Understanding the differential diagnosis of leg ulcers: focus on atypical ulcers

Jane Todhunter

The suboptimal management of leg ulcers has been identified as a UK-wide problem that involves a high financial and personal cost (Guest et al, 2015). One common omission identified in the care of patients with a leg ulcer is a failure to establish the underlying aetiology of the wound. Ideally, an accurate leg ulcer diagnosis should initiate the appropriate therapy, which should, in turn, facilitate healing; however, an inaccurate diagnosis at the outset means that the patient may not be started on an appropriate management pathway. Although vascular disorders are the major cause of leg ulcers, there are other aetiologies that should be considered when the leg ulcer has failed to respond to evidence-based therapy (Rayner et al, 2009). This article outlines some of the atypical leg ulcer types the author has encountered, as well as detailing the signs that were identified within the assessment process and which allowed the author to formulate an accurate diagnosis.

**KEYWORDS:**
- Arterial leg ulcers
- Venous leg ulcers
- Atypical ulcers
- Chronic wounds
- Assessment
- Differential diagnosis

Chronic wounds and leg ulcers are a high-profile topic within the NHS, with the recent launch of the Legs Matter campaign providing impetus for a national framework to support effective care (Legs Matter, 2018). In 2015, Guest et al outlined the extent of the burden that chronic wounds place on the health economy, prompting NHS England (2016) to focus on wound assessment as part of the ‘Leading Change, Adding Value’ campaign. A fictional account called Betty’s story formed part of this campaign, and described effective and ineffective care pathways for a person with a leg ulcer (NHS England, 2017). Betty’s story helped to highlight the human and healthcare costs of inadequate leg ulcer management. Further to this, Guest et al (2016) extrapolated NHS data to demonstrate that many people with lower limb conditions are not receiving optimal wound assessment, diagnosis or evidence-based treatment. The total number of leg ulcers was calculated as 731,035, of which 277,749 were diagnosed as venous, but 419,956 as unspecified aetiology (Guest et al, 2016). The lack of an accurate diagnosis means that a leg ulcer will be challenging to treat effectively.

While these figures are based on diagnosed leg ulcers, approximately half have no identified cause. Although inadequate lower limb treatment pathways and suboptimal training of healthcare professionals are contributing factors to this lack of accurate diagnosis (Anderson 2018), atypical ulcers, which are more difficult to assess, also contribute to a lack of effective diagnosis.

**DIAGNOSING ULCER AETIOLOGY**

A leg ulcer is a symptom of another condition and therefore it is important for nurses to ascertain the cause by implementing differential diagnostic procedures (Meyer et al, 2011). The starting point is a thorough assessment of the:
- Patient
- Leg
- Wound.

**Patient assessment**

Baseline assessment, including blood pressure, urinalysis, weight, blood screening (according to local guidelines/protocols and patient presentation), is the starting point for clinical assessment (Royal College of Nursing [RCN], 2000). The patient’s medical history and comorbidities, such as; cardiovascular disease, venous insufficiency, chronic kidney disease, autoimmune disorders and inflammatory bowel disease can provide clues as to the aetiology and are particularly pertinent to atypical ulcers, which have no significant venous or arterial involvement.

**PREVALENCE OF LEG ULCERS**

Venous leg ulcers are reported as the most common form of leg ulcer, accounting for around 80% of all cases; arterial leg ulcers account for approximately 15% of cases, while other causes, such as traumatic, vasculitic, malignant, account for 5% (NHS England, 2016; Circulation Foundation, 2018).

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The patient’s current medication profile may also have a bearing on wound healing, or may be the cause of the ulcer itself, for example, intravenous drug users often develop leg ulceration due to the trauma involved in injecting into veins. This damage can extend into muscle and nerves, as well as causing lymphatic blockage (Pieper et al, 2007).

Obesity has an adverse effect on comorbidities, mobility and patients’ mental well-being (Goldie and Brown, 2012), and may be the root cause of the ulcer. Tobón et al (2008) reviewed the literature on obesity, nutrition and venous disease and identified low levels of zinc, protein and vitamins A and C in those affected. Patients’ weight, build and nutrition are therefore important factors in the assessment of leg ulcers (Anderson, 2012).

**Leg assessment**
The shape and appearance of both legs should be visually assessed, noting the presence of any oedema, which often accompanies venous disease and may indicate lymphoedema (Wounds UK, 2016).

Legs with arterial disease may also display signs of oedema due to dependent-leg syndrome, as patients hang their legs out of bed at night or sleep in a chair to aid blood flow to the foot with gravity and ease the pain of ischaemic tissues in the lower leg or foot. The constant hanging down of the limb may impede venous return and often results in swollen feet and legs (Santilli and Santilli, 1999).

Limbs shape and size may provide clues to the ulcer aetiology, such as the classic inverted champagne-shaped leg caused by the fibrin cuff as a result of chronic venous disease. The hard ‘woody’ feel of the tissues is thought to result as fibrin gets excessively deposited around capillary beds leading to elevated intravascular pressure. This causes enlargement of endothelial pores resulting in further increased fibrinogen deposition in the tissues. The ‘fibrin cuff’, which surrounds the capillaries in the dermis, decreases oxygen permeability and inhibits diffusion of oxygen and other nutrients, leading to impaired wound healing (Burnand et al, 1982).

The patient’s mobility and ankle movement should also be noted. The calf muscle pump aids blood flow back to the heart using the muscles in the legs. Patients who have shuffling gait or fixed ankle will have lost the benefit of the pump and be at increased risk of venous hypertension and the often-resultant leg oedema (Harding et al, 2015).

The colour and condition of the patient’s skin may provide information to aid diagnosis, as systemic disease such as autoimmune disorders or vasculitis may be displayed in skin lesions or purpura.

Undertaking an arterial assessment is an essential element in differential diagnosis and will assist the nurse in excluding significant arterial disease. Calculation of the ankle–brachial pressure index (ABPI) from measurements of systolic blood pressure at the ankle and brachial artery in the arm is the method most widely used to assess peripheral arterial circulation (Beldon, 2011).

<table>
<thead>
<tr>
<th>ABPI</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;1.3</td>
<td>Arterial calcification may be present</td>
</tr>
<tr>
<td>0.91–1.3</td>
<td>Normal reading</td>
</tr>
<tr>
<td>0.8–0.9</td>
<td>No significant or mild peripheral arterial disease</td>
</tr>
<tr>
<td>0.5–0.8</td>
<td>Moderate peripheral arterial disease</td>
</tr>
<tr>
<td>&lt;0.5</td>
<td>Severe peripheral arterial disease</td>
</tr>
</tbody>
</table>

**Wound assessment**
A structured wound assessment tool such as TIME can aid diagnosis of the ulcer (Fletcher, 2007):

- **Tissue**: assess tissue quality, evidence of slough and necrosis
- **Infection**: colonisation is common in chronic leg ulcers. Assess for signs of surrounding cellulitis indicating infection
- **Moisture imbalance**: exudate should be assessed in terms of colour, viscosity and volume
- **Edge of wound**: assess for signs of over-granulation, ‘rolled’ edges, shallowness, depth and if there is a purple edge.

![Figure 1. Venous leg ulcer.](image)

A thorough assessment should allow the leg ulcer diagnosis to be noted and treatment started, or the patient referred on for further investigations and specialist treatment. The following wound types represent possible diagnoses that might arise from a comprehensive lower limb assessment.

**Wound Types**

**Venous leg ulcers**
Patients presenting with venous leg ulcers may give a history of previous varicose veins, deep vein thrombosis (DVT), leg surgery and trauma (Anderson, 2006). Leg ulcers that are venous in origin are often relatively easy to diagnose with tell-tale signs of:

- Varicose veins
- Haemosiderin staining: a ‘rusty’ discolouration of the lower limb caused by venous disease and iron released by haemoglobin when red cells break down
- Lipodermatosclerosis: a chronic inflammatory disease caused by subcutaneous fibrosis
- Atrophie blanche: white scarring that occurs where blood supply is suboptimal
- Ankle flare: collection of small blood vessels that give a ‘reddish’ tinge to the skin
- Eczema.

Venous leg ulcers are also commonly located around the malleolus or lower gaiter of the leg.

*Figure 1* shows a typical presentation of a venous leg ulcer. Treatment involves compression of the leg and a wound dressing appropriate for the ulcer.

**Arterial leg ulcers**
Elements in a patient’s medical...
Venous leg ulcers
medi’s wound care pathway

1 Step
Assess and clean
Compress with confidence and wound debridement plan
- MESI ABPI MD
- UCS Debridement

2 Step
Heal
with measureable compression
- juxtalite

3 Step
Prevent recurrence
- mediven hosiery

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history that would point to an arterial ulcer include heart disease, intermittent claudication (pain caused in the leg muscles due to occluded arteries), diabetes and hypertension. The patient may describe feeling more pain from the ulcer at night, which can be relieved by ‘hanging’ the leg out of the bed (known as rest pain). Some patients begin to sleep in a chair at night to ease the pain by resting their legs, which often results in leg oedema and wet ‘leaking’ legs, as fluid from the tissues leaks from wounds and blisters in the skin.

Arterial ulcers have a classic appearance, including:
- Slough and necrosis
- Being ‘punched-out’
- Significant depth — tendons may be visible
- Regular shape
- Usually located on the foot and lower leg.

Treatment includes revascularisation of the leg by angioplasty, with possible stent insertion or vascular surgery in the form of a bypass or endarterectomy to clean out the artery, and simple wound management.

The leg ulcer may be mixed and have underlying aetiology that is both venous and arterial in nature. *Figure 2* shows a typical presentation of an arterial ulcer.

### Inflammatory leg ulcers

Inflammatory leg ulcers are often difficult to diagnose and treat. There are a range of conditions that fall under this category.

**Pyoderma gangrenosum**

*Pyoderma gangrenosum* is an autoinflammatory disease for which the biggest sign will be the patient’s medical history, as it is associated with inflammatory bowel disease and rheumatoid arthritis (Oakley, 2016). Ulcers caused by *pyoderma gangrenosum* usually exhibit the following features:
- Rapid progression from a small pin-prick-sized lesion
- Starts with small trauma
- Involves extreme pain
- Located anywhere on the body, as well as lower leg
- Exhibits necrotic tissue or purple discoloration around the edge of the ulcer.

Biopsy will not inform the diagnosis of an ulcer caused by *pyoderma gangrenosum*, but it can be used to rule out other causes and, when used, should be undertaken under steroid suppression to prevent any potential ulcer worsening (Matthew and Pompeo, 2016).

Debridement often accelerates the progression of a *pyoderma gangrenosum* ulcer and should be avoided. Nurses should refer patients with such an ulcer to the dermatology team for systemic steroid treatment; however, they may require reduced compression to aid healing and address leg oedema. Reduced compression applies less than the standard 40mmHg of pressure at the ankle.

Treatment with topical steroids has proved beneficial in the author’s clinical practice and topical immunosuppression has been recommended in the literature. Meyer et al (2011) suggest the application of tacrolimus, corticosteroids or cyclosporine. Tacrolimus ointment suppresses inflammation in a similar way to steroids and is equally as effective as a mid-potency steroid. Cyclosporine initially developed for suppressing the immune system of transplant patients to prevent them rejecting their transplanted kidneys and other organs has subsequently been found to benefit patients with a wide range of diseases caused by immune reactions (British Association of Dermatology, 2017).

*Figure 3* shows a typical presentation of an ulcer resulting from *pyoderma gangrenosum*.

### Small vessel vasculitis

Small vessel vasculitis involves inflammation of the small blood vessels. This may be primary and associated with underlying autoimmune disorders such as...
as rheumatoid arthritis, lupus (systemic autoimmune disease), scleroderma (immune condition resulting in hardened skin) and Buerger’s disease (inflammation of the small and medium-sized blood vessels, usually in the legs), or secondary, following infection (Meyer et al, 2011). The inflammation-induced occlusion of the venules and arterioles involved in small vessel vasculitis results in palpable purpura with haemorrhage and ischaemia, often leading to ulceration (Meyer et al, 2011). Ulcers are usually painful and located on the lower legs and ankle.

Patients will require referral for skin biopsy and steroid therapy. They may also require compression bandaging and topical steroid application, in addition to systemic treatment (Oakley, 2016).

Figure 4 shows a typical presentation of an ulcer resulting from small vessel vasculitis.

Rheumatoid ulcers
Rheumatoid ulcers are often multifactorial in origin, involving a mixture of vasculitis, venous and arterial disease (Oakley, 2016). In clinical practice, rheumatoid ulcers are some of the most difficult to manage, partly because the immunosuppressants required to treat the arthritis inhibit wound healing (Meyer et al, 2011).

The clearest indication of the aetiology of a rheumatoid ulcer is a medical history of rheumatoid arthritis and foot deformities, although accompanying venous and arterial disease also need to be considered. Rheumatoid ulcers are usually:

- Sloughy
- Located on the lower gaiter and ankle area
- Prone to repeated infections
- Very painful.

Treatment of rheumatoid ulcers involves wound and exudate management and reduced compression. In clinical practice, the author has found that rheumatoid ulcers may respond well to zinc paste bandages under reduced compression.

See Figures 5 and 6 for typical presentations of rheumatoid ulcers.

Calciphylaxis
Calciphylaxis is a condition most commonly seen in patients undergoing haemodialysis and presents with vascular calcification, thrombosis and skin necrosis that eventually leads to ulcer formation (Fukaya and Margolis, 2013).

Calciphylaxis occurs in 1% of patients with chronic kidney disease and 4% of individuals undergoing dialysis (Rayner et al, 2009). The survival rate for patients with calciphylaxis is 45% at one year, with infection being the principal cause of death (Bliss, 2002). Warfarin-induced calciphylaxis has also been reported in patients with normal kidney function.

The distal form of calciphylaxis affects the lower limbs and results in ulcers on any area of the legs; the proximal form causes ulcers on the inner thighs, abdominal apron, breasts and upper arms. The ulcers caused by calciphylaxis are usually:

- Necrotic and extensive
- Prone to infection
- Quick to develop
- Extremely painful.

Treatment involves removal of the necrotic tissue and there have been some promising results using sodium thiosulphate (STS) intravenously, usually 25gm twice weekly but the optimal duration of treatment is not known. STS forms water soluble complexes with the calcium and leads to soft tissue calcium elimination (Huilaja et al, 2016).
Figure 7 is an example of a typical presentation of an ulcer due to calciphylaxis.

Calcinosus cutis
Deposits of calcium salts within the skin and subcutaneous tissue can cause tissue damage and ulceration. The pathology causing the calcium deposits can be:
- Dystrophic (arising from the deposits of calcium in the tissue following injury or inflammation)
- Metastatic (caused by an increased calcium phosphate product in the blood, and may result from hypercalcemia or hyperphosphatemia, or both. It is commonly associated with hyperparathyroidism, sarcoidosis, metastatic disease, and myeloma)
- Idiopathic (of unknown aetiology)
- Iatrogenic (relating to a condition caused by a medical intervention) (Rayner et al, 2009).

The author has most commonly come across dystrophic calcinosis where the main risk factors seemed to be chronic venous disease displayed as inflamed lipodermatosclerosis, and in one case, historical trauma in the form of a crush injury to the leg.

Chronic venous insufficiency has been suggested as a factor that promotes the deposition of calcium phosphate in the tissues. The pathogenesis is not well understood, but may result either from venous leakage caused by stasis and/or persistent inflammation, leading to phosphate binding, or from a dysregulation of intracellular calcium concentration in dying cells (Tokoro et al, 2009).

Ulcers that develop as a result of calcinosis cutis are often initially diagnosed as venous ulcers, but become chronic and fail to heal with normal wound treatment. These ulcers can exhibit the following characteristics:
- Sharp ‘gritty’ pieces of calcium may be felt within the wound bed when running a gloved finger over the ulcer or during washing of the ulcer.
- Bleeding when calcium deposits are removed.
- Tissues surrounding the ulcer may feel hard to the touch, indicating the presence of further calcium deposits.
- Not usually painful.

There is no treatment recommended within the literature; however, in the author’s clinical experience, ulcers that develop as a result of calcinosis cutis may benefit from surgical removal of the calcium, allowing the wound to proceed to healing. In the absence of surgical debridement, persistent removal of any calcium deposits during dressing changes and using forceps to loosen individual pieces, can be effective.

Figure 8 shows a typical presentation of an ulcer due to calcinosis cutis.

Drug-induced ulcers
Immunological and toxic reactions are thought to be responsible for the development of drug-induced ulceration (Rayner et al, 2009). These ulcers may often be initially diagnosed as venous, but fail to respond to treatment.

There are certain medications that should alert the nurse to a potential diagnosis of drug-induced ulcer during any leg ulcer assessment. For example, hydroxyurea (a cytotoxic chemotherapy) is probably the most well-known trigger for drug-induced leg ulcers. In her clinical experience, the author has come across cases of nicorandil-induced leg ulcers combined with lower leg and ankle oedema, although this is only reported in the literature in single case reports (Meyer et al, 2011). Drug-induced ulcers may exhibit the following characteristics:
- Often located on the ankle and lower gaiter.
- Painful.
- Sometimes surrounded by atrophie blanche.

Therapeutic alternatives to the causative drug must be identified, or doses reduced if the ulcers are to heal (Meyer et al, 2011).

Malignant leg ulcers
Basal cell carcinoma
Basal cell carcinoma (BCC) are slow-growing lesions that arise from the basal cells located at the base of the epidermis (Telfer et al, 2008).

They occur mainly in adults of fair complexions with a history of sun-damaged skin and are twice as common in men as women (Roewert-Huber et al, 2007). Because BCC lesions are slow-growing, metastases are rare (Rayner et al, 2009). BCC lesions:
- Have rolled edges.
- Have the appearance of hyper-granulation tissue.
- Are located on sun-exposed sites on the lower leg.
- Fail to respond to usual wound treatment.

Patients will require excision of the BCC and, in most cases, compression bandaging to aid healing.
### Table 1: Differential diagnoses for different leg ulcer types

<table>
<thead>
<tr>
<th>Leg ulcer</th>
<th>Typical location</th>
<th>Important factors in patient assessment</th>
<th>Important factors in leg assessment</th>
<th>Important factors in wound assessment</th>
<th>Further investigations</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venous</td>
<td>Lower gaiter/malleolus</td>
<td>Deep vein thrombosis (DVT)</td>
<td>Previous ulceration</td>
<td>Tissue may be granulating or sloughy, usually with shallow, sloping edges</td>
<td>Referral to vascular team</td>
<td>Compression. Radiofrequency ablation of superficial varicose veins</td>
</tr>
<tr>
<td>Arterial</td>
<td>Foot or ankle/lower skin</td>
<td>History of cardiac disease, intermittent claudication, diabetes, rest pain, smoking, hypertension</td>
<td>Reduced ankle brachial pressure index (ABPI)</td>
<td>Sloughy and necrotic or pale wound base</td>
<td>Urgent referral to vascular team</td>
<td>Angioplasty with stenting. Bypass surgery. Antiplatelet therapy. Steroid therapy.</td>
</tr>
<tr>
<td>Pseudomembranous</td>
<td>Anywhere on body</td>
<td>Inflammatory bowel disease</td>
<td>Significant pain</td>
<td>May have purple halo around ulcer</td>
<td>Often a diagnosis by elimination</td>
<td>Referral to dermatology. Steroid therapy. Topical and/or systemic.</td>
</tr>
<tr>
<td>Small vessel vasculitis</td>
<td>Lower legs</td>
<td>Recent infection</td>
<td>Painful, non-blanching palpable purpura</td>
<td>Necrotic tissue may be evident</td>
<td>Ulcer biopsy</td>
<td>Referral to dermatology/rheumatology. Reduced compression Steroid therapy.</td>
</tr>
<tr>
<td>Rheumatoid</td>
<td>Lower gaiter/ankle</td>
<td>Rheumatoid arthritis</td>
<td>Multifactorial aetiology</td>
<td>Tissue may be sloughy or granulating</td>
<td>Depends on underlying aetiology</td>
<td>Reduced compression. Liaise with rheumatology regarding medication.</td>
</tr>
<tr>
<td>Cinaclosis ulcers</td>
<td>Any site on legs</td>
<td>Varicose veins with ulceration</td>
<td>May have venous skin changes</td>
<td>Sharp pieces of calcium can be felt in the ulcer</td>
<td>Referral to vascular team.</td>
<td>Removal of calcium. Compression.</td>
</tr>
<tr>
<td>Drug-induced ulcers</td>
<td>Usually lower leg</td>
<td>Hydroxyurea</td>
<td>Oedema</td>
<td>May resemble a venous ulcer</td>
<td>Steroid therapy, dermatology, rheumatology, or systemic</td>
<td>Reduction in dose of offending drug, or alternative medication.</td>
</tr>
<tr>
<td>Basal cell carcinoma (BCC)</td>
<td>Sun-exposed lower leg, often front of shin</td>
<td>History of sun exposure, usually in fair complexions</td>
<td>Duration: slow growth, lack of response to standard wound treatment</td>
<td>Ulcer may resemble overgranulation tissue</td>
<td>Ulcer biopsy</td>
<td>Surgical excision with wide margin plus skin graft. Compression.</td>
</tr>
<tr>
<td>Squamous cell carcinoma (SCC)</td>
<td>Lower leg</td>
<td>History of chronic venous leg ulcers, history of trauma burns to site of ulcer, immunosuppression, actinic keratosis</td>
<td>Scar tissue</td>
<td>Rapid changes in appearance of ulcer, raised edges</td>
<td>Ulcer biopsy</td>
<td>Surgical excision. Compression. Radiation. Possible amputation.</td>
</tr>
</tbody>
</table>
Squamous cell carcinoma

Squamous cell carcinoma (SCC) causes primary cutaneous malignant lesions that arise from keratinising cells. The lesions expand and eventually ulcerate (Motley et al, 2003). SCC ulcers are locally invasive and have the potential to metastasise to other organs of the body (Rayner et al, 2009). The ulcers appear atypical and do not respond to any usual wound and compression treatment.

Chronic leg ulcers may develop into SCC ulcers known as Marjolin’s ulcers (the rare development of SCC on a scar or lesion), although the literature suggests that this malignant transformation of chronic venous leg ulcers is very rare (Reich-Schupke et al, 2015). The author has encountered up to four cases of Marjolin’s ulceration, all of which were preceded by non-healing venous leg ulcers of long duration.

The diagnosis of an ulcer due to SCC is confirmed by ulcer biopsy. Characteristics of ulcers caused by SCC include:

- Raised wound bed, often with rolled edges and hypergranulation within the wound base
- Lower-limb location, sometimes within a previously damaged area of skin or chronic ulcer
- Frequent malodour with a high volume of exudate
- Propensity for infection.

Patients with suspected SCC should receive an urgent referral to dermatology. Following excision with or without skin grafts, patients will often require compression bandaging to minimise leg oedema and encourage healing. Late diagnosis or delay in diagnosis can result in loss of the affected limb, or eventual metastasis of the tumor (Etufugh et al, 2005).

Table 1 summarises the differential diagnoses for a range of leg ulcer types.

CONCLUSION

Leg ulceration continues to be a challenge for both nurses and patients. NHS England’s current focus on chronic wounds has provided an opportunity to prioritise leg ulcers and improve patient outcomes through the national Legs Matter campaign, increased resources and training, and a national framework. However, the treatment of any ulcer must begin with accurate diagnosis, which is often still lacking.

This article has outlined some of the atypical leg ulcers that the community nurse may encounter and which can be difficult to diagnose and manage. When leg ulcers fail to respond to treatment or heal in an orderly manner despite optimal therapy, nurses should reconsider the diagnosis and, where necessary, refer on for specialist advice and management.
REFERENCES


