

Infectious endocarditis: experience of an Internal Medicine Service

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Abstract

The authors analyzed thirteen cases of infectious endocarditis and emphasize some aspects such as the cause of admission, clinical presentation, diagnostic criteria, echocardiographic al-

terations, underlying pathology, etiologic agents, complications and prognosis.

Key words: infectious endocarditis.

Introduction

Infectious endocarditis (IE) is a common pathology in the internal medicine service, and its treatment presents some problems.

It is a condition that should always be considered in the differential diagnosis of febrile syndrome.^{1,2} Some circumstances, such as sudden onset heart failure,³ pulmonary embolism in a suggestive context,⁴ systemic embolization, the presence of circulating immune complexes, and other immune disorders⁵ should alert us to the diagnostic possibility of acute endocarditis.

The form in which this condition commonly appears is also very important for the Internist, due to the major alterations that occur in the etiological and clinical spectra of the disease. The causes that may lead to more capricious manifestations of IE include advanced age, associated pathologies, and different predisposing factors, often iatrogenic, in patients admitted to internal medicine services.^{4,6,7,8}

The assessment of other pathologies in the presence of some bacterial etiologies of IE, such as endocarditis caused by *Streptococcus bovis*,⁹ and the multiorgan involvement of the disease, reinforce the need for the physician to treat this condition.

Considering these factors, the authors decided to analyze a series of cases of IE of their Service, which is part of the Coimbra University Hospitals, and which also provides independent services in Infectious Diseases and Cardiology. For this reason, it is Internal Medicine that naturally undertakes the study of patients who pose diagnostic problems, as well as those with multiple pathologies.

Material and Methods

Thirteen clinical cases were analyzed, consisting of patients admitted to the Medical Service II between January 1989 and December 1993.

The cases were selected based on the discharge diagnosis and subsequent retrospective application of Duke's diagnostic criteria for IE.^{8,10,11}

For all the cases, the following parameters were analyzed: age, sex, reason for admission, symptoms presented, diagnostic criteria, underlying pathologies, blood cultures, echocardiographic abnormalities, thromboembolic complications and prognosis.

Results

The average age of the thirteen patients was 57.4 years, ranging from 25 to 77 years; six were male and seven female.

Applying Duke's diagnostic criteria retrospectively, seven of the thirteen patients were classified as "confirmed" cases of IE and six as "probable" cases of IE.^{8,10}

Of the thirteen patients, ten (77%) had prolonged fever of unknown cause as a reason for admission; two were admitted for "pneumonia," and one due to pulmonary embolism.

All thirteen patients had fever on admission. Asthenia was a significant symptom in four cases. Cough was significant in four of the patients studied.

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Sweating was relevant in another four patients. Four patients had major headaches. Only three people complained of joint pains, and another three had chest pain.

The average duration of the symptoms described above was fifty-three days.

On clinical examination, ten patients presented heart murmurs, splenomegaly was observed in three cases, and petechiae were found in just one case.

In relation to the underlying pathology, it was known that one of the patients had subaortic interventricular communication and another had a prosthetic aortic valve. Also, there were valvular fibrodegenerative changes in three patients, all aged over sixty. Two patients had diabetes mellitus, two had alcoholic cirrhosis, one had chronic bronchitis and one had hepatoma.

Echocardiography showed alterations indicating a diagnosis of endocarditis in all thirteen patients, with significance of *major* criteria in ten of these. This means that all ten cases had vegetations, one had paravalvular abscess and another had prosthetic dysfunction. Of the remaining three patients in the study, only *minor* echographic criteria for endocarditis were observed, that is, nodular valvular thickening.⁸ Echocardiographic alterations were located in the aortic valve in six cases, five in the mitral valve, one case with mitral-aortic involvement and another with compromised pulmonary valve. Of these, three had aortic insufficiency; one mitral, and one pulmonary.

The blood cultures were positive in nine patients (69%) and negative in four (31%). The study identified the presence of: *Streptococcus Bovis* in three patients, *Streptococcus millieri* in one patient, *Staphylococcus aureus* in one, *Coagulase-Negative Staphylococcus* in two, *Escherichia Coli* in one, and *Fusobacterium Nucleatum* in one, the latter being, as far as we know, an anaerobic germ. Of the patients with positive blood cultures, this positivity was a *major* criterion of IE in five patients and a *minor* criterion in the remaining four.⁸

With regard to complications, we highlight septic pulmonary embolism in two patients, both with pleural effusion (right endocarditis, left endocarditis associated with interventricular communication) and systemic embolism in two patients (one liver abscess in the patient with endocarditis caused by anaerobic bacteria, and in the patient with endocarditis due to *Staphylococcus Aureus* with osteoarticular and skin

localizations). We also highlight the presence of heart failure (right, left or global) in four patients.

We recorded a response to antibiotic therapy in ten of the thirteen cases, and for three of these (23%) it was necessary to resort to surgery. We emphasize the fact that these two cases belonged to the group with negative blood cultures.

In all cases the evolution was favorable, and no mortalities were recorded in this small series.

The average length of hospitalization (Medicine Service) was thirty two days, ranging from a minimum of six to a maximum of fifty days. Only two patients had shorter hospitalization times, as these were transferred to surgery on the 6th and 12th days.

Discussion

Based on the results reported, we would like to make some comments with regard to particular problems that this disease presents for the internist.

The reason for admission of our patients, in 77% of the cases, was prolonged febrile syndrome. The fever was accompanied by symptoms that gave little guidance, although the presence of heart murmur in seven of these ten patients placed in doubt the existence of criteria for the definition of fever of unknown origin.² Although nowadays, IE is a less common cause of this syndrome,² probably due to the emergence of echocardiography leading to early diagnosis, for our patients, the mean evolution time of the symptoms was 53 days, which is a very long time. This is due to the fact that the clinical situation is altered by the presence of other pathologies, and also because the group analyzed included patients of advanced age, less virulent types of germs and/or the absence of traditional predisposing grounds in some patients.⁶ Thus, in the presence of persistent fever of unknown origin, blood cultures must be carried out, and in cases where the symptoms are suggestive, echocardiography should also be performed.¹ Although fever ($\geq 38^{\circ}\text{C}$) is part of the criteria for endocarditis^{8,12} and was present in all our patients, it is absent in 3% to 15% of cases, or else it barely exceeds 37°C . Therefore the possibility of IE should not be based on the presence of fever alone.³

The admissions for pulmonary thromboembolism and "pneumonia" led to the diagnosis of the remaining cases of IE. Here, we emphasize the repeated thromboembolic events, taking the form of small, multiple opacities in the chest x-ray, which coalesce,

often appearing in patients with right endocarditis. Taking into account the increase in this type of IE in the community, following intravenous drug abuse, we should consider this condition when repeated “pneumonia” is present, particularly in predisposed individuals.^{4, 9, 13}

The internist’s job is to study the symptoms with multisystemic involvement, with alterations in immunity, which include IE. The high titers of rheumatoid factor, immune complex glomerulonephritis and the presence of autoantibodies, among others, are common in IE, constituting a *minor* diagnostic criterion.^{5,8,14} Therefore, the difficulties sometimes encountered when attempting to make a differential diagnosis with other autoimmune diseases, including lupus, are hardly surprising, a fact that was observed in one of our cases.

The advent of echocardiography has facilitated the differential diagnosis of these conditions. The inclusion of echocardiographic findings in the criteria of endocarditis has increased the number of diagnoses made, compared to those made by the previously used von Reyn criteria.^{10,12,15} This development was of paramount importance in guiding the diagnosis of our patients, establishing “confirmed” IE in seven of cases and “possible” IE in six cases, a diagnosis that was not possible through the von Reyn criteria.⁸ We emphasize that in two cases with persistently negative blood cultures, whose *major* criterion was echocardiography, surgery was eventually required. Despite these benefits, echocardiography creates problems for clinical analysis. The identification of nodular valve thickening, although consistent with a diagnosis of IE (the *minor* criterion in three of these cases) may not be due to this pathology and should be evaluated only in suggestive contexts.^{8,15} Thus, the ultrasound performed in non-suggestive contexts shows low sensitivity, which may be due to injuries of marantic or other origin.¹⁵

The physician should be alert to changes in the IE spectrum with regard to predisposing cardiac injuries.^{7,16,17} Echocardiographic evaluation of our patients indicated this, revealing degenerative aortic and/or mitral valve injuries in three elderly patients as the most frequent cause, superimposed on the congenital cardiopathies (one case) and rheumatic disease. Note that in most cases (61%), there was no predisposing heart disease. These findings are also corroborated in other published series,^{7, 17} which raises additional

difficulties in making the diagnosis hypothesis.

Although rare, we also mention the presence, in our series, of a case of pulmonary valve IE. This valve is rarely affected (less than two percent of cases of IE in the post-mortem examination), and it even less frequently diagnosed while the patient is alive because the valve is more difficult to observe in the echocardiography.^{18,19,90} Compared with normal echocardiography, transoesophageal echocardiography has greater specificity and greater sensitivity in detecting vegetations. It is a technique that should be used when there is a high degree of suspicion of this type of endocarditis. For this situation, there are usually predisposing factors, particularly congenital heart disease and drug addiction, which was not observed in our case.⁹

In the cases analyzed, the prevalence of the germs involved differed from the reviewed literature.^{16,17,21} Despite being a small series, for which reason it is difficult to draw conclusions as to the distribution, we can make some comments. The absence of intravenous drug use in these patients accounts for the low prevalence of IE by *Staphylococcus aureus*, compared with the increase found in the recent literature.^{16,17} On the contrary, the presence of three patients (23%) with IE by *Streptococcus bovis* is correlated with more advanced age, since 80% of cases of IE by this etiology occur in individuals aged over 60 years,¹⁴ as was observed in our patients.

Advanced age and comorbidities such as diabetes, liver disease and neoplasias, not only predispose to IE,^{4,6,22} but also allow the installation of germs with prolonged evolution, modifying both the etiologic spectrum and the clinical symptoms.¹⁶ Also hospital “aggressions”, such as the use of intravascular catheters and other invasive methods, can lead to IE in hospitalized patients, particularly elderly and immunocompromised patients.¹⁶ These are the types of patients we normally see in the Medical wards, making this association of pathologies additional difficulties in the diagnosis. This results not only in the appearance, in our small series, of 31% of IE with negative cultures, but also 31% of cases in which the negativity is used as a *minor* criterion.^{8,10}

IE with negative blood cultures was important in our group of patients, affecting 31%. In literature consulted, the negativity of the blood cultures ranged from 2.5% to 44.5%, although a lower rate of negative blood cultures is observed in more recent studies, usu-

ally less than 5%.^{8,10,15,16,17,21,22,23,24,25,26} The frequency of this group depends on the diagnostic criteria used, increasing significantly with the implementation of Duke's criteria, as mentioned earlier.^{10,15,16} Previous use of antibiotic therapy, infection by slow-growing germs or fungi, or by fungi that are difficult to isolate by routine techniques, as well as right-side endocarditis, are sometimes responsible for the negative blood culture results.^{16,23} It is important to emphasize the seriousness of this type of endocarditis, due to the high number of embolic complications and/or heart failure, leading to high mortality in patients who do not respond to empirical antibiotic therapy at the end of the first week.^{16,27} The involvement of germs that are difficult to identify, such as fungi, means that sometimes surgery is necessary,²³ as was the case of two of our four patients. Due to the difficulties mentioned, and because it is a diagnosis of exclusion, this type of endocarditis poses problems for treatment.¹⁶

In our experience, some atypical germs were observed that are rarely involved in IE. *Staphylococcus coagulase negative*, while a cause of IE, particularly in patients with prosthetic valves and immunocompromised patients, usually comes from contamination. However, when this bacteremia is persistent, it is considered a criterion of IE.^{8,10} In our two patients, IE appeared in natural valves, these germs being responsible, in the literature reviewed, for 3% to 5% of this type of IE.^{17,21,22} Anaerobic infection is a rare etiology of IE. It is difficult to diagnose, for which reason it is usually diagnosed late.^{3,17,21,22,24,28} The germ most commonly diagnosed is *Bacterioides fragilis*, while *Fusobacterium nucleatum*, involved in one of our cases, is generally less frequently mentioned.²³ While not very virulent, with a slow course, these germs can lead to a severe outcome, with high mortality rates, especially in the penicillin resistant group,^{1,28} which did not occur in our case. Its evolution is marked by valvular destructions with valvular insufficiency, heart failure, and embolic phenomena,^{3,28,29} the latter manifested in our patient as a hepatic abscess. There is also IE due to *Escherichia coli*, for which there are few references in the literature, with frequency of between 1% and 10%.^{17,22,25,26}

An important aspect for the internist is the need to adopt certain conducts in cases of IE by *Streptococcus bovis* and *milleri*. *Streptococcus Bovis milleri*, although a rare cause of bacteremia, is often involved in IE (25% of bacteraemias), therefore echocardiographic

evaluation is indicated. What distinguishes it from other *streptococci* is its tendency to invasive, pyogenic infections often associated with abdominal, brain or lung foci.^{30,31} This type of infection generally occurs in association with predisposing factors, such as age over sixty years, liver disease, alcoholism, diabetes mellitus and malignant disease, all of which were present in our patient.³⁰ *Streptococcus bovis*, meanwhile, has been associated with a high prevalence of malignant or pre-malignant intestinal lesions, reaching 80% in some studies. Due to this fact, evaluation of the colon is essential. This evaluation was performed in our patient, but no injuries were detected. Follow up for these patients, with regular evaluations, is recommended as there are references to neoplasias that emerge years after IE. The discovery of benign colon injuries has also been associated with this etiology.^{14,32,33,34,35}

The evolution of IE was complicated by embolic events in three of the patients analyzed (1 systemic arterial, 1 lung, 1 mixed). Embolization is characteristic of IE, constituting a diagnosis criterion in itself.^{8,10,17} Its incidence varies from series to series, and it may emerge after the start of therapy^{14,16,17} as occurred in one of our cases. The development of these complications is linked to the germ involved, and it is more common in etiologies that produce large, mobile vegetations (fungi and anaerobic). The value of the echocardiographic findings in predicting embolic risk is controversial, and the correlations found are probably associated with differences between etiologies.^{36,37} A case with different implications is pulmonary embolization, which appears in right-side endocarditis in situations of left-to-right shunts. It is a frequent problem, occurring in 60% to 100% of these patients, and its clinical spectrum is highly variable, including small, repeated emboli, secondary pneumonia, pulmonary infarction and the development of empyema or pleural effusion.^{4,13}

Heart failure is the most common complication of IE, and occurred in four of our patients. It is usually referred to as the first cause of death by this entity.^{16,17} The sudden onset of clinical heart failure, especially when accompanied by fever, should alert physicians to a possible diagnosis of IE.^{3,16}

Finally, the authors report that the objective of this text was not to give an exhaustive study of a case series of IE, but to evaluate their clinical cases, commenting on some problems that arise in the practice of Internal Medicine. Considering that EI has a changing spec-

trum, and in some cases, special characteristics, the authors hope that this work will contribute increasing suspicion of this disease, which continues to have a considerable rate of complications and mortality. ■

References

- Roudaut R, Dallochio M. Le diagnostic de l'endocardite bactérienne. *Rev Prat* 1989; 67:20 – 22.
- Brusch J, Weinstein L. Fever of unknown origin. *Med Clin North Am* 1988; 72 (5): 1247 – 1261.
- Faro T, Margarido E, Mendonça M, Cardigos P, Veloso B. Insuficiência Aórtica: a propósito de um caso clínico. *Medicina Interna* 1994; 1 (1): 38 – 44.
- Remetz M, Quagliariello V. Endovascular infections arising from right-sided heart structures. *Cardiology Clinics* 1992; 10 (1):137 – 149.
- João SR, Afonso MR, Martins Junior L, Almeida Junior B, França H. Aspectos patogênicos e imunitários da endocardite infecciosa. *Arq Bras Cardiol* 1990; 54:69 – 72
- Terpenning M, Buggy, Kaufman C. Infective endocarditis: clinical features in young and elderly patients. *Am J Med* 1987; 83: 626 – 634.
- McKinsey D, Ratts T, Bisno A. Underlying cardiac lesions in adults with infective endocarditis, the changing spectrum. *Am J Med* 1987; 82 (4): 681 – 688.
- Durack D, Lukes A, Bright D. New criteria for diagnosis of infective endocarditis; utilization of specific echocardiographic findings. *Am J Medicine* 1994; 96:200 – 209.
- Pontes J, Parente F, Ruas K, Isaac J, Alexandrino B, Silva PS. Endocardite da válvula pulmonar por estreptococos bovis. *Rev Port Card* 1994; 13 (4): 329 – 334.
- Bayer A, Ward J, Ginzton L, Shapito S. Evaluation of new clinical criteria for diagnosis of infective endocarditis. *Am J Med* 1994; 96:211 – 219.
- American Heart Association ad hoc Committee. Jones criteria (revised) for guidance in the diagnosis of rheumatic fever. *Circulation* 1984; 69:203A – 208A.
- Von Reyn C, Levy B, Friedland G, Gumpacker C. Infective endocarditis: an analysis based on strict case definitions. *Ann Int Med* 1981; 94:505 – 507.
- Roberts W, Buchbinder N. Right-sided valvular infective endocarditis, the clinicopathological study of twelve necropsy patients. *Am J Med* 1972; 53:7 – 19.
- Kaye D. Infective endocarditis. In *Harrison Principles of Internal Medicine*, 12th edition 1991 McGraw-Hill, 508 – 512.
- Von Reyn, Arbeit R. Case definitions for infective endocarditis. *Am J Med* 1994; 96:220 – 222.
- Nunley D, Perlman P. Endocarditis: changing trends in epidemiology, clinical and microbiologic spectrum. *Postgrad Med* 1993; 93 (5): 235 – 247.
- Watanakunakon C, Burkert T. Infective endocarditis if a large community teaching hospital. 1980 – 1990, a review of 210 cases. *Medicine* 1993; 72 (2): 90 – 102.
- Bitar J, Alam M. Echo-doppler features of pulmonary valve endocarditis. *Henry Ford Med J* 1989; 37 (1): 41 – 42.
- Branco L, Agapito A, Oliveira JA, Gonçalves JM, Quinhina J, Velho HV, Pereira A, Ferreira ML, Antunes AM, Bento R. Endocardite da válvula pulmonar, considerações a propósito de um caso associado a comunicação interventricular e insuficiência aórtica. *Rev Port Card* 1990; 9 (3): 221 – 225.
- Shapiro S, Young E, Ginzton L, Bayer A. Pulmonic valve endocarditis as an under diagnosed disease: role of transoesophageal. *A Am Soc Echocard* 1992; 5:48 – 51.
- Mendes C, Décourt L, Grinberg M, Hemocultura em portadores de endocardite infecciosa. *Arq Bras Cardiol* 1989; 53 (2): 75 – 79.
- Garvey G, Neu H. Infective endocarditis – an evolving disease. *Medicine* 1978; 57 (2): 105 – 125.
- Tunkel A, Kaye D. Endocarditis with negative blood cultures. *New Engl J Med* 1992; 326 (18): 1215 – 1217.
- Griffin M, Wilson W, Edwards W, O'Fallon, Kurland L. Infective endocarditis: Olmsted County, Minnesota, 1950 through 1981. *JAMA* 1985; 254 (9): 1199 – 1202.
- Mansur A, Grinberg M, Galluci D, Bellotti G, Jatene A, Pileggi F. *Arq Bras Cardiol* 1990; 54: 13-21.
- Assef M, Gandra S, Franken R, Rivetti L, Miyazaki A, Chih L, Borba M, Junior P. Endocardite infecciosa, estudo em 83 casos no Hospital da Santa Casa de Sao Paulo. *Arq Bras Cardiol* 1991; 56 (3): 191 – 193.
- Pesanti E, Smith J. Infective endocarditis with negative blood cultures, an analysis of 52 cases. *Am J Med* 1979: 66:43 – 50.
- Nastro L, Finegold S. Endocarditis due to an aerobic gram negative bacilli. *Am J Med* 1973; 54:482 – 496.
- Correia J, Fonseca I, Vidigal MJ, Santos L, Santos F, Oliveira MH. Endocardite bacteriana por anaeróbios. *Cardiol Actual* 1992; 2(13): 460 – 466.
- Dall L, Jones T. Streptococcus milleri bacteremia. *Inf Med* 1991; 6 (1): 5 – 8.
- Gallis H. Streptococcus intermedius group (Streptococcus anginosus – milleri group) in Mandel. Churchill Livingstone. 1990; 1572 – 1574.
- Ben-Haim SA, Nechmad M, Edoute Y, Reisner S. Colonic villous adenoma, polyp and leiomyoma presenting with Streptococcus bovis endocarditis. *Am Heart J* 1988; 115 (11): 192 – 193.
- Grinberg M, Mansur A, Ferreira DO, Bellotti G, Pileggi F. Endocardite por Streptococcus bovis e neoplasias do colon e recto. *Arq Bras Cardiol* 1990; 54 (4): 265 – 269.
- Leport C, Bure A, Leport J, Vilde JL. Incidence of colonic lesions in streptococcus bovis and enterococcal endocarditis. *Lancet* 1987; 28:748.
- Zarkhin B, Lillemoe K, Cameron J, Effron P, Magnuson T, Pitt H. The triad of Streptococcus bovis bacteraemia, colonic pathology and liver diseases. *Ann Surg* 1990; 211 (6): 786 – 791.
- Sanfilippo A, Picard M, Newell J, Rosas E, Davidoff R, Thomas J, Weyman. Echocardiographic assessment of patients with infectious endocarditis: prediction of risk for complications. *J Am Coll Cardiol* 1991; 18:1191 – 1199.
- Steckelberg J, Murphy J, Ballard D, Bailey K, Tajik A, Tailercio C, Giuliani E, Wilson W. Emboli in infective endocarditis: the prognostic value of echocardiography. *Ann Int Med* 1991; 114:635 – 640.