International Journal of Lower Extremity Wounds

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The International Journal of Lower Extremity Wounds

Why Another?

The announcement of another wound care journal, The International Journal of Lower Extremity Wounds (IJLEW) in this case, usually evokes a medley of responses; from the groans of those straining under an information deluge and increasing workload to the glee of those who feel underrepresented—most frequently specialists. Why a new journal focused on lower extremity wounds? The reason is simple: wounds are a major clinical challenge. Wounds, especially chronic wounds, are a vast global problem. The worldwide prevalence of wounds is believed to be 1% of the world population. Most organs are liable to be affected by wounds; the lower extremities of our bodies are especially susceptible to them. Acute wounds—caused by trauma—usually follow an acceptable healing course. Chronic wounds are slow to heal and recur frequently.

Leg ulcers are most commonly caused by venous disease, whereas foot ulcers mainly result from arterial disease, diabetes, or both. The clinical management of chronic wounds can be frustrating for both the patient and the health provider, and resource implications are staggeringly high. Venous ulcers annually cost the U.K. National Health Service £600 million (US $840 million). Add the cost of diabetic foot ulcers, which can significantly increase morbidity through limb loss and, occasionally, death, and the consequences of ignoring chronic wounds grimly tower over our communities.

Chronic wounds deserve greater attention not only because of an increasing prevalence of diabetes globally but also because of an aging population in Western societies; there is a growing burden for everyone in society to shoulder. Have there been advances applicable to the clinical management of lower extremity wounds? Should we indulge in more systematic reviews? Of course there have been advances in concepts; putting advances into practice calls for strategic research and development. Wound research has been sadly neglected by major funding agencies, and this is discouraging. Wound healers should be encouraged by developments in another chronic disease entity—osteoporosis. During the last 20 years, as therapeutic advances were taking place in laboratories, it became possible to quantify the risk of hip fracture—common in patients with osteoporosis. By measuring bone mineral density, it is possible to predict hip fractures and treat to prevent them. Reducing complications aids resource planning as well as disease management. This success should invigorate wound specialists into studying the effects of preventable and modifiable risk factors for chronic wounds. Risk factor modification is applicable to diabetic as well as venous ulcers.

Who works on lower extremity wounds? Vascular surgeons, diabetic physicians, podiatrists, nurses specializing in wound care, orthopedic surgeons, orthotists, angiologists, phlebologists, and not the least, vascular and pathology laboratories, all get involved. Some rarer lesions, but chronic wounds no less, invite the opinion and support of rheumatologists and gastroenterologists. Clearly the wound management fraternity is large and, definitely, multidisciplinary. A multidisciplinary model of wound care has been developed in Denmark with success. It is also a major descriptor for this new journal. Fittingly, the inaugural issue of this journal presents reviews of basic and applied research, clinical reviews, and the opinions from 2 clinical scientists who have devoted much of their lives to studying wound healing.

IJLEW will feature original as well as teaching reviews and longer seminar papers since it is envisioned as a “rolling textbook.” It is timely that IJLEW is launched to inform, educate, and provoke wound workers, so that the pathway to progress is energized for the benefit of those who suffer, and those who care.

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Deep vein thrombosis (DVT) leads to venous ulcers in later life. Venous ulcers are the majority of chronic lower extremity wounds. Recent evidence suggests that hyperhomocysteinemia is an independent risk factor for venous thrombosis. Other evidence suggests that dietary supplementation with folic acids and vitamins helps to change hyperhomocysteinemia. This may be the key to wound management in the future.

Key words: hyperhomocysteinemia, venous thrombosis, folic acid, vitamin B₁₂, oxyradicals, coagulation

Hyperhomocysteinemia has been implicated as a risk factor for atherosclerosis, arterial and venous thrombosis, and cardiovascular disease. This review deals with the synthesis and metabolism of homocysteine, mechanism of hyperhomocysteinemia-induced venous thrombosis, and measures to reduce plasma homocysteine levels.

Deep venous thrombosis (DVT) is an initiating event leading to venous hypertension, which in turn leads to biochemical and microvascular changes that are associated with venous leg ulcers. Venous ulcers are a chronic problem in many societies in the world.

DEEP VENOUS THROMBOSIS

Deep venous thrombosis is the result of clot formation in a vein at sites of reduced blood flow. Arterial thrombosis, on the other hand, involves the formation of platelet aggregates at high shear rates at sites of vessel wall injury. The established genetic risk factors for thrombosis include factor V Leiden (resistance to activated protein C [APC]), prothrombin, and deficiencies in antithrombin, protein C, and protein S. Laboratory phenotypes such as elevated fibrinogen, antiphospholipid antibodies, and mild hyperhomocysteinemia are associated with venous thrombosis. Recently, elevated plasma levels of factor VIII have been implicated in the pathogenesis of venous thrombosis.

HOMOCYSTEINE SYNTHESIS AND METABOLISM

Homocysteine is a sulfur-containing amino acid derived from methionine. Synthesis and metabolism of homocysteine involves demethylation, transmethylation, and transsulfuration processes (Fig. 1). Demethylation converts methionine to homocysteine through intermediate metabolites, S-adenosyl methionine, and S-adenosylhomocysteine. In the transmethylation process, homocysteine is remethylated to methionine. In this process, methionine is catalyzed by methionine synthase, which uses vitamin B₁₂ as a cofactor and methyltetrahydrofolate as a substrate. In this process, methyltetrahydrofolate is converted to methylenetetrahydrofolate. Methylenetetrahydrofolate reductase converts methylenetetrahydrofolate to methyltetrahydrofolate. In the transsulfuration process, homocysteine is converted to cysteine through cystathionine. Conversion of homocysteine to cystathionine is catalyzed by vitamin B₁₂-dependent cystathionine β-synthase. Cystathionine is hydrolyzed to form cysteine, which is excreted in the urine as sulfate after further metabolism.
Normal fasting plasma levels of homocysteine are 5 to 15 µmoles/L. Approximately 70% of plasma homocysteine is bound to serum protein. Hyperhomocysteinemia is defined as a plasma level of homocysteine greater than 15 µmoles/L.

**FACTORS FOR HYPERHOMOCYSTEINEMIA**

Hyperhomocysteinemia is due to a deficiency in enzymes or vitamins, disease states, and drugs. Detailed description of causes of hyperhomocysteinemia is given in a review by Prasad. Hyperhomocysteinemia develops because of a defect in the gene for cystathionine β-synthase, methionine synthase, or 5, 10-methylenetetrahydrofolate reductase. Deficiencies in vitamin B₆, vitamin B₁₂, and folic acid, which are involved in the transsulfuration and remethylation processes of homocysteine metabolism, also cause hyperhomocysteinemia. Dietary intake of vitamin B₆, vitamin B₁₂, and folic acid is inversely correlated to plasma homocysteine. Hyperhomocysteinemia is associated with pernicious anemia and several types of carcinoma including breast, ovary, and pancreas. Homocysteine levels in plasma are elevated in diseases (chronic renal failure, coronary artery disease, hypertension, hypothyroidism, venous thrombosis, acute lymphoblastic leukemia, stroke, diabetes) and with the use of certain drugs (methotrexate, phenytoin, nitrous oxide, L-dopa, cholestyramine, niacin).

MECHANISM OF HYPERHOMOCYSTEINEMIA-INDUCED COAGULOPATHY

Endothelial cell surface glycosaminoglycans and thrombomodulin both serve as potent inhibitors of coagulation, while prostacyclin and plasminogen activators generated from the vessel wall limit platelet plug formation and fibrin deposition. Several other procoagulant properties of endothelial cells have been described.

Pathogenesis of increased thrombogenicity associated with hyperhomocysteinemia is not completely understood. Hyperhomocysteinemia could produce thrombosis through various mechanisms: (a) acting directly to increase the activity of coagulation factor and/or decrease of anticoagulant factors; (b) through release of reactive oxygen species (ROS); and (c) endothelial cell injury with subsequent impairment of the antithrombotic properties of the vessel wall.

**Homocysteine and Coagulation**

Schema of the effects of homocysteine on the coagulation pathway are presented in Figures 2 and 3. Homocysteine increases platelet activity and aggregation and adhesion. McDonald et al suggested that thrombosis might be related to abnormal platelet adhesiveness.

Homocysteine activates factor V and this results from induction of an activator of factor V. Factor V is a
critical regulatory cofactor in the coagulation mechanism. Activation of factor V by thrombin results in an approximate 30-fold increase in activity.\(^4\) Homocysteine activates factor XII\(^4\) and inhibits von Willebrand Factor (vWF) processing and secretion.\(^4\) vWF is an important factor in modulation of factor VIII.\(^4\) High factor VIII levels are caused by a rise in vWF. Inhibition of vWF would then cause a decrease.

**Reactive Oxygen Species and Coagulation**

Homocysteine could generate ROS spontaneously.\(^5\) Sulphydryl group of homocysteine is believed to act catalytically with ferric or cupric ions in a mixed function oxidation system to generate hydrogen peroxide, oxygen radicals, and homocysteine radicals.\(^4\) Superoxide anion, hydrogen peroxide, and hydroxyl radical are produced during auto-oxidation of homocysteine.\(^5\) Using chemiluminescence, Lang et al.\(^5\) showed that exposure of cultured endothelial cells to homocysteine causes an increase in the intracellular generation of superoxide anion. ROS generated by homocysteine could produce thrombosis through various ways. ROS is known to stimulate tissue factor\(^5\) and to induce tissue plasminogen activator (t-PA) synthesis but not plasminogen activator inhibitor-1.\(^5\) These effects of ROS would produce thrombus formation. This is supported by the facts that superoxide anion and singlet oxygen produced by bengal rose produced thrombus\(^5\) and that activated leukocytes contribute to disseminated intravascular coagulation and thrombosis. Inhibition of vWF by homocysteine would work against clotting for 2 reasons. First, vWF is necessary for normal adherence of platelets at a site of injury. Second, vWF forms a complex with factor VIII and regulates its plasma levels. Binding of vWF to factor VIII stabilizes factor VIII in circulation. Inhibition of vWF by homocysteine would lower factor VIII. This is sup-

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Fig. 2.  *Effects of homocysteine on clotting mechanism.*

PF-3 = platelet factor 3; HCY = homocysteine.
ported by the fact that patients with deficient vWF also have low levels of factor VIII. However, a substantial percentage of high factor VIII levels is not completely vWF-mediated.\(^{46}\) Elastase from neutrophils activates factor V.

Venous thrombosis associated with hyperhomocysteinemia could also be due to decreased anticoagulation mechanism. This decrease in anticoagulation could be mediated by decrease in thrombomodulin, protein-c activation, heparan sulfate expression, and t-PA. A schema for the effects of homocysteine on coagulation pathways is shown in Figure 3.

Thrombomodulin is an endothelial cell surface glycoprotein that promotes activation of anticoagulant protein-c and inhibits the procoagulant activities of thrombin. Protein-c is activated when thrombin binds thrombomodulin, and activated protein-c inactivates factors Va and VIIIa, and inhibitor of t-PA. t-PA converts plasminogen to plasmin, which lyases the fibrin. Homocysteine plays a major role in preventing fibrinolysis. Homocysteine directly inhibits the cofactor activity of thrombomodulin on the endothelial cells by reducing the disulfide-bond-rich epidermal growth-like structure of thrombomodulin.\(^ {47}\) It inhibits both thrombomodulin surface expression and protein-c activation.\(^ {50,51}\) It activates factor V in high concentration.\(^ {52}\)

Homocysteine inhibits expression of anticoagulant heparan sulfate by endothelium.\(^ {60}\) This effect is mediated by generation of hydrogen peroxide through alteration of redox potential. Heparan sulfate (antithrombin III) binds to thrombin and inhibits it. Homocysteine blocks t-PA binding to human endothelial cells.\(^ {61}\)

Vascular Injury

Homocysteine causes endothelial cell injury.\(^ {62-64}\) Dysfunctional endothelium would lead to a decrease in the synthesis and release of prostaglandin I\(_2\) and nitric oxide (NO), which are inhibitors of platelet adhesion and aggregation. Decreased bioavailability of NO with endothelial dysfunction has been shown by Stamler et al.\(^ {49}\) Damage of endothelium exposes the underlying
layer of collagen, which attracts platelet for platelet aggregation.

**VENOUS THROMBOSIS AND HYPERHOMOCYSTEINEMIA**

Venous thrombosis is a common disease with an incidence of 0.1% to 0.2% per year. An estimated 500,000 cases of deep venous thrombosis occur in the United States every year. This condition is a major cause of mortality because of pulmonary embolism and morbidity in the form of chronic venous insufficiency. Deep venous thrombosis occurs in the deep vessels of the arms, legs, and visceral veins. Venous thrombosis can result from any combination of venous stasis, venous endothelial damage, and hypercoagulable state.

The common causes of venous thrombosis include acquired factors (cancer, fractures of leg, knee or hip operations, use of oral contraceptives, and immobility); hereditary factors such as deficiencies of protein-c, protein s, and antithrombin; increased thromboplastin generation time; high level of Factor VIII; and mutations in Factor II gene and in Factor V gene, resulting in activated protein-c resistance. Recently emphasis has been put on the homocysteine as a major risk factor for venous thrombosis. A common and frequently lethal complication of hyperhomocysteinemia is arterial or venous thrombosis.

Prevalence of venous thrombosis in patients with homocysteinuria was first described by Mudd et al. It was not until 1991 that the first association between hyperhomocysteinemia and venous thrombosis was reported. Thereafter, numerous clinical studies have been carried out that provide the evidence in favor of the link between hyperhomocysteinemia and venous thrombosis. Most of these studies concluded that hyperhomocysteinemia is a risk factor for venous thrombosis.

**Retrospective Studies**

In a meta-analysis of 10 case control studies, the pooled odds ratio for venous thrombosis was 2.5 for fasting hyperhomocysteinemia and 2.6 for postmethionine load hyperhomocysteinemia. The pooled odds ratio for DVT in hyperhomocysteinemia was reported to be 4.37 when patients over 60 years of age were excluded from the studies. In these studies, hyperhomocysteinemia was defined as levels of above the 95th percentile, or 2 standard deviations above the mean. Fasting hyperhomocysteinemia was observed in 11% of the patients with a first DVT in comparison to 4.9% in the control individuals. Hyperhomocysteinemia is a common risk factor for recurrent venous thrombosis. Patients with hyperhomocysteinemia have most frequent thrombotic complications such as DVT. A plasma homocysteine concentration of more than 22 µmoles/L increased the matched odds ratio for DVT to 4.0. Plasma homocysteine concentrations of patients (25%) with recurrent venous thrombosis were high during fasting as well as during methionine loading tests. The combination of hyperhomocysteinemia and factor V Leiden further increases the relative risk of venous thromboembolism up to 3.6-fold.

Two studies showed that patients with plasma homocysteine levels above the 95th percentile had a risk of venous thromboembolism twice that of patients with lower levels. Falcon et al reported a high prevalence of hyperhomocysteinemia in young adults with DVT or pulmonary embolism. However, no association between homocysteine levels and risk of venous thromboembolism has been reported.

**Prospective Studies**

Prospective studies to date have been very few. Ridker et al in a study of 14,916 healthy individuals followed for 10 years reported that individuals with moderate hyperhomocysteinemia and factor V Leiden are at significantly increased risk of developing venous thromboembolism compared with men with neither or only one of these defects. Compared with men with neither abnormality, those affected with both defects had a 10-fold increase in risk of any venous thromboembolism and a 20-fold increase in risk of idiopathic venous thromboembolism. In a multicenter study, 264 patients with single episode idiopathic venous thromboembolism were prospectively followed after discontinuation of oral anticoagulant. Recurrent deep venous thrombosis was observed in 18.2% of patients with hyperhomocysteinemia compared to 8.1% of patients with normal homocysteine levels. The relative risk of recurrent deep vein thrombosis in patients with hyperhomocysteinemia was 2.7%. No association was reported in patients with systemic lupus erythematosus.

Petri et al investigated the association between homocysteine and risk of stroke and thromboembolic events in 337 patients with systemic lupus erythematosus (Hopkins Lupus Cohort Study), with follow-up of 4.8 ± 1.7 SD years. After adjustment for established risk factors, total plasma homocysteine was found to be an independent risk factor for stroke and arterial thrombosis. An increase of one log unit of homocysteine con-
centration led to a 2.4-fold increase in the risk of stroke and a 3.5-fold increase in risk of arterial thrombosis.

**THERAPEUTIC REGIMEN OF HYPERHOMOCYSTEINEMIA**

The method of treating elevated homocysteine levels in plasma remains a matter of controversy. Reduction of dietary methionine would be the appropriate approach in lowering plasma concentration of homocysteine; however, it is severely limiting and virtually impossible to comply with. The effective way of decreasing plasma homocysteine concentrations is the treatment with vitamins (folic acid, vitamin B₁₂, vitamin B₉) because they are involved in the metabolism of homocysteine. Folic acid decreases the plasma concentrations of homocysteine in normal subjects and in patients with vascular disease and chronic renal failure.¹¹ Chauveau et al.¹² used folic acid (10 mg/day) and vitamin B₁₂ (70 mg/day) and concluded that folic acid but not vitamin B₁₂ was effective in lowering plasma homocysteine concentrations. Folic acid in the doses of 0.4, 1.0, or 5.0 mg daily for 3 months reduced the homocysteine concentration by 30% in all treatment groups (coronary artery disease) but remained unchanged in the placebo group.¹³ Various doses of folic acid (0.4-10 mg/day), vitamin B₁₂ (1 mg/day), and vitamin B₉ (5-300 mg/day) have been used for reduction of homocysteine concentration in plasma.¹⁷,⁹¹ Treatment with folic acid alone reduces homocysteine levels in plasma by 40% to 50% within 6 weeks.⁹² Vitamin B₁₂ reduces the plasma homocysteine to a maximum of 10% to 15%.⁹³ In another study (Homocysteine Lowering Trialists’ Collaboration, 1998), after standardizing to pretreatment levels of 12 µmol/L for homocysteine and 12 nmol/L (the average concentrations in Western populations) for folate, folic acid (0.5-5 mg daily) reduced the homocysteine concentrations by 25%. The addition of vitamin B₁₂ (0.5 mg daily) produced an additional reduction of 7%; however, addition of vitamin B₉ (16.5 mg daily) had no effect.⁹⁴ The differences in the efficacy could be due to differences in the doses used. In a placebo-controlled study, folic acid in the dose of 127 µg daily increased the plasma folate by 31%, but the decrease in the plasma homocysteine was only 3.7%.⁹⁵ They also showed that high levels of folic acid 499 µg and 665 µg intake daily in cereals decreased the plasma homocysteine levels by 11% and 14%, respectively.

In a recent Farmingham offspring study in 350 subjects, Jacques et al.⁹⁶ showed that cereal fortification increased the plasma folate concentration from 11 to 23 nmol/L and decreased the homocysteine concentrations from 10.1 to 9.4 µmol/L. den Heijer et al.⁹⁷ studied the effects of combined folic acid (5 mg), vitamin B₁₂ (0.4 mg), and vitamin B₉ (50 mg) in patients with recurrent venous thrombosis. They showed that combined vitamin supplementation effectively reduced and normalized homocysteine levels in patients with recurrent venous thrombosis. They also showed similar effects in hyperhomocysteinemic (homocysteine level >16 µmol/L) volunteers. Folic acid (at a dose of 5 mg or 0.5 mg) in a subgroup of normohomocysteinemic volunteers was as effective as high-dose multivitamin supplementations. Oral vitamin B₁₂ had only moderate effects on the homocysteine level.

It appears that folic acid is the cornerstone in the treatment of hyperhomocysteinemia and that there are reasons for using vitamin B₁₂ and vitamin B₉. Combinations may have stronger effects in subjects with low vitamin B₁₂ and vitamin B₉ levels. Also folate administration alone might mask vitamin B₁₂ deficiency (subacute combined degeneration of the spinal cord, pernicious anemia). Mutation of the methylenetetrahydrofolate reductase (MTHFR) gene is associated with elevated levels of plasma homocysteine. Homocysteine lowering effect of folic acid in subjects with MTHFR gene mutations is even stronger than in those without this mutation.

**SUMMARY**

Mohr⁹⁸ identified skin and trophic changes as risk factors in a population that had suffered deep vein thrombosis either as single or multiple episodes. This review highlights the importance of studying the association between high homocysteine levels, DVT, and therefore venous leg ulcers. It also examined the benefits of improved nutrition by increasing intake of foliates. This line of thought must be pursued if we are to improve our understanding and management of venous ulcers, which are the majority of lower limb wounds.

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HYPERHOMOCYSTEINEMIA

Four-layer bandaging has been in existence for more than 15 years, during which time it has been used in numerous studies and in many populations throughout the world. This article will review the development of the system and new evidence contributing to the greater understanding of the effectiveness of the bandaging.

Four-layer bandaging was developed by a clinical group in Charing Cross Hospital, London, to meet the needs for an effective compression system. The concept underpinning the bandage development was the need for sustained compression. The group used Stemmer’s theoretical framework, which suggested that an external pressure of the order of 40 mm Hg at the ankle was required to achieve ulcer healing in chronic venous insufficiency, with lower levels of compression required for patients with varicose veins and higher pressures in those with venous/lymphatic disorders. The development of the bandage system also took account of the considerable clinical problems experienced, such as high levels of exudate, and disproportionate limb sizes and shapes. Reducing the number of clinical visits was also considered ideal. The aim was to develop a system that required only weekly application in the majority of patients. This feature of 4-layer bandaging has contributed to the cost effectiveness of the system through major reductions in nursing time.

Graduated Compression—Mechanisms of Action

In reviewing 4-layer bandaging, it is important to consider the accepted views on the role of compression in promoting venous ulcer healing. Compression is widely accepted as the cornerstone of venous ulcer treatment, based on sound pathophysiological principles, but the exact mechanisms that lead to healing are still understood.

The aim of compression is to reestablish normal transluminal venous pressure by increasing extravascular pressure to a level that is higher than the pressure within the venous system. In applying compression, it is important to take account of the effects of hydrostatic pressure in the upright position, which is of the order of 90 mm Hg at the ankle. The highest pressure must be obtained at the ankle, decreasing up the limb. The taper of legs will result in graduated compression providing that bandages are applied with tension. In the context of incompressible fluids, Laplace’s law relates the surface tension (T) and radius (R) and pressure (P) within a sphere as

\[ P \propto \frac{T}{R}. \]

To apply these considerations to the human leg, which is compressible, it is essential to modify Laplace’s law.

When there is loss of calf muscle altering the natural taper of the legs, it is difficult to achieve graduated compression using the same tension. When this occurs, it must be accommodated for during bandage application. The 4-layer bandage system, during its development, took account of these factors and modified the technique and number of layers based on an assess-
ment of the ankle circumference as well as the limb shape. Many of patients with chronic venous disease have large swollen legs.

Decrease in Edema

Decrease or removal of edema is an important property of an effective compression system. Compression therapy has been shown to improve superficial skin lymphatic function as well as lymph transport within the subfascial system. External compression reduces edema in a number of ways. Compression stimulates lymph formation and therefore lymph flow. Compression may also help capillary ultrafiltration. Removal of edema has been demonstrated by videomicroscopy to increase skin capillary density, though this could be an “unmasking” effect. In other words, decreasing edema permits capillaries to be visualized. Cutaneous metabolism may improve following edema reabsorption due to the enhanced diffusion of oxygen and other nutrients required for cell metabolism in the skin and subcutaneous tissues, though evidence is lacking. Compression may play an important function in preventing the cyclical reperfusion injury that has been postulated to cause venous ulceration. It has also been suggested that one of the important mechanisms of compression is through an anti-inflammatory effect rather than reliance on hemodynamic changes. Compression is thought to promote movement of neutrophils through the microcirculation; this could prevent margination and adherence to the endothelium, and the activation and release of free radicals causing tissue necrosis.

Decrease in Venous Volume

A number of studies have shown that compression decreases the venous volume in the lower limb. Compression may potentially increase venous tone (reduce diameter). Partsch using radioactive methods showed that external pressure of 40 mm Hg reduced venous volume in the horizontal position, and a similar effect was found in the upright position using air-plethysmography.

Reduction in Venous Reflux

One of the most important effects that compression may have is the reduction of venous reflux. When venous valves are damaged, reflux occurs, leading to high ambulatory pressures in the leg veins. Constant changes in position between elevation of a limb and dependency is thought to contribute to the cycles of inflammation leading to reperfusion injury. Limiting these cyclic events could be of importance to ulcer healing. Patients with venous ulceration may have ambulatory pressures in excess of 90 mm Hg.

Four-layer bandaging (elastic) and short-stretch bandaging using inelastic material have been found to decrease venous reflux in patients with proven popliteal deep venous incompetence compared to other long-stretch elastic bandages. The latter would act as a “rigid” structure during calf muscle contraction and limit expansion. This would result in pressure peaks within veins during ambulation.

These findings suggest that 4-layer bandaging acts in different ways, providing a sustained level of compression while acting as a short-stretch regime providing a rigid structure against which the calf muscle contracts forcing pressure inward and resulting in peaks of pressure during exercise. These results are not surprising given the structure of the layers within the system. While layer 3 in all 4-layer systems is highly elastic, with a wide extensible range, the outer cohesive layer has a much shorter extension; this could contribute to the short-stretch effect. The properties of 4-layer bandaging, to sustain the compression level while retaining position on the patient’s limb and its ease of use, have contributed to its success.

Improvement in Venous Pump Function

External compression has been shown to have an important effect on the venous pump, causing an increased expelled volume. Many patients with chronic venous disease have impaired calf muscle pump function. Factors such as reduced general mobility and, more important, ankle mobility may be considered to impact the calf muscle function. Studies have shown that with reduced or absent ankle function, venous ulcer healing is significantly reduced. New evidence suggests that foot deformities such as equinos deformity are extremely common in patients with ulceration with a delay in healing. Patient comfort and acceptability of the bandages is important when considering the effectiveness of compression bandaging. A number of studies evaluating 4-layer bandaging in randomized control trials and cohort populations have shown the important improvements in quality of life and reduction of pain. No explanations were offered to account for these observations.
Changes in Lipodermatosclerosis and the Microcirculation

A number of studies have shown the effect of compression on stimulating fibrinolysis. Removal of protein-rich edema through enhanced lymphatic function is also important in slowing and reversing the proliferation of liposclerotic dermal tissue.

A number of authors have sought to examine the effect of compression on the venous and arterial microcirculation. Mayrovitz and Larsen observed that compression increased arterial pulsatile flow and postulated that this could lead to fewer leucocytes being trapped in the microcirculation. This would be beneficial for tissue nutrition. Pulsatile flow was not maintained when the subbandage pressure fell over time, underlying the need to provide a level of sustained compression.

Reproducibility of Graduated Compression Profiles

Different bandages lead to different gradients along legs and therefore differing levels of compression. There is variability between bandages and bandaging systems, and nurses must be trained in bandaging. The dynamic effects of compression during exercise are under study.

During the development stage of the 4-layer bandage, studies were done to determine the system’s ability to retain pressure over time; the pressures achieved were also reproducible in a range of patients.

Hafner compared 8 different bandage systems on 10 healthy volunteers using an electropneumatic device to measure the subbandage pressure at 12 points on the legs. Four-layer bandaging lost the least pressure over the day (6.00 mm Hg, range 0.0-10.5 mm Hg) compared to short-stretch bandages (18.00 mm Hg, range 16.5-20.5 mm Hg, P = .005). Other authors have shown that elastic regimes are more likely to sustain pressure than inelastic ones.

A number of authors showed that pressures fluctuate during exercise. Partsch noted that 4-layer bandaging was associated with a rise in pressure up to 45 mm Hg during walking but that at rest the pressure never fell below 40 mm Hg. Taylor compared 2 multilayer bandage systems and found variations in pressure related to the position in which the patient was bandaged. Those bandaged in a sitting position with a 90° angle at the knee had accurate pressure gradients, compared to those bandaged in a semirecumbent position. In the latter subbandage, pressures decreased when the patient changed to a sitting position. This was likely due to the changes in calf circumference during contraction and relaxation of the calf muscle. The pressures at the knee and ankle were similar to those achieved in the semirecumbent position.

While of interest, the significance of minor changes in subbandage pressures with changes in position is unknown. The issue is further complicated by the difficulties associated with pressure measurement and the variations between different techniques. In practice, this is likely to be unimportant.

Practical Issues

The methods used to apply 4-layer bandaging have been described. However, in reviewing the concepts underpinning the system, it is important to examine the rationale for how the bandage is applied and ways of adapting it to different patient groups.

Indications for Use

Four-layer bandaging is considered a high-compression bandage system (subbandage pressure 35-40 mm Hg at the ankle) incorporating elastic layers to achieve sustained compression. The system is primarily used in the treatment of venous ulceration and achieves healing in patients with deep and or superficial venous incompetence. Four-layer bandaging may be used in patients unable to wear elastic hosiery, and this could limit recurrence. The added short-stretch effect noted in 4-layer has made this a useful treatment option for lymphoedema, although modifications to the application are required, such as full-length bandages and addition of foam and alternative upholstery material. New indications for the use of 4-layer have been recently reported, including conditions where edema is problematic to wound healing, such as pretibial lacerations and traumatic wounds (Table 1).

During the early stages of the bandage development, the system (sometimes 3 layers) was adapted so that reduced levels of compression could be applied to patients with mixed arteriovenous ulcers. These patients may need medical or surgical treatment as indicated by their vascular disease. A patient presenting with a leg ulcer should have his or her history taken and undergo a clinical examination before the ankle to brachial pressure index is determined using a Doppler ultrasound probe. When arterial or mixed arteriovenous disease is detected, a vascular opinion is needed to determine management.
Contraindications

There are circumstances in which sustained compression is contraindicated.\(^5\) Patients with decompensated congestive heart failure should not receive high-compression bandaging as it might exacerbate their condition. Patients with arterial disease should not receive compression. Patients with mixed arteriovenous leg ulcers have benefited from mild compression. However, due to the nature of the condition, careful supervision is essential. Patients with diabetes mellitus and venous ulcers often do not receive compression therapy. Each patient with diabetes mellitus and leg ulcers should be judged individually. However, it is essential that a correct diagnosis of ulceration is established. Care should be taken before offering sustained compression to patients with peripheral neuropathy as they will not be conscious of pressure on leg or foot skin, which can lead to necrosis. Similarly, patients with rheumatoid arthritis may receive high-compression therapy. Studies have shown that these patients have venous disease with an increased rate of venous filling.\(^7\) The protective function of 4-layer can be helpful in some patients who are highly susceptible to skin trauma with dermal thinning due to regular use of corticosteroids. Compression should be avoided in the small percentage of patients with vasculitic ulceration as this could exacerbate the microcirculatory dysfunction and lead to extensive tissue necrosis.\(^8\)

Patient Assessment

Clearly the most important goal of assessment is to determine the etiology of ulceration. Assessment should include careful wound and skin assessment. Simple contour tracing of the ulcer or photography is a reliable indicator of treatment effect. A number of authors have proposed that the rate of healing in the first few weeks of treatment is predictive of outcome;\(^9\) so far these proposals remain unverified.

<table>
<thead>
<tr>
<th>Table 1. Clinical Indications for Use of 4-Layer Bandaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>Four-layer Treatment of venous ulcers</td>
</tr>
<tr>
<td>Chronic venous insufficiency</td>
</tr>
<tr>
<td>Recurring ulcers</td>
</tr>
<tr>
<td>Other uses</td>
</tr>
<tr>
<td>1. Traumatic wounds with local edema, for example, pretibial lacerations</td>
</tr>
<tr>
<td>2. Lymphoedema</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 2. Recommendations for 4-Layer Bandaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>(based on the current Royal College of Nursing and Sign Guidelines(^4),(^5))</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Pressure</td>
</tr>
<tr>
<td>-----------------------------------------------------------</td>
</tr>
<tr>
<td>Full compression</td>
</tr>
<tr>
<td>ABPI &gt; 0.8 Four-layer bandaging</td>
</tr>
<tr>
<td>35-40 mm Hg</td>
</tr>
<tr>
<td>Reduced compression</td>
</tr>
<tr>
<td>ABPI &gt; 0.7 Three-layer, orthopedic wool, crepe, cohesive layer (layer 4) of 4LB</td>
</tr>
<tr>
<td>ABPI &gt; 0.5&lt; 0.7 Three-layer, orthopedic wool, crepe, long-stretch elastic layer (layer 3) of 4LB</td>
</tr>
<tr>
<td>ABPI &lt; 0.5 Compression contraindicated —</td>
</tr>
<tr>
<td>ABPI = ankle to brachial pressure index.</td>
</tr>
</tbody>
</table>

Studies have found a number of independent factors associated with delayed ulcer healing. These include increased ulcer size, long ulcer duration, levels of general and ankle mobility, and social factors such as living alone and being male.\(^3\) Some studies have found the presence of deep vein incompetence, a history of deep vein thrombosis, and lipodermatosclerosis as predictive of healing, but the results from different studies are often conflicting.\(^3\) The psychological status of the patient in relation to healing has not been examined systematically. New research has found that social isolation, levels of pain, and clinical depression are associated with delayed healing and supports the need for a comprehensive patient assessment.\(^5\) Pain occurs in some 80% of patients with venous ulceration, and practitioners frequently fail to assess or treat appropriately.\(^6\)

The quality-of-life research in this field has shown that pain reduces with compression, although a slight increase may occur during the first weeks of application.\(^2\) Patients should be warned of this fact and be advised to take regular analgesia and rest with their legs elevated. Successful use of compression requires attention to these issues. Patients must be psychologically prepared and committed to receive treatment as well as understanding the significance of compression as the central treatment modality. While practitioners frequently describe these patients as poorly compliant with compression, there is little evidence for accepting this view.\(^5\) Gaining patient acceptance of therapy is as
much the responsibility of practitioners as it is of patients.

It is beyond the scope of this article to review appropriate skin care and dressing selection. Skin hydration remains a priority, avoiding products that may cause contact dermatitis. Patients should be tested for contact allergy when indicated. The research on the use of dressings in venous ulcer healing has found little evidence that one dressing type is superior to another or that healing rates can be substantially altered provided adequate compression is used. For the majority of patients, simple, nonadherent dressings that avoid trauma to both the wound and surrounding skin are recommended.

In use, limbs should be assessed to identify foot deformities or deformed gait, as this may modify the way bandages are applied. For proper use, ankle circumference must be measured to ensure the correct combination of bandages is used and any change in the normal contour of the limb noted.

Normal Application of 4-Layer Bandaging

Table 3 outlines the application issues relating to 4-layer bandaging systems. It is important to stress that numerous multilayer combinations are mentioned in the literature and many of these do not have the same characteristics of generic 4-layer systems. The careful design of the original Charing Cross 4-layer was based on a thorough knowledge of the compression profiles of each bandage and of their combined effect, which have provided a template for other systems that have since developed. It is often assumed that any combination of bandages constitutes a 4-layer bandage system. Bandages may be designed to apply higher levels of pressure using one layer alone (subbandage pressure 35-40 mm Hg at the ankle), and developing multilayer systems using these could be counterproductive.

It is debated whether elastic bandages should be applied over the foot. In the 4-layer system, the elastic layers are applied with extension from the base of the toes to prevent foot edema. Many patients develop lymphoedematous changes of the toes. This may be overcome by bandaging the toes with a light, mildly extensible cotton bandage.

The orthopedic padding incorporated into the 4-layer systems is now considered essential beneath any compression bandage. Areas at risk of high pressure include the dorsum of the foot. It is important to note that compression damage is a well-known adverse frequent event and in extreme cases may result in reconstructive surgery or death in patients with concurrent arterial disease. The orthopedic wool layer must protect all vulnerable sites on the foot and limb. Damage to the Achilles tendon area may result from bandage slippage and subsequent pressure. The tibial crest is frequently subjected to high levels of pressure as evidenced on bandage removal in some patients with thin limbs but may also occur in men with a prominent tibial crest and little overlying subcutaneous tissue. Pleating of the orthopedic wool or addition of a strip of wool over the area is an easy way of overcoming problems. Addition of a light cotton tubular bandage next to the skin may be needed in patients particularly prone to varicose eczema; the padding layer must cover all vulnerable areas. Extra orthopedic wool may be used to recontour a limb with reduced calf muscle.

The crepe bandage adds extra absorbency and smoothes down the orthopedic layer prior to application of the 2 compression bandages. It is rarely necessary to use a second bandage even if the crepe is a little short.

The 40 mm Hg pressure within the 4-layer system is applied to the limb by the 2 outer elastic bandages. The first of these is a highly extensible bandage that is applied at 50% extension with a 50% overlap using a figure 8 technique. In “inverted champagne bottle” shaped limbs, the figure 8 application can be widened to conform with shape. If greater pressure is required over an oedematous calf, this can be achieved in a number of ways: increasing bandage extension, increasing overlap, and adding additional layers. Similarly, in patients with thin limbs the pressure can easily be reduced using the same principles, for example, decreasing bandage extension. The wide extensibility curve in these bandages prevents excessive increases in pressure even with poor technique.

The Elastic Bandage

The final layer of bandaging applies compression. A frequent misconception is that the outermost cohesive layer is merely to maintain the bandage position. However, this layer provides the higher level of compression and should not be overextended. The cohesive layer should not be applied next to the skin unless the bandage is known to be free of latex in order to diminish contact allergy from allergens.

Adaptations to the 4-Layer Bandage System

During the development stage, pressure-monitoring studies revealed the importance that ankle circumference and limb shape played in achieving correct compression profiles. Adaptations to the system have been made accordingly (Table 4). A simple ankle circumfer-
<table>
<thead>
<tr>
<th>Bandage</th>
<th>Function</th>
<th>Bandage Characteristics</th>
<th>Foot</th>
<th>Ankle</th>
<th>Limb</th>
<th>Modifications</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orthopedic wool</td>
<td>Absorbs exudate</td>
<td>Orthopedic wool with varying levels of conformability and compressed thickness</td>
<td>Apply padding to base of toes Pad tendon area over dorsum of foot</td>
<td>Ensure Achilles tendon well covered</td>
<td>Use extra padding to protect bony prominences</td>
<td>Recontour limb with loss of calf muscle</td>
<td>Density and conformability of different products vary. Extra pad of foam over postmalleolar area useful to increase pressure over ulcerated areas</td>
</tr>
<tr>
<td>Cotton crepe</td>
<td>Adds absorbency</td>
<td>Light support bandage</td>
<td>Bandage from base of toes applying tension to ensure smooth surface on which to apply elastic layers</td>
<td>Cover all padding area</td>
<td>Continue with 50% overlap up the limb</td>
<td>Second bandage not required unless excessively tall patient</td>
<td>Some 4-layer systems incorporate bandages with elastomeric fibers, which may offer higher levels of pressure than cotton-based products. Check bandage specification</td>
</tr>
<tr>
<td>Elastic, extensible bandage</td>
<td>First layer of elastic compression subbandage (pressure at ankle 17 mm Hg)</td>
<td>Light compression sufficient to maintain pressures up to approx. 20 mm Hg on ankle circumference (18-25 cm)</td>
<td>Begin extension from base of toes with 2 anchoring turns at 50% extension</td>
<td>Apply figure 8 using a high and then low turn to avoid excess layers over dorsum of foot</td>
<td>Apply in a figure 8 with 50% extension and overlap</td>
<td>Reduced pressure can be achieved by applying bandage in a spiral Increase overlap will increase the pressure</td>
<td>Bandage extensibility range is considerably important within this group</td>
</tr>
<tr>
<td>Cohesive bandage</td>
<td>Second layer of compression adds remaining 23 mm Hg of pressure Cohesiveness retains bandage position</td>
<td>Cohesive, elastic bandage able to apply pressures up to 25 mm Hg on ankle circumference (18-25 cm)</td>
<td>Applied in a spiral</td>
<td>Bandage using 50% extension 50% overlap using spiral technique</td>
<td>In “inverted champagne shaped limbs” with increased diameter figure 8 technique, This technique can be used below knee to increase pressure and prevent slippage</td>
<td>Variations in extension Nonlatex cohesive used in Robinson Ultra 4™-system</td>
<td></td>
</tr>
</tbody>
</table>
ence allows for the correct combination of bandages to ensure that a pressure of approximately 40 mm Hg is applied. Thin limbs with a circumference of 18 cm require additional padding. In these patients, the elastic bandages are substituted for those with a higher elastic modulus. Care should be taken with these bandages to ensure correct bandage extension, using bandage symbols, when present, to aid this process. The limb circumference should be regularly remeasured as rapid loss of edema in the first few weeks of treatment may require a change in bandage combination.

COMMONLY RAISED ISSUES RELATING TO 4-LAYER BANDAGING

Should 4-Layer Bandaging Be Discontinued During an Episode of Cellulitis?

The priority is to initiate antibiotic therapy. Mild compressive support may be well suited once the acute stage is overcome.

How Can the Odor Associated With Leg Ulceration Be Controlled?

Ulcer odor is common and distresses patients. It occurs frequently in the early stages of treatment. It may be managed by using dressings containing charcoal and appropriate choice of dressings to manage exudate. As ulcers heal, edema and exudate levels decrease, odor diminishes. It may be necessary to swab ulcers to deter colonizing organisms.

How Long Should 4-Layer Bandaging Be Continued before Hosiery Is Applied?

There is no clear research evidence to guide decisions relating to this issue. A pragmatic approach suggests that 4 weeks are needed to ensure that the ulcer is well covered and that the skin is strong enough to cope with elastic hosiery.

It is important to apply the hosiery immediately after bandage removal to prevent edema formation during the interim period.

Can 4-Layer Bandaging Be Applied above the Knee?

While the majority of patients only require below-knee bandaging, patients with lymphatic disorders may require full-length bandaging as well as other treatments, including manual lymph drainage and remedial exercises. It is often useful to bandage the limb in 2 sections, making sure the knee is flexed when the thigh is bandaged in a standing position.

The Effectiveness of 4-Layer Bandaging

Since its inception, the 4-layer bandaging system has been the subject of intense scrutiny since venous ulcers need effective management. A meta-analysis of randomized controlled studies by the Cochrane Wounds Group concluded that “some compression was better than none,” conferring quality statistical legitimacy to compression, a treatment hitherto based on observation. A number of cohort studies (see Table 5) have yielded varying healing rates based on 4-layer bandage use as well as the utmost importance of nurse training in bandaging and assessment skills. Regardless of variations in healing rate success using 4-layer systems, it is considered cost-effective mainly with respect to saving nurse time. Experience also suggests

(text continued on p. 24)

Table 4. Modifications to the 4-Bandage System Based on Ankle Circumference Measurement (subbandage pressure of approx. 40 mm Hg applied to all limbs)

<table>
<thead>
<tr>
<th>Ankle circumference</th>
<th>Orthopedic wool</th>
<th>Crepe</th>
<th>Elastic Conformable</th>
<th>Elastic Cohesive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 18 cm</td>
<td>2 or more</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>orthopedic wool</td>
<td>crepe</td>
<td>elastic conformable</td>
<td>elastic cohesive</td>
</tr>
<tr>
<td>18-25 cm</td>
<td>1</td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>orthopedic wool</td>
<td>crepe</td>
<td>elastic conformable</td>
<td>elastic cohesive</td>
</tr>
<tr>
<td>25-30 cm</td>
<td>1</td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>orthopedic wool</td>
<td>crepe</td>
<td>elastic conformable</td>
<td>elastic cohesive</td>
</tr>
<tr>
<td>&gt; 30 cm</td>
<td>1</td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>orthopedic wool</td>
<td>crepe</td>
<td>elastic conformable</td>
<td>elastic cohesive</td>
</tr>
</tbody>
</table>

*Increase in ankle circumference reduces subbandage pressure applied.

FOUR-LAYER BANDAGING
<table>
<thead>
<tr>
<th>Author</th>
<th>Date</th>
<th>Type of Study</th>
<th>Practice Setting</th>
<th>Inclusion Criteria</th>
<th>Number of Patients</th>
<th>Exclusion Criteria</th>
<th>Treatment Description</th>
<th>Outcome Measure</th>
<th>Comments on Methodology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blair et al</td>
<td>1988</td>
<td>Short study</td>
<td>Hospital ulcer clinic</td>
<td>Venous ulcer</td>
<td>126 (148 limbs)</td>
<td>ABPI &lt; 0.8</td>
<td>Patients previously treated with paste bandage, elastocrepe, and elastoplast</td>
<td>12-week complete healing 74%</td>
<td>Randomized controlled trial methodology would be preferable Use of historical controls may exaggerate treatment effect</td>
</tr>
<tr>
<td>Moffatt et al</td>
<td>1989</td>
<td>Cohort study</td>
<td>Pilot community ulcer clinic</td>
<td>Venous ulcer</td>
<td>13 (21 limbs)</td>
<td>ABPI &lt; 0.8</td>
<td>Original 4-layer bandaging (modifications for limb size available)</td>
<td>12-week complete healing 92%</td>
<td>No control group First attempt at restructuring community care</td>
</tr>
<tr>
<td>Moffatt et al</td>
<td>1992</td>
<td>Cohort study</td>
<td>Community leg ulcer clinics</td>
<td>Venous ulcer</td>
<td>475 (550 limbs)</td>
<td>ABPI &lt; 0.8</td>
<td>Original 4-layer bandage (modifications for limb size available) Reduced compression for ABPI 0.6-0.8</td>
<td>12-week healing rate 60% 24-week healing rate 83%</td>
<td>Other outcome measures Quality of life-symptom rating questionnaire Cost effectiveness Risk factor analysis Recurrence rates First integrated leg ulcer service Reliance on historical controls</td>
</tr>
<tr>
<td>Thomas</td>
<td>1996</td>
<td>Cohort study</td>
<td>Community leg ulcer clinics</td>
<td>Venous ulcer</td>
<td>438 (514 limbs)</td>
<td>ABPI &lt; 0.8</td>
<td>Original 4-layer bandage Modified for limb size</td>
<td>12-week healing rate 40% 17-week healing rate 50% 24-week healing rate 57%</td>
<td>Risk factor analysis Recurrence rates recorded</td>
</tr>
<tr>
<td><strong>Lambourne et al</strong></td>
<td>1996</td>
<td>Cohort study</td>
<td>Community leg ulcer clinics</td>
<td>Mobile patients able to attend community clinic ABPI &gt; 0.8</td>
<td>111 (134 limbs)</td>
<td>ABPI &lt; 0.8 Immobile patients and complex etiology</td>
<td>Profoam™ system</td>
<td>Healing rates at 12 weeks 54% 24 weeks 68%</td>
<td>Patients with complex ulcers treated by district nurses at home New clinics treated more mobile patients Patient selection obliterates the total service perspective Risk factor analysis Costing of products</td>
</tr>
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</tr>
<tr>
<td><strong>Cameron et al</strong></td>
<td>1996</td>
<td>Retrospective study—nonrandomized</td>
<td>Hospital clinics</td>
<td>&gt; 18 years of age written consent ABPI &gt; 0.9</td>
<td>70</td>
<td>ABPI &lt; 0.9 Diabetes mellitus Peripheral neuropathy Ankle circumference</td>
<td>1. Original 4-layer (30 patients) 2. Polyurethane foam Setopress™ (40 patients)</td>
<td>Healing rates 1.57% 2.36%</td>
<td>No indication of how patients were selected for treatment options</td>
</tr>
<tr>
<td><strong>Simon et al</strong></td>
<td>1996</td>
<td>Comparative study in 2 health authorities (1 area acting as cohort)</td>
<td>Community leg ulcer clinic program</td>
<td>Venous ulcer ABPI &lt; 0.8</td>
<td>233</td>
<td>ABPI &lt; 0.8 Original 4-layer bandage</td>
<td>Healing rate at 12 weeks 42% Compared to 26% in control audit (1993)</td>
<td>Only half of patients received the new treatment in the community clinic area Cost effectiveness analysis performed Healing rates in the control health authority remained static</td>
<td></td>
</tr>
<tr>
<td><strong>Vowden et al</strong></td>
<td>1997</td>
<td>Retrospective analysis Cohort study</td>
<td>Nurse led vascular leg ulcer clinic</td>
<td>Venous ulcer ABPI &gt; 0.8</td>
<td>159 (180 leg ulcers)</td>
<td>ABPI &lt; 0.8 Original 4-layer bandage Modifications to bandage applied</td>
<td>Healing rate at 12 weeks 64.5% 24 weeks 84.1% 36 weeks 91.4%</td>
<td>Risk factor analysis performed</td>
<td></td>
</tr>
</tbody>
</table>

(continued)
<table>
<thead>
<tr>
<th>Author</th>
<th>Date</th>
<th>Type of Study</th>
<th>Practice Setting</th>
<th>Inclusion Criteria</th>
<th>Number of Patients</th>
<th>Exclusion Criteria</th>
<th>Treatment Description</th>
<th>Outcome Measure</th>
<th>Comments on Methodology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stevens et al77</td>
<td>1997</td>
<td>Cohort study</td>
<td>Community leg ulcer clinics</td>
<td>Venous ulceration ABPI &gt; 0.8</td>
<td>181 (197 leg ulcers)</td>
<td>ABPI &lt; 0.8 (ABPI 0.5-0.8 treated with reduced compression)</td>
<td>Original 4-layer bandage Reduced compression for mixed disease</td>
<td>Healing rates at 12 weeks 66% 24 weeks 79%</td>
<td>Several audit cycles make interpretation of results difficult Quality of life assessment Cost analysis</td>
</tr>
<tr>
<td>Marston et al53</td>
<td>1999</td>
<td>Cohort study</td>
<td>Wound care hospital clinic</td>
<td>Clinical or duplex confirmation of venous disease ABPI &gt; 0.8</td>
<td>252</td>
<td>ABPI &lt; 0.8</td>
<td>1. Unna Boot Paste bandage + Coban™ 2. Profore™ Reduced compression on ABPI 0.5-0.8</td>
<td>Healing rates at 10 weeks 57% 16 weeks 75% Ultimately 96% healed 1 major amputation</td>
<td>No evidence of how treatment was selected Cost effectiveness analysis Risk factor analysis: initial ulcer size, moderate arterial insufficiency delayed healing</td>
</tr>
<tr>
<td>Gupta et al78</td>
<td>2000</td>
<td>Open label Cohort study</td>
<td>Not stated</td>
<td>Age &gt; 18 Venous leg ulcer ABPI &gt; 0.8 Clinical venous signs</td>
<td>15</td>
<td>ABPI &lt; 0.8 Clinical cellulitis Patients taking systemic antibiotics Diabetes mellitus Other causes, for example, rheumatoid or malignancy</td>
<td>Hydrocellular dressing Profore Extra Kit™</td>
<td>12 weeks healing 77% (10 of 13 remaining patients) Intention to treat analysis not performed</td>
<td>2 withdrawals: 1 clinical cellulitis 1 unspecified unrelated</td>
</tr>
<tr>
<td>Study</td>
<td>Year</td>
<td>Type</td>
<td>Setting</td>
<td>Inclusion Criteria</td>
<td>Group 1</td>
<td>Group 2</td>
<td>Results</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Loftus and Wheatley</td>
<td>2000</td>
<td>Cohort study</td>
<td>Large community NHS Trust</td>
<td>Age &gt; 18 years, Resident in area, Venous ulcer, Patients with diabetes and venous ulceration</td>
<td>225</td>
<td>224</td>
<td>Healing rate at 12 weeks: 1. 33%, 2. 45%, Healing rate at 24 weeks: 1. 49%, 2. 67%, Healing rate at 60 weeks: 1. 76%, 2. 80%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allegra et al</td>
<td>2001</td>
<td>Nonrandomized 2 groups</td>
<td>Hospital clinic</td>
<td>ABPI &gt; 0.8, Arterial/mixed ulcers, Use of short stretch, Nonadherence with treatment, Patients in group 1 excluded from group 2</td>
<td>Not stated</td>
<td>Not stated</td>
<td>Reduction in area significant in Profore versus Unna boot (P &lt; .001), Insufficient details of clinical outcomes, Conclusions not consistent with data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vowden et al</td>
<td>2001</td>
<td>Clinical evaluation</td>
<td>Hospital leg ulcer clinic</td>
<td>Venous ulcer, ABPI &gt; 0.8, Ankle circumference &lt; 25 cm, Informed consent “Non,” Healing over previous 12 weeks (used Margolis scoring method)</td>
<td>Not stated</td>
<td>Not stated</td>
<td>Healing rates: 12 weeks 53.2%, at 20 weeks 69.5%, No overall healing rates provided, Risk factor analysis performed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Torra, Bou, and Lopez</td>
<td>2001</td>
<td>Clinical evaluation</td>
<td>Community Health Centres (Spain)</td>
<td>ABPI &gt; 0.8</td>
<td>Not stated</td>
<td>Profore™</td>
<td>Healing rates at 12 weeks 72.9%, Risk factors Ulcer duration, Ulcer size recorded</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
that it has uses in other lower extremity wound management. The constituents of 4-layer bandages are commercially available (Table 6).

### Table 6. Commercially Available Products Used in 4-Layer Bandage System

<table>
<thead>
<tr>
<th>Generic Description and Performance Parameter</th>
<th>Original Charing Cross</th>
<th>Profore (Smith &amp; Nephew)</th>
<th>Parema (K-Four)</th>
<th>Robinson (Ultra Four)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orthopedic wool</td>
<td>Velband™ (Johnson &amp; Johnson)</td>
<td>Soffban™</td>
<td>K. Soft™</td>
<td>Solfast™</td>
</tr>
<tr>
<td>Crepe bandage</td>
<td>Crepe BCC</td>
<td>Crepe</td>
<td>K. Lite™</td>
<td>K. Lite™</td>
</tr>
<tr>
<td>Elastic conformable bandage (pressure at ankle 17 mm Hg)</td>
<td>Elset™ (Seton Scholl)</td>
<td>Litepress™</td>
<td>K. Plus™</td>
<td>K. Plus™</td>
</tr>
<tr>
<td>Cohesive elastic bandage (pressure at ankle 23 mm Hg)</td>
<td>Coban™ (3 M)</td>
<td>Coplus™</td>
<td>Ko-Flex™</td>
<td>Cohfast™ (Latex free)</td>
</tr>
</tbody>
</table>

Types of 4-Layer Bandage Systems

During the last few years, a number of other multilayer systems have been developed based on the original concept. Bandage testing has revealed some minor differences in the bandage performance and characteristics. The original Charing Cross System has been compared with Profore™ in a large, 232-patient randomized controlled trial, and no significant differences were found at 24 weeks, although a small benefit toward Profore was noted at 12 weeks. Vowden et al evaluated the healing rates of K-Four™ (Parema) in a noncomparative study and found a healing rate of 53% at 12 weeks consistent with other studies. All bandaging systems were equal at 24 weeks.

CONCLUSION

Since its introduction some 12 years ago, the use of 4-layer bandaging has grown widely, offering a reliable means of sustained compression to many patients with venous leg ulcers. Research into its use has also identified the need for bandaging skills and led to its implementation.

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Using Living Skin Equivalents for Diabetic Foot Ulceration

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Diabetic foot ulcers are a major clinical challenge with enormous socioeconomic consequence. All advances in the understanding and management of this problem are eagerly received by wound specialists. The development of bioengineered skin—living skin equivalent—is an interesting event that could be significant in the management of lower extremity wounds such as the diabetic foot ulcer.

Key words: diabetes mellitus, diabetic foot ulceration, wound healing, skin grafts, living skin equivalents

The lower extremity wounds of patients with diabetes mellitus are particularly challenging to manage. Treating diabetic foot ulcers (DFUs) carries a high economic and social burden for many healthcare systems. For example, in the United States, the direct economic cost of diabetic foot ulcers alone was estimated to be at $150 million in 1986. Each year, diabetic foot pathology afflicts approximately 7% of diabetic patients and is the leading complication resulting in hospitalization.1–6

Because of the enormous physical, psychological, and economic costs of DFUs, adherence to a comprehensive wound care regimen is paramount to enhance healing time.7 A recent meta-analysis study demonstrated that with satisfactory wound care, 24% of DFUs healed after 12 weeks and 31% healed after 20 weeks.8 While proper wound care has been shown to assist healing in DFUs, efforts to develop better methods continue largely due to the disturbing fact that failure to heal DFUs can lead to lower limb amputation.9–11 The multidisciplinary approach to treating DFUs has been demonstrated to be the most successful and cost-effective manner to prevent the potentially devastating complication of amputation. Unfortunately, DFUs continue to be challenging. Despite numerous treatment modalities, the diabetic-related lower limb amputation rate has increased over the last decade.

For several decades, researchers have sought methods to procure sheets of natural or synthetic human skin to treat skin defects. In 1975, researchers initially focused on the cellular components of the skin. From skin biopsies, researchers were able to grow sheets of keratinocytes in vitro.11 Living skin equivalents (LSEs) were the first products after years of research in tissue engineering. Consequently, scientists cultured fibroblasts in vitro, and the combination of natural, animal, and synthetic products imparted stability to these skin cells. Living skin equivalents have demonstrated promise as an adjunctive therapy for the treatment of burns and acute and chronic wounds. This review will discuss LSEs and their applications to treating DFUs.

LIVING SKIN EQUIVALENTS IN THE CLINICAL PRACTICE

The exact physiological mechanism of living skin equivalents remains unclear and under considerable discussion. However, it is theorized that epidermal cells provide a temporary coverage for the wound until the host cells can play an active role in wound healing. It is hypothesized that stimulation of host cells to proliferate occurs due to the release of growth factors and cytokines by neonatal epidermal cells. Also, the wound contains an extracellular matrix, which has been described as a “smart matrix,” thereby recruiting the cells necessary for healing to the particular wound site.
Cadaveric Allograft

Cadaveric allograft skin has been used successfully in providing temporary coverage of full-thickness burn wounds.\(^{12}\) The cadaver skin functions by closing and protecting the wound, thereby preventing life-threatening infections in an already compromised burn patient. The cadaver skin is often removed at a later date, leaving behind a well-vascularized wound base that makes autografting more likely to take. While this method has been proven to be life saving in many cases, the demand for cadaver skin is high and therefore not often readily available. Other potentially serious complications include the possibility of graft rejection and transmission of disease.\(^{13-15}\) Transmission of disease may also occur because of the potential lack of effectiveness in screening capabilities. Moreover, at the time of graft harvesting, certain transmittable diseases may not be fully expressed thereby causing further difficulty in screening procedures. The cadaveric allograft can be treated chemically to eradicate any infectious agents. However, the process itself can result in an inert, acellular dermal matrix with limited viability.\(^{16}\) The process of cryopreservation presents a satisfactory alternative to prevent cadaver allograft of transmittable pathogen.\(^{17}\) Cryopreservation also affords the allograft a longer storage life and availability. However, it may permit the allograft to become more susceptible to sloughing off the wound bed.

Cultured Epidermal Replacements

Cultured epidermal grafts have been used successfully in treating burns and chronic wounds.\(^{16,17}\) A cultured epithelial autograft technique is available for use in the United States (Epigel, Genzyme Tissue Repair Corporation, Cambridge, MA). The disadvantages with this technique include the high cost of dispensation, a mandatory biopsy prior to application, and a 2- to 3-week delay in grafting to allow for adequate epithelium to be cultured.

Conversely, cultured keratinocyte allografts were developed to be readily available with no inherent time delay prior to grafting.\(^{18}\) Keratinocyte allografts can be cryopreserved, allowing for a longer shelf life and increased viability.\(^{19}\) Cultured keratinocyte allografts are derived from neonatal foreskin cells. They can be placed in both acute and chronic wounds. Keratinocyte allografts have been used successfully to provide temporary wound coverage and stimulate wound healing.\(^{17,19}\) It has also been found that cultured cells stimulate the wound to heal from the edge, a normal healing process known as wound contraction.\(^{20}\)

Limitations to these allografts include their expense and the additional risk of disease transmission due to their allograft nature. Another disadvantage with keratinocyte sheets is that they are fragile and therefore very difficult to handle. For example, they may fall apart if not held onto a backing material. A dermal bed to support the epidermal component may add to the stability and durability of the cultured skin.

Dermal Replacements

As discussed earlier, the epidermis is fragile when not supported by a dermal layer. Therefore, the cultivation of an adequate dermal substitute was created.\(^{21}\) The dermal component plays an important role in wound healing. It can have positive effects on epithelial migration, differentiation, attachment, and growth. The first dermal graft used a collagen-based analog of bovine collagen and chondroitin 6-sulphate with an outer silastic cover (Integra, Integra Life Sciences Corporation, Plainsboro, NJ).\(^{22}\) This dermal graft was used principally in burn patients.\(^{23}\)

Dermagraft

Dermagraft is a variation of a preliminary composite graft. In place of bovine collagen, fibroblasts from neonatal foreskin were grown on a nylon mesh and covered with an outer silicone layer (Dermagraft-Transitional Covering, Advanced Tissue Sciences, Inc, La Jolla, CA).\(^{24}\) Dermagraft is designed to cover the dermal layer of skin and to provide a stimulus to improve wound healing.\(^{25}\) Histological cross sections of Dermagraft demonstrate collagen fibers arranged in parallel bundles, similar to the configuration in human skin.

Human fibroblasts are procured from newborn foreskin that is typically discarded following surgical circumcision.\(^{26}\) Supporting the fibroblasts is a mesh composed of prolactin 910, a product commonly used in surgical suture and wound support. To ensure safety of the product, maternal blood samples are screened for exposure to infectious diseases.\(^{27}\) Maternal blood samples are tested for HIV, herpes simplex virus, hepatitis virus, and numerous other pathogens. The fibroblasts themselves are scrutinized for infectious agents prior to cultivating and again at several stages during and after the manufacturing process.\(^{28}\) The Dermagraft is cryopreserved and as a result may lose some viability and therapeutic effect.

Dermagraft acts on wounds through cell colonization and provision of growth factors and cytokines.\(^{29}\)
Preclinical studies in animals indicated that Dermagraft incorporates rapidly into the wound bed and vascularizes considerably during the process. Preclinical data also suggested that Dermagraft might present the additional benefit of limiting wound contraction and scarring.

Dermagraft is supplied as a 2-inch by 3-inch graft sealed in a bag and placed in dry ice. Prior to application, Dermagraft must be rapidly thawed, warmed, and rinsed with sterile saline. The wound may be traced following application to the wound, secondary dressings are used to maintain the graft in place and produce a moist environment.

**Dermagraft in Diabetic Foot Ulceration**

Dermagraft was initially proven useful in excised burn wounds. The prevalence of diabetic wounds prompted a study to investigate the therapeutic efficacy in DFUs. A small pilot study was conducted on DFUs over a 12-week period. Fifty patients were enrolled and divided into 4 different treatment groups. Three of the 4 treatment groups received Dermagraft in numerous application techniques in addition to conventional wound care over a 12-week period while the control group received only conventional care. In all the groups, patients were matched with similar demographic characteristics. After 12 weeks, the group treated with Dermagraft in 8 separate applications achieved considerably better wound healing than the other 3 groups. Moreover, the percentage of complete wound closures in this group was considerably better than the control group. Patients treated with Dermagraft also had no ulcer recurrence over a 14-week follow-up period.

Consequently, a large, multicenter prospective study was undertaken to investigate the effectiveness of Dermagraft on DFUs. Two hundred eighty-one patients were enrolled at 20 centers. Patients were randomized to receive either Dermagraft weekly for a total of 8 applications or conventional dressing alone. The control group consisted of 126 patients who were treated with standard care and exhibited a 32% healing rate at the end of week 12. One hundred nine patients received Dermagraft treatment, achieving a 39% healing rate by the end of week 12. This finding was a statistically nonsignificant result between the 2 groups. Furthermore, there was no difference with regard to adverse events, infection, or surgical intervention in the aforementioned investigation.

Following this study, it was realized that several study patients who were not in the indicated metabolic range received an application of Dermagraft. As a result, a follow-up study was constructed. Thirty-nine patients at 12 centers completed the 12-week evaluation in this nonrandomized study and all received Dermagraft with the appropriate metabolic range to ensure fibroblast recovery and new protein synthesis after implantation. The results demonstrated that these patients had a 51% complete healing. This finding was very similar to the group that received metabolically active product in the previous study. Moreover, smaller, noncontrolled studies have shown similar success for Dermagraft. Dermagraft is currently under consideration for the application in DFUs following completion of a new multicenter study.

**Composite Replacements**

Composite replacements incorporate both epidermal and dermal components. They are allogenic, bilayered skin equivalents consisting of a well-differentiated human epidermis and a dermal layer of bovine collagen containing human fibroblasts. The first composite replacement developed, cultured skin (CSS, Ortec International Inc, New York, NY), integrated neonatal keratinocytes and fibroblasts cultured in a distinct bovine type I collagen layer. This skin replacement was found to have limited uses. Its use has been confined primarily to burn patients and has shown some efficacy for epidermolysis bullosa.

**Graftskin (Apligraf®)**

Due to limitations of the initial composite replacement, a composite graft with multiple applications was developed for the coverage of full thickness wounds. Graftskin (Apligraf) is a bioengineered, allogeneic composite graft consisting of human epidermal cells, human fibroblasts, and type I bovine collagen (Graftskin, Organogenesis Inc., Canton, MA). Apligraf simulates both the epidermis and dermis and provides 4 components: epidermal keratinocytes, well-differentiated stratum corneum, extracellular matrix, and viable allogeneic dermal fibroblasts.

The keratinocytes that form the epidermis also generate growth factors to encourage wound healing and achieve biologic wound closure. The keratinocytes initially multiply and then differentiate to replicate the architecture of the human epidermis. The stratum corneum imparts a natural barrier to mechanical damage, infection, and wound desiccation. The extra-
cellular matrix incorporates type I bovine collagen organized into fibrils and fibroblast-produced proteins. This matrix promotes the ingrowth of cells, supports the scaffold for the 3-dimensional structure of graftskin, and grants mechanical stability and flexibility to the skin equivalent.

Apligraf is produced under aseptic conditions. Both the dermal fibroblasts and keratinocytes are derived from neonatal foreskin. To ensure safety, blood samples of the maternal parent of the foreskin donor are screened and compared to normal ranges. Tests for a large number of infectious agents are performed, including anti-HIV virus antibody, HIV antigen, hepatitis, Epstein-Barr virus, and herpes simplex. Moreover, the donor cells are examined for any possible infectious pathogens and also for tumorigenic potential. Type I bovine collagen is extracted from the digital extensor tendon. This tendon is frozen, washed, dried, and then trichloroacetic acid is applied to reduce the amount of free collagen. The collagen is then extracted in a buffer to remove the cells. The resulting collagen solution is then lyophilized to remove most of the water. Finally, the collagen is dried to a solid state and then stored at -20°C for later use.

Apligraf is supplied as a circular sheet approximately 3 inches in diameter in a container with gel-cultured medium. This product contains the entire matrix of proteins and cytokines present in human skin. However, it does not contain Langerhans cells, melanocytes, lymphocytes, macrophages, blood vessels, sweat glands, and hair follicles.

Prior to application of Apligraf, the wound bed should be debrided extensively of all necrotic tissue. The graft is then removed from its container and positioned with the dermal layer in direct contact with the wound bed. Apligraf may be trimmed to size; overlap of the graft over the wound edge onto healthy surrounding tissues will not cause any harm. Also, meshing of the graft material allows for coverage of larger wounds and has the additional benefit of permitting drainage during the incorporation process. Furthermore, secondary nonadhesive dressings are used to maintain the position of the implant and to support a moist wound environment.

Graftskin (Apligraf) in Diabetic Foot Ulceration

Following the success of using Apligraf to treat venous leg ulcers, a prospective, multicenter, randomized, controlled clinical trial was conducted to evaluate the efficacy of this LSE in the treatment of chronic DFUs. 

A total of 208 patients were enrolled in 24 medical centers across the United States. Enrollment criteria included full-thickness diabetic, neuropathic ulcers of greater than 2 weeks in duration with adequate circulation as evidenced by Doppler in-sinuation of the posterior tibial and dorsalis pedis pulses. Patients were excluded from the study if there was any evidence of clinical infection at the ulcer site, significant lower extremity ischemia, active Charcot neuroarthropathy, or an ulcer of nondiabetic pathophysiology. Study patients were followed up at 12 weeks with an additional 3-month follow-up period to scrutinize any potential adverse effects.

Of the 208 patients, 96 were randomized to the control group, receiving currently available standard treatment. This treatment consisted of saline-moistened gauze changed twice daily. Also, all the patients were instructed to avoid weight-bearing on the affected foot by using crutches or a wheelchair. The remaining 112 patients were randomized to the treatment group. In the treatment group, the ulcer was debrided and graftskin was applied in the prescribed aseptic technique. Maximums of 5 applications of the living skin equivalent were applied. After the fourth week, both the treatment and control groups received identical standard wound care treatments.

The results of this multicenter study demonstrated that Apligraf-treated patients had higher rates of complete wound healing when compared to patients treated with the standard care wound regimen. Complete wound closure in the LSE treatment group required an average of 3.9 applications per patient. The median time for 100% wound closure was also reduced to 65 days in the graftskin group compared to 90 days for the control group.

Moreover, Apligraf-treated ulcerations demonstrated diminished wound undermining, maceration, eschar, and fibrin slough. Furthermore, the rate of osteomyelitis and lower limb amputations was lower in this group. Ulceration recurrence was noted to be slightly lower in the LSE treatment group. This finding may suggest that wound healing with Apligraf results in wound closure with comparable viscoelastic properties to healing by secondary intention.

Adverse events such as wound infection and cellulitis were not significantly different in either the treatment or control groups. Previous studies have demonstrated that graftskin does not elicit immunogenicity from the host and hence rejection of the graft is not a concern. It has been postulated that an immunological response does not occur because the neonatal fibroblasts lack the HLA-DR surface antigens, the antigens responsible for generating allograft rejection.

Apligraf has also been used with some success for the treatment of thermal injury, epidermolysis bullosa in newborns, acute surgical wounds, and for the donor site in split thickness skin grafts. Moreover, this LSE
may aid wound healing in difficult wounds in diabetic patients with end-stage renal disease. Unpublished data from the authors’ institution suggest that diabetic patients with end-stage renal disease on hemodialysis were able to achieve complete wound healing of chronic foot ulcers with both standard wound care and offloading techniques.

**CONCLUSION**

Although LSEs have demonstrated improved wound healing rates and improved wound closure, their use imparts a considerable financial cost and therefore should be reserved for recalcitrant, noninfected foot ulcers that have failed to respond with standard care. However, the large financial cost of foot ulceration suggests that even expensive new modalities may be cost-effective when evaluated over the long term. 47,48 Until statistically rigorous cost analysis studies are performed, LSEs will remain an adjunct for the management of DFUs that are resistant to the currently available standard of care. If a foot wound does not demonstrate significant progress in healing (closing at less than 0.1 cm²/week, after 4 weeks of standard wound care), then the use of a proven adjunctive therapy, such as LSEs, may enhance the healing potential.

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Radiological Investigation and Treatment of the Critically Ischemic Limb—A Review

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The contribution of radiological investigation and treatment in the management of the critically ischemic lower limb is reviewed. The methods of classifying and assessing the cause, level, and severity of the arterial disease causing the ischemia are discussed with comparison of the relative merits of the various invasive and noninvasive techniques of investigation. The development of the methods of interventional radiological management is described with an indication of the relative success of the different techniques. Newer interventional developments, including intravascular brachytherapy and gene therapy are discussed.

Key words: arteries, stenosis or obstruction, arteries, interventional procedures, review

Critical ischemia of the leg develops when the perfusion pressure in the arterial system is insufficient to maintain “muscular nutrition,” resulting in either severe, continuous ischemic pain or trophic changes such as ulceration and gangrene (Fig. 1). Obstructive arterial disease secondary to atherosclerosis is the usual cause. Improvement of arterial flow can relieve symptoms of critical limb ischemia (CLI).

The management of CLI is a multidisciplinary exercise. It involves a preliminary assessment to confirm the etiology of the symptoms, investigation of the specific and associated causes, primary vascular treatment, local treatment, and pain relief. Radiological input is crucial to the investigation of CLI and plays an important part in its management.

Obstructive arterial disease is only one cause of distal limb ulceration, and a full clinical examination and assessment is required to confirm the arterial nature of the symptoms. Frequently, several pathologies coexist; for example, diabetes, arterial and venous disease, and treatment of each may be required to achieve symptomatic relief. The nature of pain, site of ulceration, and signs of generalized arterial disease are all indicators of an arterial cause, but confirmation requires specific vascular assessment.

Investigation

Initial investigation should be measurement of the ankle/brachial pressure index (ABPI). If CLI is present, the ABPI is usually less than 0.5. Falsely increased values may occur in patients with extensive vascular calcification, especially diabetics, and ABPI measurements are less reliable in this situation. Levels in excess of 0.9 effectively exclude significant major vessel disease. Ankle pressure measurements may give a more accurate estimation of the severity of vascular disease with pressures of 40 mm of Hg or less generally being found in patients with CLI. Inaccurate levels may again be found in diabetic patients.

Classification of the severity of vascular disease helps in deciding on the most appropriate treatment, monitoring success, and analyzing the results of treatment. Stratification of patients with CLI is particularly important in trials of new techniques and treatments. Various definitions of CLI have been used. There are 2 systems of classification of chronic limb ischemia in common use based on a combination of clinical symptoms and ankle pressures. The Fontaine system divides patients into 4 stages; patients with CLI are included in stages III and IV. The Rutherford Classification is similar but expands the categories and uses a more objective measurement of a patient’s symptoms. A more objective definition of CLI based on clinical symptoms, ankle, and toe pressures has been formulated in the

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Second European Consensus Document on Chronic Critical Limb Ischaemia. None of these systems deals particularly well with diabetic patients or with those patients with CLI and high ankle pressures.

The limitations of ankle pressure measurements have prompted investigation into other measurements of distal limb perfusion. Ubbink et al demonstrated a more accurate classification of patients with CLI who required invasive treatment, using a combination of toe pressure and transcutaneous oxygen tension measurement (TcPO2) compared to ankle pressure measurement.5 There have been several reports predicting the likelihood of wound healing on the basis of a TcPO2 > 30 mmHg6,7 and of the benefits of TcPO2 monitoring in determining success and complications of percutaneous transluminal angioplasty (PTA).8 Laser Doppler has been used to measure foot skin perfusion and can demonstrate the postural change of precapillary sphincter resistance in the skin of the foot due to the venoarterial reflex (VAR). Using laser Doppler, Cisek et al demonstrated loss of the VAR and significant microcirculatory compensation in critically ischemic limbs.9 Castronuovo et al also reported that laser Doppler measurement of skin perfusion pressure can diagnose the presence of CLI more accurately than clinical evaluation and ankle pressures.10 However, these techniques have achieved some success in laboratory and experimental situations, consistency of results has not been obtained in clinical practice and they are not used for routine assessment.

Once the presence of occlusive arterial disease has been confirmed, an assessment of the site and severity of the disease needs to be made. Color duplex ultrasound scanning provides an overview of the peripheral vascular tree and can identify the site and severity of disease, enabling a preliminary assessment to be made of the suitability for intervention. It should be the initial imaging investigation of CLI. Vascular ultrasound is a time-consuming investigation requiring skilled operators. Although treatment can be undertaken solely on the basis of ultrasound, the technique has limitations, particularly in visualization of the aortoiliac and crural vessels.11,12

Intra-arterial digital subtraction angiography remains the “Gold Standard” for delineation of peripheral vascular disease; when using small diameter 3 or 4 French catheters, it is a low risk procedure. CLI is generally secondary to occlusive atherosclerotic disease, with most patients having disease at more than one site. Angiography must therefore demonstrate the whole of the peripheral vascular system from aorta to pedal vessels to enable a treatment plan to be formulated (Fig. 2).

The iodinated contrast agents used for arteriography are mildly nephrotoxic. Many patients with peripheral arterial occlusive disease (PAOD) have coexisting renovascular disease and poor renal function, and in these patients, arteriography can also be undertaken using CO2, a nonnephrotoxic agent (Fig. 3).

Several noninvasive techniques have been developed that are increasingly being used as an alternative to angiography. Magnetic resonance angiography (MRA) using time of flight and phase contrast sequences has been practiced for several years. However, the usefulness of these techniques is limited by long acquisition times and imaging artifacts. The introduction of ferromagnetic contrast agents and increasingly sophisticated magnets has enabled contrast-enhanced MRA to be performed.13 Peripheral vascular images that are virtually on a par with conventional arteriographic studies can now be obtained (Fig. 4). The development of new long-lasting blood pool contrast agents will further enhance the ability to acquire MRA images.

Arteriographic images can also be obtained using computed tomography (CT). With the current generation of CT scanners, peripheral vascular imaging is limited to the aortoiliac and femoral vessels. With new developments in “multislice” imaging systems, acquisition of arteriographic images of the distal circulation will also be possible (Fig. 5). In the foreseeable future, it is likely that the majority of arteriographic investigation will be undertaken using noninvasive methods, with conventional arteriography being undertaken as an immediate precursor to therapeutic intervention.
Prior to any radiological intervention, it is important, where possible, to modify any risk factors predisposing to PAOD. Although the extent of intervention required can, to a certain degree, be predicted by the Fontaine or Rutherford classification, CLI is usually caused by multisegmental disease, and healing of trophic changes in the foot usually requires restoration of foot pulses. A combined radiological and surgical approach may be required to achieve limb salvage. Updated recommendations of the American Heart Association and Society of Cardiovascular and Interventional Radiologists recommending treatment based on morphological criteria have recently been published.

Angioplasty

Dotter first described PTA of aortoiliac and femoropopliteal occlusive disease in 1964. The procedure was developed and popularized by Grünzig in 1974. The technique has been standardized since the 1980s.

When undertaken for limb salvage, aortoiliac PTA has a primary technical success rate and 1-month patency rate of between 80% and 91%. In the femoropopliteal segment, comparable figures are 73% to 88%. The reported range of medium and long-term patency is extremely variable, with different reporting criteria and disease classification affecting the results. Lammer has reported a weighted-average 5-year patency rate in the femoropopliteal segment of 48%. The following factors are generally predictive of a better result: nondiabetics, short lesions, stenoses ver-
sus occlusions, good distal runoff, and a good initial technical result.

It is unusual for aortoiliac PTA per se to result in healing of a critically ischemic limb, but it may achieve healing when combined with more distal angioplasty or surgical revascularization. The patients with trophic changes in the foot almost invariably have disease in crural vessels in addition to aortoiliac and femoropopliteal disease, and treatment of the crural disease may be required to achieve healing. Angioplasty of tibial vessels is technically more challenging, with an increased incidence of vasospasm and acute thrombosis. These complications are reduced by the use of low-profile guide wire and catheter systems and the judicious use of calcium channel blockers and nitrroglycerine (Fig. 6). Schwarten and Cutcliff reported the first large series of infrapopliteal PTA. Using low-profile systems, a 1-year patency of 51% was reported by Lofberg et al. Interestingly, the same authors reported a 3-year secondary patency of 44% but a limb salvage rate of 72%. This indicates that continued patency is not always necessary to achieve limb salvage, possibly due to alteration in the microvascular circulation between healed and ulcerated limbs. Continuing limb salvage has also been noted following occlusion of femorodistal bypass grafts.

Reduced technical success and lower patency rates occur with long-segment femoropopliteal and tibial occlusive disease compared to aortoiliac and short-segment femoropopliteal disease. To overcome some of the technical difficulties experienced with these types of lesions, angioplasty via the subintimal route has been developed. The technique has been popularized by Bolia et al. The guide wire, rather than passing intraluminally through an occlusion as in conventional angioplasty, is deliberately positioned in the subintimal space. The subintimal plane is frequently the path of least resistance, allowing easy guide wire passage. Guide wire reentry into the true lumen is performed below the occlusion followed, by balloon dilatation of the track created (Fig. 7). A technical success rate of 80% and 1-year patency of 71% for long femoropopliteal occlusions has been reported. This compares with a technical success rate of 72% for conventional angioplasty of long femoropopliteal occlusions reported by Matsi et al. The 1-year patency was only 23% in this series. The technique may have particular benefit in the re-canalization of occluded crural vessels in patients with ischemic ulcers and limited surgical options.

Several other techniques have been developed to try to increase the technical success and patency rates of
angioplasty. These include laser angioplasty, rotational wires/catheters, and atherectomy devices. While many of these have shown promising technical success, there is, to date, no convincing evidence that patency rates with these techniques are superior to conventional angioplasty.28,29

The mechanism of successful angioplasty is a rupturing of plaque tissue and overstretching of the vessel wall. This activates the intrinsic coagulation cascade, encouraging thrombus formation. Platelet activation releases platelet-derived growth Factor (PDGF) that precipitates neointimal formation. These processes can result in acute thrombosis after PTA or lead to intimal hyperplasia and late re-stenosis. The initial lumen gain following angioplasty can also be lost by elastic recoil.

The increased thrombotic tendency that occurs acutely following angioplasty is reduced by periprocedural anticoagulation. There has been extensive research into the effects of platelet inhibition following angioplasty, with most of the evidence relating to co-ro
nary vessels. However, aspirin and possibly Dipyridamole improve patency and reduce mortality following peripheral revascularization.\textsuperscript{30} Evidence for the benefit of the newer antiplatelet agents such as Clopidogrel and Abciximab further improving patency following peripheral interventions is lacking, although these agents probably further reduce vascular mortality and morbidity, mainly due to prevention of coronary and cerebral events.\textsuperscript{31}

\textbf{Intravascular Stenting}

To overcome the flow-limiting problem of elastic recoil after PTA, intravascular stents were developed. First described by Charles Dotter in 1969, stents are made from a variety of materials and can be either balloon expandable or self-expandable. They mechanically prevent elastic recoil or acute closure due to intimal dissection flaps (Fig. 8).

Good long-term primary patency of 86\% at 4 years following stenting of aortoiliac disease has been reported.\textsuperscript{32} However, there have been very few randomized trials comparing primary stenting against angioplasty. The Dutch Iliac Stent Trial Study Group demonstrated no substantial differences in clinical outcomes of patients with intermittent claudication and aortoiliac disease randomized to either primary stenting or angioplasty followed by selective stenting.\textsuperscript{33} For patients with CLI, iliac stenting performed either as a primary or secondary procedure is unlikely, on its own, to achieve limb salvage but may be employed in combination with more distal revascularization (Fig. 9).

Despite improvements in stent design, the results for femoropopliteal stenting are less satisfactory, with Strecker et al reporting a 3-year primary patency of 48\%.\textsuperscript{34} The same thrombotic and intimal repair processes initiated by PTA occur with stenting with a greater magnitude. This is probably due to the smaller

\textsuperscript{32}
diameter of the femoropopliteal vessels and reduced flow compared to the iliac vessels, with the benefit of stenting being due to an initial net lumen gain compared to angioplasty. This gain is proportionally less in smaller diameter vessels.\textsuperscript{35} While aggressive antiplatelet therapy following stenting improves patency by reducing acute thrombosis and increases survival by reducing the incidence of cardiovascular events, it is unclear whether restenosis can be prevented by drug therapy.\textsuperscript{36}

As with the aortoiliac system, comparative data of stenting versus angioplasty is lacking. In a small, randomized trial, Vroegindeweij et al reported 1-year primary patency rates in patients with intermittent claudication randomized to PTA or stent of 74\% and 62\%, respectively.\textsuperscript{37} In a larger trial of patients with both claudication and CLI, Cejna et al showed similar cumulative 1-year primary patency and concluded that the best results were obtained with primary angioplasty, with stenting reserved for PTA failures\textsuperscript{38} (Fig. 10). Currently, stenting is not suitable for treatment of occlusive crural disease.

In the femoropopliteal segment, improved patency in patients with long occlusions or diffuse stenotic disease may be achieved using covered “stent grafts.” As with “bare” stents, they may improve initial technical success by compressing intimal flaps, dissections, and ruptured plaque, and prevent elastic recoil. The covering also prevents in-growth of hyperplastic intima through the stent with resultant in-stent restenosis. Covered stents have a greater thrombotic tendency than bare stents, and aggressive antiplatelet therapy is probably required to achieve satisfactory results. Covered stents may have the potential to improve patency following intervention in long femoropopliteal obstructions with encouraging short-term primary and secondary patency rates of 79\% and 93\% being reported.\textsuperscript{39} However, there is, as yet, limited long-term evidence of their effectiveness, and further trials of their use are required.

Coated Stents

Combining the mechanical properties of stents with pharmacological treatment of intimal hyperplasia may be possible using drug eluting, coated stents. Polymer-coated stents loaded with antiproliferative drugs such as Paclitaxel, 7-hexanoyltaxol, and Sirolimus have produced significant inhibition of neointimal proliferation in animal studies and in coronary arteries in preliminary human trials.\textsuperscript{40-42} The kinetics of drug release can be modified by the binding properties of the drugs and polymers. Late thrombosis due to delayed endothelialization may be a problem, but this may be overcome by prolonged antiplatelet medication. There are no published reports of the implantation of coated stents in the peripheral circulation for the treatment of CLI. However, if the technology is successful in the cardiac field, there would be a logical progression to using the devices in the femoropopliteal and tibial vessels.
Intravascular Brachytherapy

An alternative means of modifying the intimal hyperplastic response is the use of endoluminal radiation therapy to inhibit smooth muscle cell proliferation. Several studies have shown a reduction in the degree of neointimal hyperplasia following brachytherapy. Several methods of delivering therapy have been employed, ranging from bare radioactive 90Sr, 90Y, and 192Ir wires; balloons filled with 32P, radioactive 32P, and 90Y stents; and external beam irradiation. Most experience has been gained in preventing in-stent re-stenosis in the coronary circulation, although encouraging results have also been seen following peripheral brachytherapy.43-45

Bare wires and stents have significant handling problems for staff, and uniformity and control of dose delivery is problematical. These difficulties can be overcome by the use of automated afterloading catheter-based systems.

One problem with brachytherapy is the development of “edge-effects”: stenotic lesions at the edge of the irradiated segment producing a “candy-wrapper” effect. Edge effects seem to be particularly frequent with 32P stents, probably related to endothelial injury at the stent margins produced during stent deployment.46 There is also a higher incidence of subacute thrombosis, although this may be reduced by aggressive antiplatelet therapy.

While preliminary results are encouraging, in the coronary circulation, medium-term follow-up suggests a small reduction in caliber in treated vessels compared to control groups.47-48 Thus, brachytherapy may only delay intimal proliferation and have adverse long-term effects.

Gene Therapy

The prospect of growing new blood vessels to overcome critical limb ischemia, particularly in areas inaccessible to conventional treatment, is an exciting one. Angiogenesis is a natural function in wound healing controlled by a variety of angiogenic growth factors (VEGF) and angiostatic substances. Direct local delivery of VGEF to vascular endothelium in animals has produced encouraging results.49 However, local delivery of growth factor is cumbersome, and administration of the gene encoding these factors using viral vectors may be more effective. It is unclear whether delivery of the gene to the vascular endothelium using catheter and balloon techniques or delivery of the gene to the vascular endothelium using direct injection into ischemic tissue is the most effective method of gene transfer. Trials of these methods are ongoing.50
Gene therapy is currently experimental and of uncertain benefit in the management of CLI.

CONCLUSIONS

The management and treatment of the critically ischemic limb require a multidisciplinary approach. Radiological input is a key component of both investigation and treatment. Increasingly, noninvasive methods of investigation are being used to assess the extent and severity of vascular disease. Angioplasty remains the mainstay of radiological therapeutic intervention, with the subintimal technique expanding the role of this procedure. In selected cases, vascular stenting may be beneficial.

Although long-term patency may not be a prerequisite for limb salvage or ischemic wound healing, a number of new techniques are being developed to overcome the high restenosis rate following vascular intervention in the femoropopliteal and crural vessels. These need further assessment to clarify their effectiveness.

REFERENCES

Pyoderma Gangrenosum is cutaneous manifestation of a systemic problem that should be systematically diagnosed and managed with care. When such lesions appear on legs, it is important to study and treat the systemic problem.

Key words: pyoderma gangrenosum, ulcerative colitis, arthritis, corticosteroids, immunosuppressives, graftskin

Pyoderma gangrenosum (PG) is a noninfectious cutaneous disorder of unknown pathogenesis. In 1930, Burnsting and colleagues published their observation of skin lesions in 5 patients, 4 of whom had ulcerative colitis. They defined the lesion as pyoderma gangrenosum and considered bacterial infection to be the most likely etiological factor in their causation. Since then, in the last 6 decades several studies have associated the lesion with many other chronic systemic inflammatory disorders, classified its various forms, and studied in depth its pathogenesis including the likely immunological basis. This has lead to various acceptable therapeutic modalities although complete cure has not yet been achieved. Ulcerative lesions that are PG may occur anywhere on the body including the lower extremities. As this journal is concerned with lower extremity wounds, this review seeks to update readers on the diagnosis and management of the problem as a whole.

Definition

The original definition, pyoderma gangrenosum, implied pustular skin lesions, presumed to be infective, leading to an ulcer with a necrotic base. The definition of the lesion has stayed despite the studies that have failed to show an infective organism responsible for it.

ETIOLOGY

Incidence of PG

Various studies have looked at the incidence of PG principally in association with systemic diseases, mostly with inflammatory bowel disease (IBD)\(^7\) and rheumatoid diseases.\(^7\) The incidence in IBD varies from 0.5% to 4%.\(^2\), though an incidence of 12% was also reported.\(^4\) This variation is likely to be due to the stage the lesion was at the time of inclusion. Early pustular lesions can easily get missed since they can be difficult to diagnose and may not evolve to loss of skin and ulceration. The strong association of PG with rheumatoid arthritis and other inflammatory conditions is well documented, but its incidence in these conditions is difficult to assess and is likely to be lower than in IBD. Most cases of PG occur without any underlying disease, but it is important to realize that PG can predate its association and such factors make it difficult to precisely assess the correct incidence. Adults are mostly affected\(^5\) though PG also occurs in children.\(^6\) Both sexes are affected equally.\(^7\)

Association of PG

In patients with inflammatory bowel disease, PG develops in approximately 5% of patients with ulcerative colitis and 1% of patients with Crohn’s disease.\(^8\) In a more recent study, PG has been shown to occur in about a third of the IBD population, affecting both ulcerative colitis and Crohn’s disease with equal frequency.\(^6\) Both conditions run independently, and PG may appear at either the active or the quiescent stage of IBD. PG has rarely been noted in patients after proctocolectomy for ulcerative colitis.\(^9\) PG has also been shown to heal and not recur after total colectomy.

Arthritis

Powell et al\(^7\) showed that arthritis occurs in 37% of patients with ulcerative PG. The arthropathy they describe is mostly asymmetric, seronegative mono-
articular involving large joints, the severity fluctuating independently of the skin lesion. Arthritis in PG associated with IBD has a similar distribution to “colitic” arthritis. The other types of arthritidis include rheumatoid arthritis, Felty’s syndrome, and sacroilieitis.

**Blood Dyscrasias**

Myeloid leukemia, both acute and chronic, has been reported in PG. Other hematological diseases include IgA myeloma, polycythemia rubra vera, lymphomas, and myelofibrosis. Other associations include chronic obstructive pulmonary disease, chronic active liver disease, gastric ulcer, paraproteinemia, sarcoidosis, and visceral neoplasia, to mention a few.

**Chronic Leg Ulcers**

Harland and Millard reported 3 patients with chronic venous leg ulcers complicated by PG. Two of them had Crohn’s disease and rheumatoid arthritis, respectively, the third had bowel resection for perforation. It is likely that PG was more in association with the systemic disorders in the first 2 patients. Figure 1 shows a leg lesion in a patient with PG.

**Causes of PG**

**Role of Infection**

Brunsting and colleagues in their original study proffered infection as one of the main factors in the causation of PG, since they reproduced similar lesions in experimental animals by injecting the organisms cultured from the lesion. However, their work was not reproducible by subsequent workers. The increased presence of leucocytes in the lesion, as it happens in any bacterial infection, added further support to their hypothesis. It would seem more likely that increase in leucocytes was a reflection of the activity of the associated colitis. The postulation of viral etiology has not been confirmed.

**CLASSIFICATION**

Four different variants of PG have been clearly defined and documented elegantly by Powell and colleagues. They are ulcerative, pustular, bullous, and vegetative.

**Ulcerative**

This lesion is the classical ulcerogenous one with undermined violaceous border and a necrotic base. The lesion tends to be aggressive, its frequent associations being inflammatory bowel disease, arthritis, and monoclonal gammapathy.

**Pustular**

A typical lesion is a 2- to 8-mm size pustule and frequently associated with IBD and has a tendency to remit with the treatment of the underlying bowel disease.

**Bullous**

This lesion is a painful superficial bullous eruption leading to an ulcer and is associated with blood dyscrasias. It tends to respond better to immunosuppressive therapy.

**Vegetative**

This is the most benign of all variants, progressing slowly to a superficial ulcer without an undermining border, usually responding to topical or intralesional therapy. This lesion is more often idiopathic.

**OTHER PATHOGENIC MECHANISMS**

Various theories have been postulated in the pathogenetic mechanism of PG. These include Schwartzmann phenomenon, increased stool and serum lysozymes, and proteolytic enzymes as noted in patients with PG in association with IBD. A dermato-necrotic factor in the sera of patients with PG when injected into guinea pigs has been shown to cause necrosis at the site of injection, but this factor has also been shown to be present in normal population.

**IMMUNOLGY**

In recent years, many immunological abnormalities have been shown to occur in patients with PG, as in associated conditions such as ulcerative colitis, and so on. From the available data, it is possible to accept that the skin lesion in these systemic diseases is resultant of an altered immune mechanism in the primary disease, setting off an antigen-antibody reaction at the skin level, but a specific immune defect has not been dem-
onstrated to date. Abnormalities in the humoral immunity include hypo-gammaglobulinemia and hyper-immune globulin E syndrome. Disturbed cell mediated immunity has also been implicated in PG. Cutaneous anergy to candida, purified protein derivative, mumps, and inability of lymphocytes to produce macrophage inhibitory factor have been demonstrated by Lazarus and coworkers.

Several studies demonstrated defective neutrophil function in PG. These include reduced chemotaxis, disturbed phagocytosis, and diminished oxygen uptake. PG has been described in the rare condition of congenital deficiency of leucocyte adherence glycoprotein (CDLG) as well as in immune deficiency disease, HIV infection. It has been described in immune suppressed patients following renal and bone marrow transplants. Check et al also demonstrated T-Helper/Suppressor cell imbalance in PG.

The lesion in PG occurs after a minor trauma to the area of the skin involved as a result of altered immune reactivity where the skin reacts in an exaggerated manner to trauma, the phenomenon termed as pathergy. Random neutrophil migration to the area is facilitated by a “streaking neutrophil factor,” which has been shown to be present in the serum. Dwarkanath et al hypothesized that the neutrophil migration is a result of increased stickiness of the endothelium or neutrophils.

Role of Cytokines

At the ulcer site in PG, leucocyte chemotaxis results in cytokine production, the more important ones being interleukins IL-1 and IL-8 and tumor necrotic factor. These are responsible for leucocyte recruitment, cell activation, and up-regulation of expression molecules on phagocytes and on endothelial cells. Number of events that follow include platelet activation, complement, endothelial disruption, and impaired microcirculation leading to necrosis.

HISTOPATHOLOGY

The lesion first appears following a minor trauma as discrete nodules, which multiply and coalesce, and this is followed by the disruption of the overlying skin leading to a full-fledged ulcer with a necrotic base. A typical ulcer has an undermined violaceous border and is surrounded by a rim of erythema. Any part of the body might be involved, but the more common sites of affliction appear to be the lower limbs, cubital fossae following IV sites and venepuncture, head, neck, and rarely the scalp, forehead, scrotum, and eyes.

Histological appearances are nonspecific depending on the type of lesion and the site, and timing of the biopsy. The microscopic appearance is well described by Powell et al. Earlier description is that of intraepidermal pustulation with dermal perivascular cellular infiltration. Subsequent studies have shown nonspecific cellular infiltration without blood vessel involvement to later reports of necrotizing cutaneous vasculitis and of lymphocytic vasculitis. Powell described predominant neutrophil infiltration and abscess formation centrally at the base of the ulcer. The cellular infiltrate becomes mixed toward the periphery and becomes lymphocytic nearer the erythematous region. Damage to the vasculature with fibrin deposition and thrombus formation has been noted. In the pustular form, the pustule is perivascular, the follicles dilated with neutrophils and intradermal abscesses.

DIFFERENTIAL DIAGNOSIS

Detailed examination followed by investigations for other systemic diseases are mandatory. The PG ulcer should be differentiated from other skin ulcers such as vasculitic, acute, and chronic infective skin lesions; drug reaction; and neoplastic ulcers.

TREATMENT

Once the diagnosis has been made, it is essential to investigate the underlying associated chronic disor-
ders the patient is likely to have. As PG sometimes is known to appear at the height of the activity of the systemic disease, therapy aimed at controlling the primary condition, for example, ulcerative colitis, helps to heal the early benign pyodermal lesion with less chance of recurrence. In an established ulcerous lesion, it is essential to investigate for super added microbial infection by regular swab cultures and to treat with appropriate antibiotics.

Treatment of PG can be divided into local treatment, at the site of the lesion, and systemic treatment.

Local Therapy

In early minor lesions, cure can be easily achieved with local therapy administered intralesionally. In large and multiple lesions, the local therapy can be either primary or as an adjuvant to systemic therapy. Local treatment involves injection of the drug in and around the ulcer to effect healing.

Corticosteroids

Intralesional injections of corticosteroid triamcinolone has been shown to be beneficial. Triamcinolone diacetate at a dose of 6 mg (1 ml), mixed with lidocaine injected into each quadrant of the ulcer every 2 days for 14 days has been shown to heal the lesion completely. Other workers have shown similar good results with intralesional triamcinolone at varying doses and regimen. As an adjuvant to systemic corticosteroids, intralesional triamcinolone, 100 mg, has helped healing in 5 to 8 weeks. Similar good results have also been achieved with the same drug locally along side systemic steroids, immunosuppressive agents as azathioprine and cyclosporin. The major complication of cyclosporin administered locally is tissue atrophy that occurs with high-dose regimen, but it is reported to be low in concentrations not exceeding 10 mg/ml. Immunosuppressive drugs have also been used intralesionally, but they are not recommended because of toxicity. Topical usage of drugs has also been shown to be effective when applied locally over ulcerous lesions in pyoderma gangrenosum. Corticosteroids applied locally are less effective, although good responses to complete healing have been reported in some studies. Mesalazine (Oral 5-Amino salicylic acid), which is extensively used in the treatment of IBD, used topically as a cream (10%) over the PG ulcer in a patient with Crohn’s disease, has healed the lesion completely. Another drug that has been used topically is nitrogen mustard. In general, local topical therapy used alone has very little place in the management of PG.

Systemic Therapy

Corticosteroids

Systemic corticosteroids have continued to remain as the mainstay therapy in inflammatory bowel disease and rheumatoid arthritis. These drugs have been shown to be consistently effective in the acute and severe forms of the disease. Rapid healing is effected when used in high doses. Prednisolone in high doses (40-120 mg) intravenously daily has induced rapid and complete healing and immediate reduction of toxic manifestation. Once the improvement becomes evident, the dose should be reduced gradually (less than 10 mg/wk) to prevent relapse and to avoid side effects. A small maintenance dose of prednisolone may sometimes be required to prevent recurrence. In resistant cases, very high doses of prednisolone (1 gm) given intravenously as pulse therapy from 3 to 5 days has been effective and has shown to lessen steroid side effects. Caution needs to be exercised with this form of therapy, as some studies have described severe anaphylactic shock and even death due to cardiac arrhythmias. Ideally, patients should be managed in the hospitals for pulse therapy, with careful cardiac and electrolyte monitoring and patient observation for toxic side effects such as seizures, hypertension, and signs of bleeding. This form of therapy should not be offered to people with cardiac and renal dysfunction and should be reserved for refractory PG where other initial therapies have failed.

Immunosuppressive Agents

The indications for immunosuppressive drugs are when the corticosteroids have failed to heal or if the patient becomes intolerant of the drug. They are also indicated in patients who have become resistant to steroids, needing high doses to control the lesion at the expense of serious side effects. The drugs used mostly are azathioprine and more recently cyclosporin.

Azathioprine is mostly used as adjuvant in steroid-dependent subjects. The onset of action is slow, up to 6 to 8 weeks. Azathioprine when used alone has also been effective in healing. Results of the combined therapy are favorable in some studies but are failures in others. Its serious side effects include bone marrow depression and, rarely, pancreatitis. Caution should be exercised all the time during treatment; regular monitoring of platelet and leucocyte count are mandatory.

Cyclosporin has also been proven to be effective either administered alone or in combination with corticosteroids. At a dosage of 10 mg/kg/day, it has helped healing of the lesion, refractory to other treatments, but relapse was evident when the dose was re-
Reduced to 3 mg/kg/day. Several studies showing success with cyclosporin have been published in the last few years, and the drug appears to have a major role in the future in the treatment of PG. Cyclosporin needs to be used with extreme caution because of its toxic side effects. The more important ones are microbial infections (which may lead to fatal septicemia if diagnosis and treatment are delayed), hypertension, hypertrichosisis, and convulsions.

Tacrolimus (FK506) is a newer macrolide group of antibiotic with immunosuppressive properties, more potent than cyclosporin, and is used extensively in transplant patients. Abu-Elmagd and colleagues have demonstrated complete healing of PG lesions with Tacrolimus given at a dose of 0.15 mg/kg twice daily in 8 out of 9 patients. The ninth patient was intolerant of the drug. This drug would appear to have earned an important place in the treatment of pyoderma gangrenosum. Long-term side effects with this drug include neuropathy, diabetes mellitus, and renal dysfunction.

The drugs belonging to the group described as alkylating agents have been rarely used in PG. Cyclophosphamide, chlorambucil, and melphalan have been tried with good results but are not recommended, as more recent and widely tried, less toxic drugs as described above are available. Other more recent therapies that have been tried successfully are hyperbaric oxygen therapy and plasma exchange, as well as thalidomide, cyclophosphamide, and potassium iodide.

Reports of heparin healing PG lesions by reducing leucocyte or endothelial adhesion are encouraging and serve as a message for future investigators. The prostaglandin (Pgl2) analogue (iloprost) given intravenously has also shown promising results in PG by its varied immunomodulatory functions.

Surgical treatment should be considered in the treatment of PG as an adjuvant to medical treatment to hasten healing. After initial debridement of the ulcer base, skin grafting needs to be considered especially in disfiguring large lesions. Treatment with bioengineered skin (graftskin) alongside immunosuppression with cyclosporin in an acute progressive lesion has hastened healing. In patients whose lesions are on lower extremities, advice should be obtained from vascular surgeons.

CONCLUSION

Since the first description of pyoderma gangrenosum in 1930, we have gained a considerable knowledge and insight into the study and understanding of the disease. The lesion appears differently to the different specialities. A gastroenterologist views the lesion as a manifestation of IBD, whereas a rheumatologist may view it as part of the arthritic disease process. The significance of the lesion becomes more obvious when the lesion appears abruptly, expands rapidly, and fails to heal. This causes considerable patient morbidity and, in turn, leads to the patient having to attend different specialist clinics. Increased attempts to correct both macroscopic and microscopic diagnoses and exclusion of infection as the cause have been further strengthened by the better understanding of the immunological process involved in its causation.

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Systemic Vasculitis

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The systemic vasculitides are a heterogeneous group of disorders characterized by inflammation of blood vessel walls. They can be classified according to the size of vessel affected and also into primary de novo vasculitides and secondary to other disease processes. Treatments differ and overlap depending on the type of vasculitis. It is therefore important to make the correct diagnosis and treat appropriately to achieve remission as there is a substantial mortality implication.

Key words: vasculitis, arteritis, cytotoxic, glucocorticoid, cyclophosphamide, methotrexate

Patients with systemic vasculitis get chronic ulcerative lesions of the legs or hands. Patients with rheumatoid arthritis (RA) are predisposed to chronic leg wounds. These wounds may have multifactorial etiology, although venous disease is common. In a recent study of the etiology of patients with RA and chronic leg ulcers, it was observed that 15 out of 19 patients had evidence of venous insufficiency, 4 out of 19 had arterial insufficiency, and 2 out of 19 had insulin-dependent diabetes. In 1 out of 19, no etiological cause could be attributed to the lesion. The focus of this new journal is on lower extremity wounds. This article reviews an underlying systemic disease in patients with chronic wounds who may be treated in nurse-led clinics, in vascular outpatient centers, or in the rheumatology department. With this review, our aim is to promote multidisciplinary management of chronic wounds.

The systemic vasculitides are a collection of heterogeneous disorders characterized by inflammation and necrosis of blood vessel walls, with subsequent impairment of circulation by vessel occlusion, end organ ischemia, or vessel wall weakening. They can be divided into a group of primary conditions and as secondary consequences of certain disease entities, for example, rheumatoid arthritis or systemic lupus erythematosus. Treatment modalities differ depending on the type of vasculitis. The most commonly used group of drugs are the glucocorticoids. Often, however, the disease process requires more aggressive treatment in the form of the cytotoxic agents, most commonly cyclophosphamide, methotrexate, and azathioprine, to achieve remission and maintenance.

Pathophysiology

There is infiltration of the vessel wall by neutrophils, mononuclear cells, and giant cells resulting in panmural destruction of the vessel wall with fibrinoid necrosis. This vessel wall destruction can lead to hemorrhage and perforation into adjacent structures.

Classification

The vasculitides are most commonly classified according to the size of vessel affected. Most commonly used is The Chapel Hill Classification system (Table 1). Other classification systems include the ACR (American College of Rheumatology) classification criteria, which have been devised for the individual primary vasculitides. These are classification criteria only and not diagnostic criteria; however, it is hoped that patients fitting the criteria would have the disease. Other classification systems divide the de novo vasculitides into those that are ANCA (antineutrophil cytoplasmic antibody) positive or negative.

It is recognized that small- and large-vessel disease can also affect medium-sized arteries, but the large- and medium-vessel vasculitides do not involve vessels smaller than arteries.

LARGE VESSEL VASCULITIS

Giant Cell (Temporal) Arteritis

This is relatively common, with an annual incidence of 0.49 to 27.3 per 100,000 persons aged 50 years
or older. The incidence increases with age, being uncommon under the age of 50 years. Giant cell (temporal) arteritis (GCA) is twice as common in women as in men, and siblings with GCA are at a 10-fold risk of developing the disease.

**Clinical Features**

Most patients present with symptoms and signs related to inflammation and ischemia in the territory of the affected vessel. The extracranial vessels are usually involved and may be thickened and tender. Headache is the most common feature, usually temporal and unilateral. Often, there is associated scalp tenderness and jaw and possibly tongue claudication on chewing or prolonged speaking. The temporal arteries may be thickened, erythematous, and tender, with abnormal or reduced pulsation.

Visual symptoms may be transient or fixed and include visual loss due to ocular artery involvement and also diplopia. An early fundoscopic change in blindness is ischemic optic neuritis followed by atrophy. Visual loss may be unilateral or bilateral and also may occur without headache. It is a medical emergency and should be treated without delay. Neurological sequelae occur in up to 30% of patients. Most commonly vertigo, hearing loss, transient ischemic attacks, and stroke occur when the internal carotid and vertebralbasilar arterial supply are affected. Peripheral and mononeuropathies may occur in upper or lower extremities. Large artery involvement is present in up to 15% of patients. Aortic involvement can present with upper extremity claudication, bruits over large arteries, and delayed or absent pulses. Thoracic or abdominal inflammatory aortic aneurysms may occur and rarely present as acute dissection. Constitutional features are often seen, for example, fever, weight loss, malaise.

Features of polymyalgia rheumatica are seen in 20% to 50% of patients.

**Investigations**

The ESR and C-reactive protein are markedly elevated in the majority of patients and are useful tools for monitoring disease following initiation of treatment. Normochromic, normocytic anemia of chronic disease and thrombocytosis are commonly seen. Abnormal liver function (AST, ALT, and alkaline phosphatase) may be detected. This normalizes rapidly with glucocorticoid treatment. Diagnosis is confirmed by biopsy, which shows a granulomatous inflammatory reaction. A negative biopsy, given good clinical suspicion, does not exclude the diagnosis, as there is generally patchy involvement of the artery with skip lesions.

**Treatment**

Treat with high-dose prednisolone 1 mg/kg/day if eye involvement is suspected. Patients usually respond within 48 hours of commencing treatment. The steroid dose can be tapered once clinical and laboratory measures have normalized. Most patients reduce down to 5 to 10 mg/day by 6 months and continue to reduce over the next 18 months.

Methotrexate and Azathioprine can be used as corticosteroid-sparing drugs in resistant cases, although the evidence for these drugs is limited. All patients on high-dose corticosteroid for more than 3 months should be on osteoporosis prevention treatment (whatever their diagnosis).

**Takayasu’s Arteritis**

This is a large-vessel vasculitis predominantly involving the aorta and its main branches. Onset is usually aged 10 to 30 years with a female to male ratio of 4:1. Predominantly Asian and Latin American populations are affected. Figure 1 shows large vessel stenosis typical of Takayasu’s arteritis.

**Clinical Features**

Classically (as described by Takayasu), there is involvement of the ascending aorta, resulting in dizziness and visual abnormalities. Syncope, absent pulses or blood pressure inequality, is also a presenting feature. In Western countries, involvement of the abdominal aorta is more common, causing renovascular hypertension and often localized pain and regional ischemia from stenosis and thrombosis. Musculoskeletal symptoms are common (50%). Constitutional symptoms,
malaise, weight loss, and fever are seen in 43% and 20% of patients present with cerebrovascular disease.

**Investigations**

Lab tests are nonspecific: 72% of NIH patients had an elevated ESR, and only 56% of patients in remission had a normal ESR. An electrocardiogram showing QT dispersion appears to be indicative of coronary involvement. Hypergammaglobulinemia is often seen during active disease. Radiological assessment should include magnetic resonance angiography and computed tomography angiography. For cerebrovascular disease, transcranial doppler and single photon emission computed tomography (SPECT) imaging are advised.

In one study, 70% of patients had abnormal transcranial duplex (noted by increased velocities in the anterior circulation) and 100% had abnormal SPECT. The gold standard investigation remains angiography, however.

**Treatment**

High-dose prednisolone has been shown to have a dramatic effect (1 mg/kg/day). Numerous small studies have looked at immunosuppressive treatments—cyclophosphamide, methotrexate, mycophenolate, and cyclosporin. Methotrexate seems to have the most wide and accepted use. Aggressive treatment of hypertension is mandatory to prevent cardiac and renal morbidity. Surgical techniques have classically been limited to vascular bypass surgery, but more recently there have been good results in small trials using balloon angioplasty ± stent to a variety of vessels, including carotid, aortic, renal, and subclavian arteries.

With earlier diagnosis and improved medical/surgical management, long-term survival is greater than 90%. However, the morbidity remains high, and we need to remember that acute inflammation of the vessels causes accelerated atherosclerosis and all the problems associated with this.

**MEDIUM VESSEL VASCULITIS**

**Classical Polyarteritis Nodosa (PAN)**

PAN was the first recognized form of vasculitis, described in 1866. Since that time, it has been streamlined to a precise definition of a medium-sized vessel vasculitis with no small-vessel involvement. Those with small-vessel involvement or glomerulonephritis without granulomatous change have been classified as microscopic polyangiitis (MPA) and those with lung involvement as Churg-Strauss syndrome.

PAN is a rare condition in the United Kingdom, with an annual incidence of 2.4 per million population. Increasing numbers are found worldwide in areas with a high incidence of hepatitis B infection (HBV). It most commonly presents in men and women in their fifth and sixth decades but can present at any age. It is slightly more common in men.

**Clinical Features**

Most patients present with nonspecific signs of muscle pain or weakness, weight loss, arthralgia, fever, and malaise. Acute involvement of the medium-sized vessels of the nervous system (multifocal mononeuropathies, polyneuropathies), skin (ulcers, infarcts, palpable purpura, livedo reticularis), gastrointestinal tract (hemorrhage, perforation, infarction), kidneys (renal infarcts, hypertension, renal failure), and heart (angina, myocardial infarction) can also develop. Hepatitis is seen in most patients at postmortem but rarely symptomatic unless complicated by HBV.

To attempt to identify those patients at greatest risk of a poor outcome, Guillevin et al studied 342 patients and were able to identify 5 factors associated with a higher mortality:

1. renal failure (creatinine > 1.58 mg/dl)
2. proteinuria > 1 g/dl
3. gastrointestinal involvement
4. cardiomyopathy
5. central nervous system involvement

There was an 88% 5-year survival in patients with none of these factors present, which fell to 54% if more than 2 were present. Using this information, we may be able to stratify treatment to each individual patient’s requirement.

**Investigations**

Lab tests are nonspecific, often with an elevated ESR and C-reactive protein and abnormalities specific to the system involved. Hepatitis B and C infection should be looked for, as this will alter management if positive. ANCA is negative. Neurophysiology tests may confirm neuropathy. Tissue biopsy, generally of the sural nerve, may show vasculitic lesions. PAN, however, has patchy involvement of the artery and therefore a negative biopsy does not exclude the diagnosis. Angiography may show aneurysmal dilatation, most commonly seen in the renal circulation (Fig. 2).

**Treatment**

Glucocorticoids remain the mainstay of treatment (prednisolone 1 mg/kg/day). Controversy exists over the benefit of adding cyclophosphamide to the treatment regime. Several small trials have looked at combined therapy, and it would appear that patients with a poor prognosis at outset should receive combination therapy with prednisolone and cyclophosphamide. However, no large controlled trials have confirmed this. Patients without poor prognostic indicators had as much benefit from treatment with prednisolone alone as with combined cyclophosphamide/prednisolone.

In patients with confirmed HBV infection and PAN-type vasculitis, the aim of therapy is to treat the vasculitis and also treat the HBV with antiviral treatment and plasma exchange to remove immune complexes. With treatment, the outlook in PAN has improved immensely. Untreated, the 5-year survival was as low as 13%, rising to 73% at 10 years with treatment.

**Kawasaki’s Disease**

This is a disease of childhood first described in Japanese children in 1967 by Tomisaku Kawasaki. It occurs predominantly in Japanese children although does have a worldwide distribution and is unusual over the age of 10 years. It appears to have an infectious trigger that has not yet been identified, although Staphylococcus aureus has been isolated in many individuals.

**Clinical Features**

This is a febrile illness with conjunctival congestion, mucocutaneous involvement, and changes of the peripheral extremities, a macular rash, and swollen cervical lymph nodes. The most serious manifestation of the disease is coronary involvement, which occurs in a smaller proportion of patients. This can take the form of myocarditis, infarction, and aneurysm formation.

**Investigations**

Investigations are nonspecific, with elevation of acute phase markers in the early stages of the disease. Thrombocytosis is often seen. Cardiac aneurysms are detected using 2D echocardiography. Angiography is used in selected cases.

**Treatment**

Therapy is 2-fold with 1) aspirin, first as an anti-inflammatory and then as an antiplatelet agent, and 2) high-dose intravenous immunoglobulin.

Poor prognostic features are male gender, Japanese ancestry, young age at onset (<18 months), and early clinical myocarditis; however, treatment has reduced both mortality and morbidity substantially.

**SMALL VESSEL DISEASE**

**Wegener’s Granulomatosis (WG)**

WG was first recognized in 1931, and in 1936 Frederic Wegener recognized 3 cases of necrotizing
granulomata involving the lower and upper respiratory tract and put his name to the disease. Although most commonly affecting the upper and lower respiratory tract and kidney, it is in fact a multisystem small vessel vasculitis that can affect virtually any system.

The cause is unknown, but an infectious etiology has been postulated, as there appears to be a seasonal variation noted, with the incidence being higher in the winter months. There also appear to be peaks of ANCA-associated disease every 3 to 4 years.\(^23\)

It is predominantly a disease of Caucasians and can present at any age but most commonly in the fifth decade of life. It was thought to be a rare condition but more likely rarely diagnosed. In the United Kingdom, the Norwich Health Authority survey gave an annual incidence of 8.5 per million.

**Clinical Features**

Classically, there is a triad of

1. upper airways disease: nasal and sinus disease presenting as nasal discharge, epistaxis, ulceration and thickening, destruction of the nasal septum, and saddle nose,
2. lung involvement of the parenchyma, bronchi, and pleura. There may be transient flitting infiltrates and/or nodules that may cavitate and alveolar hemorrhage. Endobronchial disease may present with cough, wheeze, breathlessness, or hemoptysis,
3. kidney involvement with necrotizing glomerulonephritis. This may initially present as abnormal urinalysis with an active sediment, proteinuria (which should be quantified), hematuria, and red cell casts. Renal function tests may be abnormal, with a decrease in creatinine clearance. Renal disease is uncommon at the onset of WG, about 20% of patients, but in several series it has been found to develop in up to 100% of cases.

In a series of 216 patients, 87% had upper respiratory tract involvement, 69% lung involvement, 48% kidney involvement, and <15% had other systems involved (skin, joints, CNS, ear and orbit, heart, salivary gland, gastrointestinal tract, spleen, and urogenital).\(^24\)

Those presenting with gastrointestinal disease, although rare, typically present with signs of peritonitis or abdominal distension within the first 2 years of their disease.\(^25\)

“Limited disease” is defined as upper respiratory tract/sinus involvement with no kidney disease. Subglottic stenosis is seen in 16% to 25% of patients and can present as an acutely compromised airway.

Constitutional symptoms of arthralgia, myalgia, fever, weight loss, and malaise are also often found.

**Investigations**

These can be divided into blood test, urine tests, imaging, and histology. Blood tests should include full blood count (normochromic, normocytic anemia, or microcytic anemia in those with pulmonary or gastrointestinal hemorrhage). ESR and C-reactive protein will be elevated at presentation in most cases and can be used to monitor disease activity and response to treatment. Renal function should be monitored at regular intervals, as renal failure is more common once the disease is established.

ANCA are circulating antibodies with 2 distinct patterns seen on immunofluorescence (cANCA and pANCA). cANCA directed against proteinase-3 is both sensitive and specific for WG. There is controversy over ANCA being a cause of vasculitis or merely a marker for it.

cANCA is found in more than 90% of patients presenting with classical WG and in 43% to 70% of those with limited disease. IgM cANCA is associated with pulmonary hemorrhage and may change to IgG ANCA on resolution.

Nonspecific ANCA can be found in many other conditions, infection, malignancy, and subacute bacterial endocarditis, and has been demonstrated in up to 90% of cystic fibrosis patients. ANCA therefore cannot be used as a diagnostic tool without clinical suspicion for the disease.

Urine dipstick should be performed at the outset and at each hospital visit, as it is a sensitive marker of early renal involvement. Red cell casts and active sediment can easily be detected. Proteinuria should be formally quantified with a 24-hour urine collection, and urinary measurements of creatinine clearance will detect renal involvement before any change in routine blood testing. Chest X-ray should be performed in all patients. This may be normal or demonstrate pulmonary pathology. High-resolution computed tomography (CT) scan has been shown to be superior in following lung involvement in WG as compared with conventional chest X-ray.

CT or magnetic resonance imaging (MRI) of the sinuses may be useful in patients with upper respiratory tract involvement. The diagnosis of WG should be confirmed with positive histology (small vessel necrotizing vasculitis with granulomata present) if at all possible, as the treatment for WG has a high degree of morbidity in itself. The likelihood of a positive yield is best obtained from renal biopsy. Nasopharyngeal bi-
opsy is often performed in limited disease with a variable yield. The yield from transbronchial biopsy is very poor; however, open lung biopsy reveals disease in up to 90% of patients.26

Treatment

Prior to treatment, mortality in WG was greater than 80% at 1 year and 90% by the end of the second year, death occurring primarily from renal and/or pulmonary disease.2 Treatment with glucocorticoid alone did not improve the outcome of renal morbidity and mortality. In the 1970s to 1980s, patients treated with daily glucocorticoid and oral cyclophosphamide achieved an 80% survival, thus revolutionizing the treatment for this disease.27,28 However, complications of treatment were seen to arise, particularly bladder cancer, superimposed infections, and other malignancies in those treated with cyclophosphamide. An incidence of 16% at 15 years was the projected estimate for bladder cancer in patients treated with cyclophosphamide on a daily basis.29 Intermittent dosing with intravenous cyclophosphamide was therefore looked at in an attempt to decrease the significant morbidity associated with daily oral dosing. It was found that there was less morbidity with intermittent dosing but a higher relapse rate seen.30-32 Currently it is suggested that for life-threatening or fulminant disease, high-dose corticosteroid (1 mg/kg/day) and either daily oral cyclophosphamide (2-4 mg/kg/day) or pulse intravenous cyclophosphamide (15 mg/kg) is given at onset.33,34 Low-dose methotrexate (20-25 mg once weekly) with glucocorticoid has been used with good effect in non-life-threatening disease and in those patients unable to tolerate cyclophosphamide to induce remission35 and also as a means of maintaining remission.36 There was a higher incidence of pneumocystis carinii pneumonia in this group, and it is recommended that prophylaxis with trimethoprim/sulphamethoxazole be given.

Other cytotoxics used include azathioprine and mycophenolate mofetil, which have predominantly been used in patients as maintenance following induction with cyclophosphamide and are probably best kept for those patients intolerant of methotrexate until further information is forthcoming. Etanercept, a powerful antagonist of TNF, has been used in preliminary work in conjunction with conventional treatment and has been found to be well tolerated, and patients may be able to stop prednisolone at an accelerated schedule without immediate disease recurrence.36,37 Other treatments used include monoclonal antibodies38 and intravenous immunoglobulin.39 Both of these treatments have been used in small numbers with reasonable outcome.

Plasma exchange is a useful addition to conventional treatment in patients with acute hemorrhagic pulmonary vasculitis or those presenting with a serum creatinine greater than 500 mmol/l, with a mortality benefit seen in these patients.

Trimethoprim/sulphamethoxazole has been reported to be useful in the treatment of limited disease and may also play a role in reducing relapse rates. Pneumocystis carinii infection is seen not infrequently in WG patients on cytotoxic and glucocorticoid treatment, and trimethoprim/sulphamethoxazole will also act as prophylaxis against this.

Microscopic Polyangiitis (MPA)

This is a small vessel necrotizing vasculitis with a predilection for kidney (100%), lung (50%), and skin (40%-44%). Many patients have systemic and constitutional symptoms for many months prior to organ presentation.

The age at onset is generally fourth to fifth decade, but this can affect any age and may be insidious or acute. There is a slight male preponderance of cases.

Clinical Features

Renal disease with a necrotizing glomerulonephritis is almost universal. Lung involvement usually takes the form of diffuse alveolar hemorrhage, often in the absence of frank hemoptysis. Skin involvement is often seen as palpable purpura. Neurological involvement occurs in the form of peripheral neuropathy, multifocal mononeuropathy, and seizures.

Investigations

The diagnosis is based on clinical suspicion, laboratory findings, and positive histology. pANCA directed against myeloperoxidase is positive in 60% to 85% of patients. Other lab investigations are the same as those for WG. Microscopic hematuria is commonly seen.

Histology is nonspecific but will feature a necrotizing small-vessel vasculitis with few or no immune complexes and differs from WG, as no granulomata are present.

Treatment

Treatment is as for life-threatening Wegener’s granulomatosis. Combined therapy with high-dose glucocorticoids and cyclophosphamide is employed. Few studies have examined the treatment of MPA. There is evidence to suggest a high degree of relapse in
and therefore rigorous follow-up is required, monitoring renal function carefully, and urinalysis.

**Churg-Strauss Syndrome**

Churg and Strauss first defined this in 1951. In 1994, the Chapel Hill International Consensus Conference classified it as a small-vessel vasculitis with an eosinophil-rich and granulomatous inflammation involving the respiratory tract and necrotizing vasculitis affecting the medium-sized vessels in association with asthma and eosinophilia. As a disease entity, it is less common than WG and is linked to atopic individuals.

**Clinical Features**

The American College of Rheumatology criteria for classification are: asthma, eosinophilia greater than 10%, neuropathy (multifocal mononeuropathy, symmetrical or asymmetrical polyneuropathy), pulmonary infiltrates, paranasal sinus abnormality, and extravascular eosinophils. Four or more criteria are required. Asthma and allergic rhinitis may precede the vasculitis by many years.

**Investigations**

Peripheral eosinophilia > 1.5 × 10^9/liter is seen in the initial stages associated with asthma. ESR and C-reactive protein are elevated. ANCA is positive in up to 70% of patients, predominantly p-ANCA. Histology, often of sural nerve, is nonspecific showing necrotizing vasculitis, eosinophilic infiltration, and extravascular granulomata.

**Treatment**

Trials are limited but would suggest that limited disease should be treated with high-dose glucocorticoids and severe disease with combined glucocorticoid and cyclophosphamide. Interferon-alpha has been shown to be effective in treatment-resistant Churg-Strauss syndrome. Five factors were associated with poor outcome: renal failure, proteinuria, gastrointestinal tract involvement, cardiomyopathy, and CNS involvement.

**RHEUMATOID VASCULITIS**

This is seen in conjunction with longstanding rheumatoid arthritis in 1% to 5% of patients. It is most often noticed as tissue ischaemia, being a small-vessel vasculitis. Variables associated with its development are male gender, extra-articular features, destructive joint disease, subcutaneous nodules, number of disease-modifying antirheumatic drugs previously prescribed, and treatment with corticosteroids at the time of diagnosis. The strongest association, however, was found with high titers of rheumatoid factor.

Rheumatoid synovitis does not have to be active for the vasculitis to present or persist. If vasculitis is present at diagnosis of RA, it is associated with a much worse outcome. Limited vasculitis is more common than systemic vasculitis and tends to present as nailfold infarcts and lower leg ulcers (Fig. 3).

It has been demonstrated that there is an excess mortality in patients with rheumatoid vasculitis as compared with patients without.

**Investigations**

Biopsy of any vascular lesion is required for diagnostic certainty. Blood tests will confirm a high acute phase response and elevated rheumatoid factor. Patients affected are more likely to have erosive joint disease demonstrated on X-ray.

**Treatment**

Patients with severe systemic vasculitis classically have been treated with intravenous pulse methylprednisolone and cyclophosphamide and low-dose aspirin. This regimen is effective but has no survival benefit. Combination azathioprine and prednisolone, however, has been shown to induce remission in patients with severe rheumatoid vasculitis, with few adverse events and a low rate of relapse.

Patients with limited disease only would benefit from combined azathioprine and prednisolone treatment. There was no outcome benefit from treating this group of patients with aggressive immunosuppressive treatment.
All patients who smoke should be strongly advised to stop.

DISCUSSION

The focus of this article is on systemic vasculitis, a condition that describes as a potential risk factor ($P < .005$) in the recurrence of chronic lower extremity wounds. The diagnosis and management of lower extremity lesions must be achieved using the vascular and pathology laboratories and the involvement of vascular surgeons and other wounds specialists. New treatments of such wounds in patients with RA may involve the use of nerve growth factor shown to have potential in treating chronic lesions in the legs, hands, and cornea.

REFERENCES


Leg Ulcers in the Tropics

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Leg ulcers are an important clinical condition and are often difficult to treat. The treatment has to continue for long periods, and the associated morbidity leads to significant loss of work. The successful treatment of leg ulcers or chronic wounds depends upon accurate diagnosis and treatment of the underlying cause. In Western societies, most leg ulcers are due to venous insufficiency, arterial disease, neuropathy (usually diabetic), or some combination of these factors. In tropical countries, however, there have been no large series of leg ulcers reported. The prevalence of leg ulcers and etiology are unknown. In this article, a short review is presented of the etiology and management of lower extremity ulcers as seen in the tropical countries.

Key words: ulcer, chronic lower extremity wounds, skin ulcer (diseases), tropical diseases

Tropical Phagedenic Ulcer

Tropical ulcers are an acute, nonspecific localized necrosis of the skin and subcutaneous tissues, endemic in tropical countries. This ulcer has a reported prevalence of 0.4%. These are distinct from necrotizing fascitis in that in tropical ulcers, the infection is usually more superficial except in cases where it spreads rapidly causing muscle necrosis and osteomyelitis. A chronic ulcer may persist after the acute stage.

ETIOLOGY

The precise etiology is unclear. A minor trauma may be the initiating factor. It is prevalent in patients of lower socioeconomic status especially in agricultural communities. Fusiform bacilli and Vincent’s spirochaetes (Borrelia vincenti) are found fairly constantly, though they may be secondary pathogens. Proteus, pseudomonas, staphylococci, and streptococci have also been cultured from these ulcers, but they are probably contaminants. Pseudomonas aeruginosa is often present. It is likely that some unidentified infective agent is involved.

EPIDEMIOLOGY

With a reported prevalence of 0.4%, the highest incidence is seen in children in the age range of 5 to 15 years. It appears to be more common in young men compared to women. Outbreaks can occur when people live in crowded conditions, who are debilitated, and suffer trauma. Tropical ulcers are seen in war refugees, prisoner of war camps, and communities affected...
by famine. A low intake of vitamin A and of protein has been observed in some cases.

CLINICAL FINDINGS

A solitary ulcer is usually seen; occasionally there may be multiple ulcers. It spreads rapidly and has raised edges that are undermined, and the surrounding tissues are edematous. There is a foul-smelling discharge of blood-stained pus. The tropical ulcer is very painful. It may be associated with widespread necrosis of skin, subcutaneous tissue, gangrene of muscles, and even osteomyelitis.

Regional lymph nodes may be enlarged due to secondary infection, and patients may have associated fever. Following the acute stage, a chronic phase supervenes in which the edges become firm and sclerotic; the floor shows unhealthy pinkish granulation tissue. The surrounding skin is thin, atrophic, and de-pigmented, and there is fibrosis in and around the ulcer. Healing is very slow and seldom occurs under natural circumstances. Epithelioma of the skin may occur in a chronic leg ulcer.

DIAGNOSIS

In the acute stage, the ulcer has a typical appearance. This is usually diagnostic. Fusiform bacilli and Borrelia vincenti may be found. In the chronic stage, a biopsy is helpful.

TREATMENT

Medical treatment is mainly useful in acute cases and to prepare chronic ulcers for surgery, whereas surgical treatment is preferred for the chronic stage.

LOCAL

Complete rest to the affected part is very helpful. A wound swab for culture of organisms and their sensitivity pattern is essential. Topical dressings with Sofratulle® is helpful and needs to be changed 3 to 4 times daily. Antibiotic cream (metronidazole) or 0.5% silver nitrate is also essential. Small ulcers usually respond to this treatment.

SYSTEMIC

Systemic antibiotics, depending upon the sensitivity profile of the organisms isolated, should be used early. Metronidazole 200 mg 3 times a day for 7 to 10
days added to the appropriate antibiotic leads to faster healing. Commonly used antibiotics include injectable penicillin and streptomycin. In chronic ulcers, surgical treatment is usually essential.

Excision of small obstinate ulcers followed by split skin grafting (SSG) leads to a complete cure. Large ulcers should be treated medically until clean and granulating, and then SSG or pinch grafts are applied. For some large ulcers, it is necessary to remove necrosed bone and tendon followed by excision of the ulcer and skin grafting. Nutritional deficiency and anemia are contributing factors and should be corrected. Recently zinc deficiency has been shown to delay wound healing, and this aspect may be important.

VELD SORE

This is an ulcer usually of the leg caused by corynebacterium diphtheria. It presents as a painful vesicle full of straw-colored fluid, which on bursting leaves a shallow, punched-out circular ulcer with undermined edges and thick margins with a chamois leather slough. Subsequently, the edges become indurated and thickened and surrounding tissue has a cyanotic appearance. The ulcer may persist for many months. Healing leads to a thin parchment-like scar. Diagnosis is established by wound swabs. The treatment is 20,000 units of Diphtheria antitoxin given subcutaneously/intramuscularly. Penicillin or erythromycin (500 mg q 6 hours) for 7 to 10 days is the preferred antibiotic.

BURULI ULCER

It is an infection caused by Mycobacterium ulcerans, the likely route being bites from mosquitoes or other insects. The Buruli ulcer is commonly seen in young people. It has been reported from several parts of Africa, notably Uganda, Zaire, Sudan, Nigeria, and Ghana.

The lesions are usually situated on an extremity. There is an initial papular stage in which a hard, circumscribed mass can be felt deep in the dermis and subcutaneous tissues. This is followed by ulceration. Ulcers have undermined edges, a necrotic base, and concomitant pitting edema of the leg, but lymphadenopathy is usually absent. Most ulcers tend to heal spontaneously over months or years. Some ulcers progress slowly, and necrosis of skin, muscle, fascia, and bone may follow. Occasionally, massive lesions have required limb amputation.

Ziehl Nelson staining of the wound smear will demonstrate the presence of the acid fast mycobacteria, thus confirming the diagnosis of Buruli ulcer. Treatment is by surgical excision and antitubercular treatment in the form of intramuscular streptomycin injection or isoniazid, rifampicin, and ethambutol.
ERYTHEMA INDURATUM (BAZIN’S NODULAR VASCULITIS)

This is a chronic recurrent nodular ulcerative condition of the lower legs, and 90% to 95% of the reported cases were in women. Peaks are seen in adolescence and at menopause. Painful lesions 1 to 2 cm or larger appear over the lower calves. Symmetric indolent nodules or subcutaneous plaques are seen, and there is edema. Such ulcers may persist for 3 to 4 months then tend to dry and heal. Overlying skin has a dusty/bluish color and may ulcerate occasionally.

Ulcers are irregular in shape and deeply excavated with undermined edges. Some ulcers heal while others persist as chronic ulceration. Histopathological examination shows lobular panniculitis. Tuberculin test is positive. Isoniazid (INH) is recommended for treatment. An algorithm for clinical management is presented in Figure 1.

DISCUSSION

Lower extremity wounds commonly seen in tropical countries have been described in this article. Although little hard epidemiological data are available, clinical observations and tests suggest that infectious agents are principally responsible for such wounds. Occasionally, lack of nutrition is also responsible. There is a pressing need to study wounds of this nature that affect populations in tropical countries as well as the more described chronic wounds due to circulatory insufficiency or diabetes.

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Common Denominators for the Low-Cost Management of Leg Conditions

Terence J. Ryan, MD, FRCP
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INTRODUCTION

The majority of lower extremity wounds may be categorized as chronic disease. The care of patients suffering with chronic wounds is heavily dependent on well-organized health care systems as found in many western societies. Self-support becomes necessary for patients when organized health care is inadequate. Since lower extremity wounds affect legs thereby impairing mobility, the drive of individual patients to seek health care support may be further diminished when health care provision is poor. Lower extremity wounds embrace problems due to circulatory dysfunction, those resulting from excess contact pressure on foot surfaces, walking inadvertently over landmines, road traffic accidents, all exacerbated by a spectrum of infections and comorbid conditions, notably diabetes.

Lower extremity wound care involves different specialists. As such, it is well suited to multidisciplinary team management. Some teams are very large, as for example, the Global Alliances for the elimination of leprosy or lymphatic filariasis. There are organizations such as World Walk for the foot ulcers of diabetes mellitus. However, in general health services, expertise may be limited to one nurse whose skills should be the distillate of experiences of the team—which in effect is the best practice of all members of the team. Written guidelines have been found to be mostly unused, but good practice must be provided as part of an oral tradition practiced by the whole community. The leg condition itself may have a variety of causes such as ischemia and/or diabetes as presented in Table 1, and its management may fall anywhere in a range of complex therapies. Systematic analyses of these therapies should yield fundamental features which constitute the basis of management.

THE STRUCTURAL UNIT AND COMMON DENOMINATORS OF PRACTICE

Most chronic lower extremity wound conditions will require a functioning blood supply with an intact arterial venous and capillary component that interacts with the tissue supplied, which in the context of this article is the epidermis. The unit of tissue is supported by a drainage system provided by the lymphatic system. The care provider may be taught with different emphasis by different members of the team—phlebologist, lymphologist, angiologist, or dermatologist—but it should be possible to distill and synthesize their common practices and deliver management principles or guidelines for each profession. Such guidelines are ultimately generalizable to all conditions to the legs. As a consequence, there should be community...
acceptance of the principles of management, which are elevation, movement, and care of the skin as well as cessation of harmful practices such as smoking. These practice principles will increasingly have evidence-based support as well as insights into pathogenesis from the fields of genetics and molecular biology. The venous system is the most easily managed of all the components of blood supply and drainage. Good management of the venous system has important perceivable effects on the health of arteries, lymphatics, and the organ supplied. In simple terms, elevation and movement are good, sitting immobile with the legs down is bad. The conditions illustrated in Figure 1 all benefit from such a simple common precept message that must become part of the oral tradition of all communities. Thus, patients with lower extremity wounds who may access health care as well as those who are self-reliant because of circumstances can benefit from simple principles.

**VENOUS SYSTEM OF THE LOWER LEG**

The main objective is to empty the venous system. This objective is encouraged by emptying the veins in the thorax by taking deep breaths. Leg elevation above the level of the heart as well as movement of ankles and toes are essential to maintain venous circulation. Moving ankles and knees contracts the muscles of the leg that act as a pump to compress the veins, thereby propelling blood through the valvular system of the main veins. Damage to the valves or excessive dilatation of the veins so that the veins are incompetent is one cause of venous failure; immobility is another. The consequences of venous hypertension and inadequate emptying of the venous system is leakage. Such leakage leads to a chronic inflammatory state, and fibrotic repair is epitomized by lipodermatosclerosis.

**LYMPHATIC SYSTEM**

The lymphatic system of the peripheries is structurally a low resistance pathway through major lymphatic trunks in the deep tissues draining into the lymph nodes of the groin and axilla. This system may fail because of blockage caused by cancer or its treatment by surgery and radiotherapy, or because of parasitic infestations such as the filaria worm. The consequence of such a block is the need to open up collaterals, which are the lymphatic network of initial lymphatics in the upper dermis. The latter normally drain into the main lymphatic trunks. They are initially effective as a drainage system following blockage of the deep lymphatic system, and they function well enough to prevent swelling of the limbs, sometimes for many years. The lymphatic system is a drainage system that removes excess water and macro molecules such as proteins and lipids, inclusive in such are many mediators of inflammation and most of the waste products of living and dying cells. When as described above the venous system fails, lymphatics have to manage the additional load consequent on the leakage from the veins and the generation of an inflammatory process. The later consequence of lymphatic failure is gradual organization of the tissues so that elastin becomes replaced by fibrosis and the tissues become hard and inelastic. Limbs affected by such a process become immobile and dependant, processes that encourage venous failure,

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**Table 1** Causes of Non Healing

<table>
<thead>
<tr>
<th>Local</th>
<th>General</th>
<th>Global</th>
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</thead>
<tbody>
<tr>
<td>Inadequate blood supply</td>
<td>Age</td>
<td>Hospital building inadequate</td>
</tr>
<tr>
<td>Haematoma formation</td>
<td>Malnutrition</td>
<td>No access and no transport</td>
</tr>
<tr>
<td>Foreign body implantation</td>
<td>Vitamin and trace metal deficiency</td>
<td>Health care worker’s knowledge and availability deficient</td>
</tr>
<tr>
<td>Necrotic tissue</td>
<td>Anaemia</td>
<td>Patient unable to comply with therapy</td>
</tr>
<tr>
<td>Wound infection</td>
<td>Systemic infection</td>
<td>Management and governance of health services defective</td>
</tr>
<tr>
<td>Radiation therapy</td>
<td>Steroid therapy</td>
<td>Support services inadequate</td>
</tr>
<tr>
<td>Recurrent trauma</td>
<td>Anti-inflammatory drugs</td>
<td></td>
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<tr>
<td>Experience of surgeon</td>
<td>Cancer and/or its chemotherapy</td>
<td></td>
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<tr>
<td>Suture material</td>
<td>Diabetes mellitus</td>
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<tr>
<td>Wound tension</td>
<td>Jaundice</td>
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<tr>
<td>Absence of nature’s secret remedy (idiopathic)</td>
<td>Uraemia</td>
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<td></td>
<td>Obesity</td>
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<td>Hypothermia</td>
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<td>Factors related to gender including pregnancy</td>
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<td>Support services inadequate</td>
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LOW-COST MANAGEMENT
thereby setting up a vicious circle of increasing lymphatic load and further failure. The factors that contribute to venous failure in the lymphoedematous limb are listed in Table 2.

**ARTERIAL SYSTEM**

The arterial system maintains blood flow to the peripheries via a balance between peripheral resistance...
Angiogenesis and overgrowth of highly permeable venular beds. Ischemia-reperfusion with the loss of protective antioxidant systems. Failure to remove and consequent accumulation of mediators of inflammation. Venous filling and hypertension gravitationally induced. Loss of venoarteriolar response.

Table 2  The Venous Component of Lymphoedema

<table>
<thead>
<tr>
<th>Failure of thoracic venous emptying</th>
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<tr>
<td>Venous filling and hypertension gravitationally induced</td>
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<tr>
<td>Loss of venoarteriolar response</td>
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<tr>
<td>Failure to remove and consequent accumulation of mediators of inflammation</td>
</tr>
<tr>
<td>Ischemia-reperfusion with the loss of protective antioxidant systems</td>
</tr>
<tr>
<td>Angiogenesis and overgrowth of highly permeable venular capillaries stimulated by a damaged epidermis and/or mechanical expansion of the upper dermis</td>
</tr>
</tbody>
</table>

and cardiac output; blood flow and pressure are finely tuned. While in general venous disease presents mostly in middle age, failure of the arterial system occurs some 20 to 40 years later in old age. A healthy artery has an elastic wall and a lymphatic system that clears the arterial wall from any undesirable macromolecules. When the lymphatic system fails, the fibrosis that results, as well as accumulation of waste materials, affects the arterial wall as much as any other tissue. Thus, venous and lymphatic diseases play a part in the aging process of the artery whereby elastic tissue is replaced by a fibrotic tissue and lipid among other molecules becomes deposited in its wall, eventually leading to arterial disease.

EPIDERMIS AND ITS BLOOD SUPPLY

Over a period of 40 years, this author has described the relationship between the epidermis and its blood supply. A healthy epidermis performs functions such as communication and cosmesis factors as well as protection of the tissues within. The last function is achieved by having a closely knit surface, which acts as a barrier to environmental exogenous irritants and prevents leakage from the inside. The epidermis perceives the environment owing to the sensory nervous system and an immunological surveillance system that uses the macrophage and lymphatic systems. It acts as a thermoregulatory system employing sweating and perspiration as well as shunting of blood. In venous disease, all of these functions can fail. The diseased state is manifested by a loss of barrier function and a change in the rate of turnover, and repair of the epidermis. It is also seen as a change in the water content of the upper dermis and in the structure of its blood supply and lymphatic drainage. Some of this is due to loss of control of the factors controlling permeability of the capillary bed, and this is, in part, due to a change in the cytokine balance.

A novel observation that has profoundly influenced understanding of the control of blood supply to the skin is the realization that the epidermis is a factory for the production of cytokines. This production is correlated with the barrier function and the epidermal cell turnover. It is also correlated with the behavior of the upper dermal blood supply. The latter ranges from a pattern of atrophy to hypertrophy. It is a pattern that helps the skin to respond to mechanical and biochemical stimuli controlling the preservation of its healthy status quo or enabling it to repair. At rest, the epidermis, being a largely anaerobic organ, requires very little oxygen, but when it is injured, it requires an instant increase in blood supply mediated by the axon reflex vasodilatation. If the repair has to be a prolonged process, then a new organ has to be grown, this is granulation tissue. A part of the protective mechanism that allows the skin to respond to its mechanical and chemical environment is the elasticity and pliability of the epidermis induced by its moisturization, most of which is generated from its underlying blood supply.

Arguably, therefore, the most important role of blood supply is the control of the water content of the epidermis and upper dermis, and its role as a provider of all that is necessary for repair becomes a secondary function. Ultrasound imaging has enabled the understanding of the water content of the upper dermis by demonstrating the features of the water reservoir at this level. Ultrasound use shows diurnal and regional variation in water content of the epidermis and the dermis, and this is affected by age and influenced by postural factors, external mechanical factors, or even by the transfusion of a liter of saline. The control of the permeability of the vascular bed supplying the epidermis is dependent on Starling’s Law (1905), but the way in which the epidermis can also modify the permeability of the blood vessels as a result of production of mediators of inflammation that include prostaglandin or cytokines has become increasingly well understood. The fact that permeability is linked to maintenance of barrier function as well as the turnover of the epidermis is relevant to venous disease. Gravitational eczema is the end point of overhydration and impairment of the relationship between the epidermis and its underlying capillary bed when there is venous hypertension due to poor venous drainage. It is characterized by a hugely increased water content, a loss of barrier function, and a disturbance of the rate of epidermal turnover. The altered structure of the venous bed has much in common with the changes that are seen in other inflammatory conditions of the epidermis such as psoriasis, and mostly it is characterized by tortuosity and elongation of the papillary vessels of the upper dermis. Such
angiogenesis has much to do with the release of a vascular endothelial growth factor from the epidermis, which is at the same time a hugely effective vascular permeability factor in severe lymphoedema. The effects of angiogenesis are perhaps the most prominent, with enormous tortuosity and overgrowth of the vasculature in the upper dermis.

ADIPOSE TISSUE AND THE LOWER LEG

One of the features of the lower leg is that adipose tissue is part of the subcutaneous structure of the skin playing a part in thermoregulation while acting as a pressure transducer, especially in the sole of the foot. The generation of adipose tissue is not entirely a separate function to that of the generation of the lymphatic system. When the latter fails, there is often an increase in adipose tissue or at least in fat cells. The typical patient with venous disease or with lymphatic disease has an increased component of adipose tissue in the lower leg; thick ankles and thick calves are part of this picture as is the condition lipodermatosclerosis. In its purest form, lipoedema is a condition of overgrowth of the adipose tissue, especially of the lower legs in which there is always a venous and lymphatic component. In gross lymphoedema, there is usually a lipodermatous component.

MANAGEMENT OF CONDITIONS OF THE LEG

The venous, lymphatic, and arterial systems may be considered to closely interact with the tissues supplied, which include the epidermis and adipose tissue. It can also be seen that one of the elements upon which management can be focused is the venous system. Components of the management include breathing, movement, elevation, and care of the skin by washing and emollients.

Breathing

Breathing empties the venous system of the thorax, promoting free drainage of the blood in the veins from the periphery while it lowers the pressure in the venous system just above the heart, thereby encouraging the lymph to exit through the thoracic duct. In the subclavian or innominate veins, lymphatic function is best promoted by rapid inspiration, holding the breath, and prolonged expiration. This is a system of breathing common in Asian medicine and may have much in common with the yawn.

Movement Versus Exercise

Movement is emphasized because it is culturally accepted by almost everyone, whereas exercise can be misunderstood. Exercise is aimed at promoting an increase in cardiac output and muscle strength, and it is usually intermittent. What the legs need is frequent small movements to promote constant emptying of the venous system. All the maneuvers that are most needed, ankle movement is perhaps the foremost. The author promotes the concept of about 40 paces per minute being the rate of movement that is satisfactory provided there is a full range of movement at the ankle. It is important for all the conditions mentioned above including venous disease, lymphatic disease, and arterial disease.

Elevation

Elevation instantly empties the venous system. In an elevated limb, increased gravitational drainage has a slow effect on the lymphatic system. However, elevation rapidly albeit indirectly offers relief by reducing the overload of leakage into the venous system. Leg elevation should be above the level of the heart ideally. In practice this may not be achievable; it is vital to remember that every inch of elevation is helpful to the venous system, and insistence that it must be above the level of the heart is a goal that cannot always be achieved. Indeed, the ideal elevation may not be desirable in a patient experiencing discomfort in an enlarged limb. In circumstances where the arterial blood supply to the limb is affected, the degree of elevation should be carefully considered.

Care of the Skin

The close relationship between the epidermal production of cytokines and the stimulus to abnormal vessel growth and excessive leakage that leads to overload of the venous system renders a constant need to soothe the epidermis. Gentle washing and emollients have been shown to be effective in all forms of eczema/dermatitis. They help to restore the barrier function and reduce the role of infective organisms as a cause of damage. Washing for about 10 minutes twice a day is optimal. Water just above body temperature is most desirable, and the more natural the emollient soap, the more supportive it is of the epidermis. The vernix caseosa is effective in the newborn, sebum is effective in the adult, and natural wool fats such as lanolin are good substitutes. Most aging skin requires a substitute. Age is accelerated by exposure to sunlight, and the
lower legs of women in particular show severe aging effects leading to dry cracked skin unable to produce its own emollients. The cosmetic industry has long emphasized that antioxidants are helpful. The literature on ischemia and reperfusion phenomena underlying venous disease also suggests a role for antioxidants.

The epidermis is a rich reservoir of interleukin-1 and quickly generates other cytokines such as tumor necrosing factors when irritated. The cosmetic and soap industries have led the way in our understanding of irritancy. The new knowledge that the cytokine profile in the dermis is a product of a complex interactions and that production of cytokines by the epidermis has to be taken into account sheds light on the failure of the removal of such by the lymphatic system. A buildup of the cytokines in the dermis affects the relationship between the epidermis and its blood supply; the increase in demand leads to angiogenesis. These effects also serve to explain why failure of the venous system in the human leg can affect both the lymphatic system and the epidermis.

DISCUSSION

Lower extremity wounds are widespread throughout our global community. Care of this problem has far-reaching consequences since all practices must be based on the simple concepts of good hygiene and physiology as well as sophisticated scientific developments. The epidermis and its substructures are connected to and dependent on functional arterial, venous, and lymphatic circulation. The latter components are mostly dysfunctional in venous disease—the underlying pathology for a majority of lower extremity wounds.

Giving up smoking helps the arterial system. Elevation and movement are beneficial to venous and lymph circulations, both essential to maintain the structure of the skin and its functions.

REFERENCES

Quantification and Stratification: Wound Research in the Future

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Advances in wound healing have been slow—from the realization of a concept through to its adoption into clinical practice. There are well-known and understood reasons for this conservative approach. One less well-tried thought is to stratify the patient’s physiological status with regard to the wound. This may be the key to quantify changes in wound milieu and therefore to progress.

Key words: hypoxia, moist wound healing, stratification

INTRODUCTION

Wounds have always been a matter of major concern to ectothermic, terrestrial animals who, from some sort of instinct or experience, learned long ago to keep their wounds moist, warm, and clean. In contrast, humans have overridden that instinct and have treated our wounds with an astonishing menu of toxic and irrelevant substances. The value of cleanliness was realized only in the 18th century, and the value of moisture came slowly in the 20th century. As for warmth—well, perhaps any day now. Most astonishing, despite our traditional and severe wound problems, it occurred to humans to quantify wounds only in the 20th century—about 85 years ago.

Nevertheless, the first known prospective trial in history (circa 1740), though focused on scurvy, began the modern era of wound-healing science. On a British naval vessel, the HMS Salisbury, the ship’s surgeon hypothesized that fresh fruits and vegetables would cure scurvy. He chose 4 groups of 2 subjects each. The 2 who received fruits and vegetables recovered quickly from their scurvy and began to heal their previously unhealed sores. The other subjects, treated with remedies then popular, remained unimproved. The study was imperfect in its design. Complete healing was not the end point, and the result was not statistically significant since the sample size was too small. Nevertheless, the captain, who had supported the experiment with a grant of the fruits and vegetables, was convinced and rescinded the unused portion of the grant. The British Navy waited to act on the finding for 50 years.

About 1920, the structure of vitamin C was deduced, and about 1925, Wolbach discovered links between vitamin C depletion and impaired collagen deposition using only histologic evidence gained from animals. In 1947, in an experimental study, Crandon and Lund established the clinical importance of vitamin C in human wound healing.

SLOW PROGRESS IN RESEARCH

Lack of quantifiable data and apathy have slowed wound research. For 150 years or so after the scurvy trial, wound measurement was almost entirely confined to infection and mortality rates in human patients. Gradually, nutrition, cleanliness, and asepsis became the preferred therapy to prevent wound problems. However, only asepsis was graced with a convincing prospective demonstration, by Joseph Lister. In this case, reducing the rate of deaths due to “hospital gangrene” was the endpoint. Again, about 50 years elapsed before Lister’s work on asepsis was recognized and became generally adapted into practice.

Wound Measurement

Actual objective measurement of human wounds combined with mathematical analysis began during World War I when Du Nouy constructed an analyzable curve for the healing of open human wounds. He noted that once a wound was established on this curve, any major departure from the curve was a warning of significant comorbidity or complications in the patient that
needed attention. This is an extremely important observation that needs reemphasis.

Pertinent animal studies had begun a few years earlier. Rudolf Virchow determined histologically the association of inflammatory cells with injury and healing in the late 19th century, and this had been quantified in human wounds by 1930. Stanley Levenson, an honoree of the Wound Healing Society, and John Schilling deduced the presence of growth factors in wounds as early as about 1940 from animal studies. Animal studies also demonstrated the importance of nutrition, but after Du Nouy, objective data from human wounds were slow in collecting for the next half century.

Wound Strength

The tensile strength assay of wound closure was first applied in animals in about 1930 and finally was applied to human subjects in the 1950s. Implanted sponges of various sorts, the most informative technique currently available, followed the same cycle except that it was not systematically applied to humans until about 1980. Since then, the porous polytetrafluoroethylene tube and the Cellstick method which is a cellulose sponge in a plastic tube, have been the most informative research tools in human wounds. Although it is often thought that acute wounds and chronic wounds are unrelated entities, the above methods have been used to document in humans the effects of uremia, steroids, hypoxia, low blood volume, warmth, smoking, age and growth hormone, arginine administration, nutrition, magnitude of injury or operation, and others.

The concept of moist wound healing was introduced many years ago and has just grown since then, mainly in the last 15 years. William Stewart Halsted made a point of it in his papers in about 1890. Maibach and Hinman demonstrated it in human studies in 1963. Since then it has gained wide acceptance. The concept of moist wound healing is based mainly on human observations, particularly from measurement of epithelium on human skin graft donor sites. Moist wound healing helps to decrease pain. Nevertheless, dry dressings are still used by a discouragingly large part of the medical world, even on skin graft donor sites.

Stratification in Wound Research

Wound healers have been trying for about 15 years without much success to stratify wounds for comparison purposes. They have laboriously recorded size, depth, volume, exudate, appearance of inflammation, duration until therapeutic intervention, location, biopsy appearance, and others without finding a method that allows us to make efficient distinctions on healing agents. Wound scores are useful, but under current regulatory conditions, they are not acceptable tools for demonstrating healing. Scoring of wounds may deserve a more circumspect appraisal by wound healers. Quantitative attempts to define wounds more precisely are being pursued.

In addition to wound scores, however, there are other methods of measuring human wounds yielding semi-quantitative data. Furthermore, as we currently select human subjects into studies, even the best methods of assessment yield a prohibitively large scatter of data. Standard deviations are big necessitating large sample sizes to detect significant changes with an appreciable power. Cost and labor are prohibitive; studies are often statistically insensitive. The variability of results will not be reduced until we make serious attempts to minimize variation in the wound environment.

A simple change is suggested. It may be advantageous to stratify the wound milieu. To achieve this end, it might serve to stratify the circulation of a leg, for example. Subjects could be stratified according to the transcutaneous oxygen pressure (TcPO2) of the peri-wound environment. Exclusion of patients with heart failure, chronic steroids, renal failure, and so on, will inevitably reduce variability.

Some of the variables that are profitably stratifiable, that is, proved or suspected to be responsible for a variability of more than about plus or minus 10% from a hypothetical mean, are listed:

- Diagnosis (venous, ischemic, mixed arterio-venous neuropathic, etc.)
- Age
- Sex (sex hormones)
Medications (steroids, Beta blockers, diuretics, etc.)
Co-morbidity (renal, diabetes, cardiac, pulmonary, etc.)
Depth, size, complexity of the wound (any tunnelling?)
Hemodynamics/TcPO2/perfusion
Smoking
Recent weight loss

The most immediate and profound influences are mediated by disorders of inflammation and the state of oxygenation/perfusion, in other words, the local hemodynamic. These are

- Peri-wound TcPO2
- Ankle/brachial index
- Smoking
- Habitual state of hydration (diuretics, etc)
- Systemic hypoxia
- Chronic pain
- Hypertension

TcPO2 is best measured in a supine position, on a warm leg (temperature 21°C-24°C), well past the postprandial diversion of blood flow, more than 1 hour after smoking, with an oxygen challenge and pain control.

Local infection could be defined as an increase of temperature in the local area greater than 1°C. Alternatively, a Doppler value showing high perfusion combined with low TcPO2 indicating that the patient has a greater ability to deliver oxygen than is being measured could be used to stratify.

Most of these variables are a result of autonomic activation. The concept remains to be tested, however.

The suggested distinction between hypoxia caused by ischemia and that due to excessive oxygen consumption to combat active infection needs further characterization. It does offer a basis to eliminate variables due to infection. Patients with low TcPO2 and high perfusion should not be included in a chronic wound study until acute infection is well controlled, or cured.

There remains, of course, the problem of end point. The authors propose that there is a need for more subtle standards for vulnerary agents. Complete healing must not be all. Wound stratification permits improvement to be documented even in the absence of total healing. Pain relief needs careful examination and study as this symptomatic improvement is very important.

In practice, important stratifications can make large differences. For instance, the likelihood is small that a wound in a tissue that has a transcutaneous oxygen pressure less than 20 mm Hg will heal. The only therapy that has been shown to affect TcPO2 on a permanent basis is hyperbaric oxygen. New or unproven agents to improve oxygenation are difficult to test under randomized controlled conditions since it appears unethical not to offer a hypoxic limb every chance to recover. Stratification as discussed above may offer a way ahead.

In general, studies in which large amounts of stratified data are collected have succeeded far better in illustrating the defined aims than others. One study illustrates the power of patient stratification. To address the question whether perioperative maintenance of normothermia would reduce the incidence of wound infection and enhance collagen deposition, patients were stratified for age and type of operation. With this robust design using colon surgery to take advantage of the high infection rate and the uniformity of injury, significant differences between groups were demonstrated in 200 patients.

In the above study, we did not stratify for sex or smoking. As it was, we were able to distinguish between premenopausal women and all others in terms of collagen deposition, a measure of wound strength. Premenopausal women deposit about 10% more collagen than men.

**DISCUSSION**

Quantification of wound healing, especially chronic wound healing, has been difficult. Many studies fail to reach statistical significance. We submit that not only should the wound be stratified for size, duration, etc, but the patient-wound milieu should be stratified as well from the point of view of perfusion and oxygenation. These are perhaps the most important variables that can be measured.

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WOUND HEALING MEETINGS 2002

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Wound-Infection-Amputation: How to Break the Cycle Conference
Monday/Tuesday April 15/16, 2002 - Glasgow Royal Concert Hall
Monday/Tuesday September 30/October 1, 2002 - Commonwealth Institute
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Organizers:
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The Malvern Diabetic Foot Conference
May 15-17, 2002
Organizers:
Anne Roscoe
C/O Professor AJM Boulton
Dept of Medicine
Manchester Royal Infirmary
Oxford Road

ITALY
Associazione Italiana Ulcere Cutanee (AIUC) Annual Meeting
November 2002
Taormina
Italy
Organizers:
Dr Marco Romanelli
e-mail: m.romanelli@med.unipi.it

SCANDINAVIA
International Workshop on Multidisciplinary Concepts in Wound Healing
April 24, 2002, Helsinger (Elsinore) Denmark
Language: English
Organizers:
www.congress-consult.com/mcwh

10 Years Anniversary Symposium of the Danish Wound Healing Society
April 25-27, 2002, Helsinger (Elsinore) Denmark
Language: Scandinavian with some English-speaking lecturers
Organizers:
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EUROPEAN TISSUE REPAIR SOCIETY FOCUS MEETING

September 12-14, 2002, Nice, France
September 11-12, 2002, Monte Carlo, France

Organizers:
ETRS Business Office
Dept of Dermatology
Churchill Hospital
Oxford OX3 7LJ

Tel: ++44 (0) 1865 228269/64
Fax: ++44 (0) 1865 228233
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2002 Joint Conference of the Wound Healing Society and the European Tissue Repair Society

May 28-June 1, 2002, Renaissance Harborplace Hotel, Baltimore, Maryland

Organizers:
www.woundheal.org

6th European Pressure Ulcer Advisory Panel Open Meeting

September 18-21, 2002, Budapest, Hungary

Organizers:
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12th Conference of the European Wound Management Association

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(eg: increased blood pressure†)


Acknowledgments

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