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Prosthetic valve endocarditis

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Abbreviation
PVE: prosthetic valve endocarditis

ABSTRACT

Introduction: Infective endocarditis in prosthetic heart valves is one of the most severe forms of this disease of difficult diagnosis and associated with high mortality.
Objective: To describe the characteristics of prosthetic valve endocarditis.
Method: An observational, descriptive and cross-sectional study was conducted from 2006 to 2019 at Hospital Hermanos Ameijeiras. The sample consisted of 40 patients. Descriptive statistics such as arithmetic mean and standard deviation were used for continuous quantitative variables, and percentage for qualitative ones.
Results: The average age of the patients was 54.29+16.07 years old, predominating those between 40-49 and 60-69 years old, as well as males (67.5%); the most frequent type of endocarditis was the late one (65%). Oral sepsis (27.5%) and previous surgery (25%) %) were the most frequent entry points. Negative cultures (40%) and coagulase-negative staphylococcus causative agents (25%) and staphylococcus aureus (10%) prevailed. Heart failure (32%) and kidney failure (22.5%) were the most frequent complications, and 20% of cases had suture dehiscence. The 52.5% of patients received surgical treatment and the mortality was of the 30%.
Conclusions: Late endocarditis predominated, with negative blood cultures and of aortic valve prosthesis. Prosthesis dehiscence was the most frequent echocardiographic finding and the heart failure, the most frequent complication. The surgical treatment was the most used, and the mortality, adjusted for this disease, was low.
Keywords: Infective endocarditis, Mechanical prosthetic heart valves, Prosthetic valve endocarditis, Mortality

Endocarditis infecciosa en válvulas protésicas

RESUMEN

Introducción: La endocarditis infecciosa sobre prótesis valvulares cardíacas es una de las formas más graves de esta enfermedad, de difícil diagnóstico y asociada con elevada mortalidad.
Objetivo: Describir las características de la endocarditis infecciosa en válvulas cardíacas protésicas.
Método: Se realizó un estudio observacional, descriptivo y transversal desde 2006 hasta 2019 en el Hospital Hermanos Ameijeiras. La muestra fue de 40 pacientes. Se utilizaron estadígrafos descriptivos como la media aritmética y la desviación estándar para las variables cuantitativas continuas y el porcentaje para las cualitativas.

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Authors' contribution
CRE, MGG and MLR: Idea and design of the research; obtaining, analyzing and interpreting the data, as well as writing the manuscript.
JOT and MNAR: Raw data collection and helped to draft the manuscript.
MHA: Conception of the research, analyzing and interpreting the data.
All authors critically reviewed the manuscript and approved the final version.

Resultados: La edad media de los pacientes fue de 54,29±16,07 años, predominaron aquellos con edades entre 40-49 y 60-69 años (27,5%), así como del sexo masculino (67,5%), y el tipo de endocarditis más frecuente fue la tardía 65%. La sepsis oral (27,5%) y la cirugía previa (25%) fueron la puerta de entrada más frecuente. Prevalecieron los cultivos negativos (40%) y los agentes causales estafilococos coagulasa negativos (25%) y estafilococos áureos (10%). En las complicaciones predominaron las insuficiencias cardíaca (32%) y renal (22,5%), y un 20% de los casos tuvo dehiscencia de sutura. El 52,5% de los pacientes recibió tratamiento quirúrgico y la mortalidad fue del 30%.
Conclusiones: Predominó la endocarditis tardía, con hemocultivo negativo y de prótesis aórtica. La dehiscencia de prótesis fue el hallazgo ecocardiográfico más encontrado y la insuficiencia cardíaca, la complicación más frecuente. El tratamiento quirúrgico fue el más utilizado y la mortalidad, ajustada para esta enfermedad, fue baja.
Palabras clave: Endocarditis infecciosa, Prótesis valvular cardíaca mecánica, Endocarditis en válvula protésica, Mortalidad

INTRODUCTION

During 17th and 18th centuries, the first reports of patients who died from a disease called "infective endocarditis" appeared. According to Grinberg and Solimene[1], Boillaud was the first one to introduce the term "endocardium" and he conceived it as the seat of an inflammation that he called "endocarditis". William Osler studied the disease extensively and his contributions to the knowledge of this entity led to name it "Osler's disease"[1]. The infection on prosthetic heart valve is a relatively recent condition in medicine, since it was not until the second half of the 20th century that the heart valve replacement surgery with the implantation of prosthesis began[2].

Infective endocarditis is a multi-modal disease, secondary to microbial colonization of the valvular endothelium, which can lead to the destruction of the heart valves, compromise of the adjacent myocardium, development of embolisms from vegetations and severe persistent sepsis[3]. The epidemiological profile of the infective endocarditis has considerably changed in recent years; previously, it was a condition that affected young adults with heart valve diseases (usually rheumatic), but nowadays it is more common in older patients who usually suffer from it as a result of healthcare related procedures, both in patients without previous heart valve compromise and those with prosthetic valves[4].

The diagnostic and therapeutic approach has also been modified, although mortality remains high[4,5]. Prosthetic valve endocarditis (PVE) is defined when the infection is based on any mechanical, biological, autologous or heterologous substitute for the native valves. It represents 10-30% of all cases of endocarditis and it is one of the most severe forms of this disease, with an in-hospital mortality of 20-40%[4]. It is estimated to occur in about 1-6% of patients with prosthetic valve, with an incidence of 1-3% in the first year, and 3-5% at 5 years; it is most frequent during the first three months after surgery and then, it gradually decreases to a relatively constant rate of 0.3%-0.6% at 12 months[3,4,6].

Different factors that may predispose to infection of the prosthesis have been assessed, although the conclusions are not homogeneous among the different studies and it is difficult as well to establish comparisons due to the variability in the design of these[7]. The factors that have been associated with a higher risk of endocarditis are: multiple heart valve replacements, valve replacement due to active endocarditis, the existence of nosocomial bacteremia in the perioperative period, prolonged time of cardiopulmonary bypass and male sex[3,8].

PVE can be early or late, the first one being defined by its diagnosis in the first 365 days after the surgical procedure, and the late one from day 366 on, due to microbiological differences observed before and after one year after the surgery. Staphylococci, fungi and gram-negative bacilli are the main causes of early PVE, while in the microbiology of late PVE, staphylococci, oral streptococci and enterococci are the most common microorganisms, behaving with a microbiological pattern similar to native valve endocarditis[9].

The diagnosis of PVE is based on the modified Duke's criteria[10], and the echocardiographic findings are a major criterion for achieving this goal; however, its diagnostic performance is lower in this disease, for this reason the use of alternative imaging

techniques is recommended in order to assist in the assessment of uncertain cases: cardiac computed tomography (CT), 18F-fluorodeoxyglucose (18F-FDG) positron emission tomography (PET)/computed tomography (PET/CT), and cardiac magnetic resonance are diagnosis techniques that constitute a new arsenal whose rational use allows optimizing the assessment of cases clinically suspicion of endocarditis. The usefulness of these diagnostic tools increases in PVE[10,11].

The best therapeutic option in PVE is still controversial. Although traditionally, the surgical treatment is considered the best alternative, the pharmacological treatment may be sufficient in some patients. Generally, surgery is the option of choice when PVE causes severe prosthetic dysfunction or heart failure; as well, urgent surgery is often equally necessary in early PVE due to staphylococcus or in that one caused by fungi or other highly resistant organisms[12]. On the other hand, patients with uncomplicated late PVE, not caused by staphylococci or fungal infection, may be susceptible to conservative treatment[13].

Despite the advances in the diagnosis and treatment of this disease, hospital mortality in patients with PVE is high and has not changed in recent decades. This is the reason why our work team carried out the current study, with the aim of describing the behavior of infective endocarditis in patients with prosthetic heart valve.

METHOD

A descriptive and cross-sectional study was carried out in patients with prosthetic heart valve infective endocarditis at the *Hospital Clínico-Quirúrgico Hermanos Ameijeiras*, from January 2006 to July 2019. The population was composed of all patients admitted with infective endocarditis according to Duke's criteria in this period of time. Patients with incomplete data in the clinical records were excluded and the sample remained composed of 40 patients with PVE.

The data were obtained from the clinical records and were recorded on a collection form prepared by the researchers for this purpose. The information was automatically processed, an Excel database was created and the 20th version of the SPSS program was used, with which the statistical processing was carried out, using summary measures such as absolute frequency and percentages for qualitative variables; and the quantitative ones were expressed as mean ± standard deviation for variables with normal distribution. The research was carried out in compliance with the International Code of Medical Ethics.

RESULTS

The presented research included a sample of 40 patients with PVE. The mean age was 54.29 ± 16.07 years old with a range between 22 and 84 years old (**Table 1**). Cases were predominantly observed in the 40-49 and 60-69 years old age groups, with 27.5% each, followed by those under 40 years old (15.0%). Regarding sex, 67.5% of the patients were men.

The predominant type of PVE was the late one (65.0%), 50.0% of patients presented endocarditis in the aortic prosthetic valve, followed by compromise of the mitral prosthesis in 45% of cases (**Table 2**).

Table 1. Distribution of patients according to demographic variables (n=40).

Variables	Nº	%
Age groups* (years old)		
Under 40	6	15.0
40 – 49	11	27.5
50 – 59	5	12.5
60 – 69	11	27.5
70 – 79	5	12.5
80 and over	2	5.0
Sex		
Male	27	67.5
Female	13	13.0

* Mean age 54.29 ± 16.07 (minimum 22, maximum 84)

In most patients (14; 35.0%) the entrance route was not detected, being identified in 11 (27.5%) with

Table 2. Distribution of patients according to the time of appearance of prosthetic valve endocarditis and its location (n=40).

Variables	Nº	%
PVE time		
Late	26	65.0
Early	14	35.0
Location		
Aortic	20	50.0
Mitral	18	45.0
Mitroaortic	2	5.0

PVE, prosthetic valve endocarditis

oral sepsis (**Table 3**), followed by previous non-cardiac surgery in 10 (25.0%) and urinary sepsis in another 4 cases (10.0%). A 25% of the studied patients had PVE due to coagulase-negative staphylococcus, 10% due to staphylococcus aureus and 12.5% due to pseudomona aeruginosa. No germ was isolated in 16 patients (40.0%).

Table 3. Distribution according to entrance route and causative agent (n=40).

Variables	Nº	%
Entrance route		
Oral sepsis	11	27.5
Previous surgery	10	25.0
Urinary sepsis	4	10.0
Dermatological	1	2.5
Non-specified	14	35.0
Causative agent		
Coagulase-negative staphylococcus	10	25.0
Pseudomona aeruginosa	5	12.5
Staphylococcus aureus	4	10.0
Enterococcus	2	5.0
Klebsiella pneumoniae	2	5.0
Gram-Negative	1	2.5
Negative blood culture	16	40.0

Regarding the echocardiographic results, –all patients underwent transthoracic and transesophageal echocardiography– suggestive of paravalvular complications, the prosthesis dehiscence predominated (8 patients, 20%), followed by perivalvular abscesses (7.5%) and, in the same percentage (5%), aortic prosthetic paravalvular leak and large vegetations, as well as prosthesis thrombosis (**Table 4**). The most frequent complications were heart failure (32.5%), renal failure (22.5%) and severe sepsis (15.0%).

Surgery was necessary in 52.5% of patients and pharmacological treatment was applied in the rest of them (**Figure, panel A**). Mortality was 30%, and 28 patients (70%) were discharged alive (**Figure, panel B**).

Table 4. Distribution of patients according to echocardiographic findings and complications (n=40).

Variables	Nº	%
Echocardiographic findings		
Dehiscence	8	20.0
Abscesses	3	7.5
Aortic prosthetic paravalvular leak	2	5.0
Prosthesis thrombosis	2	5.0
Vegetation larger than 10 mm	2	5.0
Complications		
Heart failure	13	32.5
Renal failure	9	22.5
Sepsis	6	15.0
Ictus	5	12.5
Multi-organ dysfunction	4	10.0
Aortic aneurysm	3	7.5

DISCUSSION

Patients with PVE have a history of a prosthetic valve replacement in which an inflammatory process can develop near the suture points of the prosthesis, creating the conditions for the formation of thrombi and their infestation, with the development of vegetation and perivalvular abscesses.

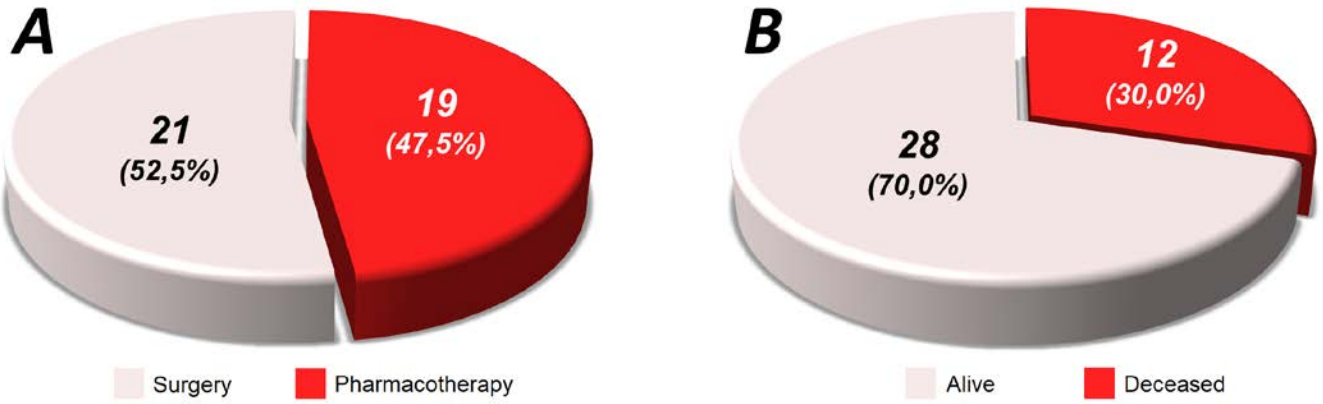

Figure. Distribution of patients according to the type of treatment received (**A**) and their condition at the moment of discharge (**B**).

These patients have a worse prognosis; heart disease prior to surgery may have affected the heart with functional sequelae, which in many cases are irreversible and compromise its hemodynamic state, thus, the presence of heart failure and pulmonary hypertension are frequent, all of which makes pharmacological and surgical treatment more difficult[14].

In the last two decades there has been a change in the clinical characteristics and microbiological origin of PVE, patients are older and predominantly male, which coincides with a decrease in the incidence of rheumatic valve disease and an increase in the degenerative disease, with an increase in infections by staphylococci, enterococci and a decrease in those produced by streptococci of viridans group[4,5]. The PVE is a more serious form of endocarditis in general, and mortality remains high despite advances in diagnosis and modifications in the therapeutic approach[4,5].

The mean age of patients included in this series is 54.29 ± 16.07 years old, with a range between 22 and 84 years old, result that is similar to that one found in other recent studies, such as those performed by Pizzi *et al*[15], Luciani *et al*[16] and Rivoisy *et al*[17], although the age range is wider. It is known that the increased incidence of PVE is one of the factors that has contributed to increase the mean age of patients with endocarditis. Predominance of males is also consistent with the reviewed literature, with a man-woman ratio of 2.07:1; although studies evaluating this are scarce, several authors[4,5,18] state that in patients with PVE the ratio is greater than 2:1.

Armiñanzas *et al*[19], in a multicenter study, assessed the epidemiological characteristics of patients with infective endocarditis in native valves and prostheses in different age groups and confirmed a predominance of males, probably due to the higher proportion of degenerative valve diseases; they also reported an increase in females while they grow older and considered that this was due to a greater life expectancy of this sex. Moreover, Sevilla *et al*[20] found a 2:1 ratio in favor of men; in women, infection on mitral mechanical prosthesis was predominant, they were older and had a higher frequency of diabetes. It has been proposed that hormonal factors may protect women from endothelial damage, but the causes of this difference are not known with certainty. Although the reason for male predominance is not clear, it is theorized that it may be a consequence of the preoperative chest hair shaving and the subsequent folliculitis. Another possible theory would be the urethral catheterization since in males the urethra is longer and more curved, and the procedure is more traumatic, which could lead to more bacteremias[21].

The clinical characteristics and the evolution of patients with early and late PVE differ, the first one being more severe and the late one behaving similarly to the native valve infective endocarditis. The early PVE predominates in the aortic valve and the late one is more frequent in the mitral valve, which may be related to the elderly patients and more frequent males' predominance of degenerative valve disease in men and mitral valve prolapse in women[9,12]. In this series, 65% of patients presented late PVE, which is consistent with the reviewed literature[3,9]. The lower incidence of early endocarditis is a consequence of improved infection prevention and

control practices, appropriate use of antimicrobial prophylaxis, adequate surgical technique and the adoption of measures to prevent and control nosocomial infection[21].

In this research, the most frequently isolated microorganism was the coagulase-negative staphylococcus (25%), followed by the pseudomonas and the Staphylococcus aureus (10%). Garrido *et al*[7] described 23.1% of coagulase-negative staphylococci and Lee *et al*[22] found 30% of Staphylococcus aureus and 22% of coagulase-negative, while Nonaka *et al*[9] found staphylococci in 80.7% of patients with early PVE, and other authors reported 14.1% affected by Staphylococcus aureus[23]. There is consensus in the literature about staphylococci being the most frequent germs in early and late PVE[5].

It is necessary to highlight the high number of negative blood cultures in the current study (40%), which is due to the administration of antibiotics prior to the admission to the cardiology department, since these patients were transferred from other institutions. There is controversy about the evolution of these patients in which no germs are isolated, some studies consider that the prognosis does not differ from the rest of patients with infective endocarditis[24], others refer that it is an independent predictor of mortality[25]. In the current research, heart failure predominated, which coincides with what other authors have described. Lopez *et al*[26] studied 257 patients with PVE and diagnosed heart failure in 145 (56.4%), with 85 (33%) deaths; this complication was an independent risk factor associated with an increase of three times in the risk of death, and heart surgery decreased mortality. However, Revilla *et al*[27] report that heart failure is the main cause of urgent surgery (57%) and does not worsen the hospital prognosis.

The most frequent complications in the cohort of patients with endocarditis studied by Romani *et al*[28] were congestive heart failure (51.5%), acute renal failure (18.2%) and embolic phenomena (12.1%), results which are similar to those of the current study. Patients with PVE researched by Glaser *et al*[29] also presented heart failure (137/355; 38.6%), systemic embolism (97/355; 27.3%), cerebral embolism (61/323; 18.9%) and intracardiac abscess (69/355; 19.4%). Another study found complications in 73.1% of patients, distributed mainly in heart failure (23.1%), embolic phenomena (65.4%) and renal failure (38.5%)[7]. Most researchers agree that heart failure is the most frequent complication in patients with PVE, worsening their prognosis, which coincides with our research.

In PVE, the expansion of infection to the valvular annulus and adjacent myocardium results in paravalvular abscess formation and partial valve dehiscence with paravalvular leak. If a large vegetation forms, it may enter the valve orifice and cause functional obstruction or it may prevent the valve from closing, causing it to become incompetent. Expansion through the aortic annulus can cause purulent pericarditis and, if it affects the membranous portion of the interventricular septum, it can cause varying degrees of atrioventricular block and intracardiac fistulas if it extends to the mitro-aortic trigone or to the ventriculo-aortic junction[30]. The sensitivity of transthoracic and transesophageal echocardiography for the detection of vegetations in PVE is 30% and 80% respectively, while the sensitivity for the detection of perianular complications is 36% and 86% respectively. The specificity of both techniques is similar and higher than 90%[31].

In 2015, the American Heart Association and the European Society of Cardiology recommended surgical treatment in PVE in the presence of heart failure or shock, severe prosthetic dysfunction or paravalvular complications, persistent bacteremia and vegetations of 10 mm or greater after an embolic event[32]. The results of a meta-analysis, including 32 articles, showed that the indication for surgery was 50%[8]; while Alonso-Valle *et al*[5] and Andrade *et al*[12] carried out a surgical treatment to 81.3% and 80.45% respectively, in patients with PVE. All of these coincide with the results of the current study.

The PVE has a worse prognosis and it is associated with a mortality rate between 20 and 50%, and the best therapeutic option is a matter of discussion. The mortality referred to in the different series varies greatly depending on the clinical characteristics and the treatment received by the patients[8]. In a study carried out in India, Abhilash *et al*[33] reported that hospital mortality associated with PVE was 23.8% and Kim *et al*[34] found an early mortality, in patients with the same diagnosis, of 11.9%. Other authors report a mortality rate of less than 30%[12,17], which is similar to −but lower than− the one of this research. Most of the current tests studying therapeutic behavior in these patients are based on observational researches and experts' opinion. Randomized clinical trials are needed to obtain reliable results[35,36]. Prevention of infective endocarditis in patients with prosthetic heart valve is essential to decrease its incidence and the patient's education concerning prophylactic measures represents an important step

towards this direction. Early diagnosis and comprehensive assessment of the patient by a multidisciplinary team, which allows the establishment of the best management in each patient, is the appropriate strategy to try for reducing mortality.

CONCLUSIONS

Most patients with prosthetic valve endocarditis are males and they are over the age of 40. The predominant type of infective endocarditis was the late one, as well as the involvement of the aortic prosthesis. No entrance route was detected in most patients and endocarditis with negative blood culture was predominant. The prosthesis dehiscence was the most frequent echocardiographic finding and the heart failure was the most frequent complication. More than half of the patients were surgically treated and were discharged alive; mortality, adjusted for this disease, was low.

REFERENCES

1. Grinberg M, Solimene MC. Historical aspects of infective endocarditis. Rev Assoc Med Bras. 2011; 57(2):228-33.
2. Palraj R, Knoll BM, Baddour LM, Wilson WR. Endocarditis sobre válvula protésica. En: Bennett JE, Dolin R, Blaser MJ. Mandell, Douglas y Bennett: Enfermedades infecciosas. Infecciones respiratorias y cardiovasculares. 8ª ed. Barcelona: Elsevier España; 2016. p. 211-26.
3. Cahill TJ, Prendergast BD. Infective endocarditis. Lancet. 2016;387(10021):882-93.
4. Olmos C, Vilacosta I, López J, Sarriá C, Ferrera C, San Román JC. Actualización en endocarditis protésica. Cir Cardiov. 2017;24(1):33-40.
5. Alonso-Valle H, Fariñas-Alvarez C, Bernal-Marco JM, García-Palomo JD, Gutiérrez-Díez F, Martín-Durán R, *et al*. Cambios en el perfil de la endocarditis sobre válvula protésica en un hospital de tercer nivel: 1986-2005. Rev Esp Cardiol. 2010; 63(1): 28-35.
6. Habib G, Lancellotti P, Antunes MJ, Bongiorni MG, Casalta JP, Del Zotti F, *et al*. 2015 ESC Guidelines for the management of infective endocarditis: The Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). Eur Heart J. 2015;36(44):3075-128.
7. Garrido RQ, Brito JO, Fernandes R, Barbosa GF, Correia MG, Golebiovski WF, *et al*. Early Onset Prosthetic Valve Endocarditis: Experience at a Cardiothoracic Surgical Hospital, 2006-2016. Surg Infect (Larchmt). 2018;19(5):529-34.
8. Mihos CG, Capoulade R, Yucel E, Picard MH, Santana O. Surgical versus medical therapy for prosthetic valve endocarditis: A meta-analysis of 32 studies. Ann Thorac Surg. 2017;103(3):991-1004.
9. Nonaka M, Kusuhara T, An K, Nakatsuka D, Sekine Y, Iwakura A, Yamanaka K. Comparison between early and late prosthetic valve endocarditis: clinical characteristics and outcomes. J Heart Valve Dis. 2013;22(4):567-74.
10. Pozo E, Olmos C, de Agustín JA, Jiménez-Ballvé A, Pérez de Isla L, Macaya C. Avances en el diagnóstico por imagen de la endocarditis infecciosa izquierda. Cir Cardiov. 2017;24(4):228-35.
11. Gomes A, Glaudemans AW, Touw DJ, van Melle JP, Willems TP, Maass AH, *et al*. Diagnostic value of imaging in infective endocarditis: a systematic review. Lancet Infect Dis. 2017;17(1):e1-e14.
12. Andrade MO, Raffoul GE, Macedo MT, Silva CN, Teixeira MA, Pontes SJ, *et al*. Experience of treatment of prosthetic valve endocarditis: a retrospective single-center cross-sectional study. Sao Paulo Med J. 2018;136(4):287-91.
13. Weinstein L, Brusch JL. Historical development of antimicrobial and surgical therapy of infective endocarditis. In: Weinstein L, Brusch JL, eds. Infective endocarditis. New York: Oxford University Press; 1996. p. 17-22.
14. Abramczuk E, Stępińska J, Hryniewiecki T. Twenty-Year Experience in the Diagnosis and Treatment of Infective Endocarditis. PLoSOne [Internet]. 2015 [cited 18 Abr 2020];10(7):e0134021. Available at: http://doi.org/10.1371/journal.pone.0134021
15. Pizzi MN, Roque A, Fernández-Hidalgo N, Cuéllar-Calabria H, Ferreira-González I, González-Alujas MT, *et al*. Improving the diagnosis of infective endocarditis in prosthetic valves and intracardiac devices with 18F-fluordeoxyglucose positron emission tomography/computed tomography angiography: Initial results at an infective endocarditis referral center. Circulation. 2015;132(12):

1113-26.
16. Luciani N, Mossuto E, Ricci D, Luciani M, Russo M, Salsano A, *et al*. Prosthetic valve endocarditis: predictors of early outcome of surgical therapy. A multicentric study. Eur J Cardiothorac Surg. 2017; 52(4):768-74.
17. Rivoisy C, Vena A, Schaeffer L, Charlier C, Fontanet A, Delahaye F, *et al*. Prosthetic valve Candida spp. endocarditis: New insights into long-term prognosis − The ESCAPE Study. Clin Infect Dis. 2018;66(6):825-32.
18. Freedman LR. Establishment of intravascular infection. En: Freedman LR. Infective endocarditis and other intravascular infections. Parte de la serie: Greenough WB, Merigan TC, eds. Current topics in infectious diseases. Boston: Springer;1982. p. 27-61.
19. Armiñanzas C, Fariñas-Alvarez C, Zarauza J, Muñoz P, González Ramallo V, Martínez Sellés M, *et al*. Role of age and comorbidities in mortality of patients with infective endocarditis. Eur J Intern Med. 2019;64:63-71.
20. Sevilla T, Revilla A, López J, Vilacosta I, Sarriá C, Gómez I, *et al*. Influence of sex on left-sided infective endocarditis. Rev Esp Cardiol. 2010;63(12): 1497-500.
21. Luk A, Kim ML, Ross HJ, Rao V, David TE, Butany J. Native and prosthetic valve infective endocarditis: clinicopathologic correlation and review of the literature. Malays J Pathol. 2014;36(2):71-81.
22. Lee JH, Burner KD, Fealey ME, Edwards WD, Tazelaar HD, Orszulak TA, *et al*. Prosthetic valve endocarditis: clinicopathological correlates in 122 surgical specimens from 116 patients (1985-2004). Cardiovasc Pathol. 2011;20(1):26-35.
23. Abdallah L, Habib G, Remadi JP, Salaun E, Casalta JP, Tribouilloy C. Comparison of prognoses of Staphylococcus aureus left-sided prosthetic endocarditis and prosthetic endocarditis caused by other pathogens. Arch Cardiovasc Dis. 2016; 109(10):542-9.
24. Ferrera C, Vilacosta I, Fernández C, López J, Olmos C, Sarriá C, *et al*. Revaluación de la endocarditis con hemocultivos negativos: su perfil es similar al de la endocarditis con hemocultivos positivos. Rev Esp Cardiol. 2012;65(10):891-900.
25. Díez-Villanueva P, Muñoz P, Marín M, Bermejo J, de Alarcón González A, Fariñas MC, *et al*. Infective endocarditis: Absence of microbiological diagnosis is an independent predictor of inhospital mortality. Int J Cardiol. 2016;220:162-5.
26. López J, Sevilla T, Vilacosta I, García H, Sarriá C, Pozo E, *et al*. Importancia clínica de la insuficiencia cardiaca congestiva en la endocarditis protésica. Estudio multicéntrico de 257 pacientes. Rev Esp Cardiol. 2013;66(5):384-90.
27. Revilla A, López J, Sevilla T, Villacorta E, Sarriá C, Manzano MC, *et al*. Pronóstico hospitalario de la endocarditis protésica tras cirugía urgente. Rev Esp Cardiol. 2009;62(12):1388-94.
28. Romaní F, Cuadra J, Atencia F, Vargas F, Canelo C. Endocarditis infecciosa: análisis retrospectivo en el Hospital Nacional Arzobispo Loayza, 2002-2007. Rev Peru Epidemiol [Internet]. 2009[cited 26 Abr 2020];13(2). Available at: https://sisbib.unmsm.edu.pe/BVRevistas/epidemiologia/v13_n2/pdf/a04v13n2.pdf
29. Glaser N, Jackson V, Holzmann MJ, Franco-Cereceda A, Sartipy U. Prosthetic valve endocarditis after surgical aortic valve replacement. Circulation. 2017;136(3):329-31.
30. Vilacosta I, Olmos C, de Agustín A, López J, Islas F, Sarriá C, *et al*. The diagnostic ability of echocardiography for infective endocarditis and its associated complications. Expert Rev Cardiovasc Ther. 2015;13(11):1225-36.
31. Habets J, Tanis W, Reitsma JB, van den Brink RB, Mali WP, Chamuleau SA, *et al*. Are novel noninvasive imaging techniques needed in patients with suspected prosthetic heart valve endocarditis? A systematic review and meta-analysis. Eur Radiol. 2015;25(7):2125-33.
32. Baddour LM, Wilson WR, Bayer AS, Fowler VG, Tleyjeh IM, Rybak MJ, *et al*. Infective Endocarditis in Adults: Diagnosis, Antimicrobial Therapy, and Management of Complications: A Scientific Statement for Healthcare Professionals From the American Heart Association. Circulation. 2015; 132(15):1435-86.
33. Abhilash KPP, Patole S, Jambugulam M, Sathyendra S, Mitra S, Rebekah G, *et al*. Changing trends of infective endocarditis in India: A South Indian Experience. J Cardiovasc Disease Res. 2017;8(2):56-60.
34. Kim YW, Jung SH, Choo SJ, Chung CH, Lee JW, Kim JB. Outcomes of reoperative valve replacement in patients with prosthetic valve endocarditis: A 20-year experience. Korean J Thorac Cardiovasc Surg. 2018;51(1):15-21.
35. Bin Abdulhak AA, Tleyjeh IM. Indications of surgery in infective endocarditis. Curr Infect Dis Rep [Internet]. 2017 [cited 26 Abr 2020];19(3):10. Avail-

able at: https://doi.org/10.1007/s11908-017-0569-6
36. San Román JA, Vilacosta I, López J, Sarriá C. Critical questions about left-sided infective endocarditis. J Am Coll Cardiol. 2015;66(9):1068-76.