

**FAST FACTS AND CONCEPTS #352
MANAGEMENT OF ISCHEMIC LIMB PAIN**

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Background: Ischemic limb pain (ILP) is a dangerous condition, most often caused by diminished tissue perfusion. It often manifests as distal lower extremity pain brought on by exertion and subsiding with rest – known as intermittent claudication (IC); or as a more severe form of limb ischemia lasting > 2 weeks duration which results in non-healing ulcers or gangrene – known as critical limb ischemia (CLI).

Illness Background: Although other medical conditions such as a vasculitis or a deep venous thrombosis can cause ILP, peripheral arterial disease (PAD) is the most common cause of ILP. PAD is usually not an isolated vascular issue. Instead, it is often indicative of a systemic vascular illness. Consequently, PAD is often associated with coronary artery disease, chronic kidney disease, delirium, vascular dementia, and other chronic medical conditions (3,5). ILP is often progressive: 20% of patients with IC develop CLI and 20% of patients with CLI die within 6 months and 50% die within 5 years (1,4).

Diagnosis: An ankle-brachial index (ABI) between 0.4 and 0.9 confirms the diagnosis of IC; CLI is associated with an ABI of ≤ 0.4 . In patients with diabetes, renal disease, or advanced age ABI results may be less accurate due to impaired vessel compressibility (3,6). For these patients, an ankle systolic pressure of ≤ 50 -70 mmHg or a toe pressure of ≤ 30 -50 can be used to diagnose CLI instead (2,3,7).

Hospice Eligibility: Hospice should be considered in patients with progressive ischemia despite amputation; significant co-morbidities (CHF, ESR, cancer, or COPD); and incurable infections.

The Palliative Role of Revascularization: An important adage in vascular medicine is: *improving the vascular flow to the ischemic tissues often improves the pain*. Therefore, if there is a suitable vascular target, revascularization may be worth pursuing even in patients with a limited prognosis, as studies suggest it can prevent limb loss, promote wound healing, and improve quality of life by rapidly improving refractory pain (5,9). Revascularization is typically performed by a vascular surgeon and often requires inpatient hospitalization (5,9). Drug eluting stents and balloon angioplasty are two examples of minimally invasive revascularization procedures which may be an option for patients with a life expectancy of <2 years. Vascular bypass surgery requires a longer healing time and therefore is only considered in patients with life expectancy of > 2 years (4,6). Even if revascularization is not possible, medical management with anticoagulation and anti-platelet agents may slow progression and play a role in analgesia (4).

The Palliative Role of Amputation: Patients with CLI who are not candidates for revascularization or have tissue necrosis may benefit from amputation as a palliative intervention. Amputation is associated with improved functional outcomes but also significant trade-offs including phantom limb pain, a relatively high peri-operative mortality rate, and the potential for subsequent amputations (3,12,16). Value-based, shared decision making is necessary when deciding which interventions to recommend.

Analgesic Strategies: Initially, ILP is classically described as an activity-induced achy pain consistent with IC. With time, the pain often progresses in intensity and occurs at rest or sleep when small changes in position prompt pain flares (17). A multi-modal analgesic approach is often required involving disease-directed interventions described above and symptom-based interventions described below.

- Supervised exercise: programs consisting of 30-45 minutes of exercise three times weekly have been associated with analgesic improvements as well as walking distances (5,6,8,9).
- Intermittent pneumatic compression therapy: Small studies have found that these devices, which usually encase the entire leg up to the thigh, can improve wound healing and pain control (10,11).
- Dependent leg positioning: ILP often worsens when the distal extremity is raised or flat. Striving for consistent positioning below the proximal extremity can promote blood flow and reduce pain.

- Topical analgesics: topical morphine, nitrates, alpha-2 receptor antagonists, or vasodilators (see *Fast Fact #327*) are often mentioned as potential agents in CLI analgesia by experts (2); however, such therapies often require a compounding pharmacist and therefore, robust clinical trial data are lacking.
- Gabapentin may help if there is a burning or neuropathic component to the pain (7). Renal dosing is often needed given the high incidence of concomitant kidney disease (see *Fast Fact #49*). Other neuropathic agents may be effective as well, but supporting evidence is sparse.
- Opioids: rapid onset IV or subcutaneous opioids such as fentanyl may be required via a patient controlled analgesia device to address CLI incident pain in a time-effective manner. For IC, clinicians may try to minimize opioid use. For CLI, given its complex nature and severity, long-term opioid use should not be used as the sole analgesic agent, but rather in conjunction with adjuvants and non-pharmacologic therapies.
- A single-dose IV ketamine IV infusion showed effectiveness in CLI analgesia in one clinical trial (14).
- Cilostazol and pentoxifylline are FDA-approved for the treatment of IC. Cilostazol 100 mg twice a day is likely more effective than pentoxifylline in reducing pain and maximizing walking distance; however, cilostazol is associated with more side effects such as headache, diarrhea, and palpitations (6,8,9,15).
- Regional Anesthesia: While interventional analgesic strategies which block appropriate nerves or nerve bundles may seem like a focused analgesic mechanism for CLI, even a dense nerve block may be inadequate for this type of pain (17). To date, no large studies demonstrate efficacy, however, collaboration with an interventional pain service may be warranted in refractory cases.
- Miscellaneous therapies: Preliminary studies of angiogenic growth factors, hyperbaric oxygen, l-arginine and spinal cord stimulation have shown benefit in relieving limb ischemia (1,3-6). For patients with a short prognosis and un-remitting pain from CLI despite an aggressive multi-modal analgesic approach, palliative sedation may require consideration (see *Fast Fact #107*).

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