REVIEW ARTICLE

CHRONIC LIMB-THREATENING ISCHEMIA: MANAGEMENT UPDATES AND COMMON QUESTIONS

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KEYWORDS

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Peripheral arterial disease

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ABSTRACT

Chronic limb-threatening ischemia (CLTI) is an advanced form of peripheral vascular disease with high rates of morbidity and mortality. Patients often present with claudication, impaired walking, and ischemic pain. Screening for CLTI and peripheral arterial disease is recommended with ankle-brachial indexing. To prevent progression to CLTI, family medicine physicians can intervene with lifestyle modification of hyperlipidemia, obesity, smoking, and encouraging well-rounded high-fiber diets. OMT can be useful in increasing lower-extremity circulation and collateral-vessel development. If refractive to optimized medical management and lifestyle modification, surgical intervention is required. Regardless of intervention, CLTI maintains a high rate of morbidity and mortality, with halting progression being the primary objective.

INTRODUCTION

Peripheral arterial disease (PAD) is a manifestation of systemic atherosclerosis affecting >230 million people worldwide.[1] PAD is a disease in which patients have plaque disturbances in their arteries that can cause blockages, be asymptomatic, cause claudication, or in 11% of cases, progress to chronic limb-threatening ischemia (CLTI).[2] Risk factors for PAD include hyperlipidemia, hypertension, and diabetes, as well as modifiable lifestyle risk factors such as smoking, poor diet, obesity, and lack of physical activity.[1] Lower-extremity PAD symptoms may include intermittent claudication, which is defined by cramping, fatigue, or discomfort in the calf muscles brought on by physical activity and relieved with rest. Many patients with PAD may not experience these classic symptoms[3]; as such, other symptoms should be investigated in patient history such as impaired walking function and ischemic pain at rest, as these could be indicative of more advanced disease.[4] Diagnosis and classification of PAD are recommended via noninvasive ankle-brachial index (ABI) testing.[4]

Those in the asymptomatic and claudication categories of PAD should first be treated with risk-factor modification and claudication medical therapy including exercise.[5] Invasive procedures in the asymptomatic and claudicant stages can complicate the disease and cause progression. Caution should be exercised in intervening in a patient who has PAD in the claudicant stage.[6] Once PAD progresses to CLTI, vascular surgeons or other qualified specialists can intervene with revascularization techniques, open bypass, minimally invasive methods, amputation, or palliative care.[7]

Chronic limb-threatening ischemia (CLTI), by definition, is PAD in addition to rest pain, gangrene, or a lower-limb ulceration greater than 2 weeks' duration.[7] Identifying patients with CLTI is important because early intervention can affect quality of life, need for amputation, mortality, and prevention. The 2020 Global Vascular Guidelines aim to improve treatment decisions for patients with CLTI.[6] The previous model for treating CLTI was based purely on ischemia due to atherosclerosis.[8] It is important to note that only those with CLTI, not those who are asymptomatic or have claudication, are classified in this algorithm.

A multimodality approach including preventative medical therapy, appropriate physical exam, objective testing, and CLTI classification determines surgical treatment (Figure 1). Surgical treatment for CLTI includes a possible endovascular approach or open bypass repair. Recently, the BASIL2[9] and BEST-CLTI[10] studies reported differing best surgical approaches to CLTI: one study reported bypass as most favorable; the other indicated an endovascular-first approach. In addition, palliative care can be offered. The criteria to determine best therapy are largely based on staging using the Wound, Ischemia, and foot infection (WIFi) clinical stage.[11]

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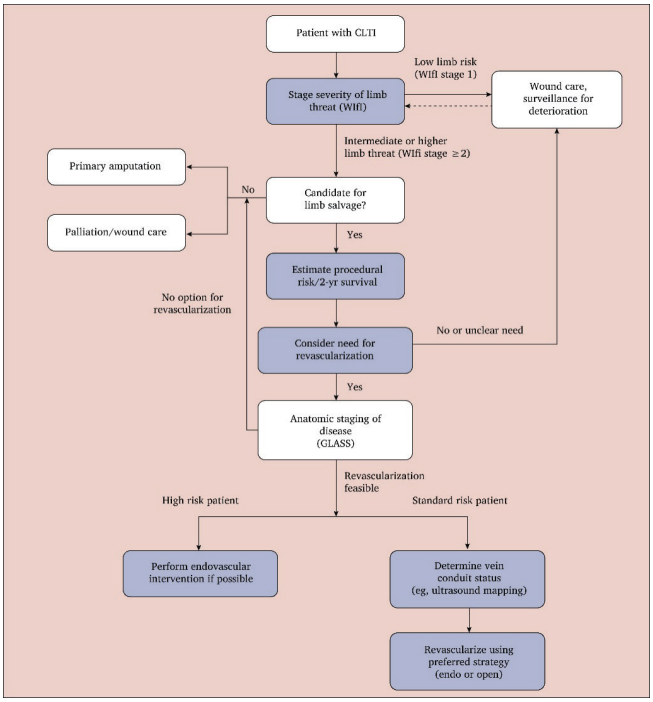
FIGURE 1:

Decision making for CLTI treatment[7]



Classification

While surgical treatment for CLTI continues to evolve and is determined by the vascular surgeon, this new system of classification, similar to TNM [tumor, node, metastasis can be helpful in guiding the family practitioner in relaying the severity of disease and risk for amputation.[7] In addition, earlier referral and medical management are prudent for limb salvage, once the diagnosis of CLTI is suspected.[12] In 2014, the Society for Vascular Surgery proposed the WIfi classification system. This system is used to determine methodology of treatment and also need for revascularization, as well as for identifying those who are not eligible for revascularization.[11] The wound is classified according to size, depth, and severity. Ischemia is scored based on ABI, along with toe-pressure indices. The last criterion measured is the extent of foot infection based on perfusion, extent, depth, infection, and sensation (PEDIS), as well as Infectious Diseases Society of America (IDSA) diabetic foot classification systems.[13] Based on the scores, a stage is defined as 1-4, with a risk of amputation assigned and a revascularization benefit score.[11] Amputation risk increases with severity of infection, ischemia, and wound, rather than solely on the level of atherosclerotic disease.

History Taking

To appropriately manage patients with signs and symptoms of CLTI, a thorough history should be taken. Risk factors should be assessed and treated appropriately, including conditions such as hyperlipidemia, hypertension, diabetes, coronary artery disease, and chronic kidney disease. History also includes lifestyle risk factors such as smoking and physical inactivity. Lack of treatment for these factors increases mortality rates and risk for a cardiovascular event.

Physical Exam and Testing

Vascular examination for PAD should include palpation of pulses, auscultation for bruits, and inspection of the legs and feet. Lower-extremity pulses are assessed and rated as follows: 0, absent; 1, diminished; 2, normal; or 3, bounding. Physical exam findings suggestive of PAD include abnormal pulses, vascular bruits, nonhealing wounds, gangrene, and elevation pallor/dependent rubor.[4] The distinction between CLTI and other forms of PAD on physical exam is the extent of pain or tissue loss, among other identifiable factors including length of onset. What distinguishes CLTI from other forms of PAD are nonhealing wounds, gangrene, and rest pain. Once a patient is identified as having CLTI, they are staged to determine which treatment is best.

Based on outcomes for staging CLTI, it is important to delineate on physical exam neuropathy, wound characteristics, evidence of infection, and vascular pulse exam. Ordering both ABIs and toe-pressures for high-risk patients is indicated. The reasoning for toe-pressure indices in addition to ABIs is that patients with diabetes mellitus or end-stage renal disease may have falsely elevated ABIs, and disease is better identified with toe pressures.[14] Toe pressures <30 mmHg and ABIs <0.4 are indicative of severe disease.[11]

For patients with diabetes, additional examination for loss of vibration with a tuning fork should be performed, as they are at higher risk for tissue loss, even if asymptomatic.[15] Attention to hair loss, muscle atrophy, cap refill time, and temperature of skin are also important.

Lifestyle Modifications

Modification of risk factors should be included in the treatment plan for all patients with PAD and CLTI, as a healthy lifestyle has been associated with risk reduction among these patient groups.[16] Diets high in fiber have been associated with reduced risk from PAD.[17] In patients with symptomatic PAD, smoking cessation can reduce the risk of CTLI, amputation, and death.[1] Exercise therapy can be a highly effective way to improve function in patients with PAD.[1]

Medical Management

Medical management can include antiplatelet agents, lipid-lowering agents, antihypertensives, glucose control, and lifestyle modifications. The goal of medical management is to protect the limb but also to prevent cardiovascular and neurovascular complications. Rivaroxaban has shown to lower incidence of acute limb ischemia, major amputation for vascular causes, myocardial infarction, ischemic stroke, or death from cardiovascular causes than aspirin alone.[17] In addition, ticlopidine, dipyridamole, and clopidogrel, may be more effective than aspirin.[7] There is level 1 evidence that a statin should be included in the treatment plan as a lipid-lowering agent. PCSK9 inhibitors such as evolocumab have also shown promise.[18] Glucose control with metformin as a first-line agent is recommended. Additional agents can be added. Sodium-glucose co-transporter 2 (SGLT-2) inhibitors for glucose control should be used with caution due to their unknown effect

on limb salvage. (Though the black box warning for canagliflozin has been lifted).[19]

Osteopathic Management

OMT is a noninvasive preventative intervention that enhances the body's natural healing mechanisms, such as promoting lymphatic drainage and increasing vascular perfusion.[20] Blood-flow dynamics is a potential determining factor in PAD, vascular claudication, and CLTI. Blood circulation in fascial tissue has been noted to be critical in maintaining biomechanical and nociceptive homeostasis.[21] A randomized controlled trial by Brandl et al. investigated the immediate effects of myofascial release treatment on lumbar microcirculation. Using ultrasound to measure blood flow, they noted an increase of 31.6% in blood flow in their experimental patients vs a vast decrease in blood flow in the placebo group.[21] A similar study by O-Yurvati et al. noted a decrease in central volume and improvement in peripheral circulation following postoperative OMT in patients who had undergone coronary artery bypass graft surgery (CABG).[22] Of note, a study by Lombardini et al. examined endothelial function in 15 participants with intermediate claudication receiving OMT vs 15 intermediate claudication patients matched for age, sex, and medical treatment. They discerned that the OMT group had increased brachial-flow–mediated vasodilation, and ABI, which were consistent in decreased claudication from the beginning of the study till the end.[23] Although OMT has been widely described for its use in musculoskeletal pain, its approach has also been noted to restore autonomic tone and physiologic function, as well as improve blood circulation and immune response.[24] These findings suggest OMT is a safe and viable adjunct for pharmaceutical and surgical therapies in the treatment of PAD.

Surgical Management/Technique

The BEST-CLI trial determined that bypass was superior for those patients with CLTI who had an adequate saphenous.[25] In bypass surgery below the inguinal ligament, an incision is made from a point of adequate blood supply to a point past the blockage to another vessel with adequate outflow.

To access the femoral artery, which many times has adequate inflow, an incision is made at the level of the groin to dissect out the femoral artery, or sometimes at the level of the popliteal artery. A tunneler is then used to create a passage for the saphenous vein bypass. Finally, an incision is made distally at a vessel that then has continuous flow to the foot: popliteal artery, peroneal artery, anterior tibial artery, posterior tibial artery, or dorsalis pedis artery.

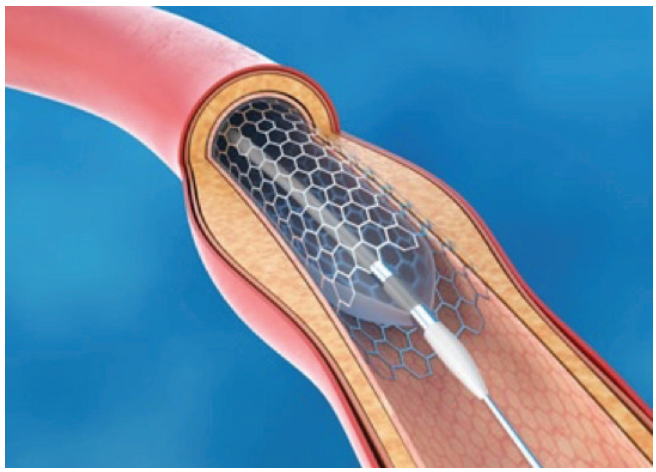
A tunneler to pass the bypass conduit is used from the distal area of anastomosis to the proximal vessel. In this case, an above-knee bypass graft to the femoral region is being performed to bypass a blockage between the two points. The above-knee popliteal is the site of the distal anastomosis. More distal areas can also be the site of an anastomosis including below the knee, on the area above the medial malleolus to reach the posterior tibial artery, and on the lateral aspect of the lower limb. An area on the anterior aspect of the distal leg would allow for a bypass to the anterior tibial artery. The peroneal artery can be reached with an incision medially or laterally on the lower aspect of the leg.

Other therapies well known for treatment of CLTI are endovascular methods (Figure 2). The BASIL2 trial concluded that the best endovascular treatment first revascularization strategy had better amputation-free survival over open surgeries.[9]

Implications

FIGURE 2:

Endo-occlusion repair



Regardless of intervention, the 5-year outcome for CLTI is poor. Approximately half of the patients enrolled in the BASIL trial had died by 5 years after randomization.[9] As noted in the BASIL trial, this disease develops over many years. In this trial, around 20% of patients noted they were still smoking, 70% had diabetes, and 90% had extensive tissue loss.[9] Regardless of the interventions for CLTI, prevention with lifestyle interventions and timely referral by primary care are opportunities to prevent future morbidity and mortality.

CONCLUSION

Regardless of intervention, morbidity and mortality for CLTI is poor. Halting disease progression through lifestyle intervention should be the primary goal of the family practice physician. Osteopathic manipulative medicine could be used as a potential adjunctive treatment modality to encourage circulation and collateral vessel growth. Optimized medical management with antiplatelet agents, lipid-lowering agents, antihypertensives, and glucose control can assist in slowing disease progression. Once a diagnosis of CLTI is made, vascular surgery should be consulted and preparations for bypass surgery made.

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