Necrobiosis lipoidica (NL) is an uncommon granulomatous inflammatory skin problem, which can be associated with diabetes mellitus (DM). NL typically appears in the third and fourth decade of life. More than half of NL patients are women and up to two thirds have DM at presentation.1,2 It should be noted that less than 1% of all diabetic patients develop NL.3 The majority of lesions occur on the lower limbs with up to 88% affecting the pretibial area. Three quarters of the lesions are bilateral and more than half of patients have multiple lesions.1 Other disease sites include thigh, upper arms and face.2 Most lesions are asymptomatic and cosmetic disability is often the greatest concern.4 Ulceration is more common in men5 and may be present in up to one third of patients.1,3 Ulceration may occur in large areas and frequently begin with minor trauma. External trauma is reported as an associated precipitant.
in up to 43% of patients. Up to a fifth of NL lesions spontaneously resolve varying between one to 34 years after onset.

**Diagnosis**

In the majority of cases, NL can be diagnosed clinically. It is useful to recognise the distinctive yellow discolouration, which may be evident in some lesions. At times, the diagnosis may not be obvious and a skin biopsy is warranted. It should be noted that skin biopsies taken from the lower legs are not without potential complications, particularly if diabetes and impaired peripheral circulation are present.

Histopathologically the epidermis of NL lesions is usually normal. The dermis often shows patches and bands of necrosis scattered throughout mid to lower layers. There may be a loss of elastic tissues. Around blood vessels, various cellular infiltrates and a granulomatous response. The exact pathophysiology of NL is currently unknown.

Defective neutrophil migration has been implicated in the pathogenesis of granulomatous inflammatory diseases including NL. NL may be related to defective collagen fibrils as well as decreased collagen synthesis. Electron microscopy studies reveal loss of cross-striation of collagen fibrils and a marked variation in the diameter of individual collagen fibrils. Histopathological examination showed vasculopathy with inflammation and thickening of vessel walls, at times leading to occlusion. Direct immunofluorescent microscopy suggests that an immune-complex vasculitis may be involved in NL pathogenesis. NL is frequently associated with other chronic complications of DM. Non-enzymatic glycosylation or other changes in collagen may be important in the aetiology of NL.

**Pathophysiology**

NL predominantly affects the dermis, but can also affect deeper fat layers. NL is characterised by collagen and elastin degeneration, cellular infiltrates and a granulomatous response. The exact pathophysiology of NL is currently unknown.

**Presentation**

Active NL often manifests shiny, round or oval lesions over the pretibial region with red, yellow and white as the key diagnostic colours (Figure 1). Usually over months or longer, NL lesions enlarge and progress to become plaques with yellow atrophic centres, surface telangiectases and an erythematous border that may be raised (Figure 2). Chronic lesions tend to become softer, less sclerotic and more atrophic. The colour then evolves to a post-inflammatory and mottled brownish hue (Figure 3). NL lesions are generally asymptomatic until ulceration occurs (Figures 4 and 5).
infiltrates including lymphocytes, histiocytes and occasional plasma, epithelioid and giant cells may be present. Neutrophils are often present if there is ulceration or infection. Vessel wall may be thickened with occasionally a loss of vessel lumen. Mucin deposits are absent or minimal in NL as opposed to granuloma annulare.

**Differential diagnosis**

Differential diagnosis of NL includes granuloma annulare (Figure 6), posttraumatic fibrosis, morphoea, sarcoidosis, stasis dermatitis, ecthyma, rheumatoid nodule, panniculitis, syphilis, tuberculid and xanthoma. Occasionally, lesions with clinical features of both NL and granuloma annulare co-exist in the same patient.

**Treatment**

A simple and effective cure for NL is lacking. For satisfactory outcomes to be achievable, a sound and committed doctor-patient relationship is vital. The crucial therapeutic components include the management of risk factors, management of
symptoms and management of active lesions with and without ulceration.

**Management of risk factors**

Local trauma, including surgery, can precipitate and exacerbate NL. Other risks would include contact sports such as hockey and tattooing. At this point of ongoing research, prospective data about the relationship between trauma prevention and incidence of NL are much needed.

Meanwhile, NL has been shown to be associated with poor glycaemic control. New continuous subcutaneous insulin infusion devices (CSII) are becoming more widely available, although they are expensive. A Cochrane meta-analysis comparing CSII versus multiple insulin injections in Type 1 diabetics showed a statistically significant difference in glycosylated haemoglobin A1c (HbA1c) improvement, favouring CSII. It will be interesting to see the effects on diabetic complications including skin diseases such as NL when long-term data become available.

**Management of symptoms**

Discomfort and disfigurement are common concerns of NL patients, especially amongst young women. Unfortunately there is limited literature about the impact and management of these issues. The use of oral analgesia may be required for local pain associated with ulceration. In terms of cosmetic appearance, referral to a camouflage or makeup specialist may be appropriate. Topical retinoids in carefully selected patients may also be useful. In sunny countries such as Australia, sunscreens need to be considered. Pulsed dye laser treatment may improve telangiectasia but care should be taken to avoid skin breakdown.

**Local management**

**Surgery**

Surgery treatment is uncommonly used, especially as first line therapy. Earlier studies showed mixed responses for surgical intervention. Muller and Winkelmann described five out of six patients relapsing after surgery and concluded surgical intervention to be ineffective. In contrast, a small series reported 100% response rate in six patients treated with excisions down to the deep fascia. It is the senior author’s opinion that, in general, surgery should be regarded as a last resort when other measures have failed. Furthermore, recurrence of NL after surgical treatment is a real concern, which can be difficult to manage (Figure 7).

**Dressings**

Treatment should include appropriate moist wound healing with hydroactive gels or occasional hydrocolloid dressing. Heavy discharge may be treated with absorptive dressings such as calcium alginites, particularly when bleeding is a problem. In general, non-adhesive materials should be used.

*Figure 6. Typical granuloma annulare.*
Topical corticosteroids

Topical steroids can be useful as initial treatment of NL, after a correct clinical diagnosis has been made. In most cases, a skin biopsy is not necessary and treatment can be commenced with ongoing clinical review. Frankly infected lesions need to be treated with appropriate antibiotics and they should not be managed under plastic occlusion. Moist and superficially ulcerated NL lesions can be treated with dilute aqueous acetic acid solutions. Once the infection has cleared, a relatively potent topical steroid ointment can be applied, particularly along the active border of the lesions. The steroid preparation should not be applied under occlusion over long periods to avoid excessive atrophy. If progress is unsatisfactory, intralesional steroid injections may need to be considered.

Intralesional corticosteroids

Intralesional corticosteroid therapy was recognised early as an effective treatment in selected patients. Amongst five patients treated with intralesional triamcinolone, three patients achieved complete resolution. The injections may halt expansion of the lesions but they should be avoided in frankly infected lesions. Moreover, the injections need to be administered at the correct depth level to achieve optimal result and minimise atrophy.

Psoralen and ultraviolet A (PUVA)

PUVA treatment may be effective in a proportion of ulcerative and non-ulcerative NL patients. A prospective study of 30 NL patients whom failed topical corticosteroids showed 17% of patients had complete clearance after a mean of 22 cycles and 37% of patients had significant improvement after a mean of 23 cycles. Smaller studies have shown similar results with up to 24 months follow-up. NL may recur in 20% of patients after 24 months, which is often responsive to further topical PUVA treatment. These treatments are not suitable for patients with a past history of skin cancers, especially melanoma.

Systemic therapy

Systemic steroids

Systemic corticosteroids remain controversial in NL treatment. Systemic corticosteroids may destabilise glycaemic control and adjustment of diabetic medications may be required. Corticosteroid therapy has been shown to be effective in several small studies. The first and largest series described complete resolution in six patients, including four diabetics, with non-ulcerating NL with mean follow-up of seven months. Oral methylprednisolone was rapidly tapered and stopped over two weeks. Half of the diabetic patients required adjustments in their diabetic treatment due to hyperglycaemia. Further success has been reported in non-ulcerating, and ulcerating NL.
Pentoxifylline

Pentoxifylline is a vasoactive drug that is commonly used in peripheral vascular disease. It not only inhibits platelet aggregation but is also believed to decrease blood viscosity by increasing fibrinolysis and red blood cell deformity. Pentoxifylline has been reported to be effective in non-ulcerating, and ulcerating NL. Improvements in size, colour and ulceration began at one month. The positive response was sustained at 10-24 months of follow-up.

Antimalarials, cyclosporin and infliximab

Antimalarials have immunosuppressive and anti-inflammatory effects. Nguyen et al. first reported complete resolution of painful NL using chloroquine. Kavala et al. demonstrated significant improvement in ulcerating NL using hydroxychloroquine.

Cyclosporin blocks the activation of T lymphocytes and the production of inflammatory cytokines. Oral cyclosporin has been shown to be effective in recalcitrant ulcerating NL. The main side effect is hypertension. Complete resolution in two patients with treatment resistant ulcerating NL occurred by three months. The addition of cyclosporin to pentoxifylline resulted in complete healing of severe recalcitrant ulcerating NL. The lesions healed completely over eight months. Further ulceration occurred three months after discontinuing cyclosporin, with improvement on re-introduction. Cyclosporin may be considered in selected patients without significant renal disease and hypertension.

Infliximab is an anti-TNF agent used in the treatment of inflammatory skin conditions including psoriasis. Kolde et al. first reported significant clinical improvement in a young diabetic man with ulcerating NL treated with infliximab. The treatment was stopped prematurely due to reactivation of tuberculosis. Intralesional infliximab was trialled in three patients with two patients achieving almost complete remission for 18 months. The true value of these therapeutic manoeuvres requires additional research to establish.

Hyperbaric oxygen therapy (HBOT)

HBOT has been used for the treatment of chronic non-healing wounds. The mechanism of action is complex but may be due to reduced matrix metalloproteinase activity through redox dependent mechanisms. Complete resolution of ulceration was demonstrated in a diabetic patient after 98 sessions. Moreover, HBOT in combination with topical corticosteroids may be trialled in selected patients. Although HBOT is considered to be safe if the therapy sessions adhere to protocols, complications including barotrauma, neurological oxygen toxicity and reversible myopia can develop.

Pancreatic transplantation

It is time to consider novel therapies. Given the known pathophysiology of NL and its association with DM, it is at least theoretically plausible that pancreatic transplantation may be effective in the treatment of NL. The concomitant effects of immunosuppressive therapy and improved skin microcirculation secondary to improved glycaemic control could explain clinical remission of NL lesions. Gullo et al. reported a case of combined pancreatic and renal transplant in a 35-year-old male type 1 diabetic with end stage renal disease and recalcitrant NL. The transplant maintained satisfactory glycaemic control without the need for exogenous insulin. His chronic resistant and progressive NL healed without any additional treatment with only small areas of scarring. In a retrospective review of NL patients with transplants, resolution of NL was seen in 45% of the patients with pancreatic transplantation with or without renal transplantation. We will have to watch this space.
**Conclusion**

NL can be difficult to manage. However it is an important, worthwhile and often rewarding challenge. NL adds complexity and increases disease burden in diabetic patients who may already have diabetic-related complications. The disease may be chronic and treatments, especially the more recently trialled and developed modalities, are not inexpensive. This can become yet another burden some diabetics have to endure. The disfigurement due to NL is an at times under-recognised source of stress and anxiety for the sufferers. Young females with obvious disfiguring lesions on the lower limbs may have depression as a result of limited work and social opportunities. Confidence can be undermined. When the lesions become advanced and badly ulcerated, pain can be distracting or debilitating. This has sometimes been overlooked by physicians and carers, and the skin lesions are downgraded to "just" leg ulcers.

With more modern therapies becoming available and hopefully affordable as well, the outlook for patients with NL should be good if not brilliant. Ongoing research and development are vital, and support from governments and communities needs to be strong and easy to access. Diabetes is not yet curable but NL is certainly treatable. Let us advance the care of NL and uplift the lives of the unfortunate sufferers so afflicted.

**References**

21. Patel GK, Mills CM. A prospective open study of topical


