REVIEW ARTICLE

Historical aspects of infective endocarditis

Max Grinberg[1], Maria Cecilia Solimene[2]

[1] Director of the Clinical Unit of Valvular Heart Diseases, InCor, São Paulo, SP

[2] Professor, Faculdade de Medicina ,Universidade de São Paulo; Assistant Physician of the Unit of Valvular Heart Diseases of InCor, Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, São Paulo, SP

Summary

Infective endocarditis was a fatal disease three generations ago. Temporal evolution of knowledge made possible important advances in diagnostic techniques, specially in echocardiography, the possibility of cardiac surgery during the active infeccious process and new guidelines for antibiotic prophylaxis before interventional procedures. Nowadays infective endocarditis is curable. In this review we describe historical aspects of endocarditis since Osler´s observations in the 19th century until the change from a "clinically possible" to a "clinically definite" disease.

Keywords: Endocarditis, bacterial; cultural characteristics; outcome assessment (health care).

Study conducted at Instituto do Coração (InCor) do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, São Paulo, SP

Submitted on: 01/20/2010
Approved on: 01/25/2011

Correspondence to:
Max Grinberg
Av. Dr. Eneas de Carvalho Aguiar,
44 -Bloco II Cerqueira Cesar
São Paulo - SP
CEP: 05403-000
grinberg@incor.usp.br

Conflicts of interest: None.

Introduction

" The infective endocarditis increases the physician's interest in the development of an infectious process".

William Bart Osler, 1893

Looking at Medicine through the infinity of Time. To employ guiding principles represented by the "good practices of now". To reinforce the benefits of the past and prevent the repetition of wrongdoing. To preserve the memory of the winding advances in the frontier of knowledge. To appreciate the impact of technological innovation on the quality of human life. To reveal the mutability of the ethical meaning of negligence and imprudence. Hence, it is useful to know the history of the knowledge of a disease.

Infective endocarditis was 100% fatal until three generations past – thus, to our great-grandparents. Research and clinical observations motivated by restlessness, creativity and collaboration supported the diagnostic and therapeutic progress in the second half of the 20th century that granted rapid applicability to the evidence on the pathogeny slowly accumulated throughout the preceding centuries. The necropsy pathognomonic vegetation became visible *in vivo*, showing how much the art of putting into practice the available scientific information is asymmetric in Time.

What can be remarkable, deserving attention in the history of infective endocarditis? Which steps contributed to reveal the unveiled of the clinical manifestation and the disease control? How did the information connections that were the basis of the current knowledge occur?

In the confluence of the anatomopathological view of the 18th and 19th centuries with the subsequent acknowledgement of germs, there were occasional reformulations in the disease concept, with different views in certain countries.

The clinical and pathogenic pieces fitted after some comings and goings. It was necessary to carry out adaptations in the current practice to construct a nosological identity that would gather the multiplicity of clinical expressions based on observed abnormalities. A crucial question was how much a clinical sign meant a disease and to what extent inflammations in distinctive tissues could share the same symptoms. Infective endocarditis contributed very much to clarify the biopsychosocial bases of current Medicine.

Pioneering aspects[1,2]

The disclosure of infective endocarditis is contemporary to the discovery of Brazil. In the beginning of the Modern Age, the renowned physicians were humanists, highly esteemed literate men and used human dissection as the means to acquire new information on organs that could cause the clinical manifestations that were carefully written down, waiting for the spontaneous course of evolution of the intractable disease.

Jean François Fernel (1497-1558) was a French physician, alias the "modern Galen", who cared for Henry II and queen Catherine de Medicis, who is also the astronomer-eponym of the lunar crater Fernelius, and became a prominent figure in history for having demonstrated a high synthesis capacity on bedside observations. He made the first comments regarding the clinical aspects of infective endocarditis.

A new mark occurred years later, when the also Frenchman Lazare Rivière (1589-1655) observed excrescences that were similar in size to a hazelnut, obstructing the left ventricular outflow tract in a patient with a clinical picture that included cardiac arrhythmia, dyspnea and edema. Sixty years passed until Giovanni Maria Lancisi (1654-1720) wrote that the small fleshy nodules were valve tissue projections and not simple appositions. History progresses for over a century and in the beginning of the 19th century, Jean Nicolas Corvisart (1755-1821) minted the term "vegetation" for the florescence that resembled the syphilis cauliflower. Years later, Jean-Baptiste Bouillaud (1796-1881) established a correlation between "typhoid" endocarditis and what he called acute rheumatoid arthritis. A little later, William Senhouse Kirkes (1822-1864) noted down that fragments of valve vegetations were found in the cerebral artery, kidneys and spleen in cases that had fever, heart murmur and purple skin spots, in addition to observing skin nodules, later called "Osler nodules" by Emanuel Libman (1872-1946). In the second half of the 19th century, renowned clinicians such as Jean-Martin Charcot (1825-1893) and Alfred Vulpian (1826-1887) understood that hyperthermia, chills and splenomegaly were symptoms of typhoid endocarditis, attributed to poisoning by a poison produced in the diseased endocardium. Subsequently, Emmanuel Winge (1817-1894) described finding "parasitic microorganisms" in aortic valve vegetation around one month after a skin suppuration episode and Hjalmar Heiberg (1837-1897) recorded a case of endocarditis after puerperal fever. The infective endocarditis secrets had started to be disclosed and could support theories.

The idea of a point of entry and transportation by blood flow was reinforced by Edwin Klebs (1834-1913) based on the presence of valve vegetation microorganisms in 27 necropsies. A matter of concern was whether the presence of microorganisms was the cause or the consequence of valve vegetations.

The idea of valvular lesion as a predisposing factor was the missing factor to clear out the doubts. Still in the 19th century, Ottomar Rosenbach (1851-1907) and Karl Koester (1843-1904) observed that valvular impairment was the preceding factor that favored the development of infective endocarditis.

In the next-to-last decade of the 19th century, Hugo Ribbert (1855-1920) performed experiences of infective endocarditis induction. He injected *Staphylococcus aureus*

cultured in potatoes into rabbits and identified bacterial colonies over particles on the surface of heart valves, especially in the *chordae tendineae* of the mitral valve. In the same year, WK Wyssokowitsch (1854-1912) obtained the colonization of bacteria injected into the bloodstream of rabbits after previous scarification of the aortic valve via the carotid artery. Based on the collection of experiments in animals of the time, two conclusions were drawn: a) the anteriority of a nonbacterial thrombotic endocardiopathy; b) the colonization of this substrate by circulating bacteria.

The 19th century ends associating valvular lesion, point of entry and circulation of microorganisms, fever and extra-cardiac manifestations under the synthetic diagnosis of infective endocarditis.

The contribution of an eponym[3-5]

William Bart Osler (1849-1919) is the eponym linked to infective endocarditis in general (Osler's disease) and one of its peripheral manifestations (Osler's nodes). He was a physician, famous for his triple nationality – a Canadian, he initially practiced in the United States of America and then in England – his name has been strongly associated with the education of young physicians. Osler was not a "parlor" physician and his knowledge, based on his being a good observer, contributed to construct a unified view of infective endocarditis.

Osler perceived that there were simpler cases and more complex ones, and therefore, used discriminative terms such as ulcerative, malignant, septic and pyemic. He established that blood elements such as fibrin and platelets deposited on the damaged endocardium – substrate of nonbacterial thrombotic endocardiopathy – and constituted the nucleus of vegetation, devaluing the concept that it depended on secretions from the endocardium. Osler called attention to the diversity of microorganisms involved in the vegetation and collected evidence in favor of the primary characteristic of the presence of germs in the etiopathogeny of infective endocarditis at a time when the detection of living germs in blood cultures was incipient.

Osler made it clear in his expositions that the infective endocarditis was a disease to be suspected in cases of fever and sudoresis; that it had a morphological basis related to the very high frequency of valvular lesion, which tended to be aggravated by infection; that it presented an evolution of weeks with extra-cardiac complications associated with the phenomenon of migration of elements involved in the endocardium, with the manifestation of petechiae, retinal hemorrhage, hematuria, splenomegaly, lower-limb embolism and multiple-organ infarction. What currently seems to be simple had to be organized just like a database by an enthusiast of bedside learning.

In the last decade of the 19th century, Osler reported his clinical experience with a woman that had a systolic murmur associated with pre-existing mitral failure, knee and ankle edema and was eupneic only at rest. The patient reported that in the beginning of the disease, small spots appeared on the hands and feet and also in the arms and face, which resembled "beehives"; they kept on appearing with an erythematous characteristic, some as small as pea and others as large as nickel, painful and that had a white dot in the center. The manifestations disappeared in a few hours and never persisted until the night of the day when they appeared. They were not plentiful and sometimes were observed at the fingertips, which became transitorily swollen. The description of the nodes made Osler an eponym.

Stimulated by Osler's presentations, Lord Thomas Jeeves Horder (1871-1955)[5], a physician of the sovereigns of England, who taught that keeping doubts on the diagnosis was essential for preventing misconceptions – in fact, the necessary concern with self-second opinion means that doubts arise more from knowledge than from ignorance – published a collection of 150 cases of infective endocarditis, with illustrations of pathological lesions, in the first decade of the 20th century. During the establishment of infective endocarditis as a nosological entity, Horder emphasized the pre-existence of valvulopathy and congenital cardiopathy, the importance of the oral and intestinal points of entry, the occurrence of mycotic aneurysm, the presence of splenomegaly and the identification of streptococcal etiology in more than 60% of the cases confirmed through necropsies.

Horder recognized five types of infective endocarditis: 1 – latent; 2- fulminant; 3- acute; 4- chronic and 5- subacute, a modality that corresponded to 70% of the cases.

Perspectives of cure[6,7]

The physician started to know more about infective endocarditis, but Medicine did not have efficient therapeutic methods. In the 1930s, some therapeutic attempts with hyperpyrexia induction led to the conclusion that "*…in spite of the increase in the cell reactions and the host's defense processes,* Streptococcus viridans *seems to resistant to high body temperatures that are safe for human body exposition…" (EP9).*

Antibiosis (in opposition to symbiosis) is a term minted by Jean Paul Vuillemin (1861-1932), in 1889, for antagonism effects of living beings in general and the term "antibiotic" was initially employed by Selman-Abraham Waksman (1888-1973) in 1942, adapting it to a substance produced by microorganisms that antagonizes the development of other microorganisms. The hope for the cure of infective endocarditis was born.

In the beginning of the 1940s, sulfanilamide, a synthetic compound, started to be used in infective endocarditis and determined some reports of therapeutic success, although most cases showed a transient benefit and subsequent fatal progression. This was the first clinical evidence that the bacteria located in the endocardium could be

a ected. Great hope was brought by Lichtman and Bierman, when they reported the cure of infective endocarditis in four (16%) of 25 cases, through the combined use of sulfanilamide and hyperpyrexia. One of the points of discussion was the strategy of hyperpyrexia sessions – at least eight sessions on alternate days, leading to an axillary temperature of 40°C for approximately, at least, five hours. Early diagnosis and treatment seemed to be factors of in uence, regarding the response to the combined treatment. Still during the 1940s, a collection of 200 cases of sulfonamide use (sulfanilamide, sulfapyridine, and sulfathiazole) presented 12 (6%) cases of cure. For some time, some authors believed that the association of heparin, hyperthermia and intravenous use of vaccine against typhoid fever was e cient.

A er penicillin availability became universal, thanks to the pioneer e orts of Englishmen such as Nobel-prize winner Howard Florey (1898-1968) and Americans such as Martin Henry Dawson (1896-1945), the treatment of infective endocarditis started an e ciency ascension. From 1944/1945 onward, the antibiotic therapy of infective endocarditis accumulated rapid experience and success.

In 1945, Dawson and Hunter concluded that infective endocarditis by *Streptococcus viridans* could be treated with penicillin. e authors used from 80,000 to 500,000 units daily of penicillin, by IV or IM route, in fractionated doses, in general every three hours, for periods of 10 to 62 days, in most cases associated with heparin as therapeutic adjuvant. ree months a er completing the treatment, 14 (70%) of the 20 patients were free of evidence of infection. One curiosity is the addendum of the original article that includes seven more patients (six cases resulted in infection control), with the observation that the continuous intramuscular infusion of penicillin had been better tolerated by the patient than the IV infusion, but the technique restricted the use of heparin. As time went by, penicillin became pure and allowed the safe administration of larger doses for longer periods of time in cases of infective endocarditis by bacteria that were sensitive to it.

As usually happens, benefits on the natural history of a disease give the opportunity for the development of survival with new clinical expressions.

ree aspects of the therapeutic e ciency with prognostic implications became the cause of growing concern: a) the evolution of the cardiac area; b) worsening in the capacity for physical e orts; c) evolution of the morphological severity of the pre-existing valvular lesion. One piece of information was clear, from the accurate observation that characterized the time and which remains valid: "*…infective endocarditis rarely occurs in the presence of severe rheumatic cardiopathy…*"

In other words, the decrease in mortality to approximately 30% (penicillin-dependent fact) brought worries concerning surviving the infection and quality of life impairment due to the worsening in the previous cardiopathy. As a consequence, the deleterious morphological e ects of infective endocarditis increased the research on the foundations of the direct intervention on the severe and symptomatic valvular lesion.

Surgery at the study phase of infective endocarditis[8]

In the 1960s, it was established that infective endocarditis was a curable disease. e perspective of controlling the infection increased the physician's restlessness regarding the cases that did not respond to antibiotics. Some thought about a direct intervention on the heart to remove the infected tissue, but the concept of imprudence was strong, in relation to operating on a patient with fever and heart failure. Andrew G. Wallace *et al.*[8] at Duke University, understood that the removal of the infected valve and its substitution by a valve prosthesis constituted an approach on the clinical manifestation cause and therefore, fever and heart failure were not exactly comorbidities that added a surgical risk.

A 45-year-old construction worker, with endocarditis by *Klebsiella* sp. that did not respond to colicimin and kanamycin and clear worsening in the aortic failure, became the first patient to have visible vegetation *in vivo*, directly in a Surgical Center, as well as perforations of right and le coronary lea ets. e implantation of a Starr-Edwards prosthesis resulted in a febrile patient, with negative blood cultures and slight paravalvular failure with no peripheral signs of aortic failure that persisted at the follow-up carried out at 15 months of postoperative evolution. e authors emphasized that the absence of the valvular annulus involvement was a factor of success, as it was a sign that there was no infection beyond the excised valve.

e assistential innovation that dismissed a research project and consequent ethical evaluation marked the beginning of the association of valvular prosthesis and infective endocarditis, both as therapeutics and etiopathogeny (endocarditis in prosthesis). Subsequently, the routine surgical indication in cases of infective endocarditis in cases with CHF grade III/IV (the most common recommendation) reduced mortality from 90% to 10%.

Echocardiography disclosing vegetation[9]

e history of the echocardiography started with the use of ultrasonography to evaluate mitral failure a er commissurotomy and pericardial e usion, as a consequence of the studies by Inge Edler (1911-2001) and Hellmuth Hertz (1920-1990), in the 1950s and the subsequent contribution of Harvey Feigenbaum, the "Father of Echocardiography".

e 1970s gathered the publication of articles emphasizing the disclosure of vegetation by M-mode echocardiography. In 1980, JA Stewart *et al*[9], from Duke University, summarized the state-of-the-art of the time, a er they identified 54% of positive signs of vegetation at the echo-

cardiography: *"... although it is a good method to document the presence or the absence of infective endocarditis, it does not seem to be reasonable to use the echocardiography as a routine diagnostic method; as only half of the patients that meet the clinical criteria manifests echocardiographic signs; moreover, the vegetation does not regress rapidly and thus, the echocardiography might have a low diagnostic power in a patient with a history of infective endocarditis…".*

Thirty years after these words by Stewart *et al.*[9] one verifies that the accumulation of experience determined a remarkable evolution in the support of the diagnostic rationale of infective endocarditis by joining the traditional clinical data and images and calculations determined by technological advancement in echocardiography (two-dimensional, Doppler and transesophageal). The term subacute endocarditis practically disappeared, due mostly to a faster diagnosis supported by the echocardiographic identification of vegetation in cases with fever and cardiopathy.

In the 1990s, Duke University gave another magnificent contribution to the knowledge of infective endocarditis through a diagnostic systematization that elevated echocardiography as a determinant method of a major criterion.

From clinically possible to clinically defined[10-12]

As the disease has a high diversity of presentations, the creation of solid criteria was the target of many researchers that realized that any increase in sensitivity caused a decrease in specificity and vice-versa.

In 1981, Fordham Charles von Reyn *et al.*[10] distributed 123 cases as defined infective endocarditis (19), probable (44), possible (41) and rejected (19). The specifications of each category were useful; however, it soon became outdated, due to two main reasons: a) the diagnosis of defined was based on anatomopathological data and therefore, the clinician, was actually treating a possible or probable case; b) the studies preceded the introduction of the two-dimensional echocardiography and the Doppler use.

For years, those who cared for cases of infective endocarditis incorporated the echocardiography in the support of the clinical diagnosis of infective endocarditis at the bedside, until 1994, when David Durack *et al.*[11], at Duke University, systematized and published the possibility of dismissing the identification of vegetation in favor of the pathological anatomy as the basis for the classification of defined infective endocarditis, substituting it for the echocardiographic image. To us, it was reduced to three categories: defined, possible and rejected.

The Duke University criteria used the strategy utilized by Thomas Duckett Jones (1899-1954) of subdividing the criteria in major and minor ones.

The echocardiography and the blood culture started to have identical diagnostic hierarchy as major criteria for the diagnosis of infective endocarditis, with evident gain in sensitivity. Two major criteria or one major and three minor criteria gave the clinician the basis to treat "a certainty" and not a possibility of infective endocarditis.

Several studies validated the new criteria; however, some gaps were perceived. In 2000, Jennifer S. Li, a professor of Pediatrics from Duke University and colleagues[12] completed the outstanding advancement in the frontier of knowledge on infective endocarditis in the 20th century, presenting a perfected version of the 1994 criteria from Duke University.

The main improvements were: a) possible endocarditis based on at least one major and one minor criterion or three minor criteria; b) elimination of "echocardiographic data consistent with infective endocarditis, but not achieving a major criteria", due to the use of the transesophageal method; c) upgrade in bacteremia by *Staphylococcus aureus* to the condition of major criterion, both in nosocomial infections as well as those associated with an eradicable source of infection; d) positive serology for Q fever started to be a major criteria with the same weight of positive blood culture.

Antibiotic prophylaxis use[13]

In approximately 60 years, there have been big changes in antibiotic prophylaxis recommendations for infective endocarditis. Time has shortened doses, restricted the number of patients considered at risk and limited the inducing procedures. The lack of controlled studies justifies the varied behavior in relation to such a severe disease.

In 1955, intramuscular penicillin was injected into the patient 30 minutes before dental procedures. In 1957, oral penicillin was administered four times a day for two days before, on the day and for two days after the dental manipulation. In 1960, the dose was a single daily one of 600,000 units of crystalline penicillin, for five days. In 1965, the first dose of penicillin was given one to two hours before the procedure. In 1977, intramuscular penicillin was applied 30 to 60 minutes before the dental manipulation, followed by eight doses of 500 mg of V penicillin every two hours. In 1984, the recommendation was 2g of penicillin V 60 minutes before the dental procedure, followed by 1g after six hours. In 1990, 3g of oral amoxicillin was recommended, 60 minutes before the procedure, followed by 1.5g after six hours. In 1997, the dose of amoxicillin was reduced to 2g, 60 minutes before the dental procedure, in a single dose.

Homage to a Brazilian

In the decades of 1960/1970, cases of fever and cardiopathy, especially in young individuals, determined the preferential diagnostic suspicion of rheumatic fever (RF) activity among us. In many cases, infective endocarditis was not even suspected, considering that microbiological support was limited.

The need to give more attention to the differential diagnosis of RF with infective endocarditis[14] was introduced to Brazilian students of Cardiology by a professor that cannot be left out of any historical record on infective endocarditis carried out in Brazil, and who was one of the Brazilian Society of Cardiology founders, in 1943: Luiz "*I believe in Medicine, which is a continuous act of improvement*" Venere Décourt (1911-2007).

References

1. Millar BC, Moore JE. Emerging issues in infective endocarditis. Emerg Infect Dis. 2004;10:1110-6.
2. Contrepois A. Towards a history of infective endocarditis. Med Hist. 1996;40:35-54.
3. Grinberg M. Epônimos em cardiologia: homenagem e exemplo. São Paulo: Roca; 1999.
4. Longcope WT. Sir William Osler and bacterial endocarditis. Bull Johns Hopkins Hosp. 1949; 85:1
5. Bourne G. Lord Horder. Br Heart J. 1956;18:123-5.
6. Lichtman SS, Bierman W. The treatment of subacute bacterial endocarditis. JAMA 1941;116:286-9.
7. Dawson MH, Hunter TH. The treatment of subacute bacterial endocarditis with penicillin. JAMA 1945;127:129-37.
8. Wallace AG, Young WG Jr, Osterhout S. Treatment of acute bacterial endocarditis by valve excision and valve replacement. Circulation 1965;31:450-3.
9. Stewart JA, Silimperi D, Harris P, Wise NK, Fraker Jr TD, Kisslo JA. Echocardiographic documentation of vegetative lesions in infective endocarditis.: clinical implications. Circulation 1980;61:374-80.
10. Von Reyn CF, Levy BS, Arbeit RD, Friedland G, Crumpacker CS. Infective endocarditis: an analysis based on strict case definitions. Ann Intern Med. 1981;94:505-18.
11. Durack DT, Lukes AS, Bright DK. New criteria for diagnosis of infective endocarditis: utilization of specific echocardiographic findings. Duke Endocarditis Service. Am J Med. 1994;96:220-2.
12. Li JS, Sexton DJ, Mick N, Nettles R, Fowler Jr VG, Ryan T *et al.* Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. Clin Infect Dis 2000;30:633-8.
13. Dajani AS, Taubert KA, Wilson W, Balger AF, Bayer A, Ferriei P *et al.* Prevention of bacterial endocarditis:Recommendations by the American Heart Association. J Am Dent Assoc. 1997;128:1142-51.
14. Décourt LV. Endocardite infecciosa. In: Décourt LV, editor. Medicina preventiva em cardiologia. São Paulo: Sarvier; 1982. p.119-39.