Neuropathic Ulcers

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13.1 Introduction

The most common cause of neuropathic ulceration to the lower limb is diabetes mellitus [1]. Primary neurological conditions (including multiple sclerosis and paraplegia), renal failure, chronic liver disease, alcohol excess, nutritional deficiencies, HIV, trauma, and surgery can also lead to peripheral neuropathy and hence to ulceration. Less common conditions that can result in neuropathic ulcers include chronic leprosy, spina bifida, syringomyelia, tabes dorsalis, poliomyelitis, and hereditary sensory and motor neuropathy (HSMN) commonly called Charcot-Marie-Tooth (CMT) disease [2, 3].

13.2 Epidemiology

Due to the heterogeneity of causes, it is difficult to provide an estimate of the prevalence of neuropathic ulcers in general; however, the prevalence of diabetic foot ulcers has been reported. The chance of an individual with diabetes developing a foot ulcer at sometime during their life has been estimated at 1 in 4 [4]. The prevalence of diabetes is increasing in every country, and it has been estimated that by 2030 there will be more than 550 million people with diabetes globally. In 2013 more than 3 million people in the UK had a diagnosis of diabetes [5], and it has been estimated that by 2030 over 550 million people globally will have diabetes.

Lower-limb ulcers are chronic, complex wounds which can be very debilitating and adversely affect patients' quality of life, often leaving them unable to work

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[6, 7]. Lower-limb ulcers also have massive economic effects on healthcare services. A European study conducted between 2003 and 2004 found that the total cost of treatment of a diabetic foot ulcer ranged from £3500 for noninfected neuropathic ulcers to £13,000 for infected ischemic ulcers [8]. In England, foot complications account for 20 % of the total National Health Service spend on diabetes care, which is around £650 million per year [9]. Not uncommonly, foot ulcers can be complicated by infection and/or need for lower-limb amputation [10]. In fact, foot ulcers precede amputation in 85 % of all non-traumatic lower-limb amputations [11]. Individuals who develop a diabetic foot ulcer are at greater risk of premature death, myocardial infarction, and fatal stroke than those without a history of diabetic foot ulceration [12].

13.3 Pathophysiology

Peripheral neuropathy may affect sensory and/or motor nerves. The sensory modalities implicated in neuropathic ulceration include pain, pressure, proprioception, temperature, and heat/cold. These sensory modalities transmit stimuli to the brain resulting in sensory awareness that enables the individual to relate to their environment, identify nociceptive stimuli responsible for local tissue injury, and respond to these by taking appropriate protective actions. Therefore, in sensory nerve damage, there is loss of protective sensation (LOPS) leading to injuries [13].

In the absence of pain sensation, foot injuries occur without the individual taking much notice [14]. Their weight exerts strain on the same foot site with relatively little discomfort resulting in repetitive mechanical forces and callous formation, followed by tissue breakdown, and eventually chronic ulceration [15]. It is not uncommon for a patient with a neuropathic ulcer to walk into the clinic without limping – they simply cannot feel pain to allow them adapt their gait/walking to prevent further injury.

Similarly, loss of pressure sensation results in individuals exerting a lot of pressure at one spot under the foot when they walk, building up a callus at that site without causing much discomfort. The pressure can become so high that it eventually leads to breakdown of tissues and ulceration. Sensory neuropathy also allows mechanical and thermal trauma with small cuts or punctures going unnoticed. Over time these may progress to ulcers. There are anecdotal reports of “holiday ulcers” where people have walked barefoot on hot sandy beaches and developed blisters and ulcers due to lack of temperature sensation.

Peripheral neuropathy can also affect motor nerves, leading to wasting of the small intrinsic muscles of the foot. This results in an imbalance between the flexor and extensor muscles [16], in turn leading to deformities and creating additional pressure points exposed to the risk of ulceration. The reduced muscle bulk also reduces the amount of soft tissue padding, therefore exposing the skin to high mechanical forces between the underlying bone and the walking surface. Autonomic neuropathy reduces sweating, consequently reducing hydration, causing the skin to be less elastic and so more vulnerable to mechanical stress [16].

13.4 Assessment of Patients with Neuropathic Ulcers

When assessing a patient with a foot ulcer, it is important to take a full history from the patient, considering both intrinsic and extrinsic factors.

Intrinsic factors include the presence of any underlying cause of neuropathy, predisposing medical conditions, diabetes, or symptoms to suggest diabetes if not yet diagnosed. A medication history [17], smoking history, and alcohol intake history are also important. Any previous history of ulcers should also be noted. A description of the ulcer itself including onset, chronicity, appearance, pain, and discharge (exudates or slough) should be elicited. Extrinsic factors include any trauma that the patient is aware of, pressure points, and their footwear. The patient's shoes should be inspected. Shoes that are too worn or too tight (too narrow or too short) for the patient are likely to lead to rubbing, blistering, and callous formation [18]. (Figs. 13.1, 13.2, and 13.3).

Neuropathic ulcers are usually painless unless an arterial component or infection is present. The wound margins tend to display callus buildup, a useful clue to the underlying high pressure load. Pedal pulses are usually present unless there is a vascular component. Foot temperature is usually normal. Despite even a large plantar ulcer, the patient may walk normally, without a limp, highlighting their lack of sensation.

Other aspects of abnormal foot pressures and neuropathy including limited joint mobility (LJM), dry skin, and various deformities (pes cavus, flattened plantar arch, hallux rigidus, hammer toes, claw toes, etc.) should also be elicited [18, 19].

13.5 Multidisciplinary Foot Teams

In many Western centers, diabetic patients with foot ulcers are managed in specialist foot clinics run by a multidisciplinary foot team (MDFT). This may include a combination of diabetes physicians, specialist nurses, podiatrists, vascular surgeons,

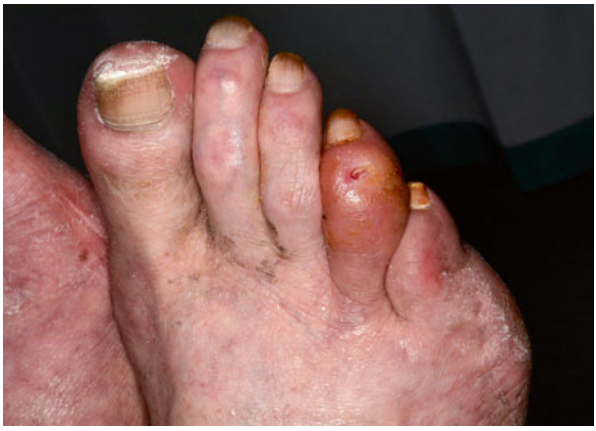

Fig. 13.1 Sausage-shaped right 4th toe with surrounding erythema; ulcer over the DIPJ probes to bone suggestive of osteomyelitis. Note the dry skin with toe deformity and callus buildup around the tip of the hallux and lateral border of the 5th toe – neuropathic ulceration from tight shoes

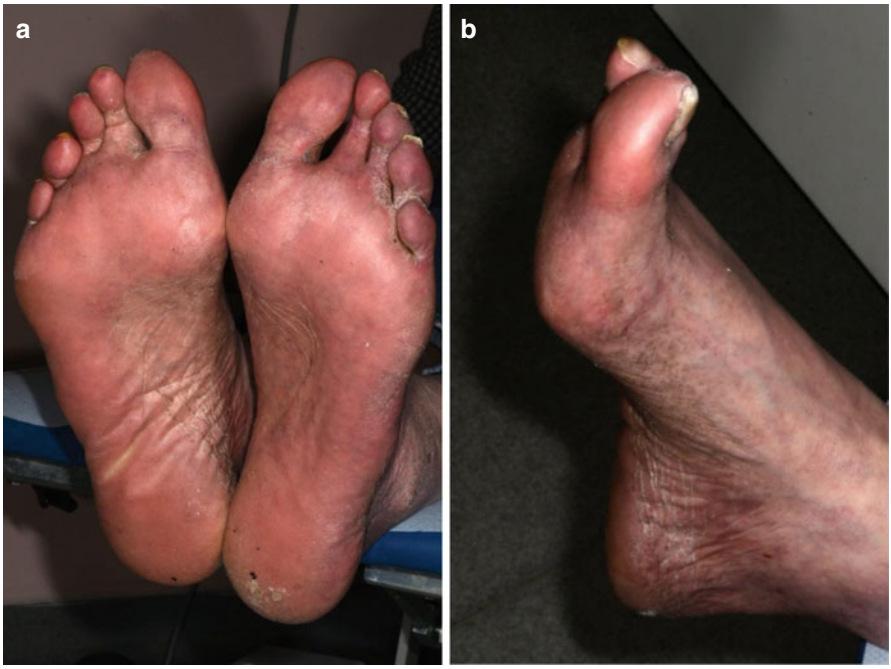

Fig. 13.2 Neuropathic foot. Note the dry skin (**a**, **b**), dystrophic nails (**b**), raised plantar arch (**b**), and distended foot veins (from autonomic shunting)

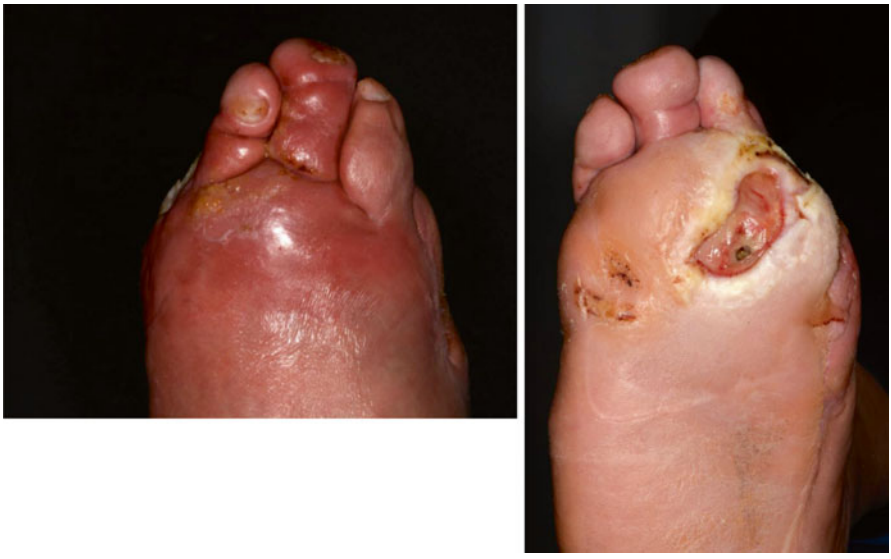

Fig. 13.3 Neuropathic ulceration in a patient with previous right hallux and 5th toe ray amputation. Like underlying infection. Not the hypertrophic callus rim around the ulcer due to inadequate offloading

orthopedic surgeons, orthotists, or psychologists. Patients with new ulcerations, swelling, or discoloration should be referred to these services promptly from primary care for urgent assessment and management. In the presence of severe infection, they may require prompt hospitalization for intravenous antibiotics. Evidence supports the role of the MDFT with one study finding that the total number of amputations fell by 70 % over 11 years following improvements in foot care services and implementation of an MDFT. [20]. The National Institute for Healthcare and Care Excellence (NICE) recommends that hospitals should have a care pathway for patients with diabetic foot problems, which should be managed by an MDFT, consisting of healthcare professionals with specialist skills and competencies [21].

13.6 Identification and Treatment of Infection

Diagnosis of infection in diabetic foot ulcers can be difficult as signs one would expect to find locally (pain, erythema, swelling, and raised temperature) may not be present [8]. Systemic signs may only be present in severe infections such as osteomyelitis or septicemia. Infection in a diabetic foot wound can produce signs such as poor blood glucose control, increased slough/exudate, pus, foul smell or change in smell, pain, and warmth. Although diagnosing infection at an early stage can be challenging, it is crucial in preventing progression of the infection and thereby preventing necrosis, gangrene, and amputation [22]. More than half of all diabetic foot ulcers will become infected at sometime so a high index of suspicion is vital [23]. The following factors increase the likelihood of an infection developing [24]: a positive probe-to-bone test, ulcer present for more than 30 days, a history of recurrent DFUs, a traumatic foot wound, the presence of peripheral arterial disease in the affected limb, a previous lower-extremity amputation, loss of protective sensation, the presence of renal insufficiency, and a history of walking barefoot.

Signs of severe infections include widespread inflammation, crepitus, bullae, necrosis, or gangrene. If a wound appears infected, appropriate cultures should be sent (soft tissue, secretions, or bone if osteomyelitis is suspected). All open wounds will be colonized with pathogens so superficial swabs are unlikely to culture the specific pathogen responsible for the infection. Empirical antibiotics should be prescribed in accordance with local microbiology advice while awaiting culture results and sensitivities. Other useful investigations include a full blood count, C reactive protein, renal function and liver function. Evidence does not support antibiotic therapy for ulcers that do not appear infected. Topical antibiotics may be useful in cases where there is poor vascular supply leading to reduced antibiotic tissue penetration, but the evidence base supporting their use is thin.

Diabetic patients with signs of infected ulceration should have a radiograph of their foot to detect any evidence of osteomyelitis. Signs of osteomyelitis on a radiograph include focal destruction of cortical bone, periosteal new bone formation, soft tissue swelling secondary to inflammation around the area, and focal osteoporosis caused by hyperemia. Conventional radiographs may not display any signs of osteomyelitis for up to 10 days so other types of imaging such as MRI should be used,

where available, if clinical suspicion remains despite a normal radiograph [25]. If MRI is contraindicated or unavailable, a labeled leukocyte imaging scan can be performed instead. Radiography can also be used to exclude a foreign body in tissues which is common with plantar neuropathic ulcers.

13.7 Identification of Deformities

As described previously, deformities of the feet can result from neuropathic changes, and these deformities create extra pressure points which are at high risk of ulceration. Feet should be inspected for common deformities including hammer toes (a fixed flexion deformity of the proximal interphalangeal joint), claw toes (flexion at the distal and proximal interphalangeal joints with dorsiflexion at the metatarsophalangeal joint), prominent metatarsal heads, and pes cavus (high arch).

13.8 Management of Neuropathic Ulcers

The basic aims of management are wound closure with prompt healing and prevention of the development of further ulcers.

These management goals can be achieved through a variety of measures including: local wound care (debridement), infection control, ensuring adequate blood supply, VAC therapy, adjunctive therapies, pressure offloading, treating underlying factors (intrinsic and extrinsic), patient education, temperature self-assessment, fat pad augmentation, and specialist shoes.

13.8.1 Debridement

This is the removal of devitalized, damaged, or infected tissue from an ulcer and hence exposure of healthy tissue. Exposure of the healthy tissue aids the healing process, and removal of devitalized tissue reduces the risk of infection. Debridement may be a single procedure, or it may need to be ongoing for maintenance of a clean wound bed [26].

Sharp debridement can be done in an outpatient setting by a podiatrist or foot specialist. A scalpel, scissors, or forceps are used to remove devitalized tissue. This procedure can be painful so adequate analgesia is essential. Assessment of the vascular supply to the feet is important before undertaking extensive sharp debridement. Patients requiring revascularization should not undergo sharp debridement due to the risk of trauma to tissues that are vascularly compromised.

Surgical debridement should be considered in cases of extensive necrotic tissue or localized fluctuance indicating pus or gas in the surrounding soft tissue. This involves excision or wider resection of both nonviable and healthy tissue from wound margins until a healthy bleeding wound bed is achieved.

Autolytic debridement is a process by which the body attempts to shed devitalized tissue with the use of moisture. If tissue is kept moist, it will degrade naturally

and deslough from the underlying healthy tissues. The presence of matrix metalloproteinases (MMPs) enhances this process. These are enzymes produced by damaged tissue, acting to disrupt the proteins that bind the dead tissue to the body. Autolytic debridement uses the body's own enzymes and moisture to rehydrate, soften, and liquify hard dead tissue and slough using semiocclusive or occlusive dressings (e.g., hydrogels, hydrocolloids) to maintain a moist environment and enhance the body's natural debridement process. This technique can be used when there is a small amount of nonviable tissue, if other methods of debridement are unsuitable, or for maintenance debridement. It is a slow process which increases the risk of infection and maceration.

Maggot debridement therapy involves applying sterile larvae of the green bottle fly to a neuropathic ulcer. This technique can achieve rapid digestion of necrotic tissue and pathogens and therefore promote granulation. Larval therapy is not recommended to be used as the only method of debridement in neuropathic ulcers as calluses cannot be removed by the larvae [27]. It is also not recommended for use in ulcers with an ischemic component as the process can cause or aggravate severe pain.

Hydrosurgical debridement uses a high-energy saline beam as a cutting implement to remove devitalized tissue [28]. The benefits of this technique include a short treatment time and the ability to remove most, if not all, dead tissue from the wound bed. Disadvantages include the need for specialist and expensive equipment.

13.8.2 Infection Control

Steps that can be taken to prevent infection developing in an ulcer include debridement of devitalized tissue, tight diabetic control (hyperglycemia leads to an increased risk of infection and also impairs healing in an established wound infection), care with footwear (checking for objects inside socks and shoes), and not walking barefoot to avoid any pathogens entering any wounds.

13.8.3 Ensuring Adequate Blood Supply

As previously described, neuropathic ulcers are commonly complicated by a degree of ischemia. Poor blood supply to the foot will impair its healing capacity. If the blood supply is good and recurrent insults are avoided, the ulcer should heal well. However, there may also be a vascular component that requires attention from surgical colleagues. It is important to recognize vascular deficits and refer early to vascular surgeons.

13.8.4 Vacuum-Assisted Closure (VAC) Therapy

VAC is an active wound therapy that applies subatmospheric or negative pressure (minus 125 mmHg) to the wound bed via a foam dressing. Applying negative pressure via a VAC pump aims to remove excess exudate and provide a moist,

wound-healing environment. It also reduces edema in the surrounding tissues that may impede local blood flow and impair healing. It also promotes increased angiogenesis and granulation tissue. VAC can be used on what is initially a complex wound to transform it into a simple wound that is then easier to close surgically. However, two Cochrane reviews of studies investigating the use of VAC in the management of diabetic foot wounds have concluded that the current evidence base is only supported by a limited number of underpowered, poorly designed studies.

13.8.5 Adjunctive Therapies

Platelet-derived growth factor (PDGF) is a protein involved with regulating cell growth and division. It has a significant role in angiogenesis. When a tissue injury occurs, platelets aggregate as part of the hemostatic mechanism, and they release PDGF which is powerfully chemotactic for inflammatory cells including macrophages. These migrate to the wound and remove necrotic tissue and fibrin. In the epidermis PDGF promotes the progression of basal epithelial cells through the cell proliferation cycle. It acts to move cells from G0 (resting phase) to G1. In the dermis PDGF stimulates proliferation of myofibroblasts. Studies have shown that treatment with PDGF significantly increases the chance of complete wound healing compared to placebo. PDGF treatment also significantly decreases the time to complete healing by 30 % [29].

Granulocyte colony-stimulating factor (G-CSF) is a hematopoietic growth factor required for the proliferation and differentiation of hematopoietic precursors of neutrophil granulocytes. G-CSF also enhances the antimicrobial functions of mature neutrophils. A meta-analysis examining the impact on rates of infection, cure, and wound healing of G-CSF in addition to normal care in diabetic patients with foot infection found that G-CSF did not significantly affect the chance of wound healing or resolution of infection. However, the addition of G-CSF was associated with fewer surgical interventions, including amputations. Addition of G-CSF was also found to reduce length of hospital stay, but it did not affect the length of systemic antibiotic therapy.

Honey has been used in the healing of leg ulcers for centuries. One theory is that honey may facilitate autolytic debridement; another theory proposes antimicrobial properties. However, there is a lack of data to support the routine use of honey in the management of neuropathic ulcers.

There is some evidence to suggest that systemic hyperbaric oxygen therapy (HBOT) may reduce the incidence of major amputations in patients with diabetic foot ulcers [30, 31].

13.8.6 Pressure Offloading

Reducing and redistributing pressures from high-risk areas to an even share throughout the foot is an important step in the management of neuropathic ulcers [32]. The gold standard method for pressure offloading is a total contact cast. This is a minimally padded cast which is molded to the foot and lower leg. It redistributes

pressure evenly across the whole of the plantar surface of the foot. It is not easy for the patient to remove so the total contact cast (TCC) has much higher compliance rates, and in turn higher success rates, compared to removable devices. In patients with a unilateral, uncomplicated plantar ulcer, using a TCC can reduce healing time by approximately 6 weeks [33]. TCCs are not suitable for patients with infected ulcers or osteomyelitis as wounds cannot be inspected regularly, allowing infection to spread without being noticed. They are also contraindicated in patients with ischemia due to the risk of inducing further ulcers. The application and removal of TCCs requires specially trained personnel [34]. If fitted by unskilled staff, ulcers can develop inside the cast. Other devices used if a TCC is either contraindicated or not tolerated by the patient include removable cast walkers, Scotchcast boots, healing sandals, crutches, walkers, and wheelchairs.

13.8.7 Treating Underlying Factors

The underlying cause of the peripheral neuropathy should be managed accordingly to prevent further deterioration. In cases of neuropathic ulcers secondary to diabetes, tight glycemic control is imperative to improve healing, reduce the risk of infection, and reduce the risk of further ulceration. Blood pressure, cholesterol, and weight also need to be controlled. Smoking cessation advice and support should be offered to all current smokers. Malnutrition should be corrected when present.

Other comorbidities that have been shown to impair wound healing must be considered and addressed. These include renal dialysis or transplant in patients with end-stage renal disease [4]. Uremia can impair white cell function and hence increase the risk of infection and impede wound healing. These patients are also likely to have peripheral edema which can adversely affect microcirculation. Anemia should be corrected and adequate nutritional support should be provided, especially in patients with low albumin.

Extrinsic factors which cause trauma and hence ulceration should be addressed. Those patients at high risk of falling should be identified. The patient's footwear should be examined for fit and presence of any foreign bodies, such as small stones, which may initiate skin damage. Those with inappropriate footwear should receive footwear education and referred to an orthotist or a shoemaker experienced in providing footwear to people with neuropathy.

13.8.8 Patient Education

The patient must be educated about the origin of neuropathic ulcers. Pain serves a purpose; it warns the individual that something is wrong and therefore alerts them to remove the stimulus. One of the leading pioneers on the management of neuropathic ulcers – Dr. Paul Brand – once said: "pain is God's greatest gift to mankind!" With impaired sensation this protective pain mechanism is lost. Patients with neuropathy should be educated and advised to check their feet regularly including

before going to bed at night. Attention to socks and shoes is important. Patients may not notice small stones or objects in their shoes because of neuropathy. Patients should be advised to check the temperature of bath water with their elbow before stepping in to avoid thermal trauma to their feet. They should also avoid electric blankets, hot water bottles, and sitting too close to a fire or heater. Patients should also be warned not to walk around the house with bare feet. Well-fitting comfortable footwear is important, as is good nail care.

Patients should be educated regarding the importance of prompt detection and treatment of ulcers. They should be advised to report any changes in current ulcers, or the surrounding skin, such as swelling, change in color, or discharge to a health-care professional.

In patients with diabetes, the importance of glycemic control needs to be highlighted. Patients should also be informed of the benefits of blood pressure, cholesterol, and weight control as well as smoking cessation.

13.8.9 Temperature Self-Assessment

High-temperature gradients between feet have been shown to precede the onset of neuropathic ulceration. The incidence of ulceration can be significantly reduced by daily at-home patient self-monitoring of foot temperatures [29].

13.8.10 Fat Pad Augmentation

Injectable silicone oil has been used in attempts to increase the thickness of tissue on the plantar surface of the foot and reduce peak foot pressures [29]. There is currently no evidence to prove that fat pad augmentation improves outcomes such as ulceration or amputation.

13.8.11 Specialist Shoes

An orthotist or specialist shoemaker should be available to assess and/or provide suitable footwear for patients with neuropathic foot ulcers. The footwear should protect the foot from trauma while ensuring that blood flow to the foot is not compromised.

13.8.12 Amputation

Surgical amputation may become necessary if there is overwhelming infection of the limb or the limb is deemed unsalvageable.

Other indications for amputation include uncontrollable neuropathic pain; a debilitating, non-healing, long-term ulcer; or a useless or disabling infected foot.

Approximately 50 % of patients who have an amputation will develop an ulcer on the contralateral foot within 18 months of the amputation [22].

Conclusion

The presence of peripheral neuropathy reduces the body's sensation of painful stimuli, while autonomic neuropathy erodes some of the natural defenses, further contributing to the insult on the integrity of the skin. The result is slow ulceration, most commonly over pressure points, where these stresses are accentuated. Diabetes mellitus is the most commonly implicated disease in the development of neuropathic foot ulcers. Of those with the condition, 25 % will go on to develop an ulcer. This has huge implications for both the patient and the financial pressures on a resource-constrained health system especially with the rising prevalence of diabetes worldwide.

An appreciation of both intrinsic and extrinsic factors is essential in the assessment of any ulcer in a diabetic patient and allows differentiation between neuropathic, arterial, or venous ulcers. Further attention to signs of infection is important in determining their severity and any complications that may be contributing to their presentation, such as osteomyelitis.

Optimal management is achieved by a multifaceted multidisciplinary approach including education, debridement, infection control, improving diabetic control, and reducing risk factors. Severe cases may require amputation. Adjunctive therapies are relatively new developments, and evidence for their efficacy will become clearer with their increasing use.

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