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# Non-bacterial Thrombotic Endocarditis

*Carmen Busca-Arenzana, Angel Robles-Marhuenda,  
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## Abstract

Non-bacterial thrombotic endocarditis or also called verrucous endocarditis or Libman-Sacks endocarditis or marantic endocarditis is a rare entity, still unknown physiopathology, which is characterized by the formation of sterile vegetations at the valvular structures. These vegetations of platelet aggregates and fibrin are sterile by definition, so for its definitive diagnosis, it is essential to rule out an infectious endocarditis. It is mainly diagnosed by echocardiography in patients with neoplasms or systemic autoimmune diseases. Its main complication is the formation of multi-systemic embolisms, preferably at the brain level, so anticoagulation will be fundamental in the treatment and evolution of non-bacterial thrombotic endocarditis.

**Keywords:** Libman-Sacks endocarditis, marantic endocarditis, non-bacterial thrombotic endocarditis, non-infective endocarditis, verrucous endocarditis

## 1. Introduction

Non-bacterial thrombotic endocarditis (NBTE) is a rare entity in which a state of hypercoagulability predisposes to the formation of sterile vegetations in heart valves and secondary systemic embolisms, mainly in the central nervous system. In many occasions, the diagnosis is made postmortem, finding up to 0.2% of the autopsies of the general population [1]. The pathogenesis is unknown, being associated mainly with the existence of neoplastic processes and systemic autoimmune diseases (mainly in systemic lupus erythematosus (SLE) or antiphospholipid syndrome (APS)).

For the diagnosis it is necessary to demonstrate the presence of valvular vegetations by echocardiography, ruling out the existence of an underlying infection. There is no specific treatment, so it is recommended to control the predisposing disease and the initiation of anticoagulation to avoid the production of systemic embolisms [2].

## 2. Epidemiology and etiology

The NBTE is a rare pathology, whose diagnosis occurs generally in autopsies, being present in 0.9–1.2% of them, according to the series [3]. However, it is believed to be an underdiagnosed entity. It is described at any age, although it is more prevalent in patients between 40 and 80 years of age. Children tend to present milder clinical forms, with a lower number of systemic embolisms [4].

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a. Malignancy
<ul style="list-style-type: none"><li>• Mucin-secreting and pancreatic adenocarcinoma</li><li>• Lung malignant neoplasm</li><li>• Ovary carcinoma</li><li>• Colon carcinoma</li><li>• Prostate carcinoma</li><li>• Cholangiocarcinoma</li><li>• Lymphoma</li></ul>
b. Systemic autoimmune diseases
<ul style="list-style-type: none"><li>• Systemic lupus erythematosus</li><li>• Antiphospholipid syndrome</li><li>• Systemic vasculitis<ul style="list-style-type: none"><li>◦ Giant cell arteritis</li><li>◦ Behçet disease</li><li>◦ Takayasu's arteritis</li><li>◦ Polyangiitis with granulomatosis</li></ul></li></ul>
c. Hypercoagulability states
<ul style="list-style-type: none"><li>• Protein S and C deficiency</li><li>• Disseminated intravascular coagulation</li><li>• Thrombotic microangiopathy<ul style="list-style-type: none"><li>◦ Thrombotic thrombocytopenic purpura</li><li>◦ Catastrophic antiphospholipid syndrome</li></ul></li></ul>
d. Chronic inflammatory status
<ul style="list-style-type: none"><li>• Tuberculosis</li><li>• Uncontrolled HIV</li><li>• Chronic pyelonephritis</li><li>• Chronic osteomyelitis</li></ul>
e. Others
<ul style="list-style-type: none"><li>• Adenomyosis</li><li>• Hypereosinophilic syndrome</li><li>• Chronic alcoholism</li><li>• Chronic renal insufficiency</li><li>• Heart failure with valvulopathy</li><li>• Toxic oil syndrome</li></ul>

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**Table 1.**  
*Causes of NBTE.*

The neoplastic disease, generally advanced, is the main risk factor for the development of NBTE. If compared with the general population, this subgroup has a higher risk of presenting it (1.25 vs. 0.2%, respectively) according to a series of autopsies [5, 6]. The adenocarcinomas (i.e., colon, ovary, lung) are the most

frequent tumors, observing a greater number of cases in the pancreatic and mucin secretors. Other pathologies that are associated are the SLE and the APS. In the SLE, different observational studies show a prevalence ranging between 6 and 11%, being more frequent among lupus patients with antiphospholipid antibodies [7]. Although exceptionally, NBTE can be a complication of systemic infections such as tuberculosis and HIV, and cases have been described in the context of uremia, adenomyosis, and even giant cell arteritis [8]. It should be said that in the cases mentioned of infectious etiology (i.e., tuberculosis, HIV), the development of NBTE is not determined directly by microorganisms, but by alterations in coagulation induced by the underlying chronic inflammatory process (Table 1).

### 3. Pathogenesis

NBTE is a type of noninfectious endocarditis whose physiopathology continues to be unknown. It is characterized by the deposition of sterile platelet thrombi in the heart valves. In certain situations of hypercoagulability, endothelial damage occurs that favors the migration of mononuclear inflammatory cells and platelet deposition, being these responsible for the formation of fibrin thrombi and immune complexes (thrombi known as “white thrombus”). The term Libman-Sacks is used when you see a large thrombus or “wart” (verruccous endocarditis).

One of the main and differential characteristics of this entity is that the valvular vegetations must always be sterile (unlike infectious endocarditis (IE)). The mitral and aortic valves are the most frequently affected (rare right endocarditis), and it is common for NBTE to appear on healthy native valves, endocardium, or chordae tendineae.

Unlike IE, vegetations of the NBTE are more friable because they develop on a tissue with an important inflammatory reaction. This makes them more likely to produce systemic embolisms. They are located in the valvular coaptation lines and



**Figure 1.**  
*ETE-3D: Three-dimensional view of the aortic valve showing a rupture of the left coronary leaflet with images suggesting multiple vegetations of the valve in a 56-year-old man with Libman-Sacks endocarditis and SLE. ETE-Velos: Short axis view of the aortic valve showing a rupture of the left coronary leaflet with images suggesting thickening and multiple vegetations in the leaflets.*

are generally not accompanied by destruction of the valvular tissue. In terms of their size, they tend to be smaller and develop on a broad and irregular basis [9].

In NBTEs associated with malignancy, it is believed that macrophages interact with tumor cells, causing a migration of cytokines (tumor necrosis factor, interleukin-1, etc.) that produces endothelial tissue damage and the formation of friable thrombi due to the deposition of platelets. On the other hand, the macrophage-tumor cell interaction favors overactivation of the coagulation cascade, which in turn worsens the state of hypercoagulability that underlies the process. For this reason, NBTE tends to develop around areas of greater valve turbulence [3].

Libman-Sacks endocarditis is the most characteristic cardiac manifestation of SLE, with pericarditis being the most frequent cardiac manifestation [10]. It was first described in 1924, by Libman and Sacks at Mount Sinai Hospital in New York. From the macroscopic point of view, these deposits, usually located on the ventricular surface of the posterior leaflet of the mitral valve, are translated into vegetations with progressive growth or only thickening of the leaflets (**Figure 1**). The classic histopathological lesion consists of a deposit of fibrin and mononuclear cells. The immunofluorescence reveals immunoglobulin deposit and complement. Valvular involvement is usually silent and occurs in approximately half of patients with SLE, although in some cases valvular dysfunction can be the origin of heart failure. As in other NBTEs, the mitral and aortic valves are affected more frequently than those on the right side, with valvular insufficiency prevailing over the stenosis. The presence of lupus anticoagulant increases the risk of suffering thrombotic and embolic phenomena in these patients [11].

## **4. Clinical presentation**

NBTE is characterized as an asymptomatic disease in early stages, whose most frequent initial manifestation is the presence of systemic embolisms. Although it can occur at any age, it is believed that young patients are less likely to suffer from embolic phenomena at a distance.

The clinic of valvular dysfunction (in the form of heart failure, syncope, etc.) usually appears in more advanced stages of the disease, and although it is recognizable by echocardiographic studies, they usually have little hemodynamic repercussion, except in advanced cases or the presence of large masses. The development of heart failure is present in less than half of patients with underlying valvular dysfunction.

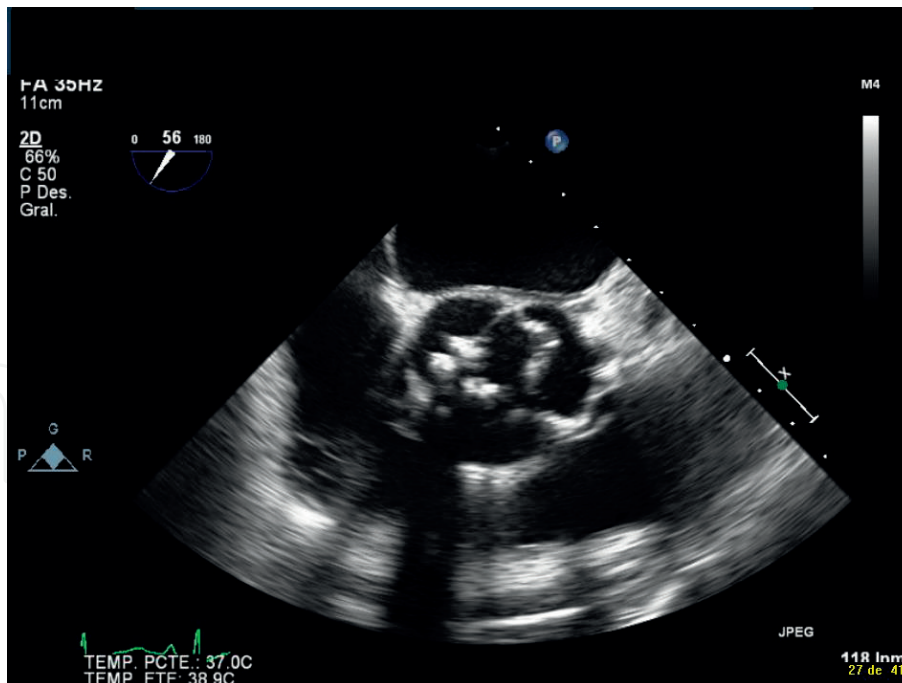
### **4.1 Characteristics of embolisms**

Given the rarity of this entity, the incidence of embolisms at the systemic level is not known. It is believed that it can appear from 14 to 91% of the NBTE. The embolisms, some with hemorrhagic transformation, are more frequent in cases associated with malignancy [12]. In these patients, embolisms are evident in up to 50% of the cases, the most frequent clinical form being the central nervous system involvement.

Patients with NBTE usually debut in the form of multiple embolisms, especially distributed throughout the brain territory in the form of multiple infarcts (sometimes casual diagnosis after performing brain imaging tests). This contrasts with IE, where typically infarcts are usually focal and/or localized.

### **4.2 Signs and symptoms**

Most patients are asymptomatic during the early stages of the disease. In fact, the appearance of fever, weight loss, and night sweats is uncommon, and its presence should guide us in the search for an underlying neoplastic process. On the other hand,



**Figure 2.**  
*ETT-IM: Four-chamber color view showing a jet of severe mitral regurgitation in a 48-year-old man with catastrophic antiphospholipid syndrome.*

the association of arthritis, photosensitive skin lesions, and arterial and/or venous thromboses requires screening for systemic autoimmune diseases (SLE or APS).

The typical form of presentation (in more than half of the cases) derives from the symptoms and signs that occur as a result of the presence of systemic embolisms. Although they can be produced in different organs (CNS, kidney, spleen, skin, etc. ), in 50% of cases, embolisms are observed at the pulmonary level, sometimes in the absence of valvular lesions in right cardiac cavities [13].

Sometimes the symptoms may be mild or nonspecific, such as hematuria, lumbar pain, and rash, in the context of renal, splenic, or cutaneous embolisms, respectively. However, the presence of coronary and CNS lesions is more specific and helps the diagnosis more early (chest pain, psychomotor agitation, delirium, stroke, etc.). The debut in the form of valvular insufficiency or decompensated heart failure is very infrequent [14] (**Figure 2**).

## 5. Diagnosis

The diagnosis of NBTE is a challenge for the clinician (which is why it is often diagnosed after carrying out necropsies) and not only due to the lack of specificity of the clinic but also because it occurs in advanced stages of the disease.

The diagnosis of NBTE is made through a high clinical suspicion after observing systemic manifestations derived from systemic embolisms and after performing complementary imaging tests (echocardiogram and transesophageal echocardiography mainly) that confirm the presence of valvular vegetations. However, the definitive diagnosis can be obtained after histologically demonstrating the presence of platelet thrombi at the level of the cardiac valves. It is a rare phenomenon, since valvular biopsies are not performed routinely. For this, it is essential to rule out the presence of a systemic infection and to identify the underlying etiology (mainly autoimmune neoplasms and diseases).

It is necessary to make a correct differential diagnosis that includes IE, degenerative valvular disease, rheumatic valvular disease, and normal anatomic variants. Applying the modified Duke's criteria can help establish the IE diagnosis [15].

Therefore, we should suspect an NBTE in those patients with active neoplasia, SLE or, APS who present coronary or CNS ischemia or, in the absence of said predisposing pathologies, in those cases in which we suspect an IE (without microbiological findings) that does not respond adequately directed empirical antibiotic treatment and that evolves torpidly with a greater number of systemic embolisms.

### 5.1 Laboratory and microbiology test

There are no specific analytical tests that suggest the presence of an NBTE. Depending on the causative disease, we can find analytical alterations that support or not a diagnosis. A complete blood test should be performed, including blood count, biochemistry, liver test, and coagulation panel. In some patients with NBTE, data of disseminated intravascular coagulation can be evidenced. In case of suspicion of autoimmune disease, a complete immunological study should be requested, mainly from SLE and APS (including antinuclear antibody, anti-double-stranded DNA, and antiphospholipid antibodies). It will be necessary to carry out a screening of the most frequent types of neoplasms taking into account the sex, the comorbidities, and the age range of the patient.

Many authors suggest that before diagnosing an NBTE, it is essential to rule out an IE after carrying out different microbiological tests. In fact, at least three sets of blood cultures must be made before any suspicion of IE. Sometimes blood cultures in the presence of valvular vegetations can be persistently negative and do not rule out the presence of IE (called “culture-negative endocarditis”). For this reason, cultures of other biological fluids (urine, feces, etc.) should be performed, and serology and PCR should be performed on those less frequent or “atypical” microorganisms that can also cause IE (e.g., *Brucella* spp., *Coxiella burnetii*, *Legionella*, etc.) (Table 2).

### 5.2 Radiological image tests

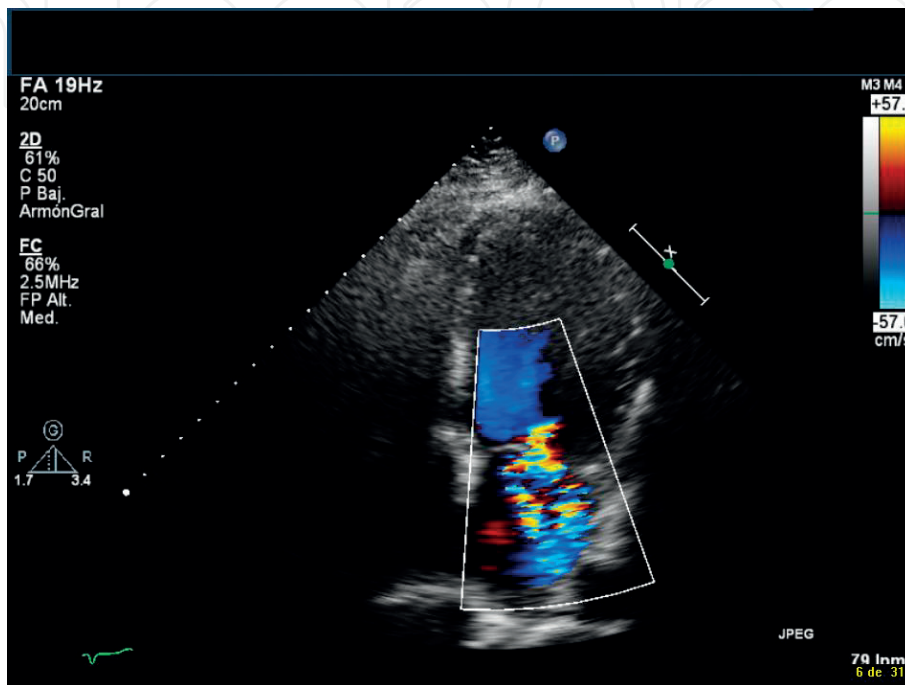
The performance of radiological image tests will depend on the symptomatology that the patient presents, since they will provide information in those cases of complicated NBTE. In chest X-ray, we can observe data that suggest heart failure (cardiomegaly, pleural effusion, etc.). Cranial computed tomography (CT) and magnetic resonance (MR) imaging are very useful for the diagnosis of cerebral embolisms, since if we suspect an NBTE, multiple infarcts will be observed, widely distributed, heterogeneous in size, and mainly ischemic. Cardiac MR or positron emission tomography may help in the differential diagnosis.

1. Previous antibiotic treatment
2. Technical problems with microbiological diagnosis
3. Acute renal failure or renal insufficiency
4. Ventricular or atrial septal defects, cardiac thrombi post-acute coronary disease, or cardiac pacemaker infection
5. Unusual microorganisms ( <i>Brucella</i> spp., <i>Coxiella burnetii</i> , <i>Bartonella</i> spp., <i>Legionella</i> spp., <i>Mycoplasma</i> spp., <i>Tropheryma whipplei</i> , mycotic infections, and HACEK group infections— <i>Haemophilus</i> spp., <i>Aggregatibacter</i> spp., <i>Cardiobacterium hominis</i> , <i>Eikenella corrodens</i> , and <i>Kingella</i> species)

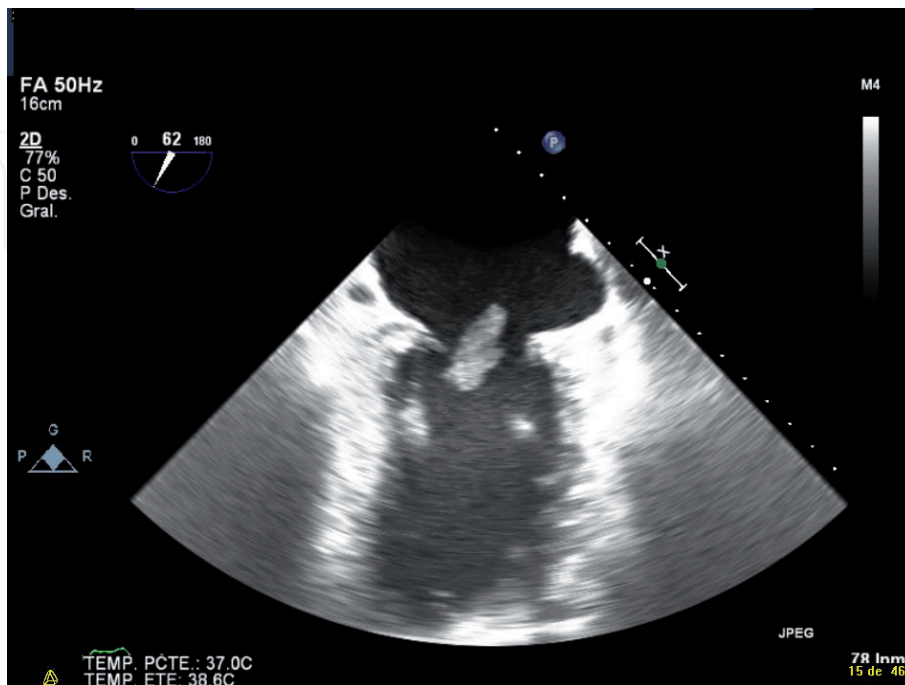
**Table 2.**  
Culture-negative endocarditis causes.

### 5.3 Echocardiography

In those patients with suspected NBTE, a two-dimensional transthoracic echocardiography (TTE) should be performed to demonstrate the presence of vegetations or valvular thickening (**Figure 3**). Vegetations in the NBTE usually appear in left valves, with the mitral valve most frequently affected (up to 75% of cases) followed by the aortic valve. Several valves can be affected simultaneously, although it is usually an uncommon finding (**Figure 4**).



**Figure 3.**  
*ETE-2C: Mid-esophageal two-chamber view showing a 28-mm vegetation in the mitral valve.*



**Figure 4.**  
*ETE-2C: Mid-esophageal two-chamber color view. A vegetation in the mitral valve can be visualized. A severe mitral regurgitation jet is shown in this figure.*



However, TTE has several limitations. Small vegetations (below 5 mm) may go unnoticed, so if the clinical suspicion is still high, there is an indication to perform a transesophageal echocardiography (TEE), since it is more sensitive and specific than the TTE in detecting smaller vegetations. Do not forget that very small vegetations (<3 mm) cannot be detected by both types of echocardiogram, being able to obtain “false negatives.” If the clinical suspicion persists, echocardiographic study should be repeated after a prudential time. Although TTE is less sensitive and specific than TEE, it should always be performed not only to confirm the presence of endocarditis but also to evaluate other fundamental parameters such as function and cardiac volumes.

Although the echocardiogram is essential in the diagnosis of valvular vegetations, it will not be useful for the differential diagnosis of the type of endocarditis (thrombotic infection vs. aggregations of platelets and fibrin).

## **5.4 Histology**

Although the definitive diagnosis is histological, most of the anatomopathological tests of valvular vegetations are obtained from necropsies or after valve replacement after the finding of a severe dysfunction or insufficiency, being very rare the biopsies of tendinous, valvular cords, or endocardial.

## **6. Treatment and management**

There is no specific treatment for NBTE. The two basic pillars are systemic anticoagulation and targeted specific treatment of the associated disease (chemotherapy, corticosteroids, etc.). In general, surgery by means of intervention, debridement, or valve replacement is usually not necessary and is rarely indicated.

### **6.1 Anticoagulation**

Anticoagulant treatment is essential in the management of NBTE since it aims to prevent the production of systemic embolisms. In fact, unlike EI, these patients have an indication for anticoagulation for long periods of time or even indefinitely (unless absolutely contraindicated), regardless of whether embolic phenomena are observed or not. This fact is based on the fragility of the vegetations and the recurrent tendency to systemic embolization, especially in the absence of antithrombotic therapy. It should always be anticoagulated with a double objective: preventive and therapeutic. There are no published randomized clinical trials or prospective studies, so the recommendations are based on case series and retrospective studies and are supported by the American College of Chest Physician’s antithrombotic therapy for valvular heart disease guidelines [16].

Anticoagulation will be carried out by subcutaneous low molecular weight heparin or intravenous unfractionated heparin at anticoagulant doses. All the evidence published to date supports the use of this pharmacological family and does not recommend the use of warfarin, direct thrombin, nor factor Xa inhibitor (direct oral anticoagulants like apixaban, rivaroxaban, dabigatran, or edoxaban) especially in patients with active neoplastic disease since they seem to have less efficacy in the reduction of systemic embolisms. There is no data to support the use of the new anticoagulants. Recently the first case of cancer-associated non-bacterial thrombotic endocarditis in the era of direct oral anticoagulants was published where a patient with a previous history of thromboembolic disease developed a NBTE with vegetations and multiple cerebral embolisms in the context of a pancreatic adenocarcinoma despite being under treatment with rivaroxaban at optimal doses [17]. This case supports the

need to carry out more studies that help to elucidate the physiopathogenic mechanisms of the NBTE with the aim of achieving an optimal anticoagulant regimen.

The most frequent complications are life-threatening bleeding and thrombocytopenia. The development of any of these complications will force clinicians to raise the risk-benefit of their use and therefore to value discontinuing their use.

## **6.2 Surgery**

In general, indications for valve replacement or vegetation excision are very limited in the NBTE. The main objective of surgery in the NBTE is to reduce or prevent the production of systemic embolisms. Because there are no prospective clinical trials, the same recommendations should be followed as in patients with IE [18].

However, unlike IE, we will try to preserve the valve as much as possible and focus all the objectives in controlling the state of hypercoagulability by treating predisposing disease.

When deciding whether a patient is going to benefit from surgery, it is essential to assess the risk-benefit individually. The surgical repair of heart valve is preferable (it is less aggressive, has less mortality, and in general decreases the need for postoperative anticoagulation), with respect to valve replacement. The latter will be considered depending on the complications and the degree of destruction or valvular insufficiency. We must take into account the prognosis of life and morbidity and mortality, especially in patients with advanced neoplastic diseases. Although there is little evidence, it is believed that anticoagulation should be maintained after surgery, especially in patients with systemic autoimmune diseases (mainly in APS).

## **6.3 Treatment for underlying disease**

The treatment of neoplasia or systemic autoimmune disease is a fundamental pillar in the management of NBTE. It is very probable that at the time of diagnosis of the neoplasm, distant metastases are already observed, which will considerably reduce the probability of therapeutic success. The same is not true in patients with SLE, where NBTE can be diagnosed at any time and whose presence does not correlate with the activity index. The treatment of patients with lupus valve disease includes prophylaxis of endocarditis, antiplatelet or anticoagulant treatment in selected cases, and valvular replacement when valvular involvement is severe; the role of corticosteroid treatment in the evolution of valvular disease is still undetermined. Regarding the type of surgical intervention, there are controversies. Some authors suggest the superiority of mechanical prostheses in this type of condition over bioprostheses, including cryopreserved homografts, as these can contract lupus valvulitis on the new valve. However, other authors have advocated reconstructive surgery to avoid the disadvantages of a mechanical prosthesis in young patients who usually require high doses of steroids and anticoagulant therapy [19].

It is unknown whether NBTE improves with antineoplastic therapy, and therefore it is believed that anticoagulation should be maintained independently of the response to treatment of the underlying disease.

## **7. Evolution and prognosis**

### **7.1 Follow-up**

The follow-up should be individualized depending on the characteristics and morbidities of each patient. It will be necessary to take into account possible

complications of the disease or treatment: systemic embolization, bleeding, or thrombocytopenia. It will be necessary to periodically perform echocardiograms to monitor valve function, control the development of new vegetations (or check their resolution), as well as monitor the appearance of an IE concomitantly.

## 7.2 Prognosis

The prognosis of NBTE has not been correctly evaluated in prospective studies. In general, the prognosis of these patients is poor, although it will depend on the type of disease and the type or location of the complications, independently of the anticoagulant treatment.

## 8. Conclusions

- The NBTE is an entity characterized by the presence of vegetations of noninfectious origin constituted by fibrin and platelet accumulations with high emboligenic potential.
- The most frequent etiologies are neoplasms (especially carcinoma of the pancreas) in an advanced or disseminated phase, without forgetting the systemic immune-mediated processes such as lupus.
- Embolism and valvular dysfunction are the two most frequent complications found in NBTE. The incidence of systemic embolisms is around 50% in malignant NTBE, with neurological manifestations being the most common.
- The therapeutic attitude in these patients should be directed toward the control of the underlying disease and the hypercoagulable state or the treatment of the embolisms.

## Conflict of interest

The authors do not present any conflict of interest.

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