CLINICAL PRACTICE

Acute Limb Ischemia

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This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the authors' clinical recommendations.*

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A 57-year-old man presents with an acute onset of left foot pain, numbness, and partial loss of motor function. Four months ago, he underwent endovascular treatment for disabling claudication, which included placement of overlapping polytetrafluoroethylene-coated stents in the left superficial femoral and popliteal arteries. His popliteal and pedal pulses are absent, and the foot is cool and mottled. Angiography reveals complete occlusion of the stent, with thrombosis extending distally into the popliteal and tibial arteries below the knee. How should his case be managed?

THE CLINICAL PROBLEM

Acute limb ischemia is defined as a sudden decrease in limb perfusion that threatens the viability of the limb.[1] The incidence of this condition is approximately 1.5 cases per 10,000 persons per year. The clinical presentation is considered to be acute if it occurs within 2 weeks after symptom onset. Symptoms develop over a period of hours to days and range from new or worsening intermittent claudication to pain in the foot or leg when the patient is at rest, paresthesias, muscle weakness, and paralysis of the affected limb. Physical findings may include an absence of pulses distal to the occlusion, cool and pale or mottled skin, reduced sensation, and decreased strength. These features of acute limb ischemia are often grouped into a mnemonic known as the six Ps: paresthesia, pain, pallor, pulselessness, poikilothermia (impaired regulation of body temperature, with the temperature of the limb usually cool, reflecting the ambient temperature), and paralysis.



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The rapid onset of limb ischemia results from a sudden cessation of blood supply and nutrients to the metabolically active tissues of the limb, including skin, muscle, and nerves. In contrast to chronic limb ischemia, in which collateral blood vessels may circumvent an occluded artery, acute ischemia threatens limb viability because there is insufficient time for new blood-vessel growth to compensate for loss of perfusion. Urgent recognition with prompt revascularization is required to preserve limb viability in most circumstances.

Clinical events that cause acute limb ischemia include acute thrombosis of a limb artery or bypass graft, embolism from the heart or a diseased artery, dissection, and trauma (from severing of an artery or thrombosis). Acute thrombosis of a limb artery is most likely to occur at the site of an atherosclerotic plaque. Thrombosis may also occur in arterial aneurysms (particularly in the popliteal artery) and in bypass grafts. Thrombosis may complicate an autogenous vein bypass at anastomoses and sites of retained valve cusps, kinks, or other technical problems. Acute thrombosis of prosthetic grafts may occur anywhere in the graft conduit, even if there is no obvious predisposing abnormality. Thrombosis may also affect a previously normal limb artery in patients with thrombophilic conditions such as the antiphospholipid antibody syn-

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KEY CLINICAL POINTS

ACUTE LIMB ISCHEMIA

- Acute limb ischemia is a sudden decrease in limb perfusion that threatens limb viability and requires urgent evaluation and management.
- Causes of acute limb ischemia include acute thrombosis of a limb artery or bypass graft, embolism from the heart or a diseased artery, dissection, and trauma.
- Assessment of limb appearance, temperature, pulses (including by Doppler), sensation, and strength is used to determine whether the limb is viable, threatened, or irreversibly damaged.
- Prompt diagnosis and revascularization by means of catheter-based thrombolysis or thrombectomy or by surgical reconstruction reduce the risk of limb loss.
- Catheter-directed thrombolysis is the preferred treatment for a viable or marginally threatened limb, recent occlusion, thrombosis of synthetic grafts, and occluded stents. Surgical revascularization is generally preferred for an immediately threatened limb or occlusion of more than 2 weeks' duration.
- Amputation is performed in patients with irreversible damage.

drome and heparin-induced thrombocytopenia. Cardiac embolism is a particular concern in patients with atrial fibrillation, acute myocardial infarction, left ventricular dysfunction, or prosthetic heart valves who are not receiving anticoagulant therapy.

Rates of death and complications among patients who present with acute limb ischemia are high. Despite urgent revascularization with thrombolytic agents or surgery, amputation occurs in 10 to 15% of patients during hospitalization.[2,3] A majority of amputations are above the knee. Approximately 15 to 20% of patients die within 1 year after presentation, often from coexisting conditions that predisposed them to acute limb ischemia.

STRATEGIES AND EVIDENCE

EVALUATION

Acute limb ischemia should be distinguished from critical limb ischemia caused by chronic disorders in which the duration of ischemia exceeds 2 weeks and is usually much longer; these conditions include severe atherosclerosis, thromboangiitis obliterans, other vasculitides, and connective-tissue disorders. Other causes of limb ischemia include atheroembolism, vasospasm, the compartment syndrome, phlegmasia cerulea dolens (deep-vein thrombosis with severe leg swelling compromising perfusion), and vasopressor drugs. Nonischemic limb pain from acute gout, neuropathy, spontaneous venous hemorrhage, or traumatic soft-tissue injury may mimic acute ischemia.

A careful examination of the limbs is necessary to detect signs of ischemia, including decreased temperature and pallor or a mottled appearance of the affected limb. Sensation and muscle strength should be assessed. The vascular examination includes palpation of pulses in the femoral, popliteal, dorsalis pedis, and posterior tibial arteries in the legs and in the brachial, radial, and ulnar arteries in the arms. The presence of flow, particularly in the dorsalis pedis and posterior tibial arteries supplying the affected foot or radial and ulnar arteries of the symptomatic hand, is routinely assessed with a Doppler instrument. If flow is audible, perfusion pressure to the ischemic limb can be measured with a sphygmomanometric cuff placed at the ankle or wrist just proximal to the Doppler probe; a perfusion pressure of less than 50 mm Hg indicates limb ischemia.

The severity of acute limb ischemia is categorized according to the clinical presentation and prognosis (Table 1).[4] This categorization guides decisions about additional testing and revascularization. Optimal management requires prompt administration of intravenous heparin to minimize thrombus propagation. In patients with viable (stage I) or marginally threatened (stage IIa) limbs, it may be reasonable to perform imaging (duplex ultrasonography, computed tomographic angiography, or magnetic resonance angiography) to determine the nature and extent of the occlusion and

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Table 1. Stages of Acute Limb Ischemia.*

Stage	Description and Prognosis	Findings		Doppler Signal	
		Sensory Loss	Muscle Weakness	Arterial	Venous
I	Limb viable, not immediately threatened	None	None	Audible	Audible
II	Limb threatened				
IIa	Marginally threatened, salvageable if promptly treated	Minimal (toes) or none	None	Often inaudible	Audible
IIb	Immediately threatened, salvageable with immediate revascularization	More than toes, associated with pain at rest	Mild or moderate	Usually inaudible	Audible
III	Limb irreversibly damaged, major tissue loss or permanent nerve damage inevitable	Profound, anesthetic	Profound, paralysis (rigor)	Inaudible	Inaudible

* Data are from the Society for Vascular Surgery standards.[4]

to plan intervention (Fig. 1). Although such types of testing have not been studied specifically for acute limb ischemia, they have sensitivities and specificities exceeding 90% for chronic arterial disease.[5-7] The availability of imaging and the time required to perform and interpret it must be balanced against the urgency for revascularization. In most patients with acute limb ischemia, catheter angiography remains the cornerstone approach (Fig. 2A). In the past, patients with immediately threatened limbs (stage IIb) were taken directly to the operating room. Hybrid operating rooms with angiographic capability and improved endovascular techniques for thromboembolectomy make it possible to perform imaging and revascularization in a single setting. Imaging and revascularization are not indicated if the limb is irreversibly damaged (stage III).

TREATMENT

Acute limb ischemia is treated by means of endovascular or open surgical revascularization. Often, the techniques are complementary. However, they are reviewed here as discrete entities.

Endovascular Revascularization

The goal of catheter-based endovascular revascularization is to restore blood flow as rapidly as possible to a viable or threatened limb with the use of drugs, mechanical devices, or both. Patients in whom ischemia for 12 to 24 hours would not be safe and those with a nonviable limb, bypass graft with suspected infection, or contraindication to thrombolysis (e.g., recent intracranial hemorrhage, recent major surgery, vascular brain neoplasm, or active bleeding) should not undergo catheter-directed therapies.

Patients are treated with concomitant low-dose unfractionated heparin through a peripheral intravenous cannula or the arterial sheath at the access site to prevent the formation of a pericatheter thrombus.[8] Before revascularization, diagnostic angiography is performed to assess the inflow and outflow arteries and the nature and length of thrombosis (Fig. 2A). Thereafter, the operator crosses the occlusion with a guidewire and a multi–side-hole catheter, which allows direct delivery of the thrombolytic agent into the thrombus.[9] Clinical and angiographic examinations are performed during the infusion to determine progress (Fig. 2B), and patients are monitored for potential complications. The blood count and coagulation profile are periodically measured.[10] Once flow is restored, angiography is performed to detect any inciting lesion, such as graft stenosis or retained valve cusps, which can be managed with catheter-based techniques or surgery (Fig. 2C).

Thrombolytic agents work by converting plasminogen to plasmin, which then degrades fibrin. The agents that are currently in use for most peripheral procedures are alteplase (Genentech), a recombinant tissue plasminogen activator; reteplase (EKR Therapeutics), a genetically engineered mutant of tissue plasminogen activator; and tenecteplase (Genentech), another genetically engineered mutant of tissue plasminogen activator. These agents are intended to selectively activate plasminogen bound in the thrombus and are administered over a period of 24 to 48 hours,[11,12] although none are approved by the Food and Drug Administration for this indication. Streptokinase, an indirect plasminogen activator, was the first agent used for intraarterial thrombolysis, but its use has been largely abandoned in the United

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Figure 1. Three-Dimensional Reconstruction of a Computed Tomographic Angiogram in a Patient with a 3-Day History of Pain and Numbness in the Right Foot.
This posterior view shows a focal occlusion of the right popliteal artery (arrow) with surrounding enlarged collateral vessels, findings that are consistent with acute thrombosis of an underlying atherosclerotic lesion. The superficial femoral and below-knee popliteal arteries are diffusely diseased. The patient underwent surgical bypass with a reversed saphenous vein graft to the posterior tibial artery.

States because of lesser efficacy and higher rates of bleeding, as compared with other thrombolytic agents, and the potential for allergic reactions.[8,13,14] The direct plasminogen activator urokinase is no longer available in the United States because of manufacturing issues resulting in a discontinuation of production.

Catheters can be successfully positioned across the thrombosed vessel (an essential prerequisite) in 95% of cases.[15] Among patients with acute limb ischemia caused by an occluded native vessel, stent, or graft, complete or partial thrombus resolution with a satisfactory clinical result occurs after catheter-based thrombolysis in 75 to 92% of patients.[3,8,15,16] Distal thrombus embolization commonly occurs as the thrombus is lysed, but the embolized thrombus typically clears during the thrombolytic infusion.[3] The adjunctive use of glycoprotein IIb/IIIa receptor antagonists may accelerate reperfusion and reduce distal embolization, but the addition of these agents does not improve outcomes.[17,18]

Bleeding occurs most commonly at the catheter-insertion site, but it can also occur remotely, particularly in recent operative fields. Major hemorrhage occurs in 6 to 9% of patients, including intracranial hemorrhage in less than 3%.[19] Factors associated with an increased risk of bleeding include the intensity and duration of thrombolytic therapy, the presence of hypertension, an age of more than 80 years, and a low platelet count.[20,21]

A variety of percutaneous mechanical devices for aspiration, rheolysis, mechanical fragmentation, and ultrasonography-assisted fibrinolysis, used either independently or in combination with pharmacologic thrombolysis, are available.[8,10,22-24] These devices may rapidly restore flow through the occluded segment and therefore shorten the duration of therapy. However, data from trials comparing these devices with pharmacologic thrombolysis alone are lacking.

Surgical Revascularization

Surgical approaches to the treatment of acute limb ischemia include thromboembolectomy with a balloon catheter, bypass surgery, and adjuncts such as endarterectomy, patch angioplasty, and intraoperative thrombolysis. Frequently, a combination of these techniques is required. The cause of ischemia (embolic vs. thrombotic) and anatomical

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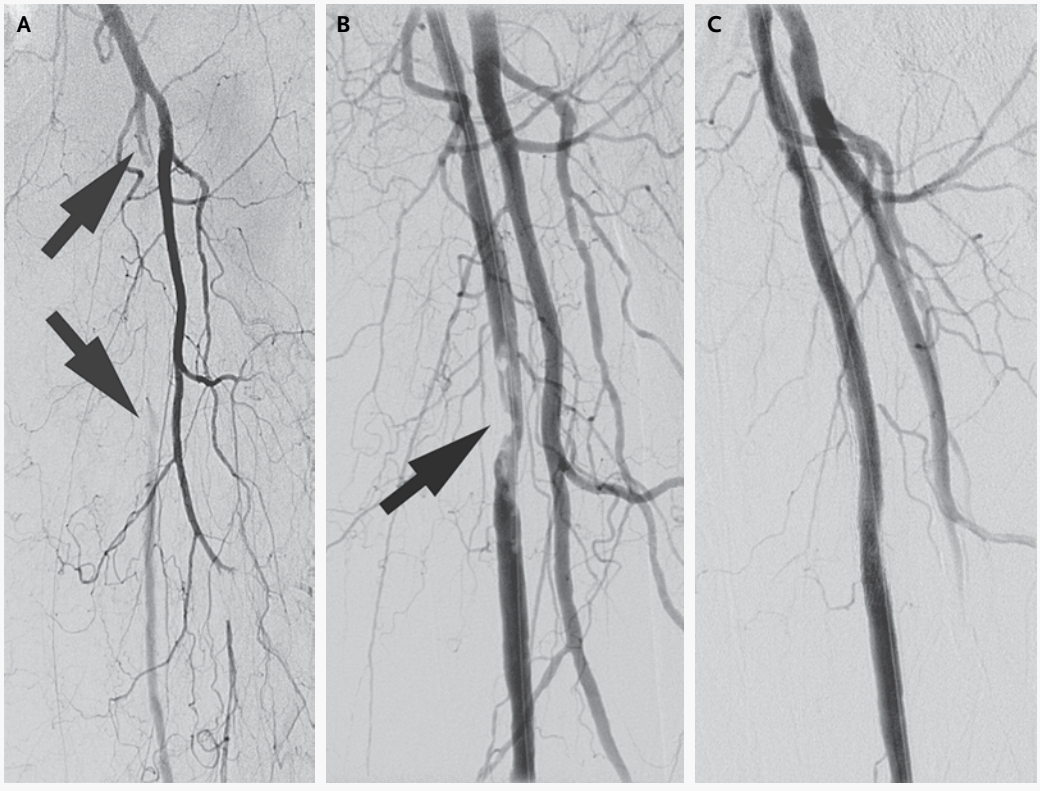


Figure 2. Acute Ischemia of the Left Leg in a 68-Year-Old Woman with Chronic Renal Failure.

In Panel A, a digital subtraction angiogram of the proximal left thigh shows occlusion of the proximal superficial femoral artery, with reconstitution in the mid-thigh (arrows). An intraluminal filling defect is present in the proximal superficial femoral artery, which is consistent with an acute thrombus. The proximal and distal arteries, which were normal, are not shown. Tissue plasminogen activator was infused for 18 hours, at a rate of 0.5 mg per hour, directly into the thrombosed segment through a multi–side-hole infusion catheter. The angiogram in Panel B, obtained after the infusion, shows that the thrombus has largely resolved, revealing the underlying stenosis (arrow). The angiogram in Panel C, obtained after angioplasty and placement of a self-expanding stent, shows a widely patent artery. After this treatment, the patient's symptoms resolved.

features guide the surgical strategy. Thrombotic occlusion usually occurs in patients with a chronically diseased vascular segment. In such cases, correction of the underlying arterial abnormality is critical. Patients with suspected embolism and an absent femoral pulse ipsilateral to the ischemic limb are best treated by exposure of the common femoral artery bifurcation and balloon-catheter thromboembolectomy.[25] A recent refinement for thromboembolectomy is the use of over-the-wire catheters, allowing for selective guidance into distal vessels. After removal of the clot, intraoperative angiography is performed to confirm that the thrombectomy is complete and to guide subsequent treatment if there is persistent inflow or outflow obstruction.

The treatment of patients with acute limb ischemia caused by thrombosis of a popliteal-artery aneurysm warrants special mention, because major amputation occurs with high frequency in such patients.[26,27] Diffuse thromboembolic occlusion of all major runoff arteries below the knee is frequently seen, and intraarterial thrombolysis or thrombectomy may be required to restore flow in a runoff artery before aneurysm exclusion and surgical bypass are performed (Fig. 3).

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) suggest treatment success. In some cases, perfusion may be incomplete and close postoperative ob-

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Figure 3. Three-Dimensional Reconstruction of Computed Tomographic Angiogram Showing Runoff in the Left Leg.

This coronal view shows a patent bypass graft (arrow) to the anterior tibial artery, performed to repair an aneurysm in a popliteal artery with acute thrombosis.

servation is required to monitor the limb status. Therapeutic anticoagulation with heparin is reinstituted after the procedure. Vasodilators (e.g., nitroglycerin and papaverine) may be useful if there is evidence of vasospasm.

Endovascular versus Surgical Revascularization

A meta-analysis[13] of five randomized trials[15,28-31] comparing catheter-directed thrombolytic therapy with surgery for acute limb ischemia showed similar rates of limb salvage, but thrombolysis was associated with higher rates of stroke and major hemorrhage within 30 days.[13] Individual trial results were inconsistent, however, perhaps because of differences in patients' characteristics, the duration and severity of ischemia, thrombolytic regimens, and length of follow-up. In one trial,[28] rates of limb salvage were similar with catheter-based thrombolysis and with surgery, but 12-month rates of survival were significantly higher in the thrombolysis group. The Surgery versus Thrombolysis for Ischemia of the Lower Extremity (STILE) trial was halted early because of higher rates of ischemia, amputation, and complications among patients undergoing thrombolysis than among those undergoing surgery.[29] However, this trial included patients with limb ischemia that had developed up to 6 months before enrollment. Post hoc analysis of patients undergoing thrombolysis, as compared with surgery, showed that the rate of amputation-free survival was higher among those with a symptom duration of less than 14 days but not among those with a longer duration of symptoms. In the Thrombolysis or Peripheral Arterial Surgery (TOPAS) trial, the rates of limb salvage and survival did not differ significantly between the thrombolysis and surgery groups, but complication rates were higher in the thrombolysis group.[15,28]

On the basis of 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 2 weeks' duration), thrombosis of a synthetic graft or an occluded stent, and at least one identifiable distal runoff vessel.[9,19,32] Surgical revascular-

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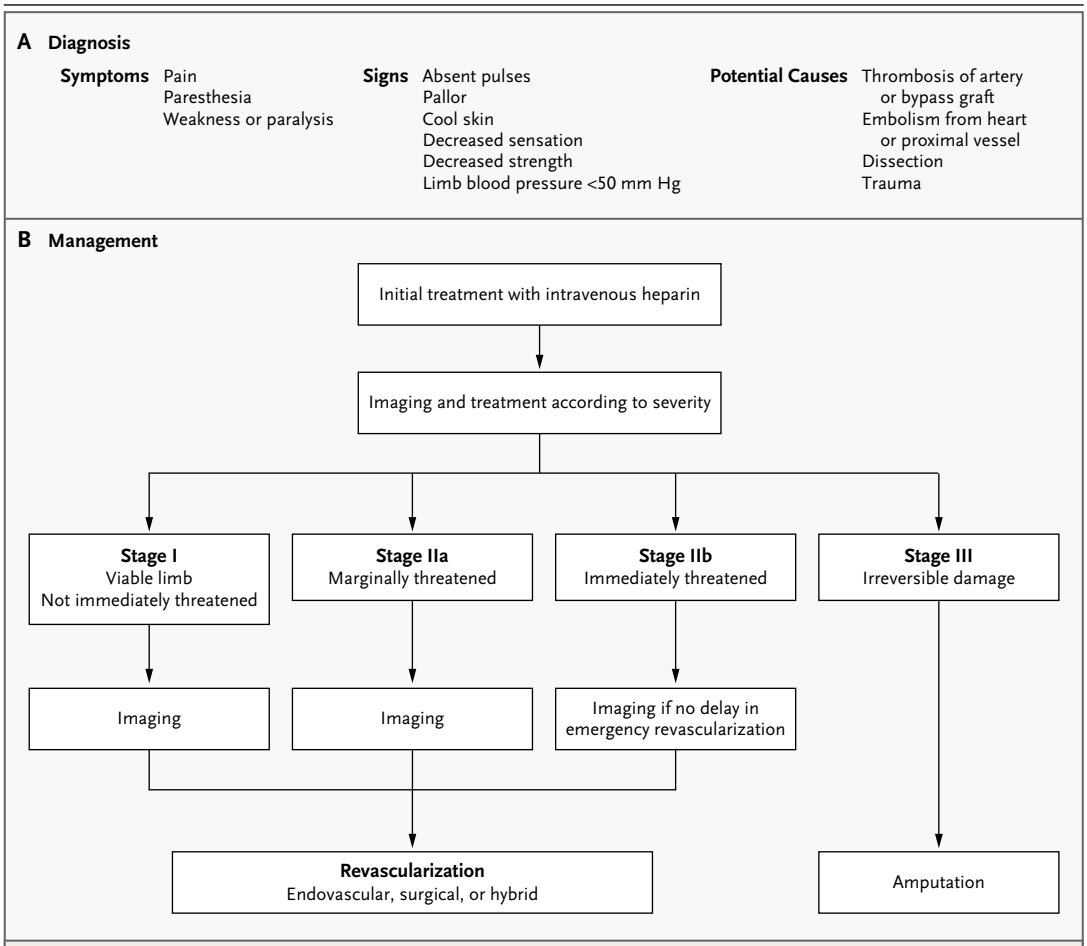


Figure 4. Algorithm for the Diagnosis and Treatment of Acute Limb Ischemia.

ization is generally preferred for patients with an immediately threatened limb or with symptoms of occlusion for more than 2 weeks.

Reperfusion Injury

Reperfusion may result in injury to the target limb, including profound limb swelling with dramatic increases in compartmental pressures. Symptoms and signs include severe pain, hypoesthesia, and weakness of the affected limb; myoglobinuria and elevation of the creatine kinase level often occur. Since the anterior compartment of the leg is the most susceptible, assessment of peroneal-nerve function (motor function, dorsiflexion of foot; sensory function, dorsum of foot and first web space) should be performed after the revascularization procedure. The diagnosis is made primarily from the clinical findings but can be confirmed if the compartment pressure is more than 30 mm Hg or is within 30 mm Hg of diastolic pressure. If the compartment syndrome occurs, surgical fasciotomy is indicated to prevent irreversible neurologic and soft-tissue damage. Since renal, pulmonary, and cardiac complications also may ensue after limb reperfusion, patients require close monitoring. Myoglobinuria should be treated by means of aggressive hydration.

LONG-TERM MANAGEMENT

Anticoagulation is continued after thrombolysis or surgical hemostasis has been ensured. Initially, unfractionated heparin is administered; alternatively, low-molecular-weight heparin may be used. Subsequent antithrombotic therapy depends on the cause of the limb ischemia. Long-term oral anticoagulation is indicated in patients with acute thrombosis of a native artery associated with thrombophilia and in those with cardiac embo-

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lism. The traditional therapy in such patients is warfarin. Novel oral anticoagulants that inhibit thrombin or factor Xa, such as dabigatran or rivaroxaban, may be considered in patients with atrial fibrillation, but the efficacy of such drugs in patients with peripheral-artery thrombosis is not known. Occluded bypass grafts may require revision if technical issues (e.g., stenoses, kinks, or retained valve cusps) are identified after successful thrombolysis; thereafter, antiplatelet agents are used to preserve patency. Long-term antiplatelet therapy is also indicated when the cause of acute limb ischemia is thrombosis superimposed on an atherosclerotic plaque and after repair of an arterial aneurysm that was deemed to underlie an embolic occlusion.

AREAS OF UNCERTAINTY

Randomized trials are needed to assess the efficacy and safety of catheter-based delivery systems for thrombolytic drugs and novel mechanical devices for thrombolysis or thrombectomy. It is not known whether outcomes are better when patients are treated in hybrid operating rooms that facilitate the use of combined endovascular and open surgical procedures, as compared with standard facilities. The optimal treatment strategy for various causes of acute limb ischemia remains uncertain.

GUIDELINES

Guidelines for the evaluation and management of acute limb ischemia include the Guidelines for the Management of Patients with Peripheral Arterial Disease of the American College of Cardiology and the American Heart Association,[33] the TransAtlantic Inter-Society Consensus on the Management of Peripheral Arterial Disease (TASC II),[1] and the American College of Chest Physicians Evidence-Based Clinical Practice Guidelines for Antithrombotic Therapy in Peripheral Artery Disease.[34] Our recommendations are consistent with these guidelines.

CONCLUSIONS AND RECOMMENDATIONS

The patient who is described in the vignette presents with symptoms and signs consistent with acute limb ischemia. This is a potentially catastrophic condition that can progress rapidly to limb loss and disability if not recognized and treated promptly (Fig. 4). Clinical evaluation includes assessment of limb color and temperature, pulses, and motor and sensory function. Heparin should be administered as soon as the diagnosis has been made. In a patient with a viable or marginally threatened limb, imaging studies can be obtained to guide therapeutic decisions. In a patient with an immediately threatened limb, such as the patient described in the vignette, emergency angiography followed by catheter-based thrombolysis or thrombectomy or open surgical revascularization is indicated to restore blood flow and preserve limb viability.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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