Chapter 5

Buerger's Disease: Clinical Aspects and Evidence-Based Treatments

Daniel Guimarães Cacione

Additional information is available at the end of the chapter

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Abstract

Buerger's disease (thromboangiitis obliterans) is a nonatherosclerotic, segmental, occlusive, and recurring progressive inflammatory form of vasculitis that most commonly affects the small- and medium-sized arteries, veins, and nerves in the upper and lower extremities. The cause is unknown, but it is most common in young men with a history of tobacco abuse. It is responsible for ischemic ulcers and extreme pain in the hands and feet. In many cases, notably in patients with the most severe presentations, there is no possibility of improving the condition with surgery (limb revascularization), and therefore, alternative therapies (e.g., sympathectomy, pharmacological agents, and many others) are used. This chapter discusses clinical aspects of Buerger's disease and evidence-based treatment available currently.

Keywords: thromboangiitis obliterans, vasculitis, limb ischemia, evidence-based treatments

1. Introduction

Thromboangiitis obliterans [Buerger's disease (BD), von Winiwarter disease, **t**hromboangiitis obliterans, presenile gangrene] is a nonatherosclerotic, segmental, occlusive, and inflammatory form of vasculitis that affects arteries with small and medium calibers, veins, and nerves in the upper and lower extremities [1]. Alexander von Winiwarter (Austrian-Belgian surgeon) described one patient with the disease in 1879 [2], but it was Leo Buerger (Austrian-American surgeon), in 1908, who published a complete description of the changes in arteries (intimal thickening, occlusive thrombus, and preservation of arterial architecture) on 11 amputated limbs in young smoker males and named the disease [3].

Buerger's disease (BD) has a global distribution, with a prevalence in patients with peripheral arterial disease (PAD) that ranges from 0.5 (in western Europe) to 66% (Asian countries, such as Japan and Korea) [1, 4, 5].

The etiology remains unknown but involves tobacco exposure (*sine qua non*), hereditary susceptibility, immune response, and coagulation changes [5]. Currently, a possible infectious role is gaining interest, especially after the findings of bacteria of the oral flora in occlusive thrombi in patients with Buerger's disease and moderate to severe periodontitis [6, 7]. Another hypothesis is the possibility of rickettsial infection (associated with environment conditions and genetic susceptibility) in Buerger's disease pathogenesis [8, 9]. Features distinguishing Buerger's disease from atherosclerosis (the main differential diagnosis) include the anatomical distribution of the occlusions (with involvement of both the upper and lower extremities in many cases), associated superficial venous thrombosis, a paucity of atherosclerotic risk factors, and normal proximal large arteries [10].

2. Clinical aspects

The "standard" or the classical profile of Buerger's disease (BD) patient is a young man, aged less than 45–50 years, and a history of previous or current smoking (in about 93% of the patients), presenting symptoms suggestive of ischemia in the distal region of limbs. Usually, ischemia restricted to the lower limb occurs in 74.7% cases, and only in the upper limbs in 20.2% cases, and in both limbs, 5.1% cases [11].

Regarding the degree of ischemia in patients with BD at admission, there is a prevalence of the most advanced degrees, and pain at rest may appear in 23.9% of cases, and ischemic ulcers and gangrene in 38% cases [11]. Intermittent claudication occurs in about 30% of cases, typically as "foot claudication," because of the more distal distribution of the disease.

Other signs and symptoms may occur, such as purpura or flushing of the extremities, coldness, migratory thrombophlebitis (16–38%) [1, 11], Raynaud's phenomenon (44%) [1], and rheumatic manifestations in joints in 12.5% usually preceding the ischemic condition. The Allen test is abnormal in 63% of the cases [1].

The frequency of arterial involvement has been demonstrated in the study by Sasaki et al. [12], including 825 patients from a national survey of intractable vasculitis in Japan. The distribution of arterial disease in this national survey presented a higher prevalence of the disease in the lower extremities presenting in the order of frequency as the anterior tibial (41.4%) and posterior tibial arteries (40.4%), followed by the dorsalis pedis artery (21.2%), fibular (18.4%), and popliteal (18.2%) in the lower extremities. In the upper extremities, there exists predominance of ulnar arteries (11.5%), digital arteries (8.1%), and radial arteries (7.0%). Left or right limb preference was not observed. The involvement of visceral, cerebral, coronary, and internal thoracic arteries is uncommon.

Because of the lack of clinical or laboratory indicators of Buerger's disease and the frequent difficulty in differentiating thromboangiitis obliterans from other vascular pathologies that

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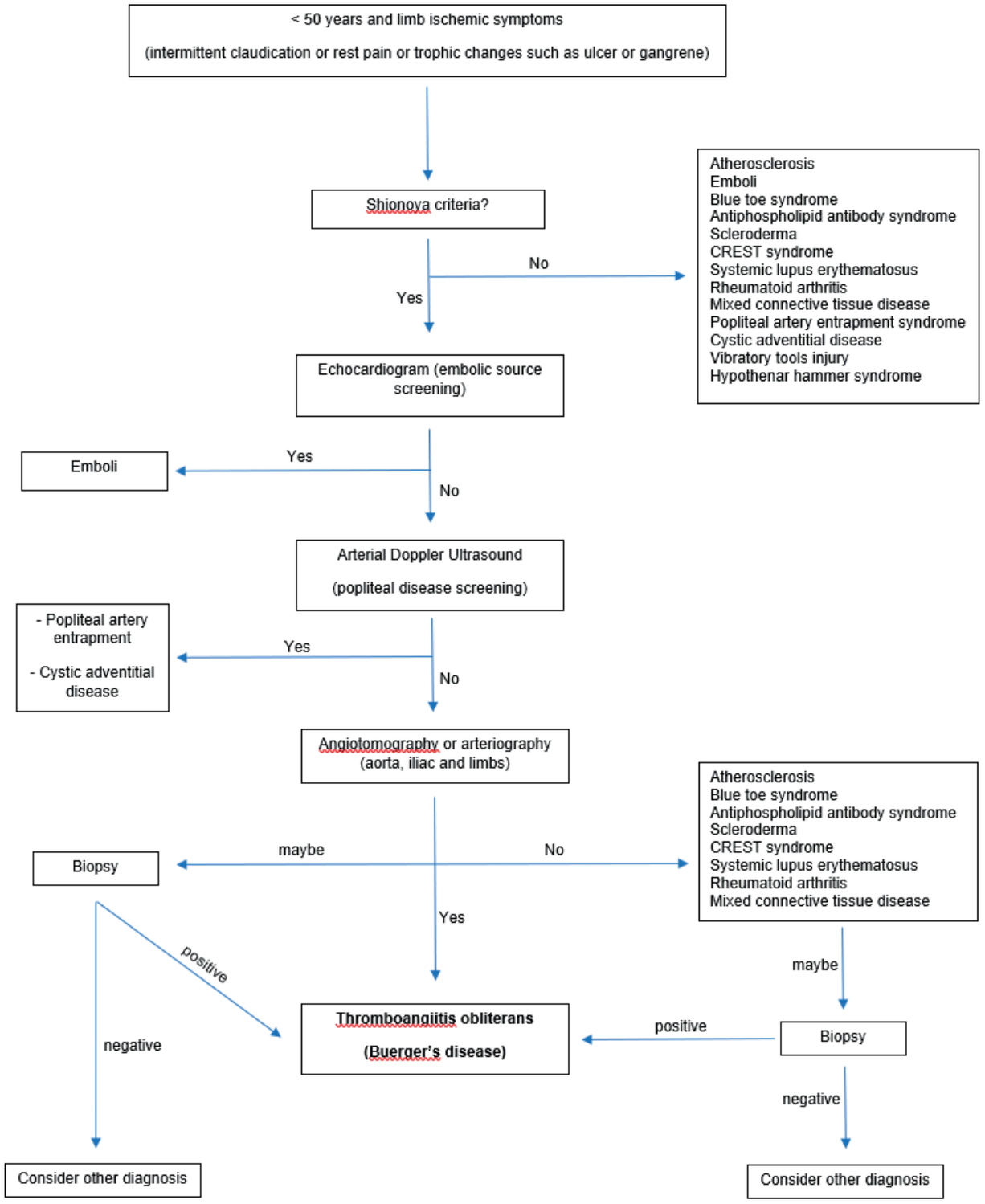

Figure 1. Fluxogram for the diagnosis of Buerger's disease.

might affect the extremities, a number of criteria have been published. The simplest criterion is Shionoya [13], which consists of the presence of five mandatory items: (1) history of smoking, (2) beginning before the age of 50, (3) infrapopliteal occlusive lesions, (4) involvement of upper limbs or migratory phlebitis, and (5) absence of atherosclerotic risk factors, with the exception

of smoking. Subsequently, other criteria were elaborated, such as those of Papa and Adar [14], Mills and Porter [15], Olin [1], and the Ministry of Health of Japan [12]. Basically, in addition to the clinical criteria for inclusion by Shionoya, exclusion criteria were added to the findings by noninvasive, angiographic, and histopathological methods (biopsy) to establish the diagnosis.

The use of ultrasound (echocardiogram, arterial, and venous Doppler) is a useful diagnostic tool for the radiographic exclusion of a possible embolic etiology (valvular heart disease, aortic aneurysm, or atherosclerotic) that can mimic the distal ischemia of BD and promote a topography of occlusion and other findings, such as arterial collateralization and phlebitis [1].

Arteriography is an important image examination for confirming the diagnosis of Buerger's disease [16]. Examination findings, which suggest thromboangiitis, include multiple segmental occlusions of the medium- and small-size arteries, mainly below the knee line and elbows, and the presence of collateral arteries adjacent to the areas of occlusion, classically described as a "corkscrew" shape (Martorell's sign) [5, 16].

Biopsy is not routine in the diagnosis of thromboangiitis obliterans, reserved for cases of diagnostic doubt [1]. The histological findings depend on the stage of the disease: in the acute phase, it includes occlusive thrombus with inflammatory characteristics and high cellularity, but with less inflammation in the walls of the blood vessels. Polymorphonuclear leukocytes, micro-abscesses, and multinucleated giant cells may exist in the intermediate phase, in which there is a progressive organization of the thrombus in the arteries and veins. Finally, in established disease, there is a well-organized thrombus with fibrosis [17].

Figure 1 illustrates a suggested fluxogram for the diagnosis of Buerger's disease.

3. Evidence-based treatments

Before studying the types of treatment for Buerger's disease, it is important to present the evidence-based method of evaluation based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) adopted in this chapter. The GRADE (Grading of Recommendations Assessment, Development and Evaluation) Working Group, formed since the year 2000 by health professionals around the world who research on health evidences, has developed a quality-of-evidence classification system [18]. The quality of a body of evidence defined by GRADE involves consideration of the risk of bias, the objectivity of the results obtained, the heterogeneity of the studies, the precision of the effect estimates, and the risk of publication bias. The GRADE system implies an evaluation of the quality of a body of evidence for each individual outcome and, consequently, how sure the authors are about the efficacy (direction and magnitude) of some intervention [19].

Evidence quality grades are classified as high, moderate, low, and very low. For research on drug efficacy, for example, the highest level of evidence is obtained through randomized controlled clinical trials [19]. From the findings of these trials for a given outcome (e.g., pain at rest), the degree of evidence may vary. Some factors may decrease the strength of evidence, such as studies with a high risk of bias, results obtained through indirect findings

(e.g., through comparisons between two interventions that were not confronted in the same study, but in different studies of meta-analysis), presence of heterogeneity in meta-analysis of studies or inconsistencies in the data collected, inaccuracy of results obtained (e.g., a very wide confidence interval), and a high probability of publication bias [19]. Other factors, however, may increase the strength of evidence such as a large magnitude of effect (very high or very low relative risk, well away from the null hypothesis) and gradient-dose response [19]. Thus, after analysis of the potential factors that might strengthen or weaken a given evidence for a specific outcome, the level of evidence available up to that moment is determined [19]. The GRADE Working Group definitions for grading the quality of evidence are among the commonly used definitions illustrating a high, moderate, low, and very low-quality definitions as follows [19]:

"**High** = Further research is very unlikely to change our confidence in the estimate of effect.

Moderate = Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low = Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low = Any estimate of effect is very uncertain."

3.1. Overview of the treatments

The treatment of patients with Buerger's disease is based primarily on the complete abolition of smoking. Concomitantly, depending on the degree of ischemia, the measurements are similar to those adopted in patients with peripheral occlusive arterial disease of atherosclerotic etiology: in patients with intermittent claudication, the performance of scheduled exercises, for patients with critical ischemia (rest pain or trophic lesions), provides conditions that increase limb perfusion (revascularization, sympathectomies, pharmacological agents, etc.), as well as analgesia and wound and extremity care.

3.2. Arterial revascularization

The surgical revascularization of limbs in patients with BD is controversial due to the high index of graft occlusion. The important distal involvement of Buerger's disease greatly impairs surgery and long-term patency [5]. Sasajima et al. [20], who present the Japanese experience of 18 years in revascularization in the infra-inguinal territory in patients with thromboangiitis, report the performance of 71 autologous vein grafts in 61 patients with BD and the occurrence of 38 (53%) graft occlusions. Among the possible causes for the high rate of graft failure is the fact that the distal anastomosis is usually performed in diseased artery and subject to frequent vasospasm, the progression of the inflammatory disease itself, the use of veins with "low quality" (because they are also affected by inflammation), and vein stenosis due to myointimal hyperplasia. Among studies about arterial revascularization, figures about a 1-year patency are around 60%. However, because of the design of the studies (prospective and retrospective case series), the evidence is **very low**.

Microsurgical delivery is performed in cases after successful revascularization, in order to reduce the recovery time of patients with superficial gangrene or ischemic ulcers [21]. However, as observed in arterial revascularization, because of the design of the studies (case series), the evidence is **very low**.

3.3. Lumbar sympathectomy

Surgical treatment through lumbar sympathectomy is a surgical modality used to prevent amputations and for alleviation of pain at rest through the vasodilatory effects, resulting from a decreased sympathetic response in the affected limb. Nakajima [22] reports improvement of up to 60% in symptoms in TAO patients according to personal experience. However, the current importance is diminished, due to the unproven effects of amputation prevention and effectiveness in the treatment of pain [22–24].

3.4. Pharmacological treatment

Pharmacological treatment in patients with Buerger's disease is an alternative for selected cases when the disease presents as diffuse and severe limb ischemia. Such critical presentation possibilities for revascularization are markedly diminished; therefore, pharmacological agents are used to improve perfusion.

Selected agents often prescribed for patients such as aspirin, cilostazol, prostanoids, and bosentan are discussed in the subsequent text.

Aspirin [25] is a drug with antiplatelet and anti-inflammatory properties often used to prevent further arterial occlusion. Pharmacologically, aspirin inhibits cyclooxygenase, the enzyme responsible for the synthesis of thromboxane and prostaglandins. Contraindications are hypersensitivity to salicylates, active gastrointestinal ulcers, use in children, patients with active hemorrhage, renal and hepatic failure, and pregnancy. Aspirin is given orally (after meals) at a recommended dosage of 75–325 mg (often 100 mg).

Cilostazol [26, 27] is a pharmacological agent frequently prescribed to patients with peripheral arterial occlusive disease of atherosclerotic etiology [Food and Drug Administration (FDA) approved in 1999). Pharmacologically, cilostazol is the derivative of quinolinone, a drug that inhibits specifically the type III cellular phosphodiesterase, which affects reversible inhibition of platelet aggregation and unequally vasodilatation of the vascular beds (femoral arterial bed is more dilatated than vertebral, carotid, or splanchnic). In other words, cilostazol "steals" a small part of the blood from other territories (gastrointestinal and cerebral) to improve perfusion in ischemic limbs. Cilostazol is contraindicated in patients with congestive heart failure, hemorrheologic disturbances or current bleeding, such as by gastrointestinal or intracranial bleeding, and in individuals with known or suspected hypersensitivity to cilostazol. Side effects of cilostazol include headache, diarrhea, abnormal stools, and tachycardia. Cilostazol is given orally and fasting, at a dose ranging from 50 to 200 mg per day [28, 29].

Prostanoids [30, 31] (prostaglandin analogs and prostacyclin) are derivatives of eicosanoids and are commonly used in the treatment of numerous diseases, including pulmonary hypertension,

sexual impotence and glaucoma, and so on. Prostanoids act by binding to specific receptors in the endothelium (causing vasodilation) and platelets inhibiting platelet aggregation, which causes a transient increase in peripheral perfusion. Arterial vasodilation in ischemic areas increases blood perfusion and, consequently, increases the chances of healing of the ulcer and improves pain at rest. By inhibiting platelet aggregation, the occlusion of small- and medium-sized arteries is prevented and, in theory, also stabilizes the disease. Due to their short half-life, about 2–3 min, these synthetic drugs should be administered by continuous intravenous infusion. The newer stable prostacyclin analogs (e.g., iloprost) with a longer half-life have allowed the oral use of these drugs. The most important contraindications are heart failure (any etiology), intracranial hemorrhage, gastrointestinal disorders, and trauma. Side effects include headache, flushing, malaise, gastrointestinal disorders, and hypotension. The maximum dose of iloprost administered is about 2 ng/kg/min of continuous infusion [31].

Bosentan is a powerful double antagonist of endothelin receptors (types A and B), causing selective vasodilator effects [32]. Bosentan has been used successfully in patients with digital ulcers and systemic sclerosis [33–35]. Some important reported side effects are hepatotoxicity and fluid retention. Bosentan is given orally, primarily in patients with pulmonary arterial hypertension, with a recommended dose of 62.5 (twice daily) or 125 mg (twice daily) [32].

It is important to cite the degree of evidence of these treatments. In a recent Cochrane systematic review on the pharmacological treatment of thromboangiitis [36], prostacyclin analog versus placebo, aspirin, and a prostaglandin analog, and folic acid versus placebo were included. Studies that evaluated pharmacological agents such as cilostazol, clopidogrel, and pentoxifylline, or studies that compared oral prostanoid versus intravenous prostanoid were not incorporated because they were not randomized controlled trials. Moderate evidence (one study) suggested that intravenous iloprost was effective in participants with critical limb ischemia (ulcers and rest pain) after 4 weeks of treatment when compared with aspirin, without differences in amputation rates [36]. Two trials indicate that prostacyclin was very effective as prostaglandin analogs in healing ulcers (very low-quality evidence) and extinguishing pain at rest (low-quality evidence), but rates of amputation were not reported by the authors [36]. Moderate evidence (one study) suggested that there was no difference between placebo and the oral prostacyclin analog iloprost (200 and 400 μg) in healing ischemic ulcers or eradicating pain at rest after 8 weeks and 6 months, and rates of amputation after 6 months [36]. Very-low-quality evidence from one study showed no difference between placebo and folic acid, in patients with thromboangiitis obliterans and hyperhomocysteinemia (abnormally high level of homocysteine in the blood), and in rates of amputation and pain scores [36]. Treatment side effects, such as headaches or nausea, were not considered serious [36].

Other pharmacological agents used are those that act on hemorrhagic properties in order to decrease the likelihood of thrombosis, such as dextran and pentoxifylline, arterial vasodilators such as calcium channel blockers and those with anti-inflammatory action in general, such as nonsteroidal anti-inflammatory drugs, phenylbutazone, cyclophosphamide, and corticosteroids. Still other drugs, used in patients with occlusive arterial disease of atherosclerotic etiology, such as carbamate pyridinol and inositol niacinate, have already been used [1]. All these agents have a low efficacy reported in a series of cases and, therefore, with a **very low** level of evidence.

3.5. Pharmacological treatment versus lumbar sympathectomy

The comparison of lumbar sympathectomy, one of the most used treatments in patients with thromboangiitis obliterans with ischemic ulcers and pain at rest with other therapies, was carried out by a recently published systematic review [37] with a finding of "**Very low** evidence suggests that intravenous iloprost (prostacyclin analogue) is more effective than the lumbar sympathectomy in the healing of ischemic ulcers and pain at rest in patients with Buerger's disease. Therefore, until now, the preference of the use of iloprost over the lumbar sympathectomy (and vice versa) is not supported by strong evidence for its routine use. In other words, disponibility and cost may interfere in clinical decision, without evidence supporting both therapies."

3.6. Other treatments

Omental transference, also known as omental transplantation and omentopexy, is a modality of revascularization whose greater omentum is elongated, preserving the native vascularization and then located distally to the ischemic member through a subcutaneous tunnel connecting the abdomen and the foot. The mechanism whose omentum promotes angiogenesis is unknown. Indian and Russian groups of researchers published good results with the technique, with highlights to the works of Singh [38] (reaching 88% of ulcer healing) and Talwar [39] (100% of limb salvage in 62 patients). However, because of the design of the studies (prospective case series), the evidence is **very low**.

Venous arterialization may be defined as the use of the disease-free venous bed as an alternative conduit for perfusion of the peripheral tissues with arterial blood. Meta-analysis of 56 studies (228 patients) published in 2006 [40] about venous arterialization demonstrated that the overall 1-year foot preservation was 71% and the secondary patency of 46% with the use of the technique. However, problems with studies (only six studies were observational and only one was controlled), mixed etiologies of limb ischemia (thromboangiitis and atherosclerosis were evaluated together) and the low number of patients, classified the evidence as **very low**.

The use of stem cells, especially bone marrow derivatives [41], umbilical cord [42], or even adipose tissue, has been the subject of many studies lately. Basically, the progenitor cells are collected, separated, and purified to be injected into the ischemic limb. This has been reported to improve pain at rest, increased healing of ulcers (about 83%) in the study by Durdu et al. [43] and the quality of life of patients undergoing this therapy.

The mobilization and in situ implantation of bone marrow cells, without the need for their processing, can also be performed through bone fenestration (tibia bone), a procedure first described as "revascularization by osteotrepanation" and that stimulates the formation of collateral circulation in the ischemic limb [44]. Allied to this technique, it can stimulate the production of endothelial progenitors through the subcutaneous injection of colony-stimulating factors [45]. Regarding the evidence of this therapy, there is a systematic review protocol [46] about the subject that was recently published, and soon we will study about the efficacy and degree of evidence of this type of treatment in patients with thromboangiitis obliterans.

Stimulation of the spinal cord for the purpose of improving limb pain and perfusion has been related to the study, without severe complications of the method [47]. However, because of the design of the studies (only case series), the evidence is **very low**.

3.7. Amputation

The final stage for the severely affected limb with Buerger's disease is amputation. A study by Cooper et al. [48] retrospectively assessed the amputation rate in 50 patients with BD listed in the Mayo Clinic patient database from January 1976 to December 1999. The authors concluded that the risk of amputation increases progressively in patients who continue to smoke, with the first amputation occurring on average 15.6 years after diagnosis. The estimated risk is 25% at 5 years, 38% at 10 years, and 46% at 20 years, and the risk of amputation higher is 11% at 5 years, 21% at 10 years, and 23% at 20 years. This study also suggests that the risk of amputation is eliminated after 8 years of cessation of smoking. In a study by Sasaki et al. [11] in a retrospective population study of 850 patients in 1993, they reported that about 25.2% of BD patients had some degree of amputation (greater or less). It also reports a 2.73-fold increase in the risk of amputation among patients who remained smokers.

4. Summary (conclusion)

Buerger's disease (thromboangiitis obliterans) is a debilitating vasculitis to the patient and challenging to the physician, as much to the diagnosis as to the treatment. Evidence for the efficacy of numerous therapeutic modalities until now is scarce, with a trend toward greater efficacy of prostacyclin analogs in the treatment of more advanced levels of ischemia (ulcer and pain at rest). Unanimity, however, refers only to the role of smoking in this vasculitis, both at the beginning of the disease and its perpetuation, making it essential to stimulate smoking cessation to minimize the damage of the disease.

Author details

Daniel Guimarães Cacione

Address all correspondence to: dancac@gmail.com

Division of Vascular and Endovascular Surgery, Department of Surgery, UNIFESP—Escola Paulista de Medicina, São Paulo, SP, Brazil

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