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MANAGEMENT OF CHRONIC LIMB-THREATENING ISCHEMIA

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ХРОНИЧЕСКАЯ УГРОЖАЮЩАЯ ПОТЕРЕЙ НИЖНЕЙ КОНЕЧНОСТИ ИШЕМИЯ

MANAGEMENT OF CHRONIC LIMB-THREATENING ISCHEMIA

Учебно-методическое пособие

Минск БГМУ 2021

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Отражены современные аспекты проблемы этиологии, патогенеза, клиники, диагностики хронической ишемии нижних конечностей. Освещены современные подходы к выбору методов ее лечения.

Предназначено для студентов 4-го курса медицинского факультета иностранных учащихся, обучающихся на английском языке.

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LIST OF ABBREVIATIONS AND ACRONYMS

ABI — Ankle-brachial index

AP — Ankle pressure

BKA — Below-knee amputation

CLI — Critical limb ischemia

CLTI — Chronic limb-threatening ischemia

CT — Computed tomography

CTA — Computed tomography angiography

DAPT — Dual antiplatelet therapy

DFU — Diabetic foot ulcer

DM — Diabetes mellitus

DSA — Digital subtraction angiography

DUS — Duplex ultrasound

EBR — Evidence-based revascularization

PAD — Peripheral artery disease

PLAN — Patient risk estimation, limb staging, anatomic pattern of disease

SFA — Superficial femoral artery

SLI — severe limb ischemia

SCLI — subcritical limb ischemia

TBI — Toe-brachial index

TcPO2 — Transcutaneous oximetry

TP — Toe pressure

WIfI — Wound, Ischemia, foot Infection

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MOTIVATIONAL CHARACTERISTICS OF THE TOPIC

Total in-class hours: 5.

In 2010, estimates suggested that > 200 million people worldwide were living with PAD. This represented a 23.5 % increase since 2000, an increase that is believed to be largely attributable to aging populations and the growing prevalence of risk factors, in particular DM. Chronic limb-threatening ischemia (CLTI) is associated with mortality, amputation, and impaired quality of life. The term CLTI is preferred over critical limb ischemia, as the latter implies threshold values of impaired perfusion rather than a continuum. CLTI is a clinical syndrome defined by the presence of peripheral artery disease (PAD) in combination with rest pain, gangrene, or a lower limb ulceration > 2 weeks duration. Venous, traumatic, embolic, and nonatherosclerotic etiologies are excluded. All patients with suspected CLTI should be referred urgently to a vascular specialist. Accurately staging the severity of limb threat is fundamental, and the Society for Vascular Surgery Threatened Limb Classification system, based on grading of Wounds, Ischemia, and foot Infection (WIfI) is endorsed. Objective hemodynamic testing, including ABI, toe pressures as the preferred measure, is required to assess CLTI. Evidence-based revascularization (EBR) hinges on three independent axes: Patient risk, Limb severity, and ANatomic complexity (PLAN). All patients with CLTI should be afforded best medical therapy including the use of antithrombotic, lipid-lowering, antihypertensive, and glycemic control agents, as well as counseling on smoking cessation, diet, exercise, and preventive foot care. Following EBR, long-term limb surveillance is advised.

The purpose is to study the etiology, pathogenesis, main clinical manifestations, diagnosis, and treatment of chronic limb-threatening ischemia.

Objectives are:

1) to learn main etiological causes of chronic limb-threatening ischemia;
2) to learn classifications of chronic limb-threatening ischemia;
3) to learn methods of examinations in chronic limb-threatening ischemia;
4) to learn common clinical features of chronic limb-threatening ischemia;
5) to make diagnosis of chronic limb-threatening ischemia;
6) to be able to assess results of diagnostic studies and laboratory tests;
7) to be able to perform preoperative preparation;
8) to be able to make plan of surgery;
9) to be able to prescribe the postoperative treatment.

Requirements for the initial level of knowledge. To learn the topic completely the student must know:

– propaedeutics of internal diseases (methods of clinical evaluation of blood vessels);

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– human anatomy (localization and structure of blood vessels);
– topographic anatomy and operative surgery (main surgical approaches to blood vessels);
– pathologic physiology (response to ischemia);
– vascukar surgery (basic principles of vascular interventions).

Test questions from related disciplines:

1. Normal and topographic anatomy of blood vessels.
2. Clinical evaluation of blood vessels.
3. Methods of investigations of blood vessels.
4. Surgical approaches to blood vessels.
5. General signs of ischemia and inflammation.

Test questions:

1. Anatomy and functions of blood vessels.
2. Classification of chronic limb-threatening ischemia.
3. Etiology of chronic limb-threatening ischemia.
4. Pathogenesis.
5. Complications.
6. Clinical manifestations.
7. Diagnosis.
8. Principles of treatment.

Target population. The target population of patients includes adults with CLTI, defined as a patient with objectively documented PAD and any of the following clinical symptoms or signs:
– ischemic rest pain with confirmatory hemodynamic studies;
– diabetic foot ulcer (DFU) or any lower limb ulceration present for at least 2 weeks;
– gangrene involving any portion of the lower limb or foot.

Successful revascularization in CLTI, particularly in patients with tissue loss, nearly always requires restoration of in-line (pulsatile) flow to the foot.

DEFINITIONS AND NOMENCLATURE

CLI / CLTI. In 1982, a working group of vascular surgeons defined CLI as ischemic rest pain with an ankle pressure (AP) < 40 mm Hg, or tissue necrosis with an AP < 60 mm Hg, in patients without diabetes. Patients with diabetes were specifically excluded because of the confounding effects of neuropathy and susceptibility to infection. CLTI is defined to include a broader and more heterogeneous group of patients with varying degrees of ischemia that may delay wound healing and increase amputation risk.

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Diagnosis. A diagnosis of CLTI requires objectively documented atherosclerotic PAD in association with ischemic rest pain or tissue loss (ulceration or gangrene). Ischemic rest pain is typically described as affecting the forefoot and is often made worse with recumbency while being relieved by dependency. It should be present for > 2 weeks and be associated with one or more abnormal hemodynamic parameters. These parameters include an anklebrachial index (ABI) < 0.4, absolute highest AP < 50 mm Hg, absolute TP < 30 mm Hg, transcutaneous partial pressure of oxygen (TcPO2) < 30 mm Hg, and flat or minimally pulsatile Doppler arterial waveforms (equivalent to WIfI ischemia grade 3) (table 1).

Table 1

Assessment of the risk of amputation: the WIFI classification

Component	Score	Description		
W (Wound)	0	No ulcer (ischaemic rest pain)		
	1	Small, shallow ulcer on distal leg or foot without gangrene		
	2	Deeper ulcer with exposed bone, joint or tendon ± gangrenous changes limited to toes		
	3	Extensive deep ulcer, full thickness heel ulcer ± calcaneal involvement ± extensive gangrene		
I (Ischaemia)		ABI	Ankle pressure (mm Hg)	Toe pressure or $TcPO_2$
	0	≥ 0.80	> 100	≥ 60
	1	0.60–0.79	70–100	40–59
	2	0.40–0.59	50–70	30–39
	3	< 0.40	< 50	< 30
fI (foot Infection)	0	No symptoms/signs of infection		
	1	Local infection involving only skin and subcutaneous tissue		
	2	Local infection involving deeper than skin/subcutaneous tissue		
	3	Systemic inflammatory response syndrome		

Pressure measurements should be correlated with Doppler arterial waveforms (fig. 1), keeping in mind that AP and ABI are frequently falsely elevated because of medial calcinosis, especially in people with DM and end-stage renal disease. For this reason, a combination of tests may be needed.

Tissue loss related to CLTI includes gangrene of any part of the foot or nonhealing ulceration present for at least 2 weeks. It should be accompanied by objective evidence of significant PAD (eg, WIfI ischemia grade 1). This definition excludes purely neuropathic, or venous ulcers (fig. 2).

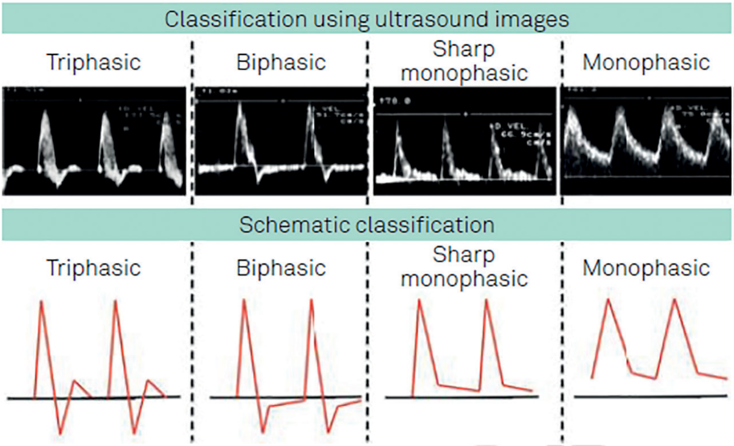


Fig. 1. Types of Doppler arterial waveforms

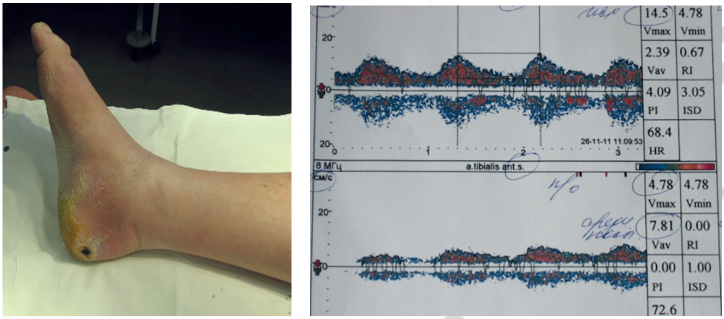
a

b

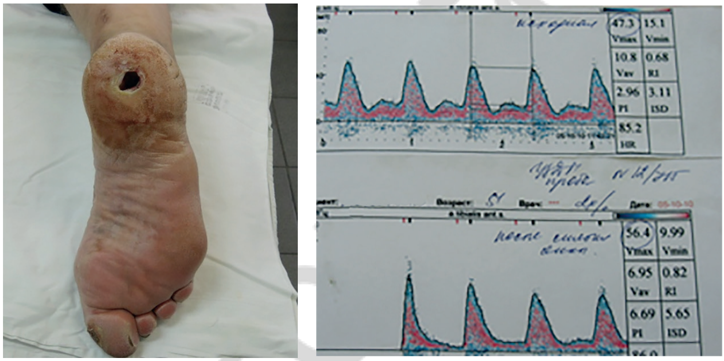
c

Fig. 2. Examples of ischemic (*a*), neuropathic (*b*), venous (*c*) tissue loss

Examples of differential diagnosis of foot ulcers using Doppler arterial waveforms is presented in the fig. 3.



a



b

Fig. 3. Ischemic (*a*) and neuropathic (*b*) foot ulcers and its Doppler arterial waveforms

CLTI is usually the result of multilevel arterial occlusive disease. Involvement of parallel vascular beds, such as the superficial femoral artery (SFA) and profunda femoris artery (PFA), is also common. Below-knee arteries typically become increasingly involved as the overall severity of disease worsens.

EPIDEMIOLOGY AND RISK FACTORS FOR CLTI

In 2010, estimates suggested that > 200 million people worldwide were living with PAD. This represented a 23.5 % increase since 2000, an increase that is believed to be largely attributable to aging populations and the growing prevalence of risk factors, in particular DM. Men have been reported to have a higher prevalence of PAD in high-income countries, whereas women seem to have a higher prevalence of PAD in low and middle-income countries. Modifiable risk factors for PAD include smoking, DM, hypertension, hypercholesterolemia. Chronic kidney disease is a strong risk factor for PAD and limb loss, especially in association with DM. People of lower socioeconomic status and educational attainment tend to have a higher prevalence of IC and probably also of CLTI, although the association is not always strong and can often be explained in part by their increased exposure to other risk factors, such as smoking. CLTI probably represents < 10 % of all PAD patients, and those undergoing amputation for CLTI are at very high risk of premature death (and so more likely to be absent from population-based studies). A systematic review found that the rate of major amputation varied considerably (3.6 to 68.4 per 100 000 per year) across the world, probably because of differences in ethnicity, social deprivation, and, in particular, the prevalence of DM.

In patients with known PAD, the risk for development of CLTI (10–21 %) appears to be greater in men, in patients who have had a stroke or are in heart failure, and in patients with DM. Patients who present de novo with CLTI (no prior diagnosis of PAD) seem more likely to be older and male and to have pre-existing CVD (including hypertension, myocardial infarction, heart failure, or stroke) and renal failure. Not surprisingly, because of the associated high prevalence of neuropathy, DM had the strongest association with a new presentation of CLTI. Approximately 50 % of patients presenting with CLTI have no prior history of PAD. The overall risk of limb loss in CLTI is estimated at approximately 25 % at 1 year.

DIAGNOSIS AND LIMB STAGING IN CLTI

History

Ischemic rest pain usually affects the forefoot, is frequently worse at night, and often requires opiate analgesia for management. If present for > 2 weeks and combined with hemodynamic evidence of severely impaired perfusion (eg, absolute AP < 50 mm Hg, absolute TP < 30 mm Hg), it is diagnostic of CLTI. Ischemic ulceration is frequently located on the toes and forefoot, but other areas may be affected in patients with diabetic neuropathy, altered biomechanics, or foot deformity. Gangrene usually occurs on the forefoot. A range of perfusion deficits may be limb threatening in different scenarios of tissue loss and concomitant infection. Thus, all patients presenting with signs or symptoms of suspected CLTI should undergo a complete vascular assessment.

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Physical examination

All patients with suspected CLTI should undergo a complete physical examination (fig. 4). Palpation of lower limb pulses can help determine the likely presence and distribution of arterial disease. Although they can be nonspecific, features such as coolness, dry skin, muscle atrophy, hair loss, and dystrophic toenails are frequently observed in patients with PAD. Buerger sign, pallor of the foot on elevation and rubor (so-called sunset foot) on dependency, is usually present in CLTI. The capillary refill time will usually exceed 5 seconds, especially when the patient is lying supine or the leg is elevated. It is leg hanging down as that may lead to false reassurance regarding the perfusion of the foot.

Many patients with CLTI, especially those with DM, have «glove and stocking» sensory, motor, and autonomic neuropathy that may be asymptomatic or be associated with tingling, numbness, weakness, and burning pain in the feet and ankles. The presence of such neuropathy is a major risk factor for tissue loss and should be carefully sought and evaluated using monofilaments and, if available, a tuning fork (loss of vibration sense is an early feature). Neuropathy often leads to abnormal foot biomechanics and deformity, and neuropathic (neuroischemic) ulcers often occur at sites of abnormal pressure (load bearing).

Noninvasive hemodynamic tests

AP and ABI. Measurement of AP and calculation of ABI (highest AP divided by highest brachial systolic pressure) is recommended as the first-line noninvasive hemodynamic test in all patients with suspected CLTI. Although many patients with CLTI will have an AP < 50 mm Hg or a markedly reduced ABI (typically < 0.4), an increasing proportion will not, especially those with DM, who may have incompressible crural arteries. ABI results should be reported as noncompressible if the value is > 1.4. However, it is important to be aware that incompressibility can lead to artifactually elevated readings between 0.4 and 1.4. This should be suspected when the ABI falls in or near the normal range but is associated with dampened, monophasic waveforms (recognized acoustically or visually on a screen). These falsely normal APs and ABI values have been reported to be an independent predictor of major amputation. In such patients, TP and toe-brachial index (TBI) or other hemodynamic measurements, as described next, should always be obtained.

Imaging of vascular anatomy

Duplex ultrasound imaging (DUS). DUS imaging is usually the first imaging modality of choice and in some health care settings may be the only modality available. DUS provides information on the anatomic location and extent of disease as well as information about flow volume and velocity. The main disadvantages of DUS are that it is time-consuming and highly operator dependent, and it does

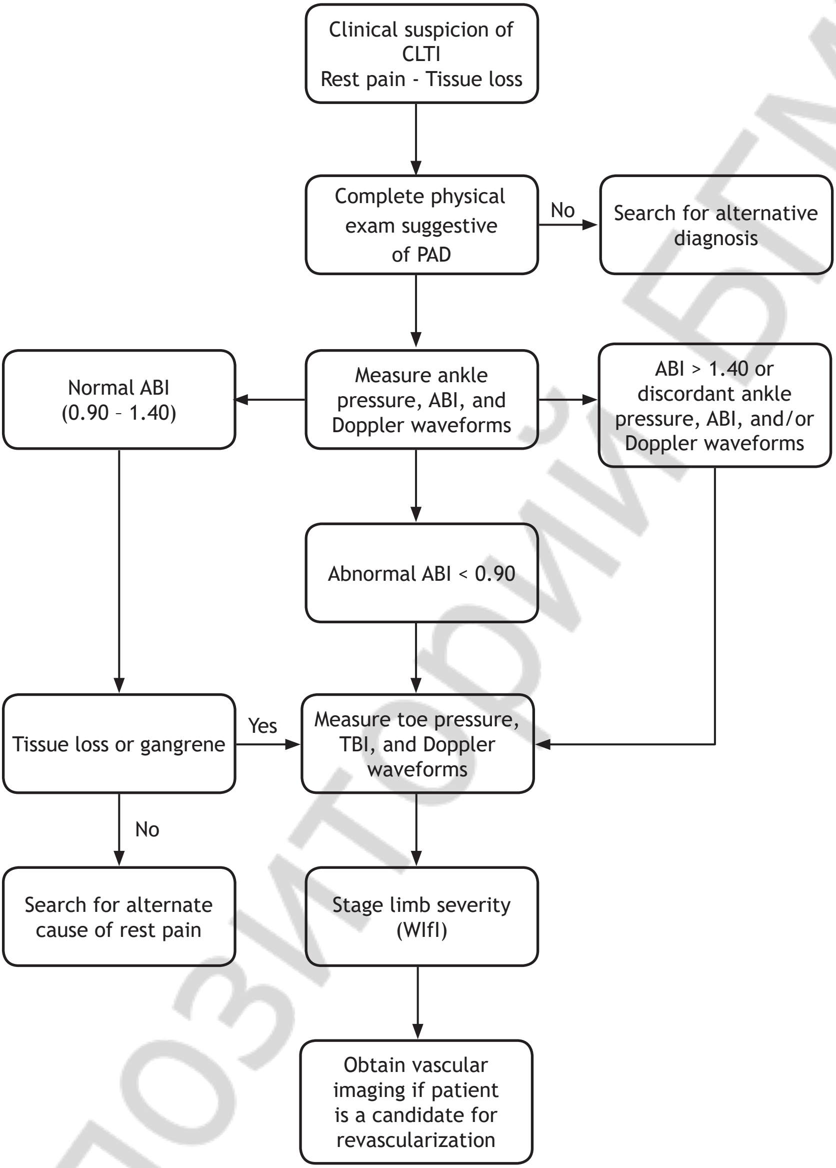

Fig. 4. Flow diagram for the investigation of patients presenting with suspected chronic limb-threatening ischemia (CLTI)

not produce a continuous lesion map. DUS is also poor at estimating collateral blood supply and reserve.

Computed tomography angiography (CTA). In recent years, CTA has advanced considerably in terms of accuracy and acquisition times. Modern CTA quickly generates high-resolution, contrast-enhanced images that can be viewed in multiple planes or as three dimensional reconstructions

Magnetic resonance angiography (MRA). MRA has the potential to produce images that are comparable in quality to DSA images but without exposure to ionizing radiation or iodinated contrast material, making contrast-induced nephropathy extremely rare.

Catheter Digital subtraction angiography (DSA). With the advent of DUS, CTA, and MRA, diagnostic DSA is probably performed less commonly now, but many vascular specialists still consider it the gold standard imaging modality in patients with suspected CLTI, particularly when Infrapopliteal disease is likely to be present. Enthusiasts for DSA will also point out that it allows intervention at the same setting. Other vascular specialists, however, argue that diagnostic DSA is outdated. The DSA technique should minimize the amount of iodinated contrast material and the dose of ionizing radiation used while maximizing imaging of the distal vasculature. In general, diagnostic DSA is widely available, and the complication rate is low

CO_2 angiography. CO_2 angiography can be used in patients with an allergy to contrast material or in individuals with severe chronic kidney disease.

Summary. Consider DUS imaging as the first arterial imaging modality in patients with suspected CLTI. Consider noninvasive vascular imaging modalities (DUS, CTA, MRA) when available before invasive catheter angiography in patients with suspected CLTI who are candidates for revascularization.

MEDICAL MANAGEMENT

CLTI is an end-stage manifestation of systemic atherosclerosis. It is frequently accompanied by clinically significant CVD, resulting in exceedingly high mortality from stroke and myocardial infarction. In the absence of aggressive identification and treatment of risk factors and associated comorbid conditions, the prognosis of CLTI is usually poor, with a mortality rate of 20 to 26 % within 1 year of diagnosis. The goal of treatment of patients with CLTI is not only to salvage a functional limb but to reduce cardiovascular morbidity and mortality through aggressive risk factor modification and best medical therapy. Whereas certain risk factors, such as age and sex, cannot be modified, others can, including hyperlipidemia, hypertension, diabetes, smoking, and sedentary lifestyle.

PenzaMTOPWARP

Antithrombotic therapy. Antiplatelet agents are strongly recommended for all patients with symptomatic PAD to reduce the risk of major adverse cardiovascular events.

Lipid-lowering therapy. Analysis showed that lipid-lowering therapy significantly reduced the risk of total cardiovascular events in PAD. The impact of statin agents may extend beyond their lipid-lowering effect by reducing inflammation in patients with PAD.

Management of hypertension. It is universally accepted that control of hypertension reduces major adverse cardiovascular events in patients with PAD. Control hypertension to target levels of < 140 mm Hg systolic and < 90 mm Hg diastolic recommended to patients with CLTI. The first-line category of oral antihypertensive does not appear to be of significance.

Management of diabetes. Type 2 DM is a significant risk factor for PAD and the extent of vascular disease appears related to the duration and severity of hyperglycemia. Glycemic control is therefore essential in all diabetic patients with PAD. Type 2 DM patients with abnormal renal function treated with metformin may be at higher risk for contrast-induced nephropathy and lactic acidosis. Whereas the matter is the subject of continued debate, it is reasonable to withhold metformin for 24 to 48 hours after the administration of an iodinated contrast agent.

Management of pain. Although pain is an important issue for most CLTI patients, it is often poorly managed. Themanagement of ischemic pain in CLTI is often complicated by the coexisting neuropathic pain, particularly in patients with DM. Guidelines usually recommend a tiered approach to pain management, with a «tradeoff» between benefits and harms (eg, constipation, drowsiness). Patients should be offered paracetamol (acetaminophen) in combination with opioids and in proportion to the severity of pain. All patients receiving opioids should also be offered laxatives and antinausea medication. If the maximum tolerated analgesic dose does not produce adequate pain relief, alternative approaches should be considered. These include tricyclic antidepressants, gabapentin, and pregabalin, all of which are used effectively for neuropathic pain.

Lifestyle modifications. In addition to controlling risk factors as discussed, it is important to encourage CLTI patients to adopt a healthier lifestyle. Stopping smoking (tobacco and other recreational drugs) completely and permanently, adopting a healthy diet and weight control, and regular exercise must be stressed as extremely important for both life and limb.

Vascular pharmacotherapy. *Prostanoids.* Prostanoids include a family of inflammatory mediators, mainly prostaglandin E1 (PGE1), prostacyclin (PGI2), and iloprost. Prostanoids act by inhibiting the activation of platelets and leukocytes, by inhibiting the adhesion and aggregation of platelets, and by promoting vasodilation and vascular endothelial cytoprotection through antithrombotic and profibrinolytic activities.

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Vasoactive drugs (Pentoxifylline). This drug improves blood flow by increasing red blood cell deformity and decreasing viscosity.

Cilostazol. This drug has been well studied in claudicants but not as much in CLTI.

Vasodilators. Because vasodilators can cause shunting of blood away from ischemic areas to nonischemic areas, they are of no value to patients with CLTI.

STRATEGIES FOR REVASCULARIZATION

Successful revascularization in CLTI, particularly in patients with tissue loss, nearly always requires restoration of pulsatile in-line flow to the foot. Because individual lesion-based schemes correlate poorly with effective revascularization in CLTI, vascular specialists must integrate approaches for arterial segments into a management strategy for the whole limb. Factors that determine a successful anatomic outcome are intrinsically different for bypass grafting and endovascular intervention. Bypass surgery requires adequate inflow and outflow and, perhaps most important, a suitable autologous conduit. By contrast, the success of endovascular intervention is largely defined by the complexity of atherosclerosis within the anticipated target arterial path (TAP) that provides in-line flow to the foot. When the TAP includes multiple lesions in series, technical success and sustained patency for the limb as a whole must be estimated as a product function of each lesion traversed.

Effective revascularization is the cornerstone of limb salvage in CLTI. Although multiple techniques are available, there are limited high-quality data to support EBR. A new, systematic paradigm is required to improve decision-making, clinical outcomes, and cost-effectiveness. To aid clinical decision-making in everyday practice it proposed a three-step integrated approach — PLAN: patient risk estimation which based on 1) patient risk estimation; 2) limb staging; 3) anatomic pattern of disease.

PLAN: Patient risk estimation

The first step involves assessing the patient for candidacy for limb salvage, periprocedural risk, and life expectancy. CLTI is associated with advanced age, multiple comorbidities, and frailty. The goals of treatment include relief of pain, healing of wounds, and preservation of a functional limb. However, revascularizationmay incur significant morbidity and mortality, requiring multiple hospitalizations, prolonged outpatient care, and thus considerable health and social care costs. Whereas the majority of patients with CLTI should be considered candidates for limb salvage, some may be appropriately treated with primary amputation or palliation after shared decision-making. Patients, families, and caregivers should have

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access to appropriate expertise in making these challenging decisions. Although maintenance of independent ambulatory status is an important goal, predicting functional outcomes after revascularization may be challenging, particularly in patients who are severely deconditioned. Palliative care consultants, where available, may be a valuable resource to optimize symptom management in patients with limited goals of care.

PLAN: Limb staging

CLTI patients present with a broad spectrum of disease severity. Staging of the limb (WIfI) is recom infection to stage CLTI. The severity of ischemia and the benefits of revascularization do not map in an exclusively concordant fashion with amputation risk across the spectrum of CLTI, as expressed in the original WIfI consensus document. Expert opinion, now supported by reports from institutional series suggests that the presumed benefit of revascularization in CLTI is linked to both the severity of ischemia and the degree of limb threat. All symptomatic patients who have severe (eg, WIfI grade 3) ischemia should undergo attempted revascularization, presuming they are appropriate candidates for limb salvage. In settings of advanced tissue loss or infection (eg, WIfI stage 4 limbs), revascularization may also be of benefit in the presence of moderate ischemia (eg, WIfI ischemia grades 1 and 2). Conversely, patients with lesser degrees of tissue loss or infection (eg, WIfI stages 1 to 3) and mild to moderate ischemia are often successfully treated with infection control and wound and podiatric care. Revascularization may be considered selectively in these patients if their wounds fail to progress (or regress) despite appropriate limb care after 4 to 6 weeks or if they have signs or symptoms of clinical deterioration. In such cases, all elements of the initial staging and treatment plan, including treatment of underlying moderate ischemia, should be re-evaluated. Whenever possible, the limb should be restaged after surgical drainage or débridement and after the infective component is stabilized.

PLAN: Anatomic pattern of disease (and conduit availability)

Although secondary to the broader context of patient risk and limb threat severity, the anatomic pattern of arterial occlusive disease is a dominant consideration in EBR. Furthermore, the availability and quality of autologous vein conduit (especially the great saphenous vein) are key considerations for bypass surgery and should be defined before revascularization decisions are taken in average-risk patients.

EBR strategies in CLTI

The technical options for treating complex patterns of disease in a minimally invasive fashion have increased markedly in recent years and led some to advocate an «endovascular-first» approach for most or all patients with CLTI, reserving

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bypass surgery as a secondary option. However, existing evidence argues strongly for a selective revascularization algorithm based on specific clinical and anatomic scenarios, as described here. Currently enrolling RCTs are eagerly awaited to provide higher quality data in support of EBR in patients with CLTI.

Thus, an important consideration is to avoid risking potential loss of bypass targets in performing endovascular interventions. Conversely, surgical bypass may incur significant morbidity and mortality despite the potential attractiveness of greater durability. Factors that may increase the risk of wound complications, graft failure, or other major postoperative complications must be carefully weighed. These considerations informed the consensus recommendations on specific EBR strategies.

The benefit of performing revascularization in chronic limb-threatening ischemia (CLTI) increases with degree of ischemia and with the severity of limb threat (Wound, Ischemia, and foot Infection [WIfI] stage). WIfI stage 1 limbs do not have advanced ischemia grades, denoted as not applicable (N/A) (fig. 5).

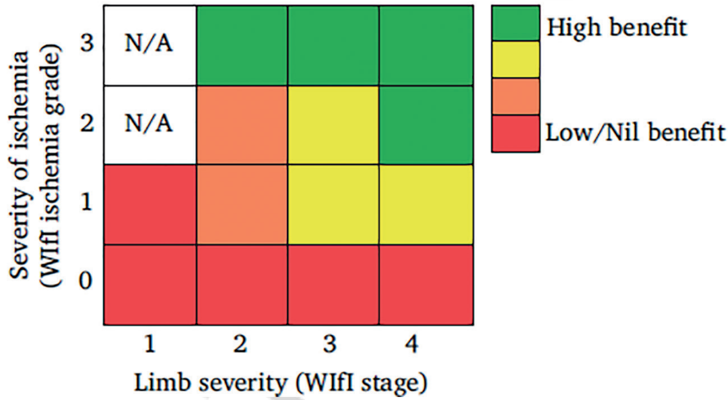

Fig. 5. The benefit of performing revascularization in chronic limb-threatening ischemia (CLTI)

EBR: Treatment of inflow disease. Inflow disease is defined here as proximal to the origin of the SFA and meeting one or more of the following criteria:

– absent femoral pulse;
– blunted CFA waveform on Doppler ultrasound;
– > 50 % stenosis by angiography in the aorto-iliac arteries or CFA;
– aorta to CFA systolic pressure gradient >10 mm Hg at rest.

Recommendations Grade 1 (Strong):

1. Correct inflow disease alone in CLTI patients with multilevel disease and low-grade ischemia (eg, WIfI ischemia grade 1) or limited tissue loss (eg, WIfI woundgrade 0/1) and in any circumstance in which the risk-benefit of additional outflow reconstruction is high or initially unclear.

2. Restage the limb and repeat the hemodynamic assessment after performing inflow correction in CLTI patients with inflow and outflow disease.

3. Consider simultaneous inflow and outflow revascularization in CLTI patients with a high limb risk (eg, WIfI stages 3 and 4) or in patients with severe ischemia (eg, WIfI ischemia grades 2 and 3).

EBR: Treatment of outflow (infrainguinal) disease. Open bypass surgery and endovascular therapy have complementary roles, with notable lack of consensus across the intermediate ranges of clinical and anatomic complexity.

Patients lacking adequate autologous (GSV) conduit must be considered separately as this is a critical factor in determining the likely success and durability of bypass surgery. For those with no suitable venous conduit, prosthetic or venous allografts are the only options. Given the inferior performance of these conduits in CLTI, endovascular intervention is preferred when possible.

Angiosome-guided revascularization may be of importance in the setting of endovascular intervention for midfoot and hindfoot lesions but is likely to be irrelevant for ischemic rest pain and of marginal value for most forefoot lesions and minor ulcers.

Wound care. CLTI is associated with a markedly shortened life expectancy, and not surprisingly, patients with unreconstructed CLTI experience poorer outcomes in terms of survival and limb salvage. In a retrospective study involving 105 patients with unreconstructed CLTI, 46 % of patients lost the limb and 54 % died within 1 year. Of the patients with a nonamputated leg, 72 % were dead within 1 year. Thus, despite advances in revascularization techniques and anesthetics, endovascular or surgical revascularization may not be appropriate in some patients, even if it is technically possible, because of significant comorbidities and reduced life expectancy.

BIOLOGIC AND REGENERATIVE MEDICINE APPROACHES IN CLTI

Biologic or regenerative medicine therapies include gene therapy and cellular therapy. These treatments offer the potential to promote wound healing and to prevent amputation in patients who otherwise have no options for revascularization. Therapeutic angiogenesis is defined as the growth of new blood vessels from pre-existing blood vessels in response to growth factor stimulation. This has been shown to occur in animal models of hind limb ischemia and can be induced either by angiogenic proteins such as vascular endothelial growth factor or by cellular therapy using stem cells or bone marrow aspirate. Various growth factors, including vascular endothelial growth factor, hepatocyte growth factor (HGF), and fibroblast growth factor (FGF), have been shown to promote angiogenesis in ani-

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mal models. The short half-life of these proteins has led to the use of gene therapy to maintain sustained expression in the ischemic limb. Most clinical trials to date have used intramuscular injection of either a gene or cellular therapy. In the case of gene therapy, expression of the protein is maintained for 2 to 6 weeks. Ongoing research in this arena includes alternative vectors to safely enhance long-term gene expression. The putative mechanism of cellular therapy involves either the differentiation of stem cells into vascular cells, after injection into the hypoxic extremity, or induction of angiogenic growth factor expression, again due to relative tissue hypoxia in the ischemic extremity. General concerns about the safety of angiogenic therapy have been related to the potential for «off-target» angiogenesis, which can result in promotion of occult tumor growth or accelerated progression of diabetic proliferative retinopathy. To date, these concerns have not occurred in angiogenic clinical therapy trials that have been completed.

Conclusions. There have been promising early safety and efficacy trial data for both gene and cellular therapies in patients with CLTI. Despite these early promising results, no phase 3 trials have shown this therapy to be effective. Still, current trial design has improved, and there are multiple phase 3 clinical trials that either are actively enrolling or are in early stages of development. These involve potentially disruptive technologies that, if proven effective, could dramatically alter how patients with CLTI are cared for in the future. Until further evidence is available, these therapies should be considered investigational.

THE ROLE OF MINOR AND MAJOR AMPUTATIONS

CLTI is associated with a reduced life expectancy, a significant curtailment in ambulation, and a high likelihood of limb loss. Preservation of a patient's ability to walk is an important aspect of care in CLTI, and vascular reconstruction is the most direct method for achieving functional limb salvage in these often critically ill patients. When properly applied, open surgical and endovascular techniques have proved useful and successful for the preservation of limb function. A successful limb salvage intervention is associated with low postprocedural morbidity and mortality, preservation or restoration of independent ambulation, improved quality of life for the patient, and lower cost to the health care system. Although most patients require a single procedure to accomplish this, many will need minor amputations to remove distal necrotic or infected tissue to achieve a completely healed and functional extremity. This is especially true of diabetics, who have a lifetime risk of foot ulceration of 25 %, with 50 % of ulcers becoming infected. Treatment of these patients requires both inline pulsatile flow to the foot and wound débridement or minor amputation.

Minor amputations. Minor amputations of the foot include digital and ray amputation of the toe, transmetatarsal amputation of the forefoot, and Lisfranc and Chopart amputations of the midfoot. Each of these can be useful to preserve foot function in appropriately selected patients. Although there is a significant risk of need for reamputation at a higher level in diabetics, the use of minor amputations, including single-digit and ray amputations, can preserve foot function in the majority of patients. There are some instances in which transmetatarsal amputation may be a better first procedure, including necrosis of the great toe requiring long ray amputation or ray amputation of the first and fifth toes, but ensuring adequate distal perfusion and appropriate offloading of the forefoot are the major principles for preservation of foot function. There are, however, situations in which an aggressive attempt at limb salvage would be unlikely to succeed, would pose too great a physiologic stress on the patient, or would be of limited value because of other causes of limb dysfunction. For these patients, major amputation may be considered a reasonable option.

Primary amputation. Primary amputation in patients with CLTI is defined as lower extremity amputation without an antecedent open or endovascular attempt at limb salvage. There are four major goals of primary amputation for patients with CLTI:

1) relief of ischemic pain;

2) removal of all lower extremity diseased, necrotic, or grossly infected tissues;

3) achievement of primary healing;

4) preservation of independent ambulatory ability for patients who are capable.

In addition, there are five major indications for primary amputation:

1. Nonreconstructible arterial disease, as confirmed by clear distal imaging studies that fail to identify patent distal vessels needed for a successful intervention. In the setting of severe distal ischemia, in particular in association with ischemic ulceration, gangrene, or infection, the inability to improve straight-line distal perfusion often results in major amputation even with a patent bypass graft. Bypasses to arteries that do not have at least large, angiographically apparent collateral vessel outflow provide little additional flow to the foot for distal limb salvage. Patients without any appropriate targets for successful distal revascularization are frequently better served with a primary major amputation.

2. Destruction of the major weight-bearing portions of the foot, rendering it incompatible with ambulation. The weight-bearing portions of the foot consist of the calcaneus, the first and fifth metatarsal heads, and a functional arch. Patients with gross destruction of the calcaneus and overlying skin should be considered for primary amputation because a functional foot can infrequently be salvaged.

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After aggressive heel ulcer excision and extensive calcanectomy, complete wound healing is infrequent and chronic pain is common.

3. Nonfunctional lower extremity due to paralysis or unremediable flexion contractures. These patients are unlikely to benefit from attempts at revascularization, and there will be little change in quality of life despite a successful intervention.

4. Severe comorbid conditions or limited life expectancy due to a terminal illness. The goal of treatment for these patients is relief from ischemic pain, if present, and an improvement in the remaining quality of life. Extensive distal revascularization, prolonged hospitalization, and protracted recovery should be avoided. Assessment of the patient's frailty may be of value to determine whether primary major amputation is more appropriate than distal revascularization.

5. Multiple surgical procedures needed to restore a viable lower extremity. As the technology and techniques of vascular surgery have improved, surgeons have advanced beyond revascularization to complex vascular and soft tissue reconstruction. This approach usually involves multiple surgical procedures to increase distal flow, removal of all necrotic tissue, and reconstruction of these areas with free flaps. The course of treatment is prolonged, involving multiple returns to the operating room, long periods of inactivity, and a difficult recovery. For these patients, if multiple procedures with high morbidity are required, primary amputation should be strongly considered to permit early ambulation. A detailed discussion with the patient to develop a comprehensive treatment plan with shared decision making is important for such advanced vascular disease.

For all patients considered for primary amputation, also consider revascularization to improve inflow in an attempt to reduce the level of the amputation. For example, those patients with extensive infrainguinal arterial occlusion, including the common and proximal PFA, might benefit from restoration of flow into the deep femoral system to reduce the amputation level from the upper thigh to the level of the knee. In such cases, despite some additional risk, proximal revascularization has the potential to offer a tangible and significant benefit to the patient.

Secondary amputation. For those in whom one or more attempts at revascularization have failed and the likelihood of a successful and durable redo procedure is limited, major amputation with a goal of rehabilitation to independent ambulation should be considered.

Level of amputation. Selecting the level of amputation that will heal primarily is critical to successful prosthetic rehabilitation and maximal functional mobility. Thus, a great deal of consideration must go into selecting the initial level of amputation. Preoperative tissue perfusion assessment can make it possible to lower the level of amputation, although there is no accurate method to predict the optimal level of amputation. In addition, whereas assessment of preoperative tissue perfusion can aid in decision-making, it still remains largely a clinical decision. Many

Perioperative

techniques to evaluate tissue perfusion have been tried, including laser Doppler flowmetry, thermography, skin perfusion pressure, fluorometric quantification of a fluorescein dye, TcPO2, and indocyanine green fluorescence angiography. In particular, TcPO2 has been extensively evaluated, and it has been shown that wound complications increase as TcPO2 levels fall below 40 mm Hg. Currently, there is still no single definitive method of evaluating tissue perfusion that can accurately predict the wound healing potential or failure at the site of amputation.

Healing rates of amputations and reamputations. Achieving primary healing is challenging in ischemic lower limbs, and it is difficult to predict early failure. Multiple débridements and reamputations are required in 4 to 40 % of patients, depending on the level of amputation. Likewise, readmission rates of 20 % have been reported even after minor amputations (toe and distal forefoot), with the majority of reamputations occurring within 1 month. Reported long-term healing rates after transmetatarsal amputations are approximately 53 %. These amputations should not be offered to patients who have poor rehabilitation potential.

The role of partial foot or midfoot (eg, Lisfranc, Chopart) amputations remains controversial. Prosthetic specialists discourage the use of these procedures as they have higher rates of delayed healing, require more revisions, and develop deformities and ulcers, and patients often struggle to achieve their full rehabilitation potential. Conversely, these amputations preserve a weight-bearing heel and allow amputees the ability to mobilize for short distances without prostheses. Transtibial amputation (below-knee amputation [BKA]) and transfemoral amputation (above-knee amputation [AKA]) are performed with an almost equal frequency in patients with CLTI. Reports have shown primary healing rates for BKA of approximately 60 %, with 15 % leading to a transfemoral amputation. The transfemoral amputation has the highest probability of successful primary healing and therefore has been the amputation of choice in individuals who are less likely to ambulate with a prosthesis.

Mortality. Survival after major lower limb amputation is poor, as seen in a systematic review that reported 30-day postoperative mortality rates of 4 to 22 %. Even after minor amputations, the 1-year and 5-year mortality rates are reported to be 16 and 25 %, respectively, for those with limb ischemia. Mortality rates for minor amputations are higher in diabetics, with type 2 diabetics having a 5-year mortality of > 50 %. The 5-year mortality after major amputations varies from 30 to 70 % and is significantly worse for AKA than for BKA. The mortality is even higher in bilateral lower limb amputees, with a 5-year survival rate of < 40 %. These mortality rates demonstrate the high rate of comorbidities and the frailty of this group of patients. In patients with diabetes who have had major amputations, survival is often worse than in some malignant diseases. Survival rates have been reported as 78 % at 1 year, 61 % at 3 years, 44 % at 5 years, and 19 % at 10 years.

POSTPROCEDURAL CARE AFTER REVASCULARIZATION FOR CLTI

Long-term antiplatelet therapy remains a cornerstone to reduce atherothrombotic events and to improve patency and limb salvage rates after peripheral interventions. Contemporary management involves the choice between single antiplatelet therapy and DAPT (aspirin plus clopidogrel). Aspirin has been a mainstay of treatment because it is efficacious and cost-effective. Clopidogrel is also effective as a single agent. Use of DAPT after intervention has become standard in the treatment of CAD and has migrated to other arenas of vascular intervention.

Tissue loss-dominant conditions. The primary issue after revascularization in CLTI is often management of tissue loss (wound healing). Therapy is based primarily on appropriate débridement, offloading, and a simple moisture-retentive dressing strategy. Pressure offloading is one of the single most important and yet neglected aspects of therapy. Whereas the total contact cast remains the gold standard for offloading noninfected, nonischemic wounds, other techniquesmay also be considered, depending on available resources. More significant degrees of tissue loss may require a strategy of filling the defect followed by skin grafting. Once the wound heals and the patient is no longer «tissue loss dominant» care then shifts to maximizing ulcer-free and activity-rich days in diabetic foot remission. This may include protecting the tissue by external (shoes, insoles, and inflammation monitoring) and internal (reconstructive surgery, physical therapy, and rehabilitation) means.

Infection-dominant conditions. Infection is often the primary factor leading to amputation, accentuated by tissue loss and ischemia. Addressing this triad involves surgical and medical therapy based on established criteria. Each member of the wound care team must work to categorize, stage, and grade the severity of each component of the «wound triad» initially and at all follow-up encounters. Appropriate and regular documentation of the wound status is crucial, including diagrams and photographs to document progress. Often, one or more of these conditions can be found to be more «dominant» and can then be targeted for care. These conditions are dynamic and will change over time. During follow-up, recurrence may be related to tissue loss (deformity, inappropriate shoes, or change in activity). As a result, nonhealing may be due to ongoing or recurrent ischemia, and intervening in the development of an infection may require additional surgical or medical intervention (table 2).

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Table 2

Summary of recommendations

Recommendation	Grade	Level of evidence
Use objective hemodynamic tests to determine the presence and to quantify the severity of ischemia in all patients with suspected CLTI	1 (Strong)	C (Low)
Use a lower extremity threatened limb classification staging system (eg, SVS's WIfI classification system) that grades wound extent, degree of ischemia, and severity of infection to guide clinical management in all patients with suspected CLTI	1 (Strong)	C (Low)
Measure AP and ABI as the first-line noninvasive test in all patients with suspected CLTI	1 (Strong)	B (Moderate)
Evaluate cardiovascular risk factors in all patients with suspected CLTI	1 (Strong)	B (Moderate)
Manage all modifiable risk factors to recommended levels in all patients with suspected CLTI	1 (Strong)	B (Moderate)
Treat all patients with CLTI with an antiplatelet agent	1 (Strong)	A (High)
Use moderate- or high-intensity statin therapy to reduce all-cause and cardiovascular mortality in patients with CLTI	1 (Strong)	A (High)
Control hypertension to target levels of < 140 mm Hg systolic and < 90 mm Hg diastolic in patients with CLTI	1 (Strong)	B (Moderate)
Offer smoking cessation interventions (pharmacotherapy, counseling, or behavior modification therapy) to all patients with CLTI who smoke or use tobacco products	1 (Strong)	A (High)
Use an integrated threatened limb classification system (such as WIfI) to stage all CLTI patients who are candidates for limb salvage	1 (Strong)	C (Low)
Offer revascularization to all average-risk patients with advanced limb-threatening conditions (eg,WIfI stage 4) and significant perfusion deficits (eg, WIfI ischemia grades 2 and 3)	1 (Strong)	C (Low)
Continue best medical therapy for PAD, including the long-term use of antiplatelet and statin therapies, in all patients who have undergone lower extremity revascularization	1 (Strong)	A (High)
Consider DAPT (aspirin plus clopidogrel) in patients who have undergone infrainguinal endovascular interventions for CLTI for a period of at least 1 month	2 (Weak)	C (Low)
Consider DAPT for a period of 1 to 6 months in patients undergoing repeated catheter-based interventions if they are at low risk for bleeding	2 (Weak)	C (Low)
Provide mechanical offloading as a primary component for care of all CLTI patients with pedal wounds	1 (Strong)	A (High)
Provide counseling on continued protection of the healed wound and foot to include appropriate shoes, insoles, and monitoring of inflammation	1 (Strong)	A (High)

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APPLICATION OF WIFI STRATIFICATION IN CLINICAL PRACTICE

The following tables (fig. 6) and examples demonstrate the application of WIfI in the clinical setting patients with chronic limb-threatening ischemia.

	Ischemia – 0				Ischemia – 1				Ischemia – 2				Ischemia – 3			
W-0	VL	VL	L	M	VL	L	M	H	L	L	M	H	L	M	M	H
W-1	VL	VL	L	M	VL	L	M	H	L	M	H	H	M	M	H	H
W-2	L	L	M	H	M	M	H	H	M	H	H	H	H	H	H	H
W-3	M	M	H	H	H	H	H	H	H	H	H	H	H	H	H	H
	fI-0	fI-1	fI-2	fI-3	fI-0	fI-1	fI-2	fI-3	fI-0	fI-1	fI-2	fI-3	fI-0	fI-1	fI-2	fI-3

a

	Ischemia – 0				Ischemia – 1				Ischemia – 2				Ischemia – 3			
W-0	VL	VL	VL	VL	VL	L	L	M	L	L	M	M	M	H	H	H
W-1	VL	VL	VL	VL	L	M	M	M	M	H	H	H	H	H	H	H
W-2	VL	VL	VL	VL	M	M	H	H	H	H	H	H	H	H	H	H
W-3	VL	VL	VL	VL	M	M	M	H	H	H	H	H	H	H	H	H
	f-0	fI-1	fI-2	fI-3	fI-0	fI-1	fI-2	fI-3	fI-0	fI-1	fI-2	fI-3	fI-0	fI-1	fI-2	fI-3

b

fI — foot Infection
W — Wound
VL — Very low = clinical stage 1
L — Low = clinical stage 2
M — Moderate = clinical stage 3
H — High = clinical stage 4

Fig. 6. Application of WIfI classification:
a — estimate risk of amputation at 1 year for each combination; *b* — estimate likelihood of benefit of/requirement for revascularization (assuming infection can be controlled first)

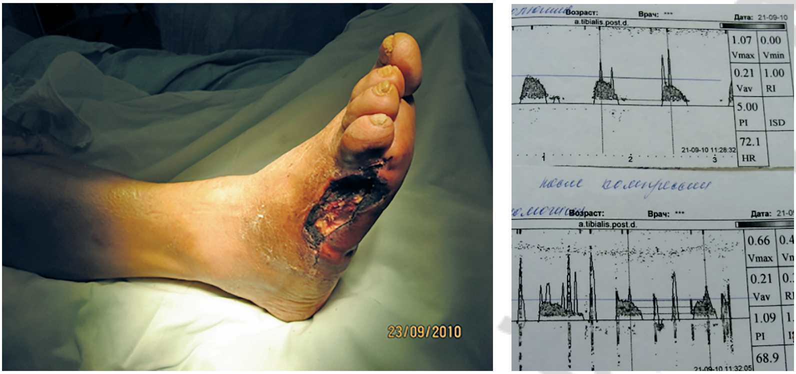
TESTS

Test 1. A patient with ischemic rest pain, an ABI of 0.30, no wounds, and no signs of infection.

Test 2. A 55-year-old man with diabetes, dry gangrene of two toes and a < 2 cm rim of cellulitis at the base of the toes, but without systemic or metabolic toxicity has absent pedal pulses. The ABI is 1.5. The TP is 35 mm Hg.

Test 3. A 44-year-old woman without a previous diagnosis of diabetes presents to the emergency room with systemic sepsis, a fever of 39.5 °C, an elevated white blood cell count of 26 000, and serum blood glucose of 600. She has a 6 cm full thickness wound on the plantar aspect of the forefoot with crepitus. The dorsalis pedis pulse is palpable, and the ABI is 1.08.

Test 4. 60-year-old diabetic woman suffer from an extensive foot wound formed after drainage of the foot phlegmon. The view of the foot is presented in the photo (fig. 7, *a*). ABI 0,47 (fig. 7, *b*). What is the optimal treatment plan?



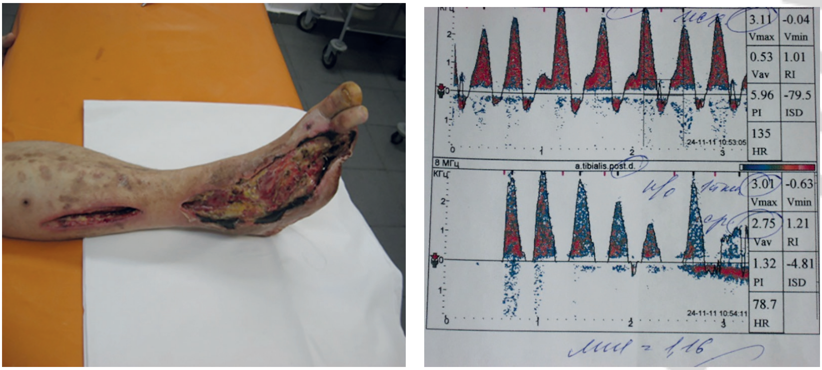
a *b*

Fig. 7. Test 4

Test 5. 57-year-old diabetic man suffers from an foot ulcer formed after callus removal. ABI 0,91. The view of the foot is presented in the photo (fig. 8). What is the optimal treatment plan?

Fig. 8. Test 5

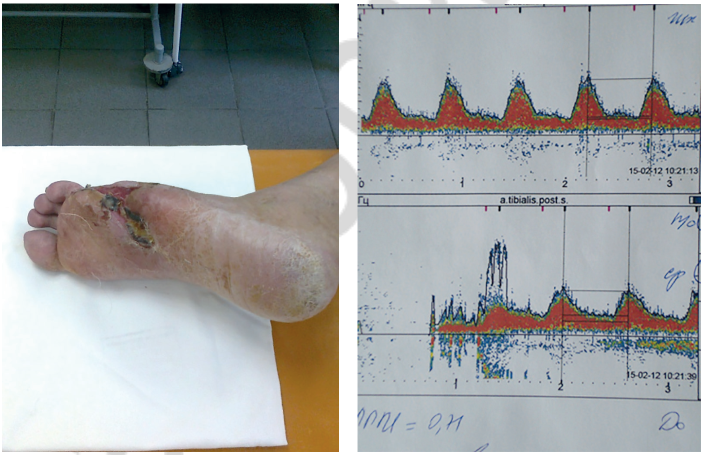
Test 6. 60-year-old diabetic man suffer from an extensive foot and ankle wounds formed after drainage of the leg phlegmon. The view of the foot is presented in the photo (fig. 9, *a*). ABI 1,16 (fig. 9, *b*). What is the optimal treatment plan?



a *b*

Fig. 9. Test 6

Test 7. 58-year-old diabetic man suffer from an foot wounds formed after use uncomfortable shoes. The view of the foot is presented in the photo (fig. 10, *a*). ABI 0,71 (fig. 10, *b*). What is the optimal treatment plan?



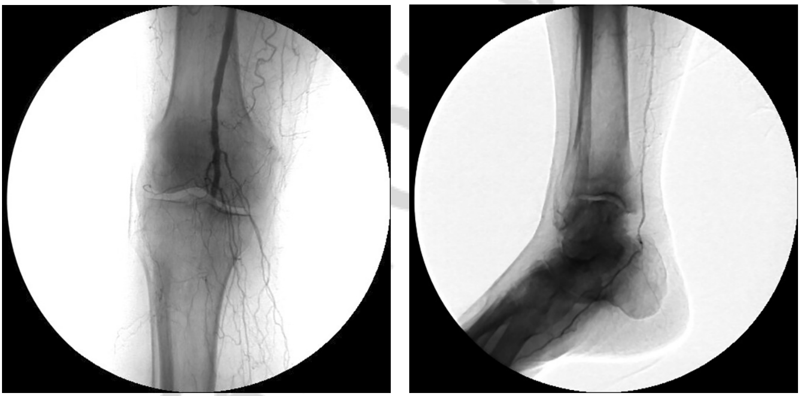
a *b*

Fig. 10. Test 7

Test 8. The view of the patient's foot from Test 7 after 2 weeks is shown in the photo (fig. 11). There is no tendency to ulcer healing despite normalization of carbohydrate metabolism and unloading of the foot. What is the optimal treatment plan?

Fig. 11. Test 8

Test 9. The patient from tests 7 and 8 was performed angiography to clarify the method of revascularization. Angiography revealed tibial artery occlusion from trifurcation of the popliteal artery (fig. 12, *a*). The posterior tibial artery is traced in the lower third of the ankle (fig. 12, *b*). Which revascularization method would be preferable in this case?



a ***b***

Fig. 12. Test 9

Answers:

1. This patient would be classified as Wound 0 Ischemia 3 foot Infection 0 or WIfI 030. The consensus clinical stage is 2 (low) with respect to risk of major limb amputation at one year. The anticipated benefit of revascularization, however, is high.

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2. He would be classified as Wound 2 Ischemia 2 foot Infection 1 or WIfI 221. The clinical stage would be 4 (high risk of amputation); the anticipated benefit of revascularization is also high.

3. She would be classified as follows: W2 I0 fI 3 or WIfI 203. The clinical stage is 4 (high risk of amputation), but the anticipated benefit of revascularization is low.

4. This patient's would be classified as Wound 2 Ischemia 2 foot Infection 1 or WIfI 221. The clinical stage would be 4 (high risk of amputation); the anticipated benefit of revascularization is also high. Angiography should be planned to determine whether endovascular or surgical revascularization is possible.

5. Patient's would be classified as follows: W1 I0 fI 0 or WIfI 100. The clinical stage is 1 (very low risk of amputation), the anticipated benefit of revascularization is very low too. Mechanical offloading the foot and optimal glycemic control are necessary for this patient. There are no indications for angiography.

6. Patient's would be classified as follows: W2 I0 fI 1 or WIfI 101. The clinical stage is 1 (very low risk of amputation), the anticipated benefit of revascularization is very low too. Mechanical offloading the foot, surgical debridement and optimal glycemic control are necessary for this patient. There are no indications for angiography.

7. Patient's would be classified as follows: W1 I1 fI 1 or WIfI 111. The clinical stage is 2 (low risk of amputation), the anticipated benefit of revascularization is Moderate. Mechanical offloading the foot, surgical debridement and optimal glycemic control are necessary for this patient. There are no indications for angiography. Requires monitoring of the dynamics of wound healing for 2 weeks.

8. Angiography should be planned to determine whether endovascular or surgical revascularization is possible.

9. Due to the extended lesion of the tibial arteries, the endovascular method of revascularization is not applicable. Autogenous popliteal-posterior tibial bypass should be performed.

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MANAGEMENT OF CHRONIC LIMB-THREATENING ISCHEMIA

Учебно-методическое пособие

На английском языке

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