REVIEW

Infective endocarditis today [version 1; referees: 1 not approved]

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Abstract

Endocarditis is an infectious disease caused by numerous microorganisms, many of which habitually colonize the oral cavity and skin. Various bacteria and bacterial factors influence the duration of bacteremia and the possible colonization of cardiac valves. If not recognized and treated early, the disease may have serious consequences until death: despite the possibility of setting up targeted antibiotic therapy, it may occur in 30% of cases. This event is related to sepsis that develops in these patients and can result in cellular functional alterations in many districts, resulting in multi-organ failure (MOF) status.

This paper is aimed to present an overview of this condition, based on the author’s own clinical experience and literature review.

Open Peer Review

Referee Status: ✗

	Invited Referees 1
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Introduction

From an epidemiological point of view, the incidence of Infective Endocarditis (IE) varies considerably, depending on the socio-economic conditions of the various countries, with significantly lower rates in industrialized countries (USA 1.6–6 cases per 100,000 people per year). In Italy, according to recent surveys, the rate of incidence is between 1.7 and 6.2 per 100,000 inhabitants, with points of 3.6/100,000 inhabitants in the city of Turin and 4–5% in Veneto and Friuli Venezia Giulia Giulia. Most studies show that the male is most affected, with an M/F ratio of about 3–4: 1, probably due to the higher prevalence of bicuspid aorta in the male. Another predisposing factor is age. All age groups may be potentially affected but with different clinical picture between young immunosupressed subjects and older than 65 years have an incidence of about 9 times that of subjects with lower age[1–4].

In the etiopathogenesis of the disease, some factors are linked to both the host and the responsible microorganism interacting with each other, which are: 1) the presence of predisposing conditions, 2) the presence of conditions capable of producing bacteriemia and 3) that the microorganisms involved are characterized by the ability to adhere and proliferate on the cardiac endothelium. In this context, mainly with regard to the predisposing conditions, mainly valvular diseases such as insufficiency and stenosis of the aortic and mitral valve (endocarditis site in 50% of cases) and the presence of valvular prostheses (12–17% of cases). Other predisposing conditions are congenital heart disease, such as interventional septal defects, Botallo's arterial channel persistence (4–18% of cases) and the use of injecting drugs (up to 30% in some cases). Causes of bacteremia can also be infectious processes in anatomic sites other than cardiovascular, as well as instrumental procedures such as bronchoscopy, colonoscopy, gastroscopy, cystoscopy, urethral and bladder catheterisation, urethrotomy, prostatectomy, hemodialysis, uterine endoscopy, and also abortion and/or delivery.

In the oral cavity, as well as the orotracheal intubation maneuvers, a source of bacteria that can give rise to endocarditis can be caused by dental infections and odontostomatologic maneuvers of treatment and prophylaxis or even poor oral hygiene, resulting in the onset of infectious diseases in periodontal tissues[1–4].

Pathophysiology and clinical features

The main host factors involved in the pathogenesis of infective endocarditis are the valvular surfaces, leukocytes and platelets. The thrombus is formed on the valve surfaces and along the sutures in the valve prostheses. This thrombus is partly composed of platelet aggregates by bacterial induction and at the same time releases microbicidal proteins (contained in the d-granules), thus having a dual role in facilitating and limiting the progression of the disease. Leukocytes, via cytokines and complement, are responsible for immunopathological manifestations of infectious endocarditis, represented by hypergammaglobulinemia, both antigen-specific and linked to polyclonal activation of B cells (which can block the opsonizing IgG response, accelerate the microvascular damage or stimulation of phagocytosis), vasculitis caused by immune circulating complexes and reduction of complement for its consumption, as well as clinical syndromes such as deposition of circulating immune complex and complement, Osler nodules, etc.[5].

The diagnosis of infective endocarditis is based on characteristic anatomopathological criteria such as the echocardiographic demonstration of pathological lesions (presence of vegetations or intracardiac abscesses confirmed by histological studies showing active endocarditis) and responsible microorganisms (proven presence by cultures or histological studies of *in situ* vegetation, or embolized vegetation or intracardiac abscess)[6].

The experienced clinician can be oriented to the diagnosis by clinical and anamnestic elements. Some of these can lead to well-founded suspicion, as clinical features such as high fever (> 38C°), general condition (asthenia, myalgia), recent onset of cardiac murmur and signs of systemic embolization. Moreover, information can be derived from the patient's history about the execution of recent endoscopic instrumental maneuvers (cystoscopy, gastroscopy, colonoscopy, hysteroscopy) or invasive maneuvers (catheterization), especially in the elderly, recent surgery (especially valvular prosthesis), recent dental interventions (dental avulsion, periodontal surgery, endodontic treatment, dental implant surgery). It is also very relevant to the patient anamnesis if they are, or have been, a drug addict with use of injectable drugs[5,7].

Among the less significant indices, the presence of a few days of febrile (around 37°C) should be mentioned, albeit associated with good systemic conditions. In addition, considering that bacterial endocarditis, if not diagnosed and treated quickly, may be burdened by poor prognosis, it is important to point out that, regardless of clinical/anamnestic suspicion, it should be considered and investigated (by serial emoculture and trans-esophageal echocardiogram), and above all, it should be excluded when the cause of the fever is not quickly detected. In addition, if a septic spot is detected elsewhere, it is advisable, to investigate the presence or absence of endocarditis, as this may also manifest itself as a complication.

The interval between the onset of infection and the onset of early symptoms is generally short (two weeks in most cases). However, it can be months, as in cases of infections caused by uncommon germs, or in the case of endocarditis on valve prostheses.

General symptomatology usually is hyperpyretis (febrile in most cases, high fever during septic shock), anorexia, asthenia, myalgia. Other symptoms may be related to so-called "local" effects: valve lesion/destruction with severe hemodynamic consequences or systemic embolization phenomena[8].

The main clinical signs are: the classic Osler nodules, small nodules purple in color at the fingertips, pathognomic of endocarditis and to be attributed to probably embolic phenomena, cardiac murmurs (which may be indicative of new appearance or aggravation of previous heart disease), petechiae, consisting of small "haemorrhagic" spots often located at the conjunctiva of the oral cavity mucosa (related to microembolic phenomena and

increased capillary permeability), and also present at the retinal level (Roth stains, red spots with a light center coming from hemorrhagic and inflammatory phenomena), as well as clubbing of the fingers.

Heart complications are related to: 1) dysfunction of the native valve or valve prosthesis, resulting in acute valve failure resulting in a clinical picture of severe hemodynamic impairment, associated with 2) heart failure (found more frequently in aortic valve infection) and burdened by an unfavorable prognosis; or 3) myocardial infarction due to cardiac abscesses (in 30% of native endocarditis and 50% of prosthesis), often complicated by atrio-ventricular block[5,8].

The prognosis of infective endocarditis, in various clinical forms, is progressively worsening in the following order: acute, staphylococcal, on valvular prosthesis, mycotic, refractory to medical treatment[5,8]

Microbiological aspects

Any microorganism can potentially cause infective endocarditis, but infection is more commonly determined by specific microorganisms, particularly streptococci and staphylococci that show tropism for valve structures. They have two properties: 1) frequent association with bacteriemia, transient or persistent, and 2) ability to adhere to the surface of valves or thrombi due to the production of certain substances. Recent scientific works, however, indicates that oral microorganisms (especially *Streptococcus spp.)* are seldom found in bacterial endocarditis, while others such as *S. aureus* and enterococci are more frequently involved. The main causal factors of bacteremia, which usually originate from the skin or oral cavity, are dental brushing or gold-dental, genitourinary and gastrointestinal procedures, poor oral hygiene and dental sepsis, but also cellulitis and soft tissue infections, injecting drugs, intravascular catheterization, cardiac surgery (including pace-maker placement)[9]. Responsible microorganisms are constituted, in addition to bacteria of the genus *Streptococcus spp.* and *Staphilococcus spp*., also from rickettsia, chlamydia, fungi, *C. burneti*. Most infectious endocarditis on native valves or on cardiac valve prostheses are caused by streptococci. Generally, the responsible strain belongs to the group of virulent streptococci (*S. sanguinis, oralis, salivarius, mutans*) normally present in oropharynx and gastrointestinal tract. These are non-virulent pathogenic bacteria, which can cause transient bacteriemia and adherence to the endocardial system, but are extremely widespread in the population and in the case of very frequent oral pathologies such as caries[10].

In the elderly population, in the lungs, the presence of *Streptococcus bovis*, a microorganism associated with polyps and colon carcinoma, or enterococci (Group D streptococci as *Enterococcus faecalis*) is commonly found in the gastrointestinal tract and can cause subacute infections after gastrointestinal clinical procedures. These bacteria are often selected by the use of broad spectrum antibiotics and are also found in the genitourinary tract and in young women, as a result of obstetric procedures, subacute infections may result. It is much less common to find, as responsible of IE, other streptococci such as *S. pneumoniae*. In the various literature available, Staphylococci are responsible for one third of endocarditis on naive valves and half of endocarditis on prosthetic valves.

Staphilococcus aureus, a highly virulent positive coagulase bacterium, causes florid vegetation of the valve flaps causing their destruction, peripheral abscesses, severe dissected and metastatic infections, and is the main cause of acute endocarditis and endocarditis in drug addicts, while coagulasi negative *S. epidermidis* is the main cause of early endocarditis on valve prostheses. This microorganism is present on the skin and can contaminate catheter and vascular access, used in the post-operative course in Cardiac Surgery Units.

Gram-negative bacteria are rarely involved as IE responsible of, but are increasingly recognized as a cause of endocarditis in drug addicts and cardiac valve prostheses, Gram-negative Bacillus species belonging to the genera *Pseudomonas, Brucella, N. gonorreae* and those that grow slowly of the so-called HACEK group (*Hemophilus, Actinobacillus, Cardiobacterium, Eikenella, Kingella*).

Statistically, 5–20% of endocarditis has negative emoculture, usually due to partial antibiotic treatments, fungal endocarditis, or to infections sustained by mutated streptococci, *C. burnetti, Clami-dia, Bartonella, Legionella*[11].

In view of the variety of microbial species involved in the genesis of IE, it is necessary to set up targeted antibiotic therapy, which is only possible if properly cultivated. This selective choice of the drug obviously aims to avoid ineffective antibiotic therapies. Indeed, as noted above, endocarditis can (though rarely) be sustained by viruses or fungi on which antibiotics do not perform any action. In fact, in the case of the *Candida* and *Aspergillus* genera, that are responsible for a fair amount of endocarditis on native and prosthetic endocarditis and endocarditis in drug addicts. They determine the formation of large vegetations, phenomena of embolization and peripheral abscesses, whose therapy is difficult and often requires surgical treatment[9,11].

Prophylaxis

Despite the possibility of performing microbiological and instrumental elective investigations and the wide availability of drugs capable of resolving pathological conditions, IE is still associated with a high mortality rate. Therefore, in addition to diagnosis and early treatment of the disease, prevention can be implemented through the application of correct hygienic-behavioral norms and by pharmacological prophylaxis protocols. In this respect, we note that, in the literature and the evidence of clinical practice, when a history of probable cause is found among the most frequent statistical-epidemiological forms, besides the forms correlated to toxic-dependencies, IE are of primary relevance related to dental procedures in general and/or oral surgery, and they have a much higher incidence than the other types of instrumental maneuvers, and endoscopic procedures in general.

Among the causes of IE, for which prevention and control are more important, one can also include: care in insertion and management of vascular access, maintenance of skin hygiene in cardiac surgery patients, and immediate removal of infected catheters, in order to prevent infectious complications, septic embolisms from "biofilm". However, as mentioned above, oral and dental hygiene plays a major role in IE prevention.

In this regard too, in patients at risk of developing endocarditis and who are undergoing oral surgery and any dental procedure, prophylactic antibiotic therapy is desirable[12].

Relations between oral hygiene conditions, dental therapeutic procedures and infective endocarditis have been studied by several cardiological scientific societies that have put forward many guidelines for pharmacological prophylaxis in subjects at risk. In 1955, the AHA (American Heart Association) recommended the antibiotic prophylaxis of bacterial endocarditis during dental procedures. Since then, despite the lack of scientific evidence of its effective preventive efficacy, antibiotic-prophylactic prescription has become common practice in all dental procedures considered at risk of infectious sequelae[13–15].

The list of subjects at risk has undergone major changes in the light of the evolution of scientific results. In 2007 guidelines for antibiotic prophylaxis were been revised and, according to the current guidelines proposed by the AHA and the British Society for Antimicrobial Chemotherapy (BSAC) and also implemented by AIFA (Italian Drugs Agency), there are four conditions that make antibiotic prophylaxis necessary before a dental procedure of any kind : 1) the presence of valve prostheses, 2) previous endocarditis, 3) previous pulmonary or systemic shunt interventions, and 4) cardiac transplant patients developing cardiac valvulopathy[16–21]. This proposal was confirmed by the European Society of Cardiology (ESC) in 2009, and later in 2015, producing a summary card for General Practice. Compared to the previous guidelines, dating back to 1997, the number of heart disease considered at risk of endocarditis was reduced, once divided into high, medium and low risk. Therefore, at present, the aforementioned cardiac conditions simply come under the only category of "heart disease with an endocarditis risk". A study was conducted to assess the doubts raised by a 2004 Cochrane review on the real effectiveness of antibiotic prophylaxis and this research would show that to prevent a few cases of infectious IE (2.7% of the population studied) the balance of the risk/benefit ratio should definitely be on the risk[20–22].

It has also been underlined that there is a need for high levels of oral hygiene in patients undergoing cardiac surgery to be maintained over time with regular oral hygiene sessions, during which a further precaution, and not only in subjects known to be at risk, is provided by the use of oral antimicrobials (liquid collutants or antibiotic gels) prior to any oral cavity manipulation that will help to reduce potentially pathogenic microbial levels.

However, it should be noted that some studies do not recognize the usefulness of antibiotic-prophylaxis in those at risk of having to undergo dental treatments of any kind, such as the aforementioned metanalysis conducted by the Cochrane Group.

Over the years numerous antibiotic-prophylaxis protocols have been proposed for dental patients, including numerous antibiotics (Penicillin, Vancomycin, Ampicillin, Gentamicin, Azithromycin) and cephalosporins (Cefalexin, Cefadroxil), but currently the most widely used antibiotic is Amoxicillin (for subjects with history of allergy to penicillin, alternative molecules may be Clindamycin or Claritromycin) to be administered orally 60 minutes before the onset of surgery, with possible extension to 24 hours in particular cases. In the case of renal failure, the single dose administration of the drug does not need to be modified.

Conclusions

Infective endocarditis (IE) is a cardiac pathology of bacterial, mycotic or more rarely viral origin, developing on the surfaces of the endocardium or heart valves. Predisposing conditions are congenital malformations of the heart or valvular acquired alterations, as well as the presence of a valvular prosthesis[5]. Still now IE causes death in 20–30% of patients.

The microorganisms involved in the etiology and pathogenesis of the damage of such infection determine the formation of the endocardic vegetations typical of this condition. Such lesions can be located on the valvular or the parietal endocardium and sometimes on the endothelium of a great artery. Despite the elevated standards of instrumental investigations and therapeutic protocols, IE represents a disease of wide interest, scientifically and socially, due to its high rate of incidence, morbility and mortality, usually due to MOF[23].

It is therefore essential to evaluate laboratory parameters, both traditional and innovative, to prevent these consequences through targeted antibiotic therapy[24].

The opportunity to implement antibiotic-prophylaxis in dental patients still remains a "*vexata quaestio*" and the analysis of literature demonstrates how the available data are somewhat controversial. Its application in everyday practice is based on other than efficacy tests: simply empirical or "traditional" tests[19–21].

Common dental, professional and non-dental procedures, as well as many oral surgery maneuvers, can result in bacteria that are sustained by particularly aggressive and resistant bacteria. It should also not be forgotten that, following such maneuvers, it is possible to cause the penetration into the bloodstream of other microorganisms commonly present in the oral cavity (viruses and fungi), which are particularly difficult to identify and treat. Considerable progress has been made in the prevention of infectious diseases and cross-contamination in the urological, gynecological, gastrointestinal and stomatological instrumental procedures. However, in the latter procedure in particuler, from the ablation of the tartar to the oral cancer surgery, this still represents an important risk factor for the development of IE in predisposed patients. However, the actual responsibility of oral bacterial flora in the

determinism of distant infections is still unclear, which is attempted to prevent antibiotic-prophylaxis during dental procedures[9,10,12,20]. This is the reason for the importance of prophylaxis in dental risk patients, which can be obtained, on the one hand, with careful patient evaluation and rational use of antibiotics and, on the other hand, with scrupulous and professional oral hygiene, associated with the main classical foundament of clinical practice, well known from antiquity: the empathy with patients[25].

In conclusion, we can state that it is very important therefore, in order to limit the risks to the health of the patient and to avoid possible legal consequences of medical treatment, the collection of a thorough history of oral and/or dental history and continuous updating of the international guidelines, considering increased risk of cardiac complications in diabetic patients[26]. In 20% of IE cases apparently there is no predisposing factor, however, the role of molecules contained in cigarette smoke and liquids used for electronic cigarettes also cannot be excluded[27].

Competing interests

No competing interests were disclosed.

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1. Is the topic of the review discussed comprehensively in the context of the current literature? No

Most writers would accept that the current literature reflects work published over the past 10 years. The majority of citations in this article are significantly older than this and largely relate to the field of dentistry rather than clinical medicine. I do not feel that the article reflects current practice, nor does it explore current controversies in the field.

There is no mention of the Duke Criteria or the modified update for the diagnosis of infective endocarditis. Diagnosis is usually made without histological confirmation at the time of surgery, which is reflected in the Duke Major criteria. Most would agree that the pathological criteria of endocarditis are largely historical.

In 2015 new imaging modalities were introduced into the ESC guideline to aid diagnosis including PET/SPECT, CT and imaging for distal embolic events. The article makes no reference to any imaging outside of TOE. Both the AHA and ESC would also recommend TTE rather than TOE as the first-line test for suspected disease.

In terms of antibiotic prophylaxis, the author does highlight that this is a controversial area. However, it might be helpful to reference current UK guidelines that do not recommend any prophylaxis, which has been the case since 2008. Potentially as a result of this, UK endocarditis rates are now rising.

The article does not reference or highlight the shift in microbiology from Streptococcus to staphylococcus or why this might be.

There is no mention of newer percutaneous valves and the signal regarding potential higher endocarditis rates.

2. Are all factual statements correct and adequately supported by citations? No

There are frequent factual statements made throughout the article that are not referenced. These need to be addressed prior to publication. At present the article reads like an opinion piece.

For example.

“endocarditis site in 50% of cases”
“12-15% of cases”
“injecting drugs (up to 30% in some cases)”
“oral microorganisms (especially Streptococcus app.) are seldom found in bacterial endocarditis”
‘Statistically 5-20% of endocarditis has negative emoculture”

3. Is the review written in accessible language? Partly

There are a number of esoteric terms used in the article that are not commonly used and make it challenging to read:

Emoculture
Anatomopathological
Odontostomatologic
Asthenia
Anamnesis
Hyperpyretis

The structure of some sentences is confusing:

“All age groups may be potentially affected but with different clinical picture between young immunosupressed subjects and older than 65 years have an incidence of about 9 times that of subjects with lower age”

“In the elderly population, in the lungs, the presence of Streptococcus bovis, a microorganism associated with polyps and colon carcinoma, or enterococci (Group D streptococci as Enterococcus faecalis) is commonly found in the gastrointestinal tract and can cause subacute infections after gastrointestinal clinical procedures”

“Despite the possibility of performing microbiological and instrumental elective investigations and the wide availability of drugs capable of resolving pathological conditions, IE is still associated with a high mortality rate”

“It’s application in everyday practice is based on other than efficacy tests: simply empirical or traditional tests”

“which is attempted to prevent antibiotic-prophylaxis during dental procedures”

4. Are the conclusions drawn appropriate in the context of the current research literature? Partly

No mention of more current risk factors for endocarditis: dialysis, immunosuppression, implantable cardiac devices or indwelling venous catheters. Agreed that mortality remains high. However, might be nice to discuss why this could be?

The reference to MOF in the second paragraph of the conclusion is rather confusing. It has not been mentioned in the article, the acronym is not described and I am unsure that mortality in endocarditis is “usually” due to it.

Agreed that antibiotic prophylaxis remains controversial.

The reference to diabetic patients at the end of the article comes out of the blue. Diabetes is a risk factor for endocarditis, but it is not highlighted anywhere else in the article. This needs to be introduced earlier.

The throw-away statement regarding cigarette smoke and electronic cigarettes is also confusing. It bears no relation to the article and seems an odd thing to conclude what is quite a traditional article on endocarditis.

Summary

All factual statements need to be referenced, ideally with articles <10 years old to ensure they reflect the current literature.

Clean up some sentences and try to move away from esoteric terms to make the article easier to read.

The second and last paragraphs of the conclusion need to be tightened up. At present they do not bear any relation to the overall article.

Is the topic of the review discussed comprehensively in the context of the current literature?
No

Are all factual statements correct and adequately supported by citations?
No

Is the review written in accessible language?
Partly

Are the conclusions drawn appropriate in the context of the current research literature?
Partly

Competing Interests: No competing interests were disclosed.

We have read this submission. We believe that we have an appropriate level of expertise to state that we do not consider it to be of an acceptable scientific standard, for reasons outlined above.