CLINICAL MANAGEMENT

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Sickle Cell Disease and Leg Ulcers

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The authors have disclosed they will discuss the off-label use of arginine butyrate, nitric oxide–releasing compounds, DNA hypomethylating agents, hematopoietic cell transplantation, gene therapy, zinc sulfate, bosentan, and pentoxifylline.

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This continuing educational activity will expire for physicians on September 30, 2013.

PURPOSE:

To enhance the learner's competence with knowledge of sickle cell disease (SCD) and its relationship to leg ulcers.

TARGET AUDIENCE:

This continuing education activity is intended for physicians and nurses with an interest in skin and wound care.

OBJECTIVES:

After participating in this educational activity, the participant should be better able to:

1. Demonstrate knowledge of SCD-associated leg ulcer pathophysiology, symptomatology, diagnostic testing, and risk factors.

2. Apply knowledge of pain management and treatment options for SCD-associated leg ulcers to patient care scenarios.

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ABSTRACT

Sickle cell disease is a genetic disorder of hemoglobin synthesis leading to a deformation of the red blood cell. This disorder is associated with painful, slow-to-heal leg ulcers. This article discusses the wound bed preparation paradigm as a guide to the treatment of sickle cell–associated leg ulcers.

KEYWORDS: sickle cell ulcers, compression therapy and sickle cell, wound bed preparation

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INTRODUCTION

Sickle cell disease (SCD) is a genetic disorder characterized by the production of a defective hemoglobin called hemoglobin S (HbS). One copy of the abnormal gene expression is known as sickle cell trait. When 2 copies of the gene are produced (homozygous), SCD is clinically manifested by ensuing rapid cell destruction and small vessel occlusion with resultant pain and ulcerations of the skin known as sickle cell–associated leg ulcers (SCUs). These ulcers are relatively common, and they result in a chronic, disabling painful condition. Release of oxygen to the tissue by the abnormal HbS causes distortion of the red blood cells (RBCs) morphing them into a sickle shape, thus increasing blood viscosity, slowing blood flow through small vessels, and setting up a clotting mechanism that leads to tissue ischemia and decreased perfusion.

Clinical research on SCD treatment often focused on increasing the levels of fetal hemoglobin (HbF). Sickle cell trait and homozygous disease are prevalent in persons who are black in the United States or Africa. Sickle cell–associated leg ulcers are multifactorial and may be precipitated by trauma, infection, and severe anemia. The most common location for these ulcers to develop is above the medial malleolus (the Gaiter area) because of chronic damage to the microcirculation of the skin in this area, and these changes may coexist with venous stasis disease, requiring concomitant compression therapy.

The therapeutic strategies for SCUs are complex and must combine the principles of wound bed preparation with optimization of SCD control including the treatment of anemia, pain management, and the diagnosis and treatment of infection. Local wound care includes debridement, moisture balance, and the use of advanced modalities when wound bed preparation of a healable wound has been optimized and the wound healing is stalled.

After reading this article, clinicians will be better able to manage SCD and to monitor the potential development of SCUs.

WHAT IS THE PATHOGENESIS OF SCD?

Sickle cell anemia (SCA) is a genetic disease with autosomal recessive inheritance in which the gene encoding the human β-globin subunit contains a DNA substitution at the 17th nucleotide of adenine for thymine.[1] This point mutation results in a subsequent translated protein having valine substituted for glutamic acid at the sixth amino acid in the β-globin chain.[2] This resultant protein is known as HbS.

Sickle cell disease is a broad term that refers to all of the different genotypes that lead to the standard clinical syndrome; SCA (homozygous form) accounts for 70% of all symptomatic cases.[1] Sickle cell disease is characterized by hemoglobin polymerization when the substituted protein undergoes hydrophobic interaction with another hemoglobin molecule in the RBCs, resulting in a distortion of the cell's shape and causing erythrocyte rigidity.[2] Disease severity is primarily determined by the rate and extent of polymerization of HbS. The presence of HbF in the erythrocyte can effectively reduce this harmful polymerization.[1]

Microvascular (small vessel) vaso-occlusion is a common clinical manifestation of HbS polymerization when rigid, deformed RBCs become entrapped in the microcirculatory system, causing tissue ischemia and associated pain. Recurrent episodes of vaso-occlusion and reperfusion can lead to progressive organ damage in all organ systems. Although not as widely recognized as sickle cell crisis or acute sickle cell chest syndrome, skin ulcers are a common manifestation of SCD.

Leg ulcers are more common in homozygous forms of SCD. Individuals at higher risk for developing SCUs include those who are older than 20 years, are male, and have reduced levels of HbF. Lower socioeconomic status and a primary level of education may also play a role in the development of ulcers as a chronic, debilitating complication.

Management options for SCUs include systemic therapies, surgical debridement, and topical treatments, including dressings.[3] The wound bed preparation paradigm as a framework[4] for the assessment, diagnosis, and treatment of patients with SCUs will be used in this article.

ETIOLOGY OF A LEG UCLER IN SCD

The exact cause of sickle cell ulceration remains unclear, but the consensus in the field is that the causation is multifactorial. The chronic damage from clotting and impeding the microcirculation plays the key role in causing SCUs. The oxygen transport capability of the RBCs (in the hemoglobin molecule) in SCD is equal to the oxygen transport of normal individuals. However, it is the abnormality of the HbS that causes distortion of the hemoglobin after the RBCs deliver the oxygen to the tissue. The sickle cells increase blood viscosity and decrease the blood flow in small vessels and subsequently lead to the clotting of the vessels. Patients experience recurrent episodes of pain over time due to small-vessel ischemia. The damage to the vessel wall results in a leaky vessel with fluid, macromolecules, inflammatory cell influx, and leaked fibrin forming a cuff around small vessels. All of the

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aforementioned abnormalities potentially aggravate ischemia of the skin, resulting in leg ulceration.

TREAT THE CAUSE

Like other wounds, SCUs are categorized on their healing potential: healable, maintenance, and nonhealable. The approach to a nonhealable wound or a maintenance wound is more complex because the inability to heal could be from an inadequate blood supply or presence of very low hemoglobin (<80 g/dL). The maintenance wound is influenced by patient behavior, including refusal of treatment (such as nonadherence to compression therapy with a venous component to the leg ulcer) or when the healthcare system cannot support the proper care (no matching blood available to achieve adequate hemoglobin for wound healing). In patients with SCD, treatment of the underlying disease and anemia is necessary for proper wound healing. It is important for patients to maintain an adequate hemoglobin level (values vary with age and sex, with women generally having lower hemoglobin values than men). Normal results for men range from 13 to 18 g/dL. For women, the reference range is 12 to 16 g/dL. Critical limits (panic values) for both men and women are less than 5.0 g/dL or greater than 20.0 g/dL. For the treatment of SCD, hemoglobin levels should be maintained greater than 10 g/dL, ideally, or a minimum of 80 g/dL for wound healing.

A careful and systematic evaluation of the patient with a leg ulcer is important for the establishment of the correct diagnosis. Accurate wound diagnosis with proper management plans is best approached through a holistic interprofessional effort because of the nature of these complex wounds. The detailed history should include: duration of the ulcer, signs and symptoms of infection, including occasional osteomyelitis, and systemic symptoms, related to SCD. The documentation of systemic manifestations, such as increasing pain and intermittent fever, is also an important part of the assessment that may be linked to infection. Specific laboratory assessment depends on the findings of the clinical evaluation. If the patient does not have a diagnosis of SCD, but there is a high index of suspicion or indicators of SCD during the differential diagnosis, laboratory testing should include a sickle cell ''prep'' and hemoglobin electrophoresis. Other clinical testing should include ankle brachial pressure index (ABPI) testing as a screening measure. The presence or absence of the pulses should be recorded, or if the pulse is weak or absent, an ABPI index (0.5 mm Hg) or toe pressure (>55 mm Hg) should be recorded, to determine if the blood supply is adequate for wound healing in these patients. The assessment of the wound ''healability'' helps clinicians to set realistic goals of treatment.[4]

COMPRESSION THERAPY

When SCUs occur in the setting of concurrent venous disease, compression bandaging is an important part of the treatment. Lifestyle and occupation are the 2 important factors in choosing a type of compression.[5] The Cochrane review of venous ulcers and compression therapy randomized controlled trials demonstrated that compression therapy is the cornerstone of venous ulcer treatment. In addition to improving the healing rate of ulcers, compression therapy reduces edema, improves venous reflux, and reduces pain.[6] Compression bandages are classified into 2 major classes: elastic bandages and support (nonelastic) bandages. The elastic system provides compression at rest and with lower compression associated with muscle contraction, but the support system has low pressure at rest, with most of the compression with muscle contraction from activities such as walking. This pressure results from the calf muscle contraction against a rigid bandage. Compression bandages are used for the treatment of existing ulcers, and the compression garments (stockings) are for prevention. Compression bandages may consist of a single component (1 bandage layer) or a system of multiple components (several different bandages used together).[7] They may be further classified into low, medium, high, and extra high compression bandages reflecting the compressive force exerted by each subclass.

A review of the literature for randomized controlled trials comparing single-component compression with multicomponent systems demonstrated statistically greater healing outcomes utilizing the higher sub–bandage pressure from multicomponent compression systems.[7] Commonly used multicomponent systems include short stretch/inelastic, inelastic paste system (Unna boot), and 3- or 4-layer elastic and inelastic systems.[7]

It has been suggested that the efficacy of any compression treatment modality may be dependent on the skills and knowledge of the person applying the bandage,[8] and where application competency is a question, the use of compression hosiery may be indicated.[7] If the ABPI is 0.8 or greater, a high compression system should be utilized; a modified lower compression system for ABPIs between 0.65 and 0.8; and very low compression used with expert guidance and caution with ABPIs between 0.5 and 0.65.

Although demonstrated to be an effective aid in the healing of venous ulcers, there are some risks associated with compression therapy, including pressure damage from reduced blood supply to the skin and impaired arterial blood supply. Uncompensated heart failure and clinically significant arterial disease have been described as contraindications for compression therapy in the treatment of venous leg ulcers.[6]

PATIENT-CENTERED CONCERNS

Sickle cell–associated leg ulcers are extremely painful. Uncontrolled pain can be devastating and stressful and affect activities of daily living. Patients with SCD may experience recurrent sickle cell painful crises. It is recommended that the World Health Organization pain assessment and treatment ladder be utilized

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as a guide for treatment. A visual analog assessment tool for consistent pain evaluation and the response to the treatment is necessary (eg, 0- to 10-point numerical verbal rating scale). Topically applied and locally injected anesthetics, including a dressing containing slow-release pain analgesics, have been successfully utilized. Systemic medications including nonnarcotic agents (such as nonsteroidal anti-inflammatory agents) for moderate pain and weak to stronger narcotics are indicated for moderate to severe pain, respectively. Short-acting agents are used to determine the dose of long-acting agents (equal analgesic effects) and also for breakthrough pain. The neuropathic component of leg ulcer–associated pain may respond to selective serotonin reuptake inhibitors, tricyclic agents, gabapentin, pregablin, or other pain-reducing agents. Proper pain control increases the patient adherence and optimizes patient-centered care. On the numerical rating scale (0–10), most patients are comfortable with a reported pain level of 3 to 4; higher levels of pain have been found to interfere with the activities of daily living.[9,10]

LOCAL WOUND CARE

Basic local wound care includes mnemonic DIM before DIME. This translates to the **D***ebridement* of devitalized tissue, control of **I***nfection* and abnormal prolonged **I***nflammation*, and maintenance of the **M***oist* wound environment before moving to the advance treatment to stimulate the **E**dge effect.

Debridement

Sibbald et al[4] proposed that the wound bed is optimally prepared via debridement of any eschar or slough. Debridement of the devitalized tissue is required after the assessment of the wound's healability. Sharp debridement may promote wound healing by removing senescent cells and bacterial biofilms; however, it is associated with risks of pain and bleeding and may not be feasible in painful SCUs.[4] If a wound does not have the ability to heal, aggressive debridement is contraindicated, and only nonviable slough should be removed from the surface. Appropriate dressings for healable wounds may provide autolytic debridement (calcium alginates, hydrogels, and hydrocolloids).

Sharp debridement is the most selective method but may be challenging in patients with SCD because of severe pain. The debridement of ulcers in these patients needs local anesthesia to control the pain. Pain management as noted earlier is mandatory during debridement.[3]

Moisture Balance

Healable wounds treated with moist wound healing are less painful and heal faster. There are numerous wound dressings available on the market. In conjunction with other therapies, the proper wound dressing can have a direct effect on healing rates. Dressings should be selected with several factors in mind, such as debridement, control of critical colonization, inflammation, and moisture balance.[4]

The selection of an appropriate dressing is also imperative for the maintenance of moisture balance in SCUs. Excess fluid may cause damage to the surrounding skin, whereas inadequate moisture can promote eschar formation, which impedes wound healing.[4] Use of occlusive, semiocclusive, absorptive, or hydrating dressings, including foams (higher levels of exudate, fluid exchange), hydrofibers (fluid lock), calcium alginates (bioresorbing converting to a sodium alginate hydrogel and promoting homeostasis), hydrocolloids (some absorption but also hydrophobic components), hydrogels (70%–90% water for hydration of wounds), and films (protection and handle minimal fluid), can all improve healing rates of chronic ulcers by controlling moisture balance.[4]

Infection and Inflammation

Patients with SCD are prone to recurrent infection and deep infections including osteomyelitis. If patients have coexisting hepatitis C virus, the risk of infections was high at 13.9% in a series of patients reported by Neto et al.[11] This series of 1415 patients also found a higher level of infection in SCD patients with adult T-cell lymphoma virus type 1 (4.7%), hepatitis B (3.1%), Chagas disease (2.8%), HIV (0.8%), and syphilis (0.4%). Radiographic assessments are indicated to rule out osteomyelitis. It is important to consider the combined radiographic test sensitivity and specificity. For example, computed tomography is more sensitive than magnetic resonance imaging, and plain radiographs are very specific but not sensitive. Therefore, by the time the osteolytic lesions appear on the X-ray, there is a lost opportunity for the early diagnosis of osteomyelitis. A bone biopsy for histology and bacterial culture gives a high degree of both sensitivity and specificity and enhances the combined sensitivity and specificity of the diagnostic tools. In the presence of fever or an increased white blood cell count (leukocytosis), rubor, color, and dolor (redness, fever, and pain), clinicians should have a high index of suspicion for local and systemic infection. Sickle cell disease patients are prone to develop infections, and these infections can include less common organisms, such as *Salmonella*.

Chronic ulcers should be evaluated for possible bacterial damage that may also contribute to wound deterioration or delayed or stalled healing. Although deep and surrounding tissue infection may require the use of systemic therapy, superficial critical colonization may be treatable with one of several antimicrobial wound dressings.[4] Silver, iodine, honey, and polyhexamethylene biguanide dressings have antibacterial properties, and their use in

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chronic ulcers has been documented to aid healing by reducing critical colonization.[4] The effect on ulcer healing rates of these dressings has yet to be evaluated specifically in the SCD population. The majority of reports on the effectiveness of topical treatments have been anecdotal in nature.[12] Minniti et al[13] conducted a randomized controlled trial of a topical, triple antibiotic preparation consisting of neomycin, bacitracin, and polymyxin B, demonstrating a significantly greater reduction in ulcer size and associated pain versus control over an 8-week period. Although the mechanism of healing is unclear, the antibiotic preparation may act on organisms such as *Staphylococcus aureus* and *Pseudomonas aeruginosa* that commonly occur in SCUs, and these organisms may impair wound healing.[14] Despite the evidence that this study demonstrated some degree of healing, the use of topical antibiotics is not recommended because of risk of contact sensitization, bacterial resistance, and the lack of moisture balance/autolytic debridement.

The control of abnormal prolonged inflammation is also an important factor. There is a role for the use of anti-inflammatory agents with protease-modulating effect, such as dressings with topical collagen, oxidized reduced cellulose, and silver. Systemic anti-inflammatory antibiotics include doxycycline, cotrimoxazole, clindamycin, and metronidazole, which can all facilitate healing if the deep and surrounding component of the wound has persistent inflammation associated with bacterial damage.[15,16]

Advanced Treatments

When wound bed preparation of a healable wound has been optimized, and the wound healing is stalled, advanced treatment modalities may be considered. Surgical interventions include sharp debridement and the use of split-thickness skin grafts and myocutaneous flaps, or alternative treatment in the treatment of some SCD leg ulcers.[3]

Recalcitrant ulcers that have failed to epithelialize may benefit from the introduction of an autologous skin graft,[3,17,18] which can provide continuous coverage, pain relief, and rapid healing of chronic ulcers.[19] Vascular insufficiency and circulatory difficulties in the sickle cell patient, however, may lead to high rates of skin graft failure.[3,17]

Microsurgical free flaps may be more effective for the treatment of refractory ulcers as they contain their own vasculature and blood supply.[3] Literature reports of successful SCD ulcers with free tissue transfers have included axial,[20] gracilis,[21] latissimus dorsi muscles,[22,23] temporoparietal fascia,[23] and split omentum[24] free flaps. Myocutaneous free flaps, however, still carry a risk of flap necrosis and failure. Some reports have suggested the use of prophylactic anticoagulation to prevent postoperative thrombosis and facilitate flap survival.[18,25]

SYSTEMIC THERAPY

Blood Transfusion

Transfusion of packed RBCs is a commonly utilized therapy for the prevention and regulation of many clinical manifestations of SCD, including anemia, acute chest syndrome, and pulmonary hypertension.[26] The aim of transfusion therapy is to increase the oxygen-carrying capacity of the blood by reducing HbS concentration and increasing normal hemoglobin concentration.[3] Transfusion is also commonly used to aid in the treatment of recalcitrant SCUs, despite a lack of organized clinical trials on this subject.[17] Potential complications, including iron overload and alloimmunization, must be monitored in patients treated with repetitive transfusions. Iron overload occurs when abnormal levels of iron accumulate in the body; the areas most commonly affected include the heart, liver, and endocrine glands. A patient with iron overload may require repetitive phlebotomies or treatment with an iron-chelating agent.[27] This problem may be minimized with the use of exchange transfusions where sickle cell–containing blood is removed and replaced with normal and ABO matching donors. Excess iron can cause severe organ damage that is generally irreversible.

Alloimmunization occurs when the transfusion recipient has an immune response to the donor blood antigens. The antigens most commonly involved include human leukocyte antigens, granulocyte-specific antigens, platelet-specific antigens, and RBC-specific antigens.[28]

What is a Realistic Hemoglobin Level? Simple blood transfusions may be utilized to reach a normal hemoglobin concentration of 8 to 9 g/dL.[1] The optimal concentration may vary in response to SCD crises, such as cerebrovascular accident, multiorgan failure, or acute neurological deficit, following which a hemoglobin concentration of 10 g/dL should be sought. Preoperative exchange transfusions may be necessary to reduce HbS concentration to less than 30% for major surgical procedures and increase hemoglobin to 10 g/dL for moderate or low-risk procedures.[1]

Hydroxyurea. Hydroxyurea (hydroxycarbamide) is a chemotherapeutic agent and the only Food and Drug Administration (FDA)–approved drug therapy for SCD. One mechanism of action is thought to be based on its reduction of deoxyribonucleotide production via inhibition of the enzyme ribonucleotide reductase. In the treatment of SCD, hydroxyurea acts to reduce disease severity by inhibiting polymerization of HbS via increased production of HbF, the precise mechanism of which is unknown.[2,29] Other therapeutic benefits include a decrease in leukocyte and erythrocyte adhesion to the vascular endothelium.[30,31]

The role of hydroxyurea in SCUs is unclear as conflicting results have been reported. Some authors have demonstrated that hydroxyurea may aid in the treatment of refractory leg ulcers in

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SCD patients,[17] whereas others suggest it has no influence on the development of leg ulcers.[9,32,33] Several reports have also indicated that hydroxyurea may augment the development of leg ulcers.[31,34] Sirieix et al[34] reported the results of a multicenter retrospective study of 41 patients who developed leg ulceration while undergoing hydroxyurea treatment. Of these patients, 70% had no prior history of leg ulceration. Complete resolution of the ulcers was noted in 80% of patients following discontinuation of hydroxyurea therapy for an average of 3 months. Definitive, randomized controlled studies are needed to further elucidate the relationship between hydroxyurea therapy and SCUs.

Arginine Butyrate (not FDA approved for SCUs). Arginine butyrate, the butyric acid salt of the amino acid arginine, has been shown to increase production of HbF with a resultant reduction in clinical manifestations in patients with SCD.[2] The relationship between arginine butyrate therapy and SCUs was first reported by Perrine et al[35] in 1993 following phase I/II dosing trials with an incidental observation of complete recalcitrant leg ulcer resolutions. Weinberg et al[36] proposed a mechanism of action by which arginine butyrate improves the efficiency of translation of hemoglobin mRNA, leading to increased production of HbF.[36]

In 2010, 23 patients with refractory SCUs of at least 6 months' duration were included in a randomized phase II trial of arginine butyrate versus standard therapy consisting of twice-daily wound cleaning, wet-to-dry dressing changes, and surgical debridement as indicated.[37] After 3 months of therapy, subjects on the treatment arm exhibited healing in 78% of ulcers as compared with 24% in the control population ($P < .001$). In addition, complete resolution was observed in 30% of ulcers treated with arginine butyrate versus 8% treated with standard therapy alone.[37]

Although increased levels of HbF have been shown to reduce SCD-associated morbidities, the wound-healing activity of arginine butyrate is thought to occur via a separate, unknown mechanism.[37] This study demonstrated the commencement of wound healing within 3 weeks of initiation of therapy, although HbF levels did not significantly increase until 6 to 8 weeks after introduction of arginine butyrate. Further studies encompassing larger patient populations are indicated.

Nitric Oxide. Nitric oxide (NO), also known as nitrogen monoxide, is a naturally occurring free radical that serves as a cellular signaling molecule. Nitric oxide has been demonstrated to act by a number of mechanisms, including oxidation of iron-containing proteins, activation of guanylate cyclase, and activation of iron regulatory factors. Nitric oxide has receptors in the endothelium of blood vessels, which initiate relaxation of the surrounding smooth muscle, resulting in vasodilatation and increased blood flow, and also serves to reduce neutrophil adhesion.[1,38] Reduced bioavailability of NO in patients with SCD has been linked to a hemolytic-vascular dysfunction syndrome, the characteristics of the syndrome include priapism, pulmonary hypertension, and cutaneous leg ulcers.[39] Hemolysis of sickled RBCs in patients with SCD leads to extrusion of cell contents into the plasma, causing a disturbance in the diffusion barrier of plasma hemoglobin.[39] These activated molecules react with NO to form inert nitrate, which is bioinactive. The ensuing NO deficit results in vasoconstriction, contributing to clinical morbidities associated with SCD outlined previously.

Small studies concerning inhaled NO gas in patients with SCD suggest that the inhaled molecules bind preferentially with plasma hemoglobin, preventing these molecules from scavenging NO and limiting the vasoconstriction process.[39] Similar results have been demonstrated utilizing intravenously administered nitrite (NO2)[40] and dietary supplementation of L-arginine.[39]

Nitric oxide has also been noted to play a role in the healing process of burns and other cutaneous wounds.[41–43] The increase in NO levels in SCD patients may thus have implications in the treatment of persistent leg ulcers, in addition to reducing morbidities associated with hemolysis-vascular dysfunction syndrome. Similar to other potential therapeutic intrinsic or extrinsic substances, overproduction in the case of NO may cause untoward consequences. ''Nitric oxide–releasing compounds'' may be used off-label for the treatment of SCD, including Viagra for pulmonary hypertension and SCD.[44,45]

Hypomethylating Agents and Other Systemic Treatments of SCD (not FDA approved). DNA hypomethylating agents such as 5-azacytidine and decitabine have been reported in small groups of patients to markedly increase HbF, resulting in a reduction of pathogenic mechanisms in patients with SCD.[29] There is, however, a paucity of long-term data on patients treated with such therapies, and the relationship with SCUs is unknown.

The effects on wound healing of other systemic SCD treatments such as hematopoietic cell transplantation and gene therapy are unknown. The relatively small population of patients who have undergone such therapies does not provide sufficient clinical data from which to draw such conclusions, and further study is necessary.[1]

In addition to arginine butyrate, periodic transfusions, and hydroxyurea, other systemic medications and preparations, such as zinc sulfate, bosentan, and pentoxifylline, have been shown anecdotally to positively affect ulcer healing rates.[3,46] Zinc deficiency has been described in patients with SCD,[17] and the addition of oral zinc sulfate 220 mg three times a day to other SCD treatment modalities has been shown to significantly heal or improve the SCUs (21/29 in the active group and 11/29 of the placebo pill–treated population).[47]

Bosentan is a dual endothelin receptor antagonist used for the treatment of hypertension and well accepted as an important treatment for pulmonary hypertension. A study done by Serarslan et al[48] on 88 patients with SCD demonstrated a high incidence of pulmonary hypertension, 31.6% of 76 patients without leg ulcers,

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CASE STUDY UTILIZING WOUND BED PREPARATION PARADIGM

Mrs C. is 37 years old and has SCA (homozygous disease) and a leg ulcer that resulted from a traumatic event 3 years ago (foreign body removed). The ulcer on the left medial malleolus changes in size but currently measures 5.7 × 3.4 cm with healthy granulation on part of the ulcer but some slough (10%) and maceration. The chart documents the concepts for the management of SCUs.

Parameter	Finding	Comment
Treat the cause		
Anemia (hemoglobin)	• Now Hg 90 g/dL with exchange transfusions as often as every 2 wk • Previous hydroxyurea	Adequate level for healing Hydroxyurea may have delayed or prevented the leg ulcer from healing
Infections: cultures of methicillin-resistant *Staphylococcus aureus*, *Streptococcus* B, and *Pseudomonas* (in past)	• Hepatitis C virus (HCV) positive • Recurrent bacterial infections requiring intravenous piperacillin-tazobactam, meropenin, and numerous courses of oral antibiotics	HCV virus makes other infections more likely Hospitalizations with severe infections as complication of the leg ulcer
Sickle cell crises (3 episodes) since onset of ulcer	• Required hospitalizations and treatment of infections, severe pain, other complications—acute gallbladder attack and cholecystomy	Lower hemoglobin, infections, or other coexisting disorders
Venous disease	• 2 pregnancies in the past • 2 episodes of deep vein thrombosis in the past • Leg swelling at end of day • Varicosities, pigment • Biopsy: hyalinizing vasculitis—the clots in the blood vessels that are relatively noninflammatory from sickling/↑ viscosity	There are several risk factors here for venous disease. The use of multilayer inelastic or elastic high compression systems has been limited with pain, and 1 to 2 layers of elastic tubular bandage often been used as a low-compression alternative.
Patient-centered concerns		
Pain/ability to work and function	• Severe pain often 10/10 on a verbal rating score • Nalbutone—synthetic cannabis to help with pain management • Nociceptive: nonsteroidal anti-inflammatory drugs, hydromorphone—long-acting/short acting breakthrough, fentanyl patch • Neuropathic: Gabapentin • On disability and father is custodian of children	Pain and its control have been a major issue for this patient. She has required high doses of pain medication with variable effects including delirium and confusion that lead to a hospitalization (extra doses, lower hemoglobin with ↑ drug delivery). The pain and ulcer have severely disabled this patient.
Local wound care	• Debridement—surgical often painful and used calcium alginates • Critical colonization: silver dressings • Persistent inflammation + pain: foam with ibuprofen (available in Canada, not in the United States)	Local wound care needs to be gentle; avoid irrigation and harsh adhesives that can increase the local pain and discomfort. It is very difficult to debride this ulcer even with injected local anesthetic because of the severe pain.
Edge effect or advanced therapies	• Consider skin grafting if all components are corrected + wound healing is stalled • Potential for hyperbaric oxygen therapy: arterial Doppler results are normal, but small vessel occlusion may be decreasing transcutaneous oxygen to the skin	This patient has limited financial resources, and other treatment options are not available to her. A skin graft with a flap may be a reasonable alternative to heal this stalled chronic wound.

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but this percentage increased to 91.6% of the 12 patients with leg ulcers. Patients with SCD and leg ulcers should be screened for pulmonary hypertension. The use of bosentan to treat pulmonary hypertension in a patient with SCD was reported with the unintended adverse effect of complete resolution of the patient's chronic lower-leg ulcers of 18 years' duration.[46] Although the mechanism of action is unknown, the facilitation of healing is thought to be due to the endothelial receptor blocker characteristics of bosentan and its effects on the high levels of endothelin 1, which may be found in patients with SCD.[49]

Wound healing in vascular leg ulcers has been reported with propionyl-L-carnitine; however, a randomized, double-blind, placebo-controlled pilot study showed no significant improvement in ulcer healing rates of SCD patients treated with propionyl-L-carnitine, versus placebo.[50] Pentoxifylline has also demonstrated efficacy in vascular leg ulcers, but there is a paucity of data regarding its efficacy in SCUs. Frost and Treadwell[51] reported the successful treatment of a sickle cell patient with pentoxifylline, which is thought to act by reducing the RBC sickling, decreasing erythrocyte deformability, and increasing leukocyte flexibility. It may also inhibit platelet aggregation, reduce blood viscosity, and decrease plasma fibrinogen levels,[3,17,51] although clinical data to support these mechanism have yet to be found. Randomized controlled trials are needed to evaluate the efficacy of this and many of the other therapies for SCUs.

Conclusion

Leg ulcers are a common and challenging cutaneous complication in patients with SCD. The treatment strategies in the diagnosis, treatment, and the management of infection and pain require an interprofessional team with a mastery of system-based management. The success of the management of SCUs involves treatment of underlying SCD and its associated anemia, pain management, unlikely but potential narcotic dependency, and local and systemic infections. The use of hydroxyurea may impair the healing of SCUs, whereas blood transfusions may facilitate healing. Local wound care for healable SCUs includes debridement, moisture balance, and topical treatment of critical colonization and abnormal inflammation. When a wound is stalled, despite optimal care and correction of the components of wound bed preparation, various skin grafting modalities and techniques should be considered.

Systemic agents promoting increased HbF (arginine butyrate, 5-azacytidine, decitabine) and NO (free radical signaling molecule)–enhancing preparations need further study in order to become accepted therapies of the future. In the meantime, patient education regarding risk of recurrence, compression therapy for coexisting venous disease, and methods of prevention are all important patient-centered considerations. ●

PRACTICE PEARLS

- For the healing of sickle cell disease–related leg ulcers, fetal hemoglobin (HbF) levels should be greater than 8 g/dL (ideally 10 g/dL).
- Sickle cell disease (SCD) patients require pain control with a numerical rating scale less than 3-4: use agents for neuropathic and nociceptive pain.
- Hydroxyurea may impair healing of sickle cell–associated leg ulcers (SCUs).
- Check SCD patients with SCUs for pulmonary hypertension (>90%).
- Local wound care: nonhealable/maintenance wounds—conservative debridement and bacterial/moisture reduction.
- Local wound care: healable wounds—active debridement and bacterial/moisture balance.

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