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Review article

Acute ischemia of the upper and lower limbs: Tailoring the treatment to the underlying etiology

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ABSTRACT

Acute limb ischemia (ALI) can be a devastating clinical emergency with potentially limb- or life-threatening consequences. It is defined as a quickly developing or sudden decrease in limb perfusion producing new or worsening symptoms and signs, often threatening limb viability. ALI is commonly related to an acute arterial occlusion. Rarely, extensive venous occlusion can lead to upper and lower extremities ischemia (ie, phlegmasia). The incidence of acute peripheral arterial occlusion causing ALI is approximately 1.5 cases per 10,000 people per year. The clinical presentation depends on the etiology and whether the patient has underlying peripheral artery disease. Except for traumas, the most common etiologies are embolic or thrombotic events. Peripheral embolism, likely related to embolic heart disease, is the most common cause of acute upper extremity ischemia. However, an acute thrombotic event may occur in native arteries, at the site of a pre-existing atherosclerotic plaque, or as a failure of previous vascular interventions. The presence of an aneurysm may predispose to ALI for both embolic and thrombotic mechanisms. Immediate diagnosis, accurate assessment of limb viability, and prompt intervention, when needed, play important roles in salvaging the affected limb and preventing major amputation. Severity of symptoms is usually dependent on the amount of surrounding arterial collateralization, which may often reflect a pre-existing chronic vascular disease. For this reason, early recognition of the underlying etiology is crucial for choice of best management and definitely for treatment success. Any error in the initial evaluation may negatively affect the functional prognosis of the limb and endanger the patient's life. The aim of this article was to discuss diagnosis, etiology, pathophysiology, and treatment of patients with acute ischemia of the upper and lower limbs.

1. Introduction

Acute limb ischemia (ALI) is one of the most common emergencies in vascular surgery, and it is likely to be the most frequent emergent circumstance faced by young vascular surgeons at the beginning of their career. It is defined as the sudden decrease in limb perfusion that threatens the viability of the limb [1]. Classically, the signs and symptoms of ALI can be described using the six Ps—pain, pallor, paresthesias, poikilothermia, pulselessness, and paralysis. To make the diagnosis of ALI, these symptoms should be present for fewer than 15 days. Although the diagnosis may seem easy, some factors

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Fig. 1 – Acute limb ischemia of left lower limb (Rutherford class IIa).

may be difficult to interpret, such as the role of clinical examination and radiological investigations, optimal timing of intervention, and treatment modalities. Any error in the initial evaluation and management can jeopardize the functional prognosis of the affected limb as well as the patient's life. The management process, aimed to choose the most appropriate treatment option, consists of establishing severity, site, and etiology of the acute ischemia. According to Rutherford's classification, severity of clinical presentation is classified as follows [2]:

I. Viable (not immediately threatened): no ischemic pain, no neurologic deficit, adequate capillary circulation, and clearly audible pulsatile flow signal.
II. Threatened viability (reversible ischemia and limb salvage in case of prompt treatment): ischemic pain and/or mild and incomplete neurologic deficit, only venous flow signal audible. It can be divided into marginally threatened (IIa) and immediately threatened (IIb) (Figs. 1 and 2).
III. Major (irreversible ischemic change): profound sensory loss and muscle paralysis, absent capillary skin flow or evidence of more advanced ischemia (eg, muscle rigor or skin marbling), neither arterial nor venous flow signals audible, generally requires major amputation regardless of therapy (Fig. 3).

Fig. 2 – Acute limb ischemia of right lower limb (Rutherford class IIb).

Fig. 3 – Acute limb ischemia of right lower limb (Rutherford class III).

With an incidence of approximately 1.5 cases per 10,000 people per year [3], together with a generally long hospitalization and a high rate of major amputation (10% to 30% at 30 days), especially for lower extremities, ALI remains a major disease entity with not-negligible social and economic implications.

2. Etiology

Excluding trauma, the most common etiologies of ALI are embolism, thrombosis, aneurysms, and failure of vascular reconstructions. ALI may occasionally develop as a complication of an acute aortic syndrome, such as acute aortic dissection. Moreover, it is worth separately discussing ALI secondary to coagulation defects described with respiratory viruses, including SARS-CoV-2 and its related disease COVID-19.

2.1. Embolism

The fragmentation of the thrombus is the main mechanism at the basis of this phenomenon. In this case, the arterial occlusion is generally located at an arterial bifurcation, such as the femoral or brachial bifurcation or the tibial trifurcation, but any artery can be affected.

Thromboembolism is the most common cause of acute upper extremity ischemia. It is responsible for approximately 60% of cases and typically affects older patients [4,5].

The most common etiologies include atrial fibrillation, valvular heart disease, and ischemic heart disease with left ventricular hypokinesis [6]. Other sources of cardioembolism include left atrial myxoma, left ventricular aneurysm, and valvular vegetations in infective endocarditis. Atrial fibrillation contributes to 80% of the cases of cardioembolic events. Post-infarction intramural cardiac thrombus, as well as left ventricle aneurysm, are other important causes of emboli of cardiac origin. Usually, in such cases the prognosis of the ALI is also worse due to the precarious concomitant general condition of the patients [7].

Paradoxical embolism to lower as well as upper extremities via a patent foramen ovale from a site of deep venous thrombosis can also occur [8]. The paradoxical embolism typically occurs in young subjects as sequelae of a deep vein thrombosis. It is due to the migration of a thrombus from the venous system to the arterial system through the patent foramen ovale.

Endocarditis and atrial myxoma represent other possible causes of cardioembolism and justify any histologic investigation, especially in young patients without a known heart disease.

Peripheral embolic events responsible for ALI may also occur as a result of an atheroembolism. In these cases, the emboli do not originate from the heart, but rather from other arterial districts. Atherosclerosis of the ascending aorta or the aortic arch, innominate or subclavian arteries, or aneurysm affecting the subclavian or axillary arteries may be sources of upper extremity embolism. Similarly, atherosclerosis or aneurysms of the thoracic and abdominal aorta, as well as of the iliac, femoral, and popliteal arteries may be the cause of acute lower limb ischemia. Unlike heart emboli consisting generally of platelet aggregates, atherosclerotic emboli may include cholesterol particles. In the lower limbs, occlusion of the skin capillaries by these cholesterol particles may manifest as the so-called "blue toe syndrome." These distal lesions are often inaccessible for any kind of procedure and partly explain the serious prognosis of this syndrome.

Despite the improvement in clinical examinations and radiological investigations, approximately 20% of embolic peripheral events remain idiopathic.

2.2. *Thrombosis*

Acute thrombosis of a native artery is most likely to occur at the site of a pre-existing atherosclerotic plaque. Thrombosis can also occur at the location of an aneurysm, or at sites previously affected by dissection. Native artery thrombosis is currently the most frequent etiology of acute ischemia of the lower limbs. In fact, clinical manifestations of ischemia from acute native arterial thrombosis in a pre-existing stenosis of an upper extremity artery are rare, presumably due to the rich collateral network of this district.

Thrombosis of a previously patent but stenotic artery is a well-known complication of atherosclerosis. Occlusion of atherosclerotic vessels may occur on the basis of progressive atherosclerotic narrowing of the artery, with resultant low flow, stasis, and eventual thrombosis, or intraplaque hemorrhage and local hypercoagulability [9]. The causes of thrombosis may be secondary to a state of hypercoagulopathy (eg, myeloproliferative syndrome, polyglobulia, and dehydration) or secondary to hemodynamic deficiencies (eg, septic shock and heart failure). Recognition of the latter etiology is essential because correction of the hemodynamic insufficiency may help in the treatment of ALI.

The clinical manifestations of lower extremity ischemia resulting from arterial thrombosis on a background of underlying atherosclerosis are usually less dramatic at onset and less severe compared with those after an acute embolism or vascular thrombosis in patients without atherosclerosis. This difference is primarily due to the collateral circulation that generally develops over time in patients with chronically diseased vessels. Collaterals are frequently so hypertrophic that the patient notices no change or only a mild increase in symptoms of chronic ischemia when an atherosclerotic vessel undergoes an acute occlusion.

A completely different scenario may be seen in case of acute thrombosis of the abdominal aorta. This is an uncommon but potentially devastating event. Acute aortic thrombosis may be the result of a large saddle embolus to the aortic bifurcation, in situ thrombosis of an atherosclerotic aorta, acute occlusion of an abdominal aortic aneurysm, or previous aortic surgical reconstructions. Clinical presentation is usually sudden and can vary depending on the level of the aortic occlusion. Generally, patients present with a bilateral severe lower limb ischemia that can often be mistaken for a stroke or similar neurologic disease. Revascularization of the ischemic lower limbs as soon as possible is the primary aim in the therapy for acute aortic thrombosis to avoid further ischemic damage. One of the largest case series of acute aortic occlusion was reported by Grip et al [10] on the basis of the Swedish nationwide vascular database, including 715 cases collected in a 20-year study period. Bilateral ALI was the clinical presentation in $> 80\%$ of these patients. The most common operative approach was thromboembolectomy, followed by thrombolysis, axillary–bifemoral bypass, and aorto–bi–iliac/bifemoral bypass. Interestingly, endovascular techniques became more frequent over time: 15.6% before 2000 versus 43.8% after 2008 ($P < .001$). The results of this study suggest a flexible approach with different techniques: open aortic surgery, extraanatomic bypass, and endovascular approach. The treatment strategy should be based on the type of occlusion, patient's status, and experience of the center. Current research also underscores that endovascular therapy is used more often in selected patients with acute aortic occlusion, with results similar to those of open surgery. However, the reported in-hospital or 30-day mortality rates of endovascular procedures in these patients remain not negligible at between 20% and 52% [11,12]. It seems paradoxical that most of the patients with acute aortic occlusion die as a consequence of reperfusion injury or postperfusion syndrome that occurs after revascularization of acute ischemic limbs.

2.3. *Aneurysms*

The presence of an aneurysm may predispose to ALI for both embolic and thrombotic mechanisms. Aneurysm-related peripheral embolism can be caused by atheroma of the arterial wall, such as in shaggy aorta and penetrating atherosclerotic ulcer, as well as aortic and peripheral aneurysms with high thrombotic content.

Acute thrombosis of an aneurysm can lead to severe lower extremity ischemia. This clinical scenario is most commonly associated with popliteal artery aneurysm. Acute thrombosis of a popliteal aneurysm has a catastrophic functional prognosis for the limb, with an amputation rate of approximately 50%, mainly due to poor distal run-off secondary to diffuse thromboembolism (Fig. 4). A thrombosed popliteal aneurysm may be the underlying cause of ALI in 3.5% of cases, and approximately one-half of the popliteal artery aneurysms present with ALI [13,14]. Therefore, thrombosed popliteal aneurysm should always be considered in case of acute lower limb ischemia. In fact, when endovascular treatment is attempted without noticing the presence of a popliteal artery aneurysm, there is a high risk of exacerbation of thromboembolism due to guide wire or catheter manipulations.

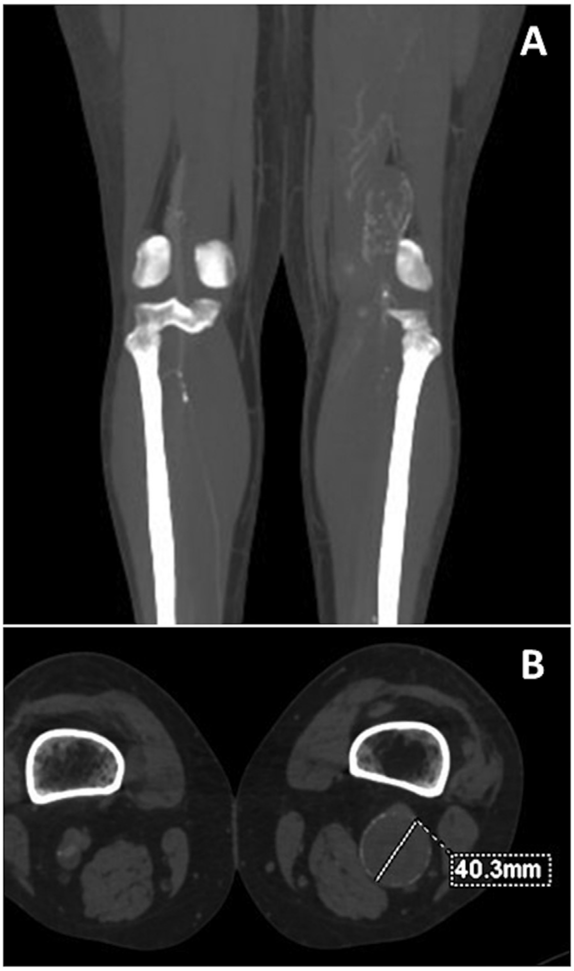

Fig. 4 – Acute left popliteal aneurysm thrombosis in maximum intensity projection (A) and axial (B) view.

2.4. *Failure of vascular reconstructions*

Development of vascular and, even more, endovascular procedures has increased the number of ALIs from bypass, stent, or stent-graft thrombosis. In the setting of an acute lower limb ischemia, the failure of vascular reconstruction may occur in the suprainguinal as well as infrainguinal district. The main causes of acute lower limb ischemia secondary to the failure of a suprainguinal intervention are the thrombosis of aorto–iliac, aorto–femoral, or ilio–femoral bypasses, as well as the occlusion of iliac stents or iliac legs in the setting of a pre-existing aortic endografts. The occlusion of femoropopliteal/distal bypasses or peripheral stents in the superficial femoral or popliteal artery are the main causes of ALI secondary to the failure of previous infrainguinal interventions. Failure of previous vascular reconstructions may have different clinical manifestations based on whether they occur above or below the inguinal ligament. Usually, the more distal the failed reconstruction, the more severe the clinical presentation; this is easily explained by the theoretically greater chance of compensation in case of more proximal occlusion.

The time of ALI onset with respect to the initial procedure is primary to understanding the underlying mechanism that predisposed to failure and, therefore, to choose the most appropriate treatment option. Early bypass thrombosis (within 1 month) is generally secondary to technical defects or an insufficient distal run-off. Thrombosis of the bypass during the first year after surgery is mainly due to myointimal hyperplasia, which may predispose to anastomotic stenosis. Late thromboses (after 1 year) are usually secondary to the evolution of the atherosclerotic disease proximally or distally to the revascularization site. Symptoms may vary widely in case of acute bypass occlusion. Some patients with acute bypass occlusion will experience symptoms similar to those before the initial revascularization, and others will have symptoms that are even worse, and potentially limb-threatening, due to concomitant occlusion of vessels proximal or distal to the revascularized segment. However, the occlusion of a bare metal stent is usually associated with a return to the initial clinical manifestation because the collateral network is generally preserved in this kind of interventions. However, the use of peripheral covered stent in the treatment of both occlusive and aneurysmal disease may predispose to severe limb ischemia in case of acute stent-graft occlusion. In fact, in both occlusive and aneurysmal disease, collateral pathways are largely sacrificed by the use of a covered stent, leaving little opportunity for distal compensation (Fig. 5). Moreover, when a covered stent is used in the treatment of an aneurysmal lesion, such as popliteal artery aneurysm, collateral vessels are usually unprepared to cope with a sudden occlusion, effectively mimicking the clinical manifestations of an acute native popliteal aneurysm thrombosis [15].

Iliac leg occlusion of an aortic stent-graft represents a new etiology with the development of endovascular procedures in the treatment of abdominal aortic aneurysms. One of the risk factors of this unwanted event is the distal landing of the leg in the external iliac artery. This complication is observed in up to 5% of patients with an aortic stent-graft [16].

Given the high capability of vascular compensation of the upper limb in case of failure of previous vascular reconstruction or stenting, ischemic post-surgery symptoms of the upper extremities are likely related to hemodialysis accesses, and generally present as forearm or hand ischemia after creation of an arteriovenous fistula [17]. Ischemic complications of hemodialysis arteriovenous fistula are uncommon, but can result in significant limb dysfunction or even limb loss. Ischemia can occur for a variety of reasons that almost always include decreased blood flow to the distal extremity resulting from blood flow through the fistula. The incidence and timing for the development of hemodialysis access–induced distal ischemia may vary with the type and location of the access, and clinical symptoms can be graded from mild to severe. Rarely, a severe presentation known as ischemic monomelic neuropathy, characterized by severe sensory and motor deficits in the hand, may be observed. This variant may lead to irreversible neurologic deficits and requires an aggressive management strategy. Treatment options for hemodialysis access–induced distal ischemia include access ligation for severe ischemia, banding procedures to reduce flow to the fistula, or procedures to modify access hemodynamics and improve distal blood flow [18].

Fig. 5 – Acute thrombosis of covered stent in the right popliteal artery in volume rendering (A), maximum intensity projection (B), and axial (C) view.

It is worth mentioning, among other causes after vascular interventions, the in situ thrombosis of the femoral bifurcation after use of a percutaneous closure system device. This event is directly related to the malposition of the system in the artery, especially in case of severe calcifications. In this case, symptoms of acute ischemia generally appear right after the procedure, but sometimes may be of delayed onset.

2.5. *Acute aortic dissection*

Acute aortic dissection (AAD) is a life-threatening event and its management remains highly challenging. The development of complications, such as rupture, aneurysmal dilatation, or malperfusion syndrome, necessitates immediate surgical or endovascular treatment. Malperfusion may involve renal, visceral, spinal cord, and limb arterial circulations. Few studies have specifically analyzed ALI secondary to AAD because it is generally reported together with other malperfusion complications, such as abdominal organ ischemia.

Limb or other end-organ ischemia is caused by malperfusion from the dissection flap occluding or inducing thrombosis in aortic branches. Recent case series have reported that ALI may complicate an AAD in up to 20% of cases, and represents the most common presentation in patients with complicated AAD, with an incidence between 40% and 70% [19–21].

Patients with Stanford type A AAD usually require urgent open repair of the ascending aorta. Patients with Stanford type B AAD are generally managed with medical therapy unless the dissection is complicated, as in the case of malperfusion syndrome. In such cases, open or endovascular aortic repair, with the aim of occluding the primary entry tear and re-expanding the true lumen, is often needed. Nevertheless, some patients may have persistent symptoms of limb ischemia, despite urgent primary aortic treatment. Such patients require urgent peripheral revascularization. The primary goal of treatment is to restore perfusion of the limbs as soon as possible. Extraanatomic bypass grafting (ie, femoro–femoral, axillo–femoral, or axillo–bifemoral) or surgical fenestration represent the traditional treatment options. However, less invasive treatments using an endovascular approach have been proposed. Endovascular fenestration and/or spot stenting, especially in case of isolated single-limb involvement, are attractive options. These procedures may be combined as an adjunct to a primary endovascular aortic repair or occasionally may be proposed as isolated treatment without central aortic repair. Plotkin et al [22] reported a single-center institutional experience including 769 patients with type A or type B AAD, of whom 42 had lower extremity malperfusion. Few of these patients had a limb-first intervention with extraanatomic revascularization. The authors noted that limb-first patients were more likely to have early failure compared with aortic-first–treated patients (50% *v* 8%; $P = .029$), emphasizing the usefulness of urgent thoracic endovascular aortic repair for complicated type B and open repair for type A AAD before lower extremity intervention.

Limb malperfusion is statistically associated with higher in-hospital mortality. This can be explained by the high chance, in such patients, to have a concomitant mesenteric ischemia. In a large case series from the University of Texas including 1,015 patients with AAD (49.4% Stanford type A and 50.6% Stanford type B), lower limb ischemia was present in 104 patients (10.3%) and was more common in type A than type B dissections (65.4% *v* 34.6%; $P = .001$). In this series, patients requiring limb revascularization were more likely to have mesenteric ischemia compared with the rest of the cohort in both type A ($P = .037$) and type B dissections ($P < .001$), with worse 10-year survival rates (21.9% *v* 59.2%; $P < .001$). This underscores that the need for limb revascularization is a marker for more extensive dissection and should always prompt evaluation for visceral malperfusion [23].

2.6. *COVID-19*

Thromboembolic complications in patients with COVID-19 is a topic of great relevance. Clinical presentation may widely vary. Symptoms are most commonly related to venous thromboembolism, but also to ischemic complications due to limb, cerebral, coronary, and visceral ischemia. Early recognition and intervention for ALI can help to reduce mortality in these critical patients and maximize the chance for limb and life salvage.

In patients with COVID-19, ALI is predominantly due to large or medium artery thrombosis and embolism, although other etiologies can also occur. As with acute ischemia in the general population, the lower extremities are affected more commonly than the upper ones [24].

Although ALI is generally a complication of hospitalized patients with severe COVID-19, it can sometimes occur in patients with mild symptoms of COVID-19 and, moreover, can be the primary presenting symptom even in the absence of respiratory manifestations. In addition, ALI has also been reported in association with vaccine-induced immune thrombocytopenia and thrombosis. The European Society for Vascular Surgery recently published an update of the clinical practice guidelines on the management of ALI in light of the COVID-19 pandemic. First of all, the results collected in this update must be interpreted with caution, as most of the data are observational and derived from case reports or small case series. Data are conflicting concerning whether the incidence of ALI increased or remained unchanged during the pandemic. However, the incidence was higher in patients younger and healthier than usual, with a greater proportion affecting the upper limbs. Most of the treatment recommendations from the European Society for Vascular Surgery guidelines about ALI remained valid, although some minor modifications are suggested in case of concomitant COVID-19. These additional recommendations include the need to perform computed tomography angiography (CTA) before revascularization, which includes the entire aorta and iliac arteries, given the risk of venous and arterial thrombosis in multiple locations. The preferential use of local or locoregional anesthesia during revascularization procedures is also recommended [25].

3. Clinical evaluation

Recognition of the typical signs of acute upper and lower extremity ischemia is primary for limb salvage.

The diagnosis of ALI is purely clinical and based on the combination of the following three signs:

- pain for fewer than 15 days;
- alteration of the microcirculation, which leads to lowering of the skin temperature and/or to abnormal skin color (pallor/cyanosis); and
- disappearance of the peripheral pulses.

Signs of severity leading to immediate surgical treatment include:

- compartment syndrome; and
- severe neurologic deficit.

Neurologic deficit may include paresis or paralysis. In lower limbs, it starts from the toes and gradually goes up toward the root of the limb. It preferentially affects the extensors of the foot and/or toes. Paresthesia is not a main sign of gravity. Clinical presentation depends on the etiology and pathogenic mechanism, and its severity is directly related to the lack of pre-existing collateral network. Generally, in the initial stage of acute ischemia, the limb is white with empty veins. Over time, with the stagnation of the blood, the cutaneous capillary network fills with venous blood and the limb appears more marble. A completely cyanotic limb is evidence of the extension of thrombosis to the capillary system, with a consequent poor prognosis. Clinical management includes an interrogation to determine the time of symptoms onset, as well as other important elements to clarify the pathogenic mechanism and its etiology. The presence of pre-existing intermittent claudication, absence of pulses in the contralateral limb, and the presence of cardiovascular risk factors are important elements in favor of a pre-existing peripheral artery disease. However, an embolic cause can be suspected for the presence of all pulses in the contralateral limb and an arrhythmic heartbeat.

4. Instrumental examination

ALI may be diagnosed on the basis of medical history and physical examination. However, vascular ultrasonography and whole-body examination with CTA may be crucial to determine the affected site and the underlying disease, and to distinguish among multiple embolisms. It is not uncommon at all that an unrecognized concomitant mesenteric embolism could irreparably complicate the postoperative course of a patient who has undergone a simple upper or lower limb thromboembolectomy. When CTA cannot be performed, such as in severe renal dysfunction and/or in case of iodinated contrast medium allergy, simple CT alone can provide important information regarding aneurysms and arterial calcification. The role of echocardiography remains controversial. In fact, failure in visualizing embolic sources does not definitively exclude a cardiac cause. To identify the cause and evaluate the patient's general conditions, electrocardiography, chest radiography, blood examination (including coagulation and thrombophilia screening tests), urine analysis, and blood gas analysis, may be useful. In particular, blood and urinary myoglobin, blood creatine kinase, lactate dehydrogenase, potassium, and lactic acid levels at blood gas analysis are important parameters to determine the severity of ischemia and to predict the onset of ischemia–reperfusion injury.

5. Management

5.1. *Evaluation of limb viability*

The first question the vascular specialist should ask himself is: How much time do I have to avoid irreversible ischemia? The answer to this question should guide the treatment choice. Although it is well established that surgical thromboembolectomy is the treatment of choice for patients with thromboembolic etiology, endovascular approach is usually the first-line option for those cases due to acute vascular thrombosis.

However, the overwhelming majority of endovascular techniques need hours or even days to give the first results. The need for urgent blood flow restoration will depend on the severity of the clinical presentation, graded using the Rutherford clinical classification. If there is a neurologic deficit in the limb, particularly involving motor loss (Rutherford IIb), urgent revascularization is mandatory [26]. Hence, in particular cases in which one cannot wait, immediate surgical revascularization is preferred as last chance for limb salvage. Fortunately, in the last few years, some percutaneous techniques aimed to restore blood flow as quickly as possible, such as thromboaspiration and mechanical thrombectomy, have been implemented.

In general, the first approach to a patient with ALI should include urgent anticoagulation with unfractionated heparin to prevent thrombus propagation and preserve microcirculation [27]. Analgesic treatment is often necessary. Routine blood and coagulation tests should be performed. In patients with critically threatened limbs, acidosis should be assessed to predict adverse outcomes and reperfusion injury. If present, acid–base and electrolyte imbalances should be corrected as soon as possible. Careful assessment of renal function before and after revascularization is recommended, especially in older patients or in patients with prior kidney disease.

In the evaluation process, a special mention goes to patients presenting with Rutherford class III. These scenarios, fortunately rare, generally include bedridden patients on a very altered general status. For a severe clinical presentation, often represented by a marble limb with complete neurologic deficit, livid skin, and major compartment syndrome, the decision oscillates between therapeutic abstention associated with palliative care and major amputation as first intention. Attempting revascularization is not recommended and even dangerous. Obviously, in this group, the prognosis is particularly poor [28].

For patients with Rutherford class I to IIb, the therapeutic strategy will depend on etiology, location, type of conduit (native artery of graft), duration of ischemia, age, comorbidities and therapy-related risks, and outcomes. Different revascularization strategies can be proposed, either surgical or endovascular.

5.2. *Open surgery*

Patients with an immediately threatened limb (Rutherford IIb), especially in case of contraindication to thrombolysis, should undergo open surgical revascularization. Moreover, the surgical approach may be preferred in patients with ischemic symptoms for more than 2 weeks [29]. Surgical procedures include thrombectomy with a balloon catheter (Fogarty), bypass surgery, and surgical adjuncts, such as endarterectomy, patch angioplasty, and intraoperative thrombolytic agent injection. Frequently, a combination of these techniques is required. A recent refinement for thrombectomy is the use of over-the-wire catheters, allowing for selective guidance into distal vessels. A large meta-analysis including six clinical trials reported that, in patients presenting with ALI, endovascular and surgical approaches had similar rates of short- and mid-term mortality, limb amputation, and recurrent ischemia [30]. However, open surgery is recommended as the best option for thromboembolism and for patients with Rutherford class IIb. However, endovascular treatment should be preferred for patients presenting with Rutherford class I and IIa [31]. ALI secondary to thrombosed popliteal aneurysm deserves special mention because major amputation occurs with high frequency in such patients [14]. Diffuse thrombotic occlusion of all major run-off below-the-knee vessels is observed frequently here, and percutaneous thrombolysis or thrombectomy may be required to restore flow in the run-off arteries before performing aneurysm exclusion and surgical bypass. However, patients with evidence of sensory loss or motor weakness (Rutherford class IIb) need urgent revascularization and must proceed immediately to the operating theater. These patients cannot tolerate additional ischemic time required by arteriography and thrombolysis. A delayed-phase CTA may be helpful to identify a patent run-off vessel useful to proceed to bypass surgery. Inflow is generally provided by the distal superficial femoral artery via a medial approach. The superficial femoral artery can be used as inflow unless there is evidence of severe ectasia or coexistent atherosclerotic disease, which requires the use of the proximal superficial femoral artery or common femoral artery as inflow vessel. A below-the-knee medial approach is usually used to expose the distal popliteal artery, tibioperoneal trunk, or proximal posterior tibial artery for the distal anastomosis. In this phase, a thromboembolectomy and/or intraoperative injection of thrombolytic agent into below-the-knee vessels may be required. Aneurysm exclusion with proximal and distal ligation above and below the knee may be accomplished easily with this medial approach. Autologous vein, including arm vein if necessary, should be used preferentially because of its superior patency in comparison with prosthetic conduit (77% to 100% *v* 29% to 74% at 5 years) [32]. If the patient presents an ALI secondary to popliteal aneurysm thrombosis without neurologic deficit (Rutherford class I or IIa), an arteriography performed via ipsilateral or contralateral common femoral artery may show a thrombosed popliteal artery with the below-the-knee vessels not always visible. In these cases, prompt in situ thrombolysis is initiated to restore patency of at least one below-the-knee artery, which can later be used as distal run-off vessel for the bypass.

5.3. *Endovascular techniques*

Although thromboembolectomy or bypass grafting still plays a major role in the treatment of ALI, there is a trend for these patients to have complex and multilevel occlusive disease. These conditions may benefit from a combination of open and endovascular techniques. In fact, in situ thrombolysis or percutaneous mechanical thrombectomy and aspiration can be used to remove any possible residual clot after a simple thromboembolectomy. In addition, when completion angiography reveals an underlying chronic stenosis, balloon angioplasty or stenting can be performed to treat the underlying lesion. Although the endovascular and hybrid approaches have gained widespread acceptance, there are few data evaluating their potential benefit for ALI. A recent multicenter retrospective study analyzed the short-term outcomes of 1,480 patients after open surgical, endovascular, or hybrid treatment for ALI. Interestingly, a total endovascular approach was used in 55% of the patients, followed by hybrid revascularization (32%) and open surgical repair (13%). The most common endovascular procedures were angioplasty (93%) and thrombolysis (50%), whereas the most common surgical revascularization was femoropopliteal bypass (33%), femorotibial bypass (28%), and thrombectomy (19%). Endovascular treatment was associated with a reduction in the amputation rate versus open and hybrid procedures ($P < .001$). However, there was no difference in 30-day freedom from mortality and reintervention [33].

The goal of the endovascular approach is to restore blood flow as quickly as possible to the threatened limb with the use of thrombolytic agent; mechanical devices for thrombectomy and aspiration; balloon angioplasty and stenting; or, more frequently, a combination of these techniques.

5.3.1. *In situ thrombolysis*

The action mechanism of in situ thrombolysis is the stimulation of plasminogen conversion to plasmin. The latter is a protease capable of degrading fibrin and inducing the dissolution of the thrombus. Treatment of ALI by systemic fibrinolysis is not very effective, at the price of a not-negligible morbidity. Direct instillation of the fibrinolytic agent in contact with the thrombus by means of an endovascular catheter allows the maximum efficacy to be obtained, with acceptable systemic complications. As mentioned above, because of the relatively long time to restore blood flow, catheter-directed thrombolysis is generally not indicated in Rutherford class IIb.

Three large trials (Rochester study, STILE [Surgery vs Thrombolysis for Ischemia of the Lower Extremity], and TOPAS [Thrombolysis or Peripheral Arterial Surgery]) [34–36] analyzed more than 1,000 patients with ALI randomly assigned to in situ thrombolysis or surgical revascularization. Clinical outcomes were similar in the two groups and amputation-free survival rates at 6 and 12 months were not significantly different. In the thrombolytic-treated group, patients with graft thrombosis benefited more than patients with native artery occlusion. Patients assigned to in situ thrombolysis had lower rates of procedure-related morbidity and mortality compared with the surgery group, at a cost of higher bleeding complications. Factors associated with an increased risk of bleeding include the amount of administered fibrinolytic agent, duration of the therapy, presence of uncontrolled hypertension, age older than 80 years, and low platelet count [37]. During the infusion through a multihole catheter, coagulation profile monitoring is mandatory. Daily angiographic examinations should be performed to determine the effect of the treatment. The duration of the procedure varies between 48 and 72 hours. An early arrest may be indicated in case of complications, intolerance to treatment, or lack of improvement or worsening of the angiographic findings and/or clinical status. After successful restoration of blood flow, a final angiography is performed to detect possible pre-existing arterial lesions, which can be managed by endovascular or surgical procedures. In situ fibrinolysis for acute popliteal aneurysm thrombosis remains a special case. Because there is a high risk of distal embolization, an attempt to revascularize the popliteal aneurysm itself is not recommended, and it is preferable to perform the in situ fibrinolysis at the level of below-the-knee vessels in order to recover an acceptable distal run-off useful for bypass grafting. The in situ thrombolysis can be terminated when at least one below-the-knee artery in continuity with the pedal arch is demonstrated or there has been no progress in recanalization. If the patient shows progression in limb ischemia or failure of thrombolytic therapy, exposure of below-the-knee and/or ankle-level vessels is needed to perform a thrombectomy, followed by attempts at bypass grafting. Failure to establish a bypass target by either thrombolytic or surgical means may necessitate an immediate amputation according to patient's clinical condition.

5.3.2. *Percutaneous mechanical thrombectomy*

Percutaneous removal by mechanical thrombectomy is often used as first-line therapy for patients with ALI due to arterial thrombosis. It is characterized by an endovascular thrombus fragmentation and removal with the use of dedicated devices. It is mainly indicated in Rutherford class IIb because the time needed for reperfusion is significantly shorter than with in situ thrombolysis alone. Patients with contraindications to thrombolysis and high surgical risk can also benefit from mechanical thrombectomy. In patients with high risk of bleeding, this technique can be used to debulk the thrombus before the in situ thrombolysis to shorten the treatment time, thereby limiting the dose of thrombolytic agent needed [38]. Mechanical thrombectomy may also be used as an adjunctive procedure for incomplete thrombolysis or to treat distal embolic complications after in situ thrombolysis. Distal microembolization when using this kind of devices remains a concern. For this reason, devices with additional fragment aspiration, such as Rotarex (Straub Medical AG), AngioJet (Boston Scientific), and Trellis (Bacchus Vascular) are usually preferred [39–41]. Occasionally there is a need to perform balloon angioplasty or stenting after successful removal of the thrombotic material.

Comparative studies between mechanical thrombectomy and in situ thrombolysis found that, in patients with ALI, use of a Rotarex device represents a safe and effective alternative to thrombolysis and is associated with a reduced rate of major bleeding, shorter hospitalization time, and lower costs [42,43]. The Indigo system (Penumbra), another interesting device widely used in interventional neuroradiology, features important advantages; it does not usually require the use of thrombolytic agents and it generally provides immediate flow re-establishment. It can be used when thrombolysis has failed or is contraindicated. The Indigo system promotes active thrombectomy using a powerful vacuum pump that generates substantial suction, enabling aspiration of clots of various sizes and lengths [44]. de Donato and co-authors [45] recently published the results of the Indigo system in the treatment of ALI in 150 patients in a multicenter experience, reporting an assisted primary technical success of 95.3% in a population overwhelmingly Rutherford class II. Adjunctive procedures included angioplasty or stenting of chronic atherosclerotic lesions, thrombolysis, covered stenting, and supplementary Fogarty embolectomy. At 1-month follow-up, primary patency and re-intervention rates were 92% and 7%, respectively. Another interesting thrombectomy device is the Clearlumen-II system (Walk Vascular). This device, unlike conventional vacuum-based automatic aspiration devices, simultaneously aspirates the thrombus and performs pulse spray thrombolysis with a high-pressure jet of saline solution [46].

5.3.3. *Balloon angioplasty and stenting*

The role of adjunctive endovascular procedures like percutaneous balloon angioplasty with or without stenting in the setting of an ALI has always been a subject of debate. The belief that angioplasty and stenting may play only a marginal role, or even be harmful, in an acute setting, has been overturned by several studies that reported interesting results of these procedures in combination with other open surgical or endovascular techniques. In fact, when completion angiography reveals an underlying chronic stenosis, balloon angioplasty or stenting can be performed to treat the underlying lesion. In addition, in case of ALI secondary to failed previous open or endovascular interventions, these adjuncts may prove helpful to treat the possible cause of failure, such as an anastomotic stenosis secondary to a myointimal hyperplasia. In a single-center experience including 322 patients with acute lower limb ischemia, 112 patients (35%) received urgent surgical treatment using only a Fogarty balloon catheter, and a combined hybrid approach with endovascular adjuncts was performed in the remaining 210 cases (65%). The adjunctive endovascular procedures consisted of balloon angioplasty with or without stenting, as completion of thrombolysis or thrombus aspiration procedure, in 92% of the cases. This hybrid approach was associated with significantly higher primary patency and freedom from reintervention rates at 5 years compared with pure open surgical repair (87% *v* 66%; $P <$ .01 and 89% *v* 74%; $P = .04$, respectively) [47]. Therefore, the different endovascular techniques should not be viewed as competitive treatment options, but much more as complementary modalities aimed to offer a synergistic approach.

5.3.4. *Postoperative care*

The restoration of a palpable pulse, audible arterial flow signals, and visible clinical improvement suggest treatment success. Patients with thromboembolism or thrombophilia will need long-term anticoagulation. Novel oral anticoagulants should be considered in patients with nonvalvular atrial fibrillation and a cardioembolic etiology. According to results of the VOYAGER PAD (Vascular Outcomes Study of ASA [Acetylsalicylic Acid] Along with Rivaroxaban in Endovascular or Surgical Limb Revascularization for Peripheral Artery Disease) trial, the 3-year cumulative incidence of ALI in patients who had undergone lower extremity revascularization for chronic peripheral artery disease is 7.8%. The authors found that the combination of rivaroxaban and acetylsalicylic acid is able to reduce the occurrence of ALI relative to a placebo group by one-third at 3 years ($P = .0001$), with benefit starting early at 30 days ($P = .0068$). This would suggest that in patients who underwent successful urgent endovascular or surgical revascularization for ALI secondary to a chronic peripheral disease, especially in the case of previous vascular reconstructions, the postoperative administration of rivaroxaban 2.5 mg twice daily on a background of aspirin could theoretically reduce the recurrence of ALI [48].

Dorsiflexion of the foot and sensory function should be assessed after the revascularization procedure to screen for compartment syndrome. This unwanted complication may result after blood flow restoration, especially in case of advanced stages of ischemia and when the revascularization is performed after a prolonged ischemic time of more than 6 hours [49]. Severe limb swelling, with a dramatic increase in compartment pressures, is the trademark of this phenomenon [50]. After revascularization, the muscles of the extremity may develop edema due to fluid extravasation or inflammatory responses after an ischemia–reperfusion injury, with resultant rapid increase in compartment pressure. Compartment syndrome results in local ischemia of the intracompartment structures, including muscles and nerves. Therefore, delayed recognition can lead to irreversible ischemia of the nerves and muscles of the extremity, resulting in a nonfunctional limb or limb loss. Early recognition and management of compartment syndrome will optimize the chances of full recovery of limbs. Patients admitted for ALI presenting inadequate backflow, high level of serum creatine kinase, positive fluid balance volume, and Rutherford class IIb, have a significantly higher risk of compartment syndrome [51]. The diagnosis of compartment syndrome is clinical, with a tense and painful muscle lodge. The anterior compartment of the leg is the most susceptible to this phenomenon, leading to peroneal nerve dysfunction. If the compartment syndrome occurs, surgical fasciotomy of one or more compartments is indicated to prevent irreversible neurologic damage. After revascularization, it is also necessary to monitor the occurrence of acute renal insufficiency. In fact, during this period, an intense systemic inflammatory response, which can lead to a multiorgan failure, may be observed.

6. Discussion

ALI is one of the most common emergencies in vascular surgery. The goal of therapy is the reperfusion of the ischemic limb as soon as possible. Although most patients with ALI present with a typical constellation of symptoms and signs, it is unknown how frequently the diagnosis is delayed as a result of inexperienced assessment (patients are usually evaluated initially by nonvascular specialists) or atypical presentations. Patients with ALI should be treated by specialists in vascular and endovascular therapies in centers with a full range of facilities to manage patients with vascular diseases. This may mean that a patient will need to be transferred for treatment, if appropriate. The urgency of transfer will depend on the severity of the symptoms. As we mentioned, any error in the initial evaluation and the following management, including a delayed transfer to a vascular center, may jeopardize the functional prognosis of the affected limb as well as the patient's life. When a strong diagnostic suspicion is present, patients should be promptly anticoagulated with heparin on presentation, even before the diagnosis of limb ischemia is fully established. This can prevent propagation of the thrombus or embolus and maintain patency of any collateral vessels.

It is worth considering the differences between upper and lower limb acute ischemia. Acute upper limb ischemia is not as common as acute lower limb ischemia. In addition, in upper limbs, the ischemia is more likely to be embolic and less likely to be limb-threatening. It is also less likely to be immediately life-threatening than lower limb ischemia, although late mortality remains high, owing to the underlying disease and comorbidities. Some patients with upper limb ischemia appear to have no immediate threat to the limb (Rutherford

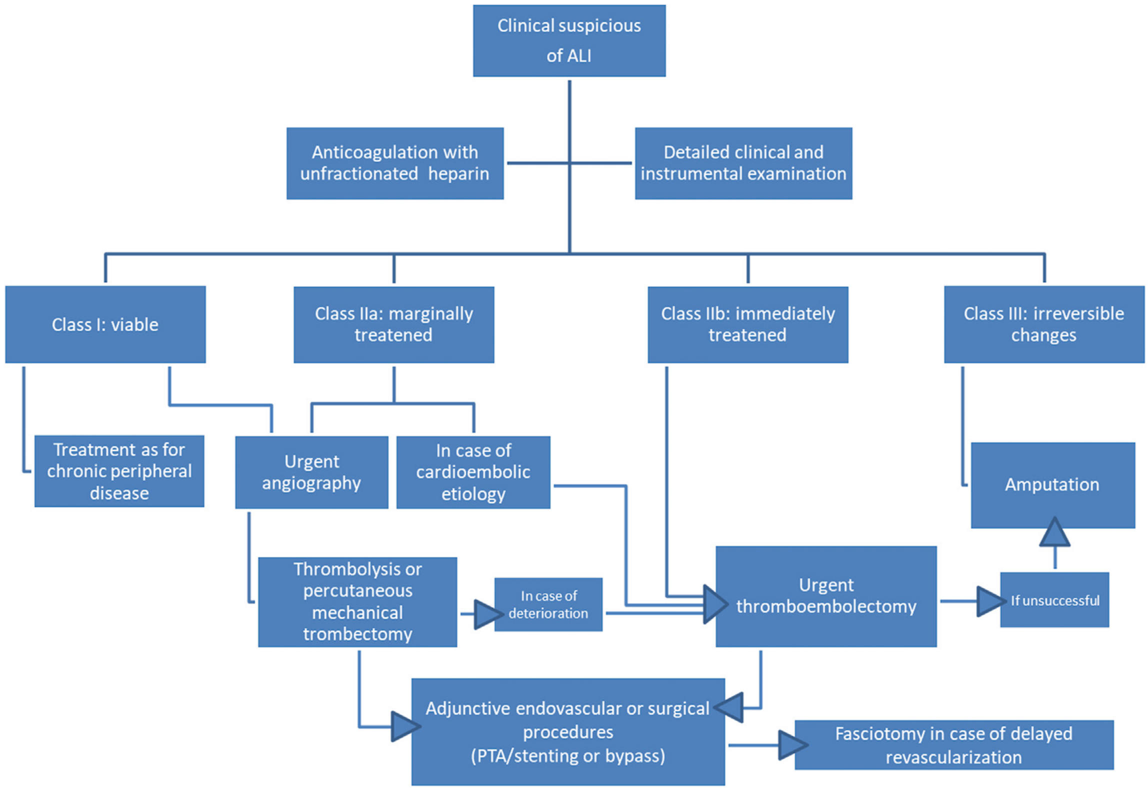

Fig. 6 – Treatment algorithm according to clinical presentation. ALI, acute limb ischemia; PTA, percutaneous transluminal angioplasty.

class I or IIa) and conservative treatment with anticoagulation therapy alone may be appropriate. The risk is that although the limb may remain viable, the patient may have forearm claudication, which can affect quality of life. As for lower limb ischemia, there should be a discussion about therapeutic options, individualized to risks and benefits for each patient. Aside from the severity of the symptoms, other factors that may be taken into account for treatment indication are whether the dominant hand is affected and the age, condition, and occupation of the patient. In the case of conservative treatment chosen as first approach, the arm should be reviewed regularly over the next few days to ensure it does not deteriorate. Anticoagulation alone has been suggested as primary therapy, however, several studies have suggested that poor functional outcomes are reported more often after a conservative approach [52]. For patients with upper limb immediately threatened by embolic occlusion, a surgical approach represented by brachial embolectomy is usually the first-choice treatment. Endovascular treatments, such as percutaneous thrombectomy or aspiration and in situ thrombolysis have been used, but only case reports exist to describe their benefits and complications. A percutaneous approach through femoral artery, with the devices in the aortic arch, may be associated with the risk of supraaortic vessels embolism, but it can also be performed with a brachial approach, minimizing that risk [53]. Primary distal thrombosis of the hand or residual distal ischemia after embolectomy may also benefit from thrombolysis.

Management of acute lower limb ischemia is definitively more complex compared with upper limb ischemia. Patients with acute lower limb ischemia presenting with Rutherford class I usually pose no immediate threat, and may often be treated as deferred urgency. Many of these patients may, in fact, have significant comorbidities and conservative measures may be more appropriate. In addition, old and sedentary patients may actually end up ultimately asymptomatic after a course of anticoagulant therapy. Functional class I patients deserve revascularization and should be treated similarly to class IIa patients, who are defined by having a threatened limb that is salvageable if treated promptly. Therefore, after CTA imaging, percutaneous angiography represents an appropriate first step in these cases, often allowing limb salvage with endovascular techniques, such as in situ thrombolysis or percutaneous mechanical thrombectomy. In this phase, a bail-out surgery can always be considered if the procedure is not successful. An immediately threatened limb (Rutherford class IIb) is still salvageable if immediate revascularization occurs. Surgery, most often embolectomy, is the default treatment of choice to reperfuse the affected limb in adequate time and maintain its viability. Embolic occlusions may only require embolectomy, whereas thrombotic occlusions may require endarterectomy or more likely bypass. Like endovascular intervention, completion arteriography is generally recommended unless embolectomy results in complete restoration of normal distal pulses. Distal clot may be treated by a popliteal cutdown with embolectomy or thrombolysis. Class III ischemia is con-

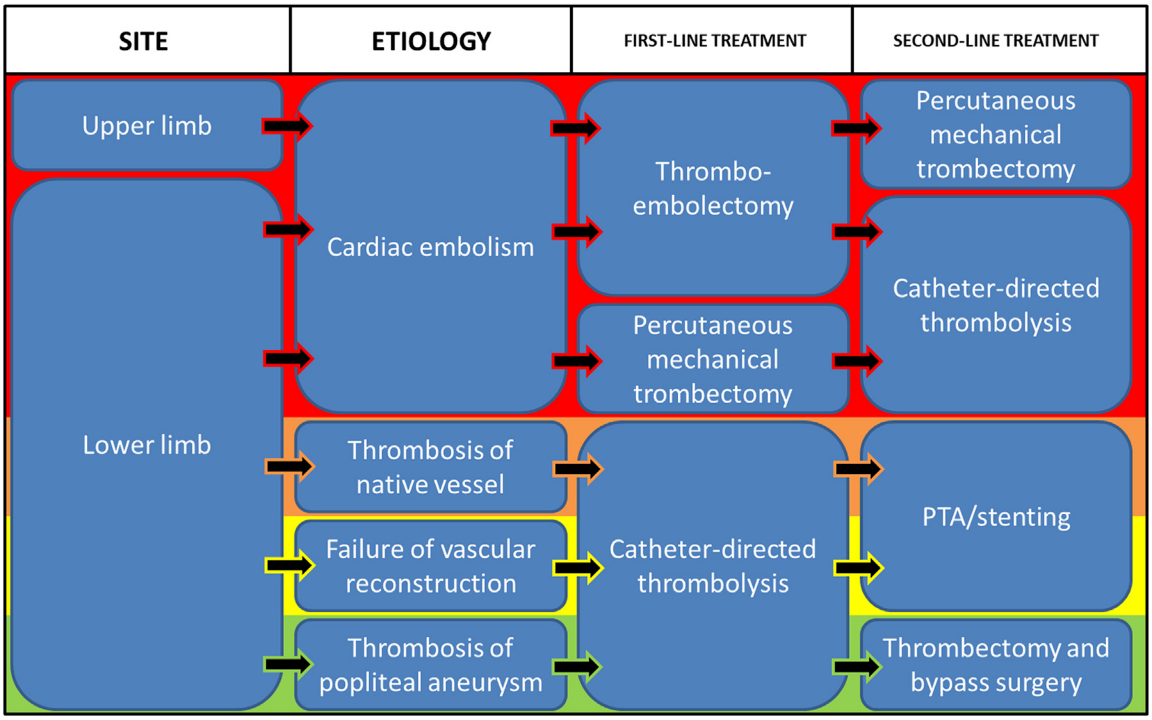

Fig. 7 – Treatment algorithm according to the most common etiologies. PTA, percutaneous transluminal angioplasty.

sidered to be irreversible. In addition to inaudible arterial and venous Doppler signals, these patients exhibit profound anesthesia and paralysis, along with muscle rigor and fixed mottling. Any revascularization attempts are unlikely to result in limb salvage, but often result in renal failure due to rhabdomyolysis, as well as a nonfunctional ankylosed limb, which may compromise future amputations.

In common practice, the use of endovascular techniques has usually been limited to class I and IIa patients, as the awareness is that surgery is able to offer the fastest reperfusion for patients presenting with class IIb and III ischemia. In the past, in situ thrombolysis was associated with prolonged treatment times, with infusion of lytic agents even for days to achieve a sufficient recanalization. It has become increasingly apparent that the choice of intervention is often not that clear cut. Advances in technology, such as accelerated thrombolytic regimens and the use of mechanical thrombectomy, have resulted in a considerable decrease in the time to reperfusion. Although thrombolysis may take longer to restore full patency, it must be kept in mind that improvement in limb perfusion, during thrombolysis, occurs before complete thrombus removal. Thrombolysis may also have the added benefit of a gradual return of arterial flow, which may result in a reduction in reperfusion injury. Overall, it is common that several patients with class IIb and III ischemia receive various endovascular treatments during their hospital course, possibly in combination with an open surgical approach. Ultimately, the choice of technique incorporates many additional factors, such as the etiology of the ischemia, presence of underlying medical conditions, local capabilities, and expertise. The advantages of an endovascular approach in comparison with open surgery are that it is minimally invasive, performed under local anesthesia, may result in improved thrombus resolution in smaller vessels, and it allows for subsequent endovascular and surgical procedures (Fig. 6).

In summary, with the certainty that any type of intervention must be as timely as possible, the choice of the best treatment option remains strictly related to clinical presentation. The underlying etiology at the basis of ALI plays a primary role in the decision-making process, with the most recent evidence in favor of a combined approach in which surgical and endovascular techniques with complementary features are both involved in the therapeutic process (Fig. 7).

7. Conclusions

Despite the development of several therapeutic options for upper and lower limb acute ischemia, the optimal management remains to be determined. Prognoses for limbs and patients' survival vary according to the accuracy of the evaluation process and the promptness of the therapeutic interventions, including revascularization and limb amputation. An adequate preoperative assessment, including medical history, time of symptom occurrence, severity of clinical presentation, and etiology of ALI are crucial in determining the best treatment strategy. The greatest benefit of surgical treatment remains early restoration of blood flow. Further studies are needed to differentiate which injuries may benefit more from conventional treatment from those that primarily require in situ fibrinolysis or other endovascular solutions. Endovascular techniques, with the development of new fibrinolytic agents and new dedicated devices, will definitely improve the prognosis of these patients.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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