Critical limb ischaemia: an update for the generalist

**Abstract**

Critical limb ischaemia (CLI) occurs in those people with severely impaired peripheral circulation which can threaten the limb if not recognised or managed appropriately. It is more common in those with diabetes and is associated with poorer outcomes. Importantly, CLI is also a marker of associated cardiovascular disease.

This paper describes how to recognise CLI, whether with or without tissue loss in the foot (ulceration and/or gangrene), and explains the importance of rapid and appropriate referral to a foot multidisciplinary team as part of an integrated pathway of care.

In addition, it reviews the further clinical assessment of the person, and discusses the various more detailed investigations available for CLI.

Finally, the treatment options available for the management of the individual with CLI are presented. Copyright © 2014 John Wiley & Sons.

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**Key words**

critical limb ischaemia; foot protection team; multidisciplinary team; revascularisation; amputation

**Introduction**

Foot disease is one of the most common complications in patients with diabetes, with peripheral arterial disease (PAD) being a major factor in the pathogenesis of both foot ulceration and amputation. Despite foot disease being costly to the individual, with half of all amputations in England occurring in people with diabetes,¹ and to the NHS in financial terms,² it remains a relatively neglected complication.

This review will concentrate on the detection,³⁴ subsequent investigation and specialist management of critical limb ischaemia (CLI). However, the article will not cover the specific management of intermittent claudication, or the acutely ischaemic limb.

**Peripheral arterial disease**

**How common is it?**

Peripheral arterial disease (PAD) affects 5–10% of the general population overall, rising to over 15% in those aged over 70 years,³ with cigarette smoking and diabetes being the two most common potentially modifiable risk factors in its development.⁶ In those with diabetes the risk of PAD is increased 2–4-fold.⁶ In Scotland, data have shown that the annual incidence of PAD development is 5.5 per 1000 patients with type 1 diabetes and 13.6 per 1000 patients with type 2 diabetes.⁷

**Why is PAD important?**

PAD (whether symptomatic or not) should be recognised as a strong surrogate marker for cardiovascular and cerebrovascular disease.⁸–¹⁰ The pathological processes of atherosclerosis in those with and without diabetes are broadly similar, as are the main risk factors which include smoking, diabetes, increasing age, abnormal lipid profile, hypertension, and renal disease.

Increasing HbA1c is associated with an increasing risk of PAD.¹¹ All patients with PAD should therefore have their diabetes and hypertension well controlled, receive appropriate statin and antiplatelet therapy unless contraindicated, and smoking should be discouraged.

In diabetes patients with PAD there is a greater tendency for the below knee (‘tibial’ or ‘crural’) vessels to be diseased than in the non-diabetic population.¹² This propensity for more distal disease influences the types of endovascular and surgical treatment required to revascularise a compromised limb.

PAD can result in increased morbidity and impair quality of life through intermittent claudication, rest pain, lower limb ulceration,¹³ or
amputation. The overall incidence of amputations (minor or major) is significantly higher in those with diabetes (2.51 per 1000 person-years) than in those without (0.11 per 1000 person-years). The term ‘critical limb ischaemia’ (CLI) is reserved for the most advanced form of PAD where limb viability is becoming threatened.

The prevalence of CLI has been reported as 0.24% in an unselected population of 40–69 year olds, with diabetes increasing the risk. Survival in patients with CLI is poor, with one-year mortality rates being over 30% and approximately 25% of patients undergo major amputation within one year.

### Critical limb ischaemia

**How do you define CLI?**

There are a number of definitions and classifications of PAD available to define the presence and severity of disease, but they are not used consistently in clinical practice. Formalising a precise and workable definition for CLI has been problematic. In simple terms, CLI is characterised by ‘chronic rest pain (over two weeks), or ulceration, and/or gangrene due to objectively proven arterial occlusive disease’.

In an attempt to identify those patients with true limb threatening ischaemia more precisely, ankle or toe arterial occlusion pressures were added to the diagnostic criteria for CLI. Examples of these are an occlusion pressure of 50mmHg at the ankle or 30mmHg at the toe, or in the presence of tissue loss higher levels of 70mmHg and 50mmHg respectively. Unfortunately, the problem with arterial occlusion pressure measurements is that not all patients with low ankle and/or toe pressures will end up with tissue loss, and some patients with higher pressures than these may develop tissue loss.

The diabetes population may have artifically elevated ankle pressures due to calcification of the vessel walls. This makes them incompressible for accurate arterial pressure measurement and hence the ankle brachial pressure index (ABPI) may be falsely elevated. In addition, in clinical practice it is clear that patients with larger areas

- Foot colour – may be normal, red or blue 'Elevation pallor, dependent rubor': elevate the foot and it may go pale, then hang the foot down and it may go redder
- Ulceration and/or gangrene
- Nail dystrophy
- Reduced foot temperature
- Absence of clearly palpable foot pulses

**Box 1. Potential signs of critical limb ischaemia in the foot**

of tissue loss require higher foot perfusion pressures to allow healing. Recently, NICE used a simple definition for CLI of ‘people with severely impaired circulation who are at imminent risk of limb loss without undergoing revascularisation’.

Finally, there are a group of patients who fall outside this definition of CLI. They have no symptoms of rest pain (see below), and currently intact feet, but have significant PAD and low foot pressures and are at risk of future tissue loss. Managing these ‘sub-critical’ patients can be difficult as most vascular interventions carry risks.

### How can CLI present?

**Symptoms.** Some patients with CLI may have a preceding history of intermittent calf claudication, but in patients with diabetes the presentation is often less obvious. Intermittent claudication, if present, is typically described as tight, cramp-like pain most commonly in the calf, and comes on with exercise and is relieved at rest. The calf is the most distal large muscle in the lower limb vasculature, and hence the most susceptible to impaired lower limb circulation. Claudication pain may also involve the buttock and thigh muscles when more proximal arterial disease predominates.

Rest pain, conversely, tends to occur in the forefoot and is worst when lying down at night in bed. The nocturnal pain often causes the patient to get out of bed and walk around or hang their foot out in a dependent position (or even sleep upright in a chair) to try to increase perfusion to their foot and reduce symptoms. It is postulated that rest pain is worse at night due to a reduced nocturnal cardiac output, the loss of the benefits of gravity in supplying blood to the foot when supine, and an increased metabolic rate of the foot when warmed in bed. Importantly, patients with diabetes more commonly develop ulceration or gangrene without experiencing any preceding claudication or rest pain, unlike the non-diabetic population, as concomitant neuropathy may mask the symptoms of CLI. In addition, patients with poor mobility may not experience claudication due to their limited walking distance.

**Signs.** Clinical assessment starts with a general inspection of the feet and legs particularly looking for any foot discolouration, swelling, nail dystrophy, hair lack, ulceration or gangrene, as well as any deformity of shape (Box 1). The presence of ulceration or gangrene should be obvious but careful inspection of heels and interdigital spaces is needed to ensure ulceration is not missed. The location of neuroischaemic, or pure ischaemic ulcers on the borders of the foot, tips of toes or heels can indicate the likelihood of PAD being a causative factor in ulceration.

Foot temperature and any temperature asymmetry should be assessed. It is sometimes difficult to decide if one foot is warmer than normal (e.g. due to infection or Charcot foot) or, if in fact, the other foot is cooler due to PAD. Redness of the foot may occur in infection, but is also seen in severe PAD (Figure 1). PAD may also mask the inflammatory response to infection so the signs of infection may be very subtle or missed. Infection can also lead to discomfort or pain in the ischaemic foot and can be the trigger for the development of CLI in an ‘at risk’ foot.

Palpation of the foot pulses includes the presence or absence of the posterior tibial, and dorsalis pedis pulses (up to 10% of the normal population do not have a palpable dorsalis pedis). It is exceedingly unusual to have a clearly palpable foot pulse in advanced CLI. The main exception to this would be distal small vessel embolisation causing localised tissue infarction. When there is uncertainty about the presence of a pulse it is best to assume
that the pulse(s) is absent and arrange further investigation. Assessment for any lower limb neuropathy is also vital.5,20

Foot screening
All people with diabetes should undergo annual foot screening, including palpation of foot pulses5,20 by a suitably trained health care professional,4 with subsequent classification of their current risk status, and a management plan then agreed with the patient. If found to be other than at low current risk (i.e. increased/ moderate or high risk), without current active foot disease, then they should receive review by a member of the ‘foot protection team’3,4 or a podiatrist20 at regular intervals.5,20,22 Although, as mentioned above, the diagnosis of CLI is highly unlikely in the presence of a clearly palpable foot pulse, the presence of a foot pulse does not exclude the diagnosis of PAD. ABPI may be useful in this situation as a supporting diagnostic test.

Of course, all active foot disease, e.g. new (or deteriorating) foot ulcer, discoloration, swelling, or CLI (with or without tissue loss) should be referred rapidly (within 24 hours) to the specialist diabetes ‘multidisciplinary foot team’ (MDFT).5,20,22,25

When should you refer the person with CLI?
Although further investigation is possible outside specialist centres, e.g. ABPI (see below), if CLI is suspected on the grounds of a simple but thorough history and examination, then urgent onward referral is indicated. For patients with diabetes and associated tissue loss or ulceration then this would usually be to the specialist diabetes MDFT. Where pain is the predominant symptom, without tissue loss, this may be to the vascular team depending on local pathways. No matter what the local pathway, it is vital that urgent referral and subsequent review are arranged.5,20,22,23

Specialist care
Clinical assessment
This should involve a more detailed assessment of the peripheral vasculature as well as investigation (and, importantly, management) of cardiovascular risk factors, a review of medication (including statins and antiplatelet therapy)5,10 and measurement of renal function. More detailed investigations can be organised on an individual basis. If the patient is admitted to hospital, then relevant NICE recommendations should be followed.24

What investigations are needed?
Ankle brachial pressure index (ABPI). Although there is controversy and confusion regarding the interpretation of ABPIs in diabetes patients, the recommendation is still that all patients should have a measurement recorded. This reading, however, should be interpreted carefully. Recent NICE guidance in PAD10 gives details on the practicalities of ABPI measurement.10 Incompressible vessels at the ankle can make ABPI interpretation difficult, and the measured pressure artificially elevated. There should be a low threshold for obtaining formal vascular assessment in patients with ABPI values >1.3, particularly when wound healing is delayed, or when foot pulses are absent on palpation. Waveform patterns heard with a hand-held Doppler are useful but take time to learn. ABPIs of <0.5 signify the presence of severe PAD; however, the result in itself does not establish the diagnosis of CLI. Most patients with ABPIs <0.5 will not require intervention in the absence of rest pain or tissue loss. The absolute pressure in mmHg is a more useful value than the ABPI ratio as a predictor of wound healing.

Toe pressures. Toe pressures have the advantage of being more representative of the perfusion to the distal extremity than ankle pressures and are useful when the calf arteries are incompressible. In the healthy individual the toe pressure is usually 0.8–0.9 of the brachial pressure. Ischaemic rest pain usually exists when the absolute toe pressure is <30mmHg,5 and recommendations from the European Society of Vascular Surgery suggest that healing is severely impaired when the toe pressure is <30mmHg.25 The authors’ opinions are that ankle pressures of 50–70mmHg and toe pressures of 30–50mmHg remain a ‘grey’ area for healing and the feet require close observation.

What vascular imaging is indicated?
Recent NICE guidance in PAD10 has recommended Duplex ultrasonography as the first-line investigation in all patients in whom revascularisation is being considered. If further imaging is then required, contrast enhanced magnetic resonance angiography (MRA) is advised with computed tomography (CT) angiography only if MRA is contraindicated, not tolerated or not available.

Figure 1. Image of peripheral arterial disease feet. The left foot has erythema due to ischaemia. The right foot was previously treated with angioplasty.
**Duplex.** Duplex imaging has the advantage over other forms of imaging as it gives real-time information about blood flow in a vessel. It can also provide functional information on the severity of an arterial stenosis and its effect on blood flow. The calf vessels can be more difficult to assess due to their size, calcification and in the presence of more proximal disease.

**MRA.** MRA avoids the need for ionising radiation and is better at assessing the lumen of calcified vessels than CT. This has obvious value when looking at calcified tibial vessels. However, optimal imaging does require contrast.

**CTA – CT angiogram.** Modern CT angiography can provide detailed information on arterial anatomy and allows for complex 3D reconstructions, but does expose patients to ionising radiation and potentially nephrotoxic contrast media. Arterial calcification can also make interpretation of the images more difficult, although the information may be beneficial in planning some forms of intervention.

**Angiography.** Conventional angiography has traditionally been the ‘Gold standard’ and has the added advantage that it can be combined with simultaneous intervention. Diagnostic angiography alone is rarely performed as it is an invasive procedure that requires cannulation of the femoral vessels to inject intra-arterial contrast.

**How do you manage CLI? Organisation and delivery of care**

The management of CLI in patients with diabetes should be planned within the MDFT, including diabetologists and vascular specialists, along with the patient. Amputation rates do vary considerably across England and could in part be due to variations in care delivery. MDFTs have been shown to reduce amputation rates. Multidisciplinary working with integrated pathways of care has been increasingly emphasised over recent years for optimal care of the diabetes patient with foot disease.

**General management of the foot and person**

General management should include a review of metabolic control, assessment and management of cardiovascular risk factors, and antiplatelet therapy instigated (unless contraindicated).

It is of vital immediate importance to treat any associated foot infection early on as this can cause a rapid deterioration in an ischaemic or neuroischaemic foot. If surgical drainage of the foot is needed, then this should not be delayed. The combination of PAD and infection has a significant negative impact on ulcer healing.

**Treatment options**

Historically, the treatment for CLI has relied on bypass surgery, amputation or conservative measures. The role of surgery as the primary treatment strategy has changed with the development of minimally invasive endovascular techniques (angioplasty, with or without stenting). Endovascular treatment is less invasive practically and physiologically, and so is an attractive option; however, both surgical and endovascular treatments are not mutually exclusive, and can be performed together (‘hybrid’ techniques) to simultaneously manage multi-level arterial disease.

Patients with diabetes often have arterial disease involving the below knee vessels which are more complex to treat due to their small calibre and lower blood flow. Fortunately, the majority of patients with CLI can still be offered some form of revascularisation in the form of endovascular intervention or open surgery including distal revascularisation. Revascularisation techniques, either initially angioplasty or open surgery, have tended to show similar medium-term outcomes although, in patients who survive for more than two years following intervention, surgery may be more effective.

With large quantities of evidence influencing most major medical treatments it may come as a surprise that there is very little evidence guiding the clinician with the treatment of a patient with CLI. PAD as a whole is a relatively ‘evidence free’ zone in comparison to aneurismatic or carotid artery disease. First-line treatment therefore depends on a number of factors including comorbidities, vascular disease pattern, vein graft availability and, importantly, patient preference. Treatment goals in CLI can often be shorter term in terms of relief of rest pain and increased extremity perfusion to allow a wound to heal. Many patients with CLI have a poor life expectancy and treatment choices therefore often reflect what is safest for these patients.

**Endovascular treatment.** Angioplasty (Figure 2) and stenting have
become highly successful when treating large-diameter, high-flow vessels such as the iliac arteries, with five-year patency rates of over 60%.

With improvements in equipment, angioplasty has also become established as first-line treatment in many centres for managing suitable infrainguinal arterial disease. Technological developments have created smaller diameter and longer balloons suitable for treating tibial arteries down to foot level. Other advances currently being evaluated include drug eluting balloons and stents, absorbable stents and devices to directly remove atheroma from occluded small vessels.

Although endovascular treatment is often viewed as a low-risk option compared with open surgery, it is not without risk, e.g. contrast nephropathy, bleeding, distal embolisation. Endovascular treatment has the same pre-requisites as those of open surgery with the requirement for good proximal inflow and a good good distal target vessel. Outcome is usually best when inline (uninterrupted) blood flow can be achieved to the foot.

The UK BASIL trial (Bypass versus Angioplasty in Severe Ischaemia of the Leg) demonstrated similar outcomes for surgery and angioplasty in the short and medium terms. Restenosis in endovascularly treated vessels may be increased in diabetes; however, with close follow up and re-intervention, good limb salvage rates can be obtained.

Vascular surgery. Bypass surgery is the mainstay of treatment in managing complex occlusive or stenotic disease of the lower limb vessels. Bypass surgery requires suitable patent inflow and outflow vessels for the bypass graft (vein or prosthetic) to be joined to. The surgeon’s conduit of preference remains the great (long) saphenous vein, which has patency rates of over 80% in large specialist institutions.

Due to the pattern of vascular disease in diabetes, bypasses to the pedal vessels are more frequently required (Figure 3). Large specialist units can demonstrate good patency and limb salvage rates for pedal bypasses: >50% primary patency rate and >70% limb salvage at five years.

There is a commonly held misconception that bypass grafts fare badly in diabetes. In contrast to this, there are studies showing superior patency rates in diabetes. Renal dialysis has been shown to be a marker of worse outcome in patients undergoing infrainguinal bypass surgery, and patients with renal failure or diabetes have also been shown to have an increased mortality at one year following bypass surgery.

Hybrid techniques. If required, it is often beneficial to perform both open surgical and endovascular techniques at the same sitting. An example of this is in the presence of combined femoral artery occlusive disease in the groin and an iliac stenosis proximally. In this case, access for iliac angioplasty via the femoral artery is not possible. The ‘hybrid’ option would be to perform a femoral endarterectomy (removal of intimal atheroma) combined with iliac angioplasty at the same sitting.

Amputation. Major amputation should still be considered as a treatment option in CLI. In patients who truly have no suitable distal target vessels for revascularisation, major amputation can provide a definitive treatment for pain or tissue loss or where mobility is already severely compromised.

However, it is vital that this decision is not taken until a multi-disciplinary team discussion has been undertaken, all options for revascularisation considered, and the patient’s views sought. This may help in reducing the current variability in amputation rates across England. It is important to involve the prosthetics and rehabilitation services in assessing a patient’s potential to rehabilitate prior to surgery.

Conclusion
Peripheral arterial disease is more common in patients with diabetes and is associated with worse outcomes and a higher risk of limb loss. Critical limb ischaemia is a manifestation of diabetic foot disease and requires early recognition with urgent onward referral and management.

This demands good communication between the community and specialist teams with agreed integrated pathways of care if amputation rates are to be minimised.

Declaration of interests
There are no conflicts of interest declared.

References
References are available in Practical Diabetes online at www.practicaldiabetes.com.
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References


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