-CT findings to be a new major diagnostic criterion of IE,¹⁵ this technique is not yet available in all centres, is not performed according to a standard protocol in all hospitals, image quality varies and like any new technique, is associated with a certain learning curve for those professionals responsible for carrying it out.

The therapeutic challenges of IE are varied and include factors such as antibiotic therapy and surgical indications and techniques to achieve a definitive cure. From the point of view of antimicrobial treatment, there are very few randomised studies on which to base guideline recommendations, particularly in the case of IE caused by *S. aureus*. Although this is currently the most frequent cause of IE, the best (most effective and least toxic) antibiotic treatment remains unclear and in-hospital mortality remains high.¹⁶ Current therapeutic guidelines contain multiple options for staphylococcal endocarditis, all of them with a low level of scientific evidence.^{15,17,18} Some authors have called for a new approach: abandon the search for consensus, which may be difficult to achieve, and describe the different antibiotic regimens used in reference centres. This will show that mortality most probably depends on the existence of multidisciplinary teams in the management of this complex entity and not on following these guidelines.^{19,20} In any event, well-designed comparative studies are needed, particularly after the launch of new antibiotics such as ceftaroline and dalbavancin. Ceftaroline is a potent cephalosporin with activity against *S. aureus* (regardless of its sensitivity to methicillin) and is indicated in rescue therapies generally associated with other antibiotics with activity against this microorganism.²¹ Dalbavancin is a lipoglycopeptide with an extremely long half-life that permits administration once-weekly or even once-fortnightly, thus

enabling treatment to continue in the outpatient setting in some circumstances.²²

In the special case of IE caused by *M. chimaera*, the fact that all infections are caused by the same strain makes it, *a priori*, easier to establish an effective antibiotic combination. However, because of the low prevalence and severity of this entity, there is a pressing need for international collaboration to determine the best antimicrobial therapy.

Another challenging aspect of antibiotic treatment is establishing the optimal duration, since the standard 2–6 week regimens are only applicable to “traditional” native or prosthetic valve endocarditis. Clinical practice guidelines are unclear on the duration of antibiotic treatment in several circumstances, such as patients contraindicated for surgery and/or those with IE associated with aortic valve devices or with prosthetic valves, to give just a few examples. In these cases, the duration is based on the experience of the treating centre and can differ enormously among hospitals. In this context, new imaging techniques (angio-CT, PET-CT) could help establish the duration of antimicrobial treatment at an individual level.

There is also the possibility of concluding treatment with oral antibiotics. Although this is common in some centres, the practice is not standardised. The POET study published in 2013 hypothesised that oral antibiotic treatment can be both effective and safe in the case of left-sided valve IE.²³ Although the full results have yet to be published, there is already some evidence that certain patients with staphylococcal IE can be treated orally.²⁴

A fundamental, recurrent and unresolved aspect of IE involves surgery, and in particular, the best time to operate.²⁵ Moreover, widely used surgical risk classification systems (EuroSCORE I and II) do not show the real risk of patients with IE and this can distort decision making. This has led to the development of specific surgical risk scores for patients with IE.²⁶

In our setting, TAVI is indicated in patients with a high risk of mortality in open surgery. Therefore, valve replacement surgery, which is technically more complex, is not currently indicated in IE. However, the best surgical approach when the indications for TAVI are broadened (to include moderate or low risk patients) remains to be seen. IE patients with congenital heart defects present a major surgical challenge. These are often patients who will likely have undergone previous surgery and will probably require more interventions during their lifetime; therefore, the possibility of conservative treatment should always be considered in these cases. If surgery is unavoidable, it must be performed by highly specialised surgeons in hospitals capable of providing ventricular assistance if repair is suboptimal and a heart transplant is indicated. In this respect, there is already some evidence of successful outcomes in IE patients that have undergone heart transplantation when corrective heart surgery has been ruled out.²⁷ Finally, technical advances have made it possible for a growing number of IE patients, given their frailty, to benefit from percutaneous treatment of heart defects, once resolution of the infection has been confirmed. These procedures include periprosthetic leak closure and TAVI on valves severely impaired by IE.

Whatever the approach, we will only overcome all these challenges if we pay attention to epidemiological changes, anticipate problems and work together rigorously in multidisciplinary, patient-centred teams. It is important to bear in mind that, as in many other diseases, no single medical professional is capable of addressing all the problems arising from IE.²⁰

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