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REVIEW

Infective endocarditis in intravenous drug abusers: an update

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Abstract Infective endocarditis despite advances in diagnosis remains a common cause of hospitalization, with high morbidity and mortality rates. Through literature review it is possible to conclude that polymicrobial endocarditis occurs mainly in intravenous drug abusers with predominance in the right side of the heart, often with tricuspid valve involvement. This fact can be associated with the type of drug used by the patients; therefore, knowledge of the patient's history is critical for adjustment of the therapy. It is also important to emphasize that the most common combinations of organisms in polymicrobial infective endocarditis are: *Staphylococcus aureus*, *Streptococcus pneumonia* and *Pseudomonas aeruginosa*, as well as mixed cultures of *Candida* spp. and bacteria. A better understanding of the epidemiology and associated risk factors are required in order to develop an efficient therapy, although PE studies are difficult to perform due to the rarity of cases and lack of prospective cohorts.

Introduction

Infective endocarditis (IE) despite advances in diagnosis remains a usual cause of hospitalization, with high morbidity and mortality rates. According to the Guidelines on Prevention, Diagnosis and Treatment of Infective Endocarditis report [1], IE is defined as "an endovascular microbial infection of cardiovascular structures including endarteritis of the large intrathoracic vessels or of intracardiac foreign facing the bloodstream."

IE still is an important clinical problem that can lead to native valve endocarditis (NVE) and prosthetic valve endocarditis (PVE) with an annual incidence of approximately 1.7–6.2 cases per 100,000 patients [2]. PVE has an alarming mortality rate of 40–50 %, being more frequent in men than women (in a ratio of 2:1), and the occurrence gradually increases with age. The management of IE is a challenge because the usually proposed standard antibiotics often are not very efficient, which can be attributed to several factors, namely, allergic reactions, antibiotic toxicity due to prolonged therapy and increasing microbial resistance to antibiotics used as first-line therapeutic options [3]. In fact, this high tolerance to antimicrobial treatment is mainly due to the fact that infective microorganisms are generally in the biofilm form, i.e., as sessile communities of cells irreversibly attached to cardiac surfaces and enclosed in a protective matrix of exopolymeric products [4].

When the infecting organism of NVE is identified, the treatment of choice is expanded antibiotic therapy. Patients with PVE most of the time require surgery to replace the infected prosthesis, as medical treatment alone is generally insufficient. This failure of antimicrobial treatment is often related with biofilm formation on the surface of the prosthetic valve. Biofilms are up to 1000-fold more resistant than planktonic cells and are associated with numerous pathologies, such as PVE, normally correlated with a more deleterious prognosis than NVE. Amongst other causes, improper visualization of a collection of platelets, fibrin, microorganisms, and inflammatory cells—the so called "vegetation"—in PVE, in the transthoracic echocardiography, is responsible for the poor diagnosis. Even though NVE is significantly more recurrent than PVE [5], medical treatment for PVE is rarely successful [6, 7]. Nevertheless, since transoesophageal echocardiography

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was introduced into clinical practice, the diagnostic sensitivity and specificity for the detection of vegetations located on prosthetic valves has been improved [8].

IE is mainly caused by *Staphylococcus aureus*, *Pseudomonas aeruginosa*, streptococci, enterococci, *Staphylococcus epidermidis*, and the HACEK organisms (*Hemophilus parainfluenzae*, *Hemophilus aphrophilus*, *Actinobacillus* [*Hemophilus*] *actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella* species, and *Kingella* species) [9]. In the recent prospective study of Rostagno et al. [7], staphylococci were the more frequent IE etiological agents, in agreement with previous reports [10]. In fact, in a recent study, it was concluded that the strongest predictor of mortality in patients with IE was MRSA infection, followed by staphylococcal infection, especially in association with older age and/or with large vegetations [11]. According to Bouza et al. [12], nosocomial infection contributes to endocarditis in 22 % of the cases, with mortality greater than 50 %. Predominant pathogens are staphylococci and enterococci, often related to IVs or surgical procedures, and fewer than 50 % of patients had underlying structural heart disease. A particular risk group includes immunosuppressed patients with CVCs and those undergoing haemodialysis [13]. Coagulase-negative staphylococci (CNS) are the most common cause of PVE [14]. It is important to highlight that *Candida* and *Aspergillus* species cause the majority of fungal IE [15].

The diagnosis of IE is simple in patients with classic oslerian manifestations: bacteremia or fungemia, evidence of active valvulitis, peripheral emboli, and immunologic vascular phenomena. Nevertheless, if the characteristic peripheral stigmata is discrete or absent, during the acute phase of IE, particularly among IVDA patients with *S. aureus* and HACEK [9], and is not detected in time, the final outcome for the patient will be deleterious.

Despite improvements in health care, the incidence of IE has not decreased in recent decades and still persists with substantial morbidity and mortality related to this infection [13]. This apparent contradiction can be explained by the fact that there is a progressive development in risk factors: classic predisposing conditions, such as rheumatic heart disease (still not eradicated), and new IE risk factors such as IV drug use, sclerotic valve disease in elderly patients, use of prosthetic valves, and nosocomial disease. Recently identified pathogens, which are difficult to grow *in vitro*, e.g. *Bartonella* spp. and *Tropheryma whipplei*, were found in few patients, as well as resistant microorganisms to conventional antimicrobial therapy [16].

Polymicrobial endocarditis (PE) is a variant of IE, which occurs when the infection is carried out by more than one organism and, despite being uncommon, is often fatal, especially when the polymicrobial community includes *Candida* species.

Taking into consideration all the facts described previously, it is important to understand IE and PE pathogenesis to develop new strategies for their control, including new drugs and new prosthetic valve materials.

The main goal of this review is to summarize the current knowledge of IE and PE, especially associated with intravenous drug abuse.

Infective endocarditis of intravenous drug abusers—IVDA-IE

IE continues to be a preeminent health hazard among IVDAs. Although the exact incidence of IE in IVDAs is still unknown, an increase in the number of hospitalization of IVDAs with IE is noticed [17]. IE related to IVDAs occurs more recurrently in IVDAs who are HIV positive, particularly those with advanced immunosuppression [18, 19]. *S. aureus* is responsible for most of the IE cases among IVDAs [20]. IVDAs IE etiology is changing, comprising other staphylococci and *Pseudomonas*, as well as pathogenic fungi [21, 22]. The most commonly isolated fungi are *C. albicans* (24 %), and non-*Candida albicans* accounts for 24 % of the fungal isolates [21]. Also, due to IVDAs high-risk behaviors, they are subjected to needle-borne infections by organisms that are usually non-pathogenic. Owing to the habit of cleaning their needles with saliva and using the saliva to dissolve the drug, IVDAs are therefore prone to infection from normal oropharyngeal flora microorganisms (e.g., *Haemophilus parainfluenzae*, *Eikenella corrodens*, and *Streptococcus milleri*) [23].

Right-sided IE accounts for 5–10 % of cases of IE [19], and it may occur in patients with a permanent pacemaker, implantable cardioverter defibrillator, CVC, or congenital heart disease, although this situation is more common in IVDAs [24]. Among the pathophysiological hypotheses that support the incidence of right-sided IE in IVDAs are abnormalities on the immune system, contaminated drug solutions and reduced injection hygiene [25].

IVDA-IE patients have a high recurrence rate of right-sided IE and most of these patients develop severe sepsis, congestive heart failure, embolization, or other complications that lead to organ failure and to intensive care unit admission (ICU), as well as to surgery [26]. It must be noted that a new pattern of IE in IVDAs is rising, characterized by infections on the left side of the heart with a severe clinical course, and requiring surgery in the active phase [27]. Left-sided endocarditis, in comparison to right, and polymicrobial compared to single organism, are thus risk factors for an increase in morbidity and mortality in IVDAs with IE [28]. A preponderance of tricuspid valve involvement seems to exist, but the reason is still unknown. One of the hypotheses proposed is that the physical discharge of impurities contained in injected drugs or adulterants can lead to endothelial injuring [23]. Whilst the

tricuspid valve is the usual site of infection in IVDAs, pulmonary and Eustachian valve infection may also be observed, with left-sided IE being common in this group [27, 29].

Polymicrobial multivalve endocarditis infection on the biventricular valve is uncommon; it is also generally described in patients with prolonged IV infusion, in patients with congenital heart disease with shunt, and particularly in IVDAs [26, 30, 31]. It is also noteworthy that the greater number of IE identified by echocardiography occurs on a single valve; on two valves is less common; and on triple or quadruple-valves has barely been addressed. Nevertheless, multivalve endocarditis is an independent clinical entity which has higher risks for the patient and generally with a fatal outcome [30]. Thus, a polymicrobial multivalve IE, although rare, represents an extremely elevated risk of high morbidity as well as mortality.

According to Levine et al. [32], the pathogens and the valves infected among patients with IVDA-IE may depend on the type of illicit drug used, as they noted that the use of certain drugs was associated with particular pathologies. More recently, Jain et al. [33] demonstrated that tricuspid valve endocarditis occurs more frequently in heroin users than in other IVDAS. In the study of Saydain et al. [34], all patients were heroin users, and the majority had right-sided endocarditis; however, to establish the use of heroin as a key factor for right-sided endocarditis it is necessary to carry out further studies in a larger cohort of patients.

Saydain et al. [34] reported the outcome in a retrospective study of 33 patients with IVDA-IE admitted to an ICU. Accordingly, *S. aureus* was the more frequent pathogen, as it was found in 31 patients (94 %), with 16 (52 %) being methicillin resistant (MRSA). PE was detected in 5 (15 %) patients with four having *S. aureus* + *Streptococcus* or *S. epidermidis* or *Acinetobacter* or *Candida*. One patient had *Staphylococcus hominis* + *Corynebacterium* and another patient had *Streptococcus viridians*. Initial empiric antibiotic therapy was administrated in 29 patients and considered appropriate based on the activity against the specific microorganisms. MRSA are, thus, well-known nosocomial pathogens with high levels of incidence in IE patients. Nevertheless, community-associated methicillin resistant *Staphylococcus aureus* (CA-MRSA) have been increasingly reported recently and have become emerging pathogens of IE in adults and children [35].

The initial selection of empiric antimicrobial therapy should rely upon the suspicion of the infecting microorganism, type of drug and solvent used by the addict, and the infection location [36]. In right-sided NVE, *S. aureus* must always be taken into account, especially in IVDAs or venous catheter-related infection. Initially, therapy included either penicillinase-resistant penicillins or vancomycin, depending on the local prevalence of MRSA [32, 37]. In the case of a patient being a pentazocine-tripelennamine addict, infection with *P. aeruginosa* is usually correlated, due to contamination during drug preparation for self-administration, and an anti-*Pseudomonas* agent must be administered [38]. If an IVDA is addicted to brown heroin dissolved in lemon juice, *Candida* spp. (not *C. albicans*) should be considered and antifungal treatment given [39]. In the case of IVDAs with critical valve lesions right and/or left-sided involvement, antibiotic treatment should comprise protection against streptococci and enterococci [36]. Once the causative organisms have been isolated and identified therapy should be adjusted accordingly.

Polymicrobial endocarditis related to intravenous drug abusers—IVDA-PE

Polymicrobial endocarditis is increasing, thus posing a huge challenge to the medical community over the past decade, as its outcome is often fatal [40]. The infection occurs primarily and with increasing frequency in IVDAs with IE rather than in non-IVDAs [26, 32]. It remains a rare and poorly understood cardiac complication, with a predominance of tricuspid valve involvement, but few data exist on IVDA-PE. Nevertheless, in recent years, rates of PE among IVDAs have increased, leaving a growing number of patients at risk with health complications [41].

Besides IV drug use, fundamental cardiac structural abnormalities, prosthetic heart valves, and CVCs are among the major risk factors for PE [42], but with low incidence. Although, with the increasing broader employment of CVCs and the current progress in medical devices, an increase in PE incidence in the coming years is expected, which is already starting to be noted [36, 43].

The most common combinations of organisms in PE include *S. aureus* and *Streptococcus pneumoniae* followed by *S. aureus* and *Pseudomonas aeruginosa*. *Candida parapsilosis* endocarditis carries a mortality rate of 45 %, and each infection with *Candida* or *Pseudomonas* per se carries a very high mortality rate approaching 85 % and 80 %, respectively [41]. PE has a low survival rate, and patients with this type of endocarditis need to be identified as soon as possible and treated aggressively, with the appropriate antibiotics, if available, or surgery [44]. Therefore, combined therapy, medical and surgical, represents the standard of care, but long-term suppressive therapy duration in cases of polymicrobial fungal endocarditis is still discussed.

Polymicrobial endocarditis also sustains a very high mortality rate (greater than 30 %) and an uncommonly large number of patients (more than 50 %) need heart surgery either to control the infection or to repair cardiac failings resulting from the PE infection. According to Saravolatz et al. [45], the prognosis relies on the species rather than the number of microorganisms isolated or antimicrobial and surgical therapy.

In 1991, Adler et al. [46] reported the first case of an IVDA with a tricuspid valve endocarditis involving seven pathogens (*Eikenella corrodens*, *Streptococcus intermedius*, *Corynebacterium* spp., *Hemophilus parainfluenza*, Bacteroids sp., *Fusobacterium necrophorum* and *Eubacterium lentum*). Besides antimicrobial therapy, the patient required surgery for the treatment of tricuspid valve endocarditis. In this study it was demonstrated that the organism responsible for infection may be neglected due to the presence of fastidious pathogens in blood culture tests. Therefore, not all the pathogens might be identified, with consequent treatment failure and hemodynamic decompensation. This fact suggests that, in many cases, PE may be not detected due to the presence of such fastidious pathogens. If PE it is not properly diagnosed, it will often result in the application of an inadequate therapy, which will not be effective for eradication of the infection.

Raucher et al. [47] reported cases of PE in IVDAs with *Haemophilus parainfluenzae* and other organisms of the normal oral flora, such as *S. aureus* and commensal oral streptococcal species. Oh et al. [31] presented a case of PE caused by *Actinomyces odontolytica*, *Veillonella species*, and *Prevotella melaninogenica* in a patient with a history of injection drug abuse. It should be noted that the bacteria implicated in this patient's PE are all anaerobes primarily found in the human oral cavity. This means that the habit of this patient of licking the needle to estimate the strength of the injection exposed him to infection by these oral microbes. The patient was successfully treated with a 6-week course of penicillin G and metronidazole. This report points out very clearly that contamination from non-skin flora and PE should be considered in an IVDA with non-sterile injection drug use practices. Indeed, another work identifies the same organisms, as a part of a group of microorganisms that are particularly profuse in saliva and on the dorsal and lateral surfaces of the tongue [48]. Therefore, the patient's history and the absence of other microorganisms in blood culture tests confirm that these bacteria were the probable cause of the PE in that particular patient. This highlights how important it is to be aware of the detailed history of the patients injection drug use habits, because it may reveal a risk factor for more abnormal infections and thus enables modification or adjustment of the therapy of PE [31]. In another case [49], a successful operative case of tricuspid infective endocarditis in an IV drug user was described, but despite IV drug use cessation, there were additional recurrences. Six different microorganisms with multiple portals of entry were identified, including one episode of fungal endocarditis. This was the first case of recurrent IE involving *Candida dubliniensis* in an HIV-negative patient [49]. The achieved success in this case must be pointed out, given that *Candida* IE or PE is uncommon but often fatal [50] and, despite vigorous antifungal and surgical therapy, mortality approaches 80 % in some cases and hence, a better understanding of this infection is needed [21, 51]. Taking into account that an effective treatment of a bacterial endocarditis requires the use of high doses of antibiotics over extended periods of time, and frequently via the IV route, it is thus expected that, in some cases, *Candida* opportunistic infection will complicate bacterial endocarditis, becoming a serious PE, due to *Candida* virulence.

Despite the advances in antimicrobial therapy and the development of better diagnostic and surgical techniques, PE is still a fatal infection. Therefore, an early diagnosis of infective endocarditis is critical for the final outcome. The use of new clinical criteria, emphasizing echocardiography, is a positive guide for the practitioner correct diagnosis.

Conclusion

The frequency of polymicrobial endocarditis is rising, with significant morbidity and mortality rates and economic costs, thus it is critical to widen the research on endocarditis. This in turn will provide more information on the pathophysiology of the disease, as well as novel and better treatment and prophylactic strategies. These novel insights should help redefine preventive and therapeutic strategies against PE. Infection by staphylococci and streptococci is already being analyzed at the molecular level and new ideas for antimicrobial agents and prosthetic valve materials have been developed in recent years.

A better understanding of the epidemiology and associated risk factors of PE is required to develop more efficient therapies for PE. Although, the factors associated with this disease are poorly defined, essentially due to the rarity of PE as a single institution. Therefore, PE studies are mostly derived from single-site case studies and case reports.

In summary from this review it is possible to firmly conclude that:

- PE is still poorly understood and sustains a very high mortality.
- PE occurs mainly on IVDAs.
- A predominance in the right side of the heart, often with tricuspid valve involvement, is noticed.
- A meticulous knowledge of the patient's history is critical for the adjustment of PE therapy, medical and/or surgical.
- The most common combinations of organisms in PE are: *Staphylococcus aureus* and Streptococcus *pneumonia*, and *Staphylococcus aureus* and *Pseudomonas aeruginosa*; and *Candida* spp. with bacteria.
- In IVDA-PE, the organisms are often anaerobes primarily found in the human oral cavity.

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