ACUTE LIMB ISCHEMIA (ALI): AN OVERVIEW OF CLINICAL DIAGNOSIS AND TREATMENT

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ABSTRACT

Acute limb ischemia (ALI) is one of vascular emergency. It is defined as a rapid and sudden decrease in limb blood flow due to acute occlusion It is considered to be acute if it occurs within 14 days after the first symptom onset. The incidence of ALI is around 1.5/10.000 people per year. It has reported a mortality rate of 15%-20% in 30 days and high amputation rates 10%-15% if appropriate treatment not administered. The causes of ALI are divided into embolism and thrombosis. Thrombosis can occurred due to atherosclerotic lesion while most cases of embolism are cardiogenic one. Classic features of ALI are known as 6Ps: pain, pallor, paralysis, paraesthesia, pulselessness, poikilothermia. A good history taking and physical examination are needed to assess further treatment needed. Severity of ALI also need to be set based on Rutherford Classification. If the limb was diagnosed as irreversible damage, amputation should be taken as treatment choice without hesitation. ALI can be treated with administered of heparin, endovascular and open surgical. Post treatment follow up also needed to rule out any possible complication such as compartment syndrome and ischemic-reperfusion injury.

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INTRODUCTION

Acute limb ischemia (ALI) defined as a rapid and sudden decrease in limb blood flow due to acute occlusion and represented as a vascular emergency[1]. It is considered to be acute if it occurs within 14 days after the first symptom onset. Different from chronic limb ischemia in which collateral vascularization often present, ALI threatens limb in a short time. The rapid ischemia period affects all tissue of the limb, such as skin, tissue, and nerve[2]. It can result in amputation unless appropriate management is administered. Thus, emergency treatment with revascularization is needed to preserve limb viability. Acute upper limb ischemia (AULI) is different from lower limb ischemia. AULI is less common than lower ischemia. In clinical appearance, the shoulder and elbow part much more tolerant of ischemia due to well collateral development, therefore it is more common to serve in below-elbow which brachial artery is the most common side of occlusion[1,3].

The incidence of ALI is around 1.5/10.000 people per year. It has reported a mortality rate of 15%-20% in 30 days and amputation rates 10%-15%[4,5]. A study by Baril et al. also showed that ALI patients experience increased in-hospital major adverse events, including myocardial infarction, congestive heart failure, renal failure, and respiratory complications[6].

ETIOLOGY

Several different factors can cause ALI. The causes of ALI, excluding trauma, are divided into embolism and thrombosis. Arterial thrombosis due to plaque complication (40%) has the highest number followed by an arterial embolism (30%), thrombosis of a popliteal aneurysm (5%), trauma (5), or graft thrombosis (20%)[7,8]. Another study by Belle et al. showed that arterial embolism (46%) has the highest number that can cause ALI followed by in situ thrombosis (24%), complex factor (20%), and stent- or graft related thrombosis (10%)[9]. In 2012 annual report of the Japanese Society for Vascular Surgery based on data from the National Clinical Database showed that patients with embolism and thrombosis are half of the total patients on the database[10].

Potential embolic that caused an acute decrease in limb perfusion is cardiogenic embolism; the majority arises from left atrial appendage associated with atrial fibrillation (80%)[11]. These emboli form due to poor cardiac wall motion leading to stagnant blood in cardiac chambers and clot formation. Other emboli can be caused by post valve replacement, left ventricle wall thrombosis following myocardial infarction, cardiac/aortic tumor, and embolus carried from venous side of circulation to the arterial side called as paradoxical embolism[12]. Shaggy aorta

syndrome[13] that can cause spontaneous atheromatous visceral embolization from diffuse aortic atherosclerotic disease can be caused by ALI as well as aneurysm associated with mural thrombus and iatrogenic embolism by catheter manipulation. Intraarterial drug administration can cause ALI by intense spasm and microvascular thrombosis[14]. Peripheral embolism caused by popliteal artery aneurysm and thrombotic occlusion from a true aneurysm is not rare and needs more caution. Some conditions such as intracardiac masses (myxoma, vegetation), calcified debris post transcatheter aortic valve implantation (TAVI), dissection of pelvic and lower extremity arteries are essential to be identified because of different treatment. The most common side of embolism is the femoral artery[15].

Thrombotic limb ischemia occurs in patients with underlying peripheral artery disease (PAD). Chronic stenotic lesions in occlusive atherosclerosis cause acute obstruction resulting from plaque breakdown, circulatory failure, or a hypercoagulable state. It can be caused by occlusion of stents and bypass graft. Thrombosis in situ may arise from acute plaque rupture, hypovolemia, or pump failure. Usually, limbs that have stable chronic ischemia do not suddenly worsen without any reason[16]. It is often challenging to distinguish embolism from thrombosis. Trauma can occur because of non-iatrogenic ALI. The commonest are limb fractures and dislocations, blunt injury and stab wounds. Trauma can lead to vascular injury that results in vascular damage. Compartment syndrome results from trauma that can be caused by compression inside the vascular compartment lead to ALI[17–19]. Some orthopedic procedures on the limb, especially with a tourniquet and pelvic surgery in a patient with the aortoiliac disease in which pelvic collaterals are ligated, form the main blood supply to the legs. Lower limb ischemia needs further assessment if there is the presence of epidural or spinal anesthesia. Hugl et al. reported a case of upper acute limb ischemia caused by thoracic outlet syndrome (TOS). TOS caused by compression or irritation of the neurovascular bundle at the level of the costoclavicular passage is an unusual case of ALI. Upper extremity ischemia caused by TOS is less than 5% of patients[20,21].

PATHOLOGY

The longer time the limb without oxygen, the greater chance it becomes irreversible. The ischemia starts from the most sensitive part, which is nerve, skin, and subcutaneous tissue to skeletal muscle. Ischemia causes a decrease in oxygen level in tissues, leading to the inability of mitochondrial oxidative phosphorylation. In ischemia, the condition occurs obstruction

of blood vessels causes dysfunction in the electron transport chain[22,23]. Lack of ATP production that leads to anaerobic metabolism, which produces a low level of pH in the cell. In ischemia condition, Sodium-dependent pH regulatory including Na+/H+ exchanger and Na+ - HCO3 transporter are activated. Hydrogen ions are excreted by Na+/H+ exchanger, which produces a large influx of sodium to balance the accumulation of hydrogen ions due to the decrease of pH In ischemia conditions. Cellular ATP depleted, which Inactivates ATPases leads to ultrastructural damage to mitochondria[4,24].

Ischemia tissue produces oxygen-free radicals. Peroxidation of membrane lipids, increase in capillary permeability and swelling can be caused by oxygen free radicals. Inflammation and leukocyte-activated platelets in ischemia conditions cause activation of the complement system and platelet aggregation. This results in the no-reflow phenomenon lead to the release of cell death into the systemic circulation. Prolonged ischemia can caused a condition such as myonephropatic metabolic syndromes. MNMS is a condition where muscle cell is liquefactive necrosis and accumulation of K^+ ion, myoglobin creatine, lactic acid and superoxide occur in affected limb. This condition can cause sudden death from heart failure and renal failure[22,25].

4. DIAGNOSIS

4.1 Signs and Symptoms

Symptoms of ALI usually develop in several minutes, to hours or day. In total arterial obstruction, irreversible change in nerves happened in 4-6 hours, muscles in 6-8 hours, and skin in 8-12 hours. It starts with intermittent claudication end develop until it becomes severe rest pain, paraesthesia, muscle weakness, paralysis, and gangrene. Clinical features of ALI are mnemonic known as the Six Ps: pain, pallor, paralysis, paraesthesia, pulselessness, poikilothermia[3,26]. Pain is usually the first symptom of ALI, start from the distal part of the limb and gradually progressing proximally with increased duration of ischemia. After ischemia progress to the neurological damage stage, the pain may begin to diminish. Numbness is a common complaint associated with persistent limb ischemia. As ischemia progresses, anesthesia and paralysis become more prominent[27].

A good history taking and physical diagnosis are very important to ALI for further management. It is often difficult to distinguish between embolic or thrombotic, and clinically possible only in around 15% ALI cases. In general, sudden onset development of ischemia symptoms in a patient with previously asymptomatic is most consistent with an embolus, and sudden worsening symptoms in a patient

with a history of chronic ischemia and claudication is more indicative of thrombosis. Patient with thrombosis usually has significant comorbidities such as coronary artery disease, stroke, diabetes, and renal failure. At the same time, the prior history of embolism, arrhythmia suggesting atrial fibrillation, aneurysm are comorbidities for embolic. Unclear onset and confusing complaints can be caused by atherosclerotic plaque. Collateral vessels to the distal regions of limb usually occur with gradual progression of atherosclerosis. Vascular spasm and marble white of limb appear on acute arterial occlusion. After the vessel relax, the deoxygenated blood will fill the skin leading to mottled that blanches on pressure (Table 1)[11]

Table 1. The Difference between Embolism and Thrombosis[11]

	Embolism	Thrombosis
History		
Onset of pain	Rapid onset of symptoms	Sudden worsening of claudication symptoms
Past medical history	No known PAD history ± atrial fibrillation, recent MI, valvular disease	Known history of PAD ± coronary artery disease, cerebrovascular disease
Prior vascular surgery	Usually none	Often yes
Physical examination		
Appearance	Mottled, distinct demarcation	Bluish, no distinct demarcation
Temperature	Cold	Cool
Neurologic	Paralysis	Paresthesias
Contralateral limb	Normal	Abnormal pulse examination, hair loss, shiny skin, thickened nails
Most common cause	Cardiac thromboemboli	Plaque rupture
Most common ischemic class	Immediately threatened (IIb)	Marginally threatened (IIa)

The severity of ALI is classified using the Rutherford classifications. Classification of severity is important because the evaluation and treatment of ALI are based on the degree of tissue ischemia and limb prognosis (Table 2)[27,28]

Figure 1. Clinical condition of Acute Lower Limb Ischemia and Upper Limb Ischemia (Tahalele & Gerardo's documentation and Fauzan's documentation[28])

Table 2. Acute Limb Ischemic (ALI) Severity Based on Rutherford Classification[11]

Category	Description/Prognosis	Sensory Loss	Muscle Muscle Weakness	Arterial Arterial Doppler	Venous Venous Doppler
Viable (I)	Not immediately threatened	None	None	Audible	Audible
Marginally threatened (IIa)	Salvageable if promptly threatened	Minimal (toes) or none	None	Often inaudible	Audible
Immediately threatened (IIb)	Salvageable with immediate revascularization	Extends beyond toes; pain at rest	Mild to moderate	Usually inaudible	Audible
Irreversible damage (III)	Major tissue loss or permanent nerve damage inevitable	Profound, anesthetic	Profound, paralysis or rigor	Inaudible	Inaudible

4.2 Imaging

Duplex ultrasound (DUS) is the first imaging choice to assess ALI because it is widely available, low cost, non-invasive, non-irradiant procedure, and it takes a relative time to perform. DUS shows important information like anatomic location, degree of obstruction (complete or incomplete), hemodynamics (proximal and distal to the obstruction), and is highly useful for the follow up of revascularization treatment[29]. DUS imaging uses 2D ultrasound, a color Doppler, and a pulsed

wave Doppler. This procedure provides excellent data at femoral and popliteal levels, while aortic and iliac arteries may be difficult to evaluate, especially in obese patients or gas interposition[2]. A non-pulsatile artery, without color flow, with a thrombus within the lumen, indicated the site of arterial occlusion. DUS can also differentiate between a thrombosis on a preexisting chronic and severe stenosis and an embolic event. Venous examination using DUS may also be useful for the differential diagnosis and appropriate staging of ALI[30].

Computed Tomography Angiography (CTA) and Magnetic Resonance Angiography (MRA) is high-resolution imaging tools and usually used to confirm the diagnosis and demonstrate the location and extent of arterial occlusion. The ability to visualize calcification, stents, and bypasses is the most significant advantage of CTA. Contrast agents can worsen renal failure and contraindicated in patients with a glomerular filtration rate (GFR) lower than 60 mL/min[30]. Gadolinium-enhanced MRA has excellent sensitivity (93–100%) and specificity (93–100%) compare to digital subtraction angiography (DSA) for assessing peripheral arterial disease[4,5]. MRA is useful in patients with allergies or moderate renal failure but contraindicated in patients with severe renal failure (GFR below 30 mL/min) and the presence of pacemakers or metal implants. CTA and MRA are reserved for patients with a non-immediately threatened limb because of long imaging sessions[30].

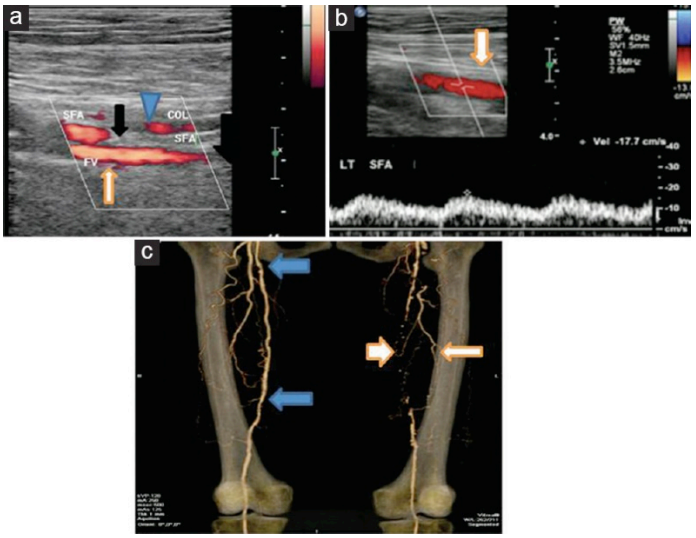

Figure 2 (a) Absent color flow at superficial femoral artery (SFA) because of intraluminal thrombosis (black arrow) with normal color filling of the SFA (white arrow) and noted collaterals beside the SFA (arrowhead). (b) Distal SFA monophasic low velocity flow Doppler (arrow). (c) Left SFA thrombosis showing absent opacification with distal collateral refilling (white arrows). Right SFA stenotic segments (blue arrows) computed tomography angiography[15,31]

DSA is an invasive angiogram procedure and was considered as the "gold standard" for ALI diagnosis. This procedure is useful to distinguish an embolic occlusion from in situ thrombosis and shows the site of occlusion and distal arterial tree. However, because it is an invasive procedure so there is a potential risk of complications, DSA should not be used as a first diagnostic method and should not

replace DUS for positive diagnosis of ALI. DSA is complementary to DUS and plays an essential role in the theurapeutic strategy[30]

4. Treatment

All patients with ALI, an intravenous injection of unfractioned heparin (50-100 units/kg) is immediately administered to prevent further clot propagation and allows time for assesment of adequancy of collateral flow and preparation for operation, as long as heparin therapy is no contraindicated[32]. For patients with viable or a marginally threatened limb (Rutherford class I and IIa), it is indicated to perform imaging (duplex ultrasonography, computed tomographic angiography, or magnetic resonance angiography) and endovascular revascularization is the appropriate initial treatment. In severly threatened limb (Rutherford class IIb), immediate revascularization is required within 3 to 6 hours for limb salvage and may best be served with surgical intervention. Class IIb patients should be examined by imaging where it is rapidly availble to guide management and aid prompt revascularization[30]. Amputation is appropriate in patients with irreversible limb (Rutherford class III) without attempt at vascular revascularization, as it is may expose the patient to the serious hazards of reperfusion caused by release of acidic and hyperkalemic venous blood from dying tissue[26]. Intaoperative angiography may be performed after revascularization procedure to detect pre-existing arterial lessions or outflow obstruction[30].

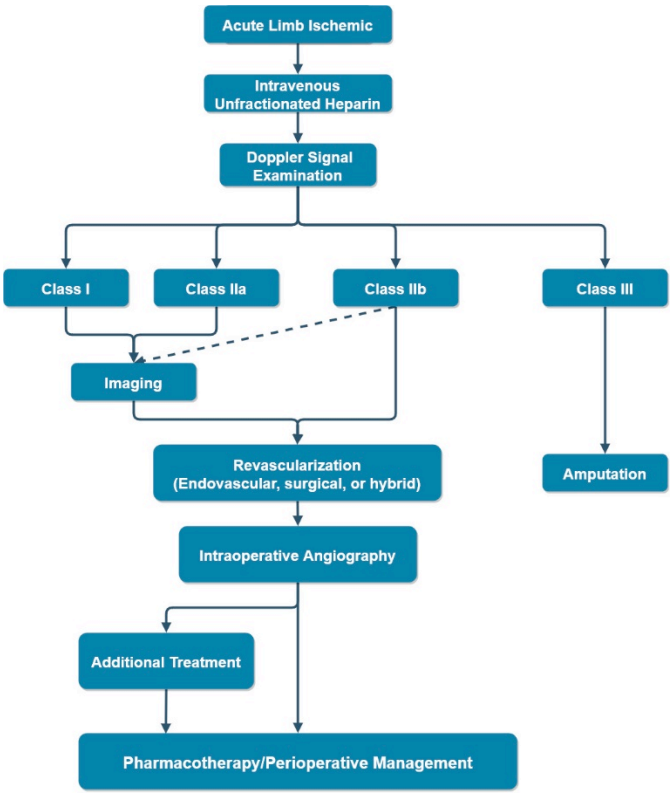

Figure 3 Algorithm for the treatment of acute limb ischemia

Endovascular treatment includes catheter-directed thrombolysis (CDT), percutaneous thromboaspiration (PAT), with or without thrombolytic therapy, or percutaneous mechanical thrombectomy (PMT), to restore blood as quickly as possible to the threatened limb, with the use of drugs, mechanical devices, or both. Generally, CDT is not indicated in class IIb patients because of a long time to reperfusion. CDT is often indicated for ALI, which affects the femoral artery and arteries distal to the femoropopliteal arteries.

Thrombolytic agents are injected within the thrombus by inserting 6-F sheath guidewire anterogradely in the common femoral artery of the affected side, then followed by a 4-F multihole catheter positioned in the thrombus[15]. Thrombolytic agents degrade fibrin by converting plasminogen to plasmin[33]. The main thrombolytic agents that are currently used for ALI are alteplase, urokinase, and streptokinase. During infusion of thrombolytic agents, patients should be admitted to an intensive care unit, blood count, and coagulation profile are mandatory to be periodically measured. Patients should not undergo CDT if suspected graft infection, symptom duration > 14 days, contraindication for thrombolysis (listed in Table 3), and failure to position the catheter across the thrombus

Tabel 3 Contraindicaitons to thrombolytic therapy (*adapted from Schwartz*)

Absolute contraindications
Established cerebrovascular events (including transient ischemia attack) within the last two months
Active bleeding diathesis
Recent (<10 days) gastrointestinal bleeding
Neurosurgery (intracranial or spinal) within the last three months
Intracranial trauma within the last three months
Intracranial malignancy or metastasis
Relative contraindications
Cardiopulmonary resuscitation within the last ten days
Major nonvascular surgery or trauma within the last ten days
Uncontrolled hypertension (>180 mmHg systolic or >110 mmHg diastolic)
Puncture of noncompressible vessel
Intracranial tumor
Recent eye surgery
Minor contraindications
Hepatic failure, particularly with coagulopathy
Bacterial endocarditis
Pregnancy
Diabetic hemorrhagic retinopathy

PAT and PMT may extend the applicability of endovascular treatment to patients with more advanced degrees of ALI (class IIb) and contraindicate to thrombolysis[32]. PAT provides a low-cost and rapid technique that uses large lumen catheters (6–8F) connected to a syringe. Furthermore, it is highly effective for acute iatrogenic distal embolization during an endovascular procedure. The concurrent use of CDT with PAT is recommended and is expected to shorten the duration of ischemia more compared with that by CDT alone, with the primary success rate reached 90%[o30,32]. PMT is defined as endovascular thrombus maceration and removal using percutaneous

thrombectomy devices and mainly indicated in class IIb patients because the time to reperfusion is significantly shorter than CDT. PMT may also be used as an adjunctive procedure for CDT that followed by incomplete thrombolysis or to treat distal embolic complications[30]. Conjunction with thrombolytic agents enhance clot lysis and limit the doses and time required for thrombolysis[15]. In one study by Blaisdell F., the amputation-free survival at 12 months was better in PMT compared to CDT or surgical thrombectomy[34].

The surgical approach of ALI includes thromboembolectomy with a balloon catheter (Fogarty), bypass surgery, and other adjuncts such as endarterectomy, patch angioplasty, and intra-operative thrombolysis. A combination of these techniques is frequently required. Surgical revascularization is preferred in a patient with an immediately threatened limb, suspected infection bypass graft, occlusion symptoms have been present for more than two weeks, or contraindication to thrombolysis[35]. Fogarty catheter for thromboembolectomy developed by Thomas Fogarty in 1963, it changed the treatment for ALI and largely improved the associated treatment results[32,34]. In surgical intervention, the groin is opened through a vertical incision, exposing the common femoral artery and its bifurcation. The location of the embolus at the femoral bifurcation can be detected by distally disappeared of the proximal femoral pulse. The artery is clamped and opened transversely over the bifurcation. The thrombus is extracted by passing a Fogarty balloon embolectomy catheter. The procedure is repeated until back-bleeding, and antegrade bleeding occurs, which suggests that the entire clot has been removed[30]. A recent refinement treatment is the use of the over-the-wire type Fogarty catheter. This procedure enabling intraoperative selective fluoroscopically assisted thromboembolectomy into distal vessels[30,32]. Additional endovascular treatments are performed (hybrid treatment) when sufficient peripheral blood flow cannot be obtained despite thromboembolectomy. If there are good distal vessels, and the saphenous vein is suitable, the surgical bypass is recommended because it is fast, durable, and reliable. In the absence of a good distal target and saphenous vein, or a patient at high risk for surgery, thrombolysis is recommended[35]. Patch angioplasty should be considered to avoid the narrowing of the artery[36].

One meta-analysis of five randomized trials with a total of 1283 participants was included comparing catheter-directed thrombolytic therapy with surgery for acute limb ischemia showed similar rates of limb salvage and mortality

rates. Still, thrombolysis was associated with higher rates of stroke, major hemorrhage, and distal embolization within 30 days[37]. Based on these trials and more recent case series, catheter-directed thrombolysis has the best results in patients with a viable or marginally threatened limb, recent occlusion (no more than two weeks' duration), thrombosis of a synthetic graft or an occluded stent, and at least one identifiable distal runoff vessel. Surgical revascularization is generally preferred for patients with an immediately threatened limb or with symptoms of occlusion for more than two weeks.

Successful revascularization manifested by relief of pain, restoration of a palpable foot pulse, audible arterial Doppler signals, and visible improvement of foot perfusion (e.g., capillary refill, increased temperature, and sweat production)[37,38]. Once revascularization successful, a reperfusion injury may develop with significant swelling requiring surgical fasciotomy to treat the compartment syndrome that may accompany the reperfusion injury to prevent irreversible neurologic and soft-tissue damage. Peroneal nerve dysfunction may occur due to compression of the anterior compartment of the leg because it is the most susceptible to this phenomenon. Renal insufficiency from myoglobin release should be anticipated after the reperfusion of ischemia muscle. Treatment consists of aggressive hydration and alkalinization of the urine.

Oral anticoagulant with unfractionated heparin is continued after thrombolysis, or surgical hemostasis has been ensured. For thrombosis and cardiogenic embolism associated with the thrombophilic conditions and localized lesions, long-term anticoagulant therapy with warfarin is needed to decrease the recurrence rate[39]. All patients with a history of ALI need long-term follow-up with a cardiovascular specialist. In those with identified peripheral arterial disease, appropriate secondary preventive measures such as daily exercise, smoking cessation, diabetic control, blood pressure and treatment of hyperlipidemia should be instituted[39].

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