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# Leg Ulceration in Sickle Cell Disease: An Early and Visible Sign of End-Organ Disease

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## Abstract

**Introduction:** Leg ulcers are a frequent and debilitating complication of sickle cell disease (SCD), particularly of the SS genotype. The prevalence of leg ulcers in patients with sickle cell disease (SCD) varies geographically ranging widely from 75% in Jamaica to as low as 1% in Saudi Arabia. The prevalence of leg ulcers in the Cooperative Study of Sickle Cell Disease (CSSCD) in the United States was 5% in SS genotype with the incidence increasing with age. As patients with SCD have increasingly improved survival, the prevalence of leg ulcers is likely to be higher. These ulcers are slow to heal, have a high rate of recurrence, and are associated with severe unremitting pain and depression, thus leading to high healthcare costs. Despite being a well-recognized complication of SCD, there are no specifically designed evidence-based guidelines to help clinicians manage these patients.

**Methods:** To prepare this manuscript, we searched PubMed using the search terms “sickle cell,” “ulcer,” “sickle cell,” and “wound.” We also appraised the references mentioned in the identified articles. Inclusion criteria included case reports, case series, retrospective reviews, clinical trials, randomized controlled trials, systematic reviews, and meta-analyses from 1945 to 2016. We present our extensive personal observations and expert opinion, whenever there is a lack of reliable data.

**Conclusion:** Our understanding of the pathophysiology of leg ulceration in sickle cell disease is improved, though still limited since the first described case in the English literature over 100 years ago. Moreover, there remains a paucity of good quality randomized clinical trials to test new and effective therapies. No evidence-based guidelines for the management of these patients are available. Currently, a holistic multidisciplinary approach is recommended with adequate systemic control of SCD as well as aggressive local therapy, with a focus on targeting pathways involved in potentiating healing of these ulcers including novel approaches like topical nitric oxide donors. SCD patients with leg ulcers represent a cohort of patients who are at an increased risk of developing other vasculopathic complications that have a potentially common mechanism including pulmonary hypertension, renal and retinal disease, and

priapism. Prospective trials are needed to better evaluate the natural history of these patients in the modern era and develop preventative and therapeutic strategies for the management of this serious complication.

**Keywords:** leg ulcers, wounds, sickle cell disease

## 1. History

The first patient with SCD described in the English medical literature more than 100 years ago suffered from leg ulceration [1, 2, 4–7, 9]; however, it was not until 1939 that the causal role of SCD in leg ulceration was established [3].

## 2. Epidemiology

### 2.1. Prevalence and geographic variation

Leg ulcers are a frequent and debilitating complication of sickle cell disease, particularly of the SS genotype. The prevalence of leg ulcers in patients with sickle cell disease (SCD) varies geographically widely ranging from 75% in Jamaica to 1% in Saudi Arabia [4–5]. In the Cooperative Study of Sickle Cell Disease (CSSCD) in the United States, the overall prevalence was 2.5%, in persons 10 years of age and older and was higher in patients with SS disease (4.97%) and SS-alpha thalassemia (3.92%) compared to patients with SC disease and SS-beta thalassemia [6]. However, over 70% of the study population was under the age of 30 years, and along with improved survival of SCD patients, the prevalence of leg ulcers is likely to be much higher. In a sickle cell clinic in West Indies, 58% had a history of leg ulcers out of 102 patients who survived beyond 60 years of age [8]. About 20% of the 505 patients screened at the National Institutes of Health (NIH) recalled having had an ulcer [9]. The incidence of leg ulcers in sickle cell patients is hard to elucidate given the lack of any recent large prospective trials. The incidence of leg ulcers in patients with SS genotype was 9.97/100 persons in the Cooperative Study of Sickle Cell Disease [6]. In comparison, the prevalence of venous ulcers in the general population in the United States is approximately 600,000 annually [10] with 1% of the population is affected at any given time. Thus, the incidence of leg ulcers in patients with SCD exceeds that of the general population by more than tenfold and also occurs at a younger age.

The striking geographic differences in leg ulcer prevalence may be attributed in part to the differing age structure of the studied populations; however, there does seem to be a difference even after adjusting for age. Different SCD haplotypes differ in their clinical severity. The Bantu haplotype usually has more severe clinical manifestations compared to others; however, there exists a considerable variation within haplotypes as well [11]. Leg ulcers have been reported to be more common in carriers of the CAR beta-globin gene cluster haplotype [12]. Among patients who have the Asian haplotype, leg ulceration is rare among

adults in both the eastern province of Saudi Arabia [5, 13] and central India [4, 14]. Though not yet defined, environmental, socioeconomic, and genetic factors are most likely responsible for the variations in incidence.

## 2.2. Age

Studies from Jamaica and personal observations indicate that leg ulcers' first occurrence is rare before 10 years of age, is most frequently seen between 10 and 25 years of age, and continues to increase in frequency after 30 years [2, 4]. In the CSSCD, incidence increased sharply after second decade of life, ranging from 14.59 to 19.17 in hemoglobin SS patients and from 7.57 to 11.13 in patients with hemoglobin SS-alpha thalassemia [6].

## 3. Risk factors

### 3.1. Gender

Some studies found a male preponderance with the rates being 15 and 5/100 person-years in men and women, respectively, in the CSSCD cohort [6]. Similar patterns were observed in Ghana [15]. However, no difference was seen in studies from Nigeria and Jamaica [4] nor in more recent reports [12].

### 3.2. Hematology

#### 3.2.1. Type of SCD

The prevalence of leg ulcers is higher in patients with SS and SS-alpha thalassemia than among those with SC, SB+, or SB0 genotypes. Alpha thalassemia with two alpha gene deletions seems to be protective against development of leg ulcers in patients with sickle cell disease [6]. In CSSCD, incidence of leg ulcers was significantly lower in SS patients with two alpha gene deletions compared to patients with SS disease and SS patients with three alpha gene deletions. More recent data have shown that alpha thalassemia (one gene deletion) is not protective [12].

#### 3.2.2. Hemoglobin and hemoglobin F level

Data from CSSCD suggest that higher hemoglobin level as well as higher fetal hemoglobin percentage is protective against development of leg ulcers in SS patients, whereas only fetal hemoglobin is protective in SS- alpha thalassemia patients [6].

Incidence of leg ulcers was 43.2 events per 100 person-years in patients with hemoglobin levels <6 g and 2.4 events per 100 person-years in patients with hemoglobin >12 g.

In both genotypes, the incidence of leg ulcers decreased with an increase in fetal hemoglobin. Incidence was 0.7/100 person-years in patients with HbF levels of >10% compared to 13/100 person-years in patients with HbF levels of <5%. Most recent series [12, 16] did not show a relationship between HbF and leg ulcers. Of note is that the latter study included individuals

that received hydroxyurea (HU) therapy and whose elevated HbF levels were not constitutional, but induced by the use of this drug. Patients did not enjoy its protecting effects since birth, as in the case of the older studies. Furthermore, hydroxyurea's other (negative) effects on angiogenesis could have blunted the benefits of high hemoglobin F.

## 4. Pathogenesis

### 4.1. Mechanical obstruction of microcirculation

Sickle cell disease is characterized by vasoocclusion. The rigid deformed sickle cells get entrapped in the microcirculation leading to hyperviscosity, decreased blood flow through venules and capillaries, and chronic hemolysis resulting in anemia, ischemia-reperfusion injury, and inflammation causing end-organ damage [4]. Studies have shown that the hematocrit to viscosity ratio as well as red blood cell (RBC) deformability was reduced in sickle cell patients with leg ulcers [17, 18]. The marginal circulation of the malleoli is particularly susceptible to this obstruction of microcirculation, making them the most common site for sickle cell leg ulcers.

### 4.2. Hemolysis-vascular dysfunction syndrome

Nitrogen oxide (NO) is a natural occurring free radical found in plasma. Receptors for NO present on the endothelium initiate relaxation of vascular smooth muscle causing vasodilation and increased blood flow along with reduced neutrophil adhesion. Chronic hemolysis is a hallmark of SCD and results in red blood cell (RBC) membrane damage, cell breakdown, and extrusion of free hemoglobin into plasma. This free hemoglobin scavenges NO, reducing its bioavailability and thus linked to hemolysis-vascular dysfunction syndrome which is characterized by chronic vasoconstriction contributing to leg ulcers, priapism, and pulmonary hypertension [19, 20].

### 4.3. Venous incompetence

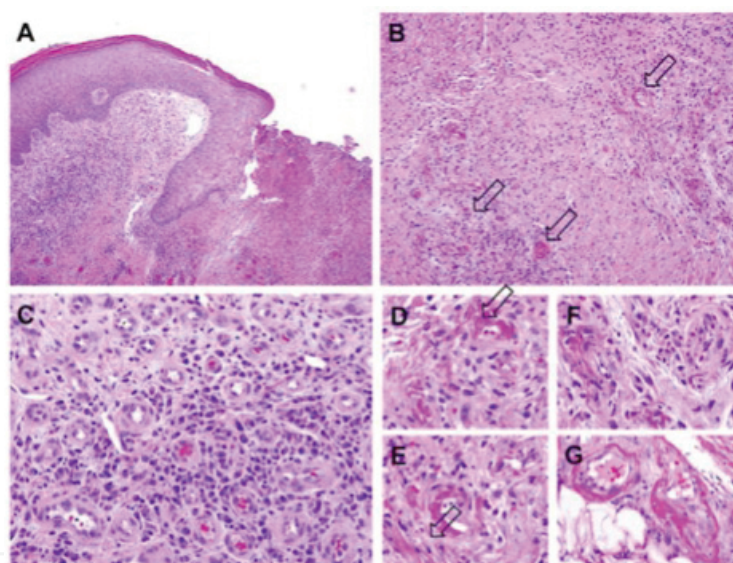
An early study of 16 SCD patients with leg ulcers using manometry and the Doppler studies failed to demonstrate venous insufficiency as a primary factor in development of leg ulcers in SCD [21]. However, edema and pain often precede ulceration in these patients, and numerous studies since then have linked venous stasis with sickle cell leg ulcers [7]. Venous stasis in the calf muscles was suggested by the delayed clearance of  $^{99m}\text{Tc}$  [22] and by magnetic resonance spectroscopy studies [23] in SS patients with leg ulcers as compared with those without.

Mohan et al. described reduced venous refilling time and cutaneous red blood cell flux recovery time after exercise in patients with SS disease with leg ulcers compared to SS and AA patients without ulcers. They proposed incompetence in venous valves around the ankle resulting in venous hypertension and development as well as delayed healing of leg ulcers [24]. The Jamaican cohort study of 183 SS and 137 age- and sex-matched AA controls showed significant association of venous incompetence and leg ulcers in SCD. Contributing factors

were hypothesized to include sluggish circulation with dependency, turbidity and impaired linear flow at venous valves, hypoxia-induced sickling, rheological effects of high white cell counts, and activation of coagulation cascade [25]. Cummings et al. obtained similar results in 2007 with venous incompetence significantly linked to development of leg ulcers in SCD [26]. Minniti et al. used laser speckle contrast imaging (LSCI) and infrared (IR) thermography to study regional blood flow of ulcer beds. The presence of venostasis was confirmed by their finding of increased number of blood vessels with fibrin thrombi and vascular occlusion [16]. Cutaneous hemosiderosis, dermatosclerosis, and prominent superficial veins are frequently found in SCD patients and further support the role of venostasis in the pathogenesis of leg ulcers. Further clinical evidence comes from the fact that ulcers tend to worsen on prolonged standing and improve with bed rest and compression therapy [7, 16, 25, 26].

#### 4.4. Hypercoagulability, thrombosis, and inflammation

Ischemic injury caused by microvascular occlusion by sickle cells initiates a pro-inflammatory and procoagulant cascade that is initiated by the upregulation of RBC integrins. This is



**Figure 1. Microscopic analysis of skin biopsies. Evidence of increase in vascularity, chronic inflammation, vasculopathy with blood vessels occlusion, fibrin deposition in the intima, and microthrombi.** *Panel A:* Scanning magnification view of the skin punch biopsy showing edge of an ulcer from the right ankle of patient MD. The epidermal changes adjacent to the ulcer are characterized by acanthosis, hyperkeratosis, and attenuated rete ridges. There are increased vascularity and inflammation in the dermis (H&E, 100× original magnification). *Panel B:* The histological changes subjacent to the ulcer bed are characterized by chronically inflamed granulation tissue with vasculopathic changes involving some of the small blood vessels (H&E, 200× original magnification). *Panel C:* High magnification view of the superficial dermal vessels peripheral to the ulcer shows proliferation of thick-walled capillaries and venules, consistent with chronic stasis. There is a lymphoplasmacytic inflammatory infiltrate in the dermis (H&E, 400× original magnification). *Panels D–F:* Very high magnification view of involved vessels subjacent to the ulcer bed reveals eosinophilic fibrin deposits within the vessel wall and partial occlusion of the vascular lumen (H&E, 600× original magnification). *Panel G:* Scanning magnification view of the skin punch biopsy obtained from the right dorsal foot of patient DD shows vasculopathic changes involving a cluster of small blood vessel in the deep dermis (H&E, 40× original magnification). *Panel H:* High magnification view of the involved vessels reveals eosinophilic fibrin deposits within the vessel wall associated with intimal hyperplasia and narrowing of the vascular lumen (H&E, 400× original magnification). Reproduced with permission from Minniti et al. [16].

followed by RBC adhesion to the endothelium, platelet aggregation, and granulocyte recruitment with the release of pro-inflammatory cytokines [27]. The cycle of vessel obstruction and ischemic injury is hence perpetuated, culminating in further end-organ damage. Minniti et al. provided histopathologic evidence of vasculopathy characterized by mural fibrin thrombi causing luminal narrowing and progressive vascular occlusion in small vessels in ulcer beds of SCD patients with leg ulcers [16] (**Figure 1**). Earlier studies also alluded to the procoagulant state in SCD patients including elevated levels of factor VIII and low levels of antithrombin III and prothrombin complexes [28, 29]. SCD ulcer patients have higher levels of soluble ICAM-1 and the key inflammatory cytokine IL-1 beta [30]. Oxidative stress has been shown to play a role in leg ulcer pathogenesis in sickle cell patients, and patients with glutathione S-transferase polymorphism (GSTM1 and GSTT1 null phenotypes) have been shown to have a high risk of developing ulcers [31].

#### 4.5. Autonomic dysfunction

Cardiac output is increased in patients with SS disease, and this may affect the distribution of peripheral blood flow and reflex vascular responses [4]. Normal microcirculation of the lower extremity (LE) is characterized by the venoarteriolar vasoconstriction reflex and the disappearance of vasomotion in the dependent position. It was noted that the venoarteriolar reflex was abolished and vasomotion preserved in the dependent position of the leg in SCD patients [32]. In addition to a high resting perfusion in patients with SCD to maintain normal integrity of cutaneous tissue, there occurs a pronounced vasoconstriction on dependency that exacerbates ischemia and pain, delays healing, and promotes recurrence of leg ulcers [7, 33].

#### 4.6. Bacterial colonization

The role of bacteria in the pathogenesis of leg ulcers is uncertain. Secondary bacterial colonization is inevitable and usually not considered to be clinically significant. Commonly isolated bacteria in African reports include *Staphylococcus aureus*, beta-hemolytic *Streptococci*, *Pseudomonas aeruginosa*, and *Salmonella*. Anaerobes comprised >50% of isolated bacteria in an African series, whereas bacterial flora is predominantly aerobic and polymicrobial in Jamaican reports. Bacterial colonization although unlikely to initiate ulceration may contribute to persistent inflammation of surrounding tissue that results in delayed healing [7]. Baum et al. reported improved healing with topical antibiotics; however, this carries the risks of bacterial resistance, contact sensitization, and disruption of wound moisture balance [7]. Researchers no longer rely solely on culture for identification of bacteria and are utilizing sophisticated sequencing techniques to elucidate the full diversity of microbial communities on the human body [34]. The ulcer skin microbiome, which has been thought only as a commensal on healthy skin, can contribute to delayed healing of ulcers in patients with sickle cell disease by causing excessive activation of both the innate and adaptive immune systems [35]. Emerging data from the study of diabetic wounds shows that the diversity of the skin microbiome correlates with ulcer characteristics [36], and it is likely that similar mechanisms are at play in sickle cell leg ulcers that may explain the variability in their occurrence.

## 4.7. Genetic factors

Studies suggest that the expression of certain genes may contribute to the development of leg ulcers in SCD; however, the data on genetic associations with leg ulcers remains limited [12].

### 4.7.1. Candidate gene studies

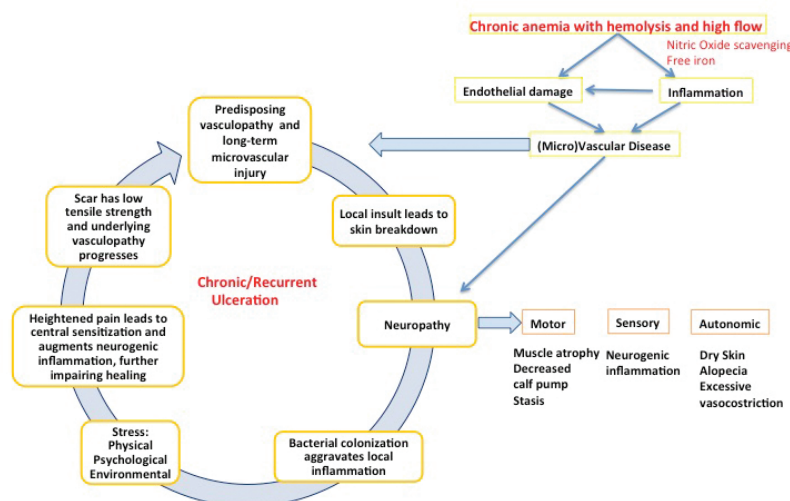
Ofusu et al. published a study of 9 cases and 29 controls in 1987 suggesting a possible association of HLA-B35 and CW14 alleles, with carriers of both alleles having a 17-fold increased risk of developing leg ulcers. This study was limited due to its small size as well as the identified region being hard to study due to long-range disequilibrium [12, 37].

Another candidate gene study of 243 cases and 516 controls from the CSSCD by Nolan et al. identified associations with single nucleotide polymorphisms (SNPs) in Klotho (promotes endothelial NO production), TEK (involved in angiogenesis), and numerous genes in the transforming growth factor- $\beta$  (TGF- $\beta$ )/BMP pathway (modulates angiogenesis and wound healing) [38].

Some of the same SNPs have been reported to be associated with risk of stroke, pulmonary hypertension, and priapism, further supporting the observation that leg ulcers are often associated with other sickle cell sub-phenotypes [12].

### 4.7.2. Genome-wide association studies

Preliminary results from genome-wide association studies of 219 cases and 1180 controls from the CSSCD identified 30 SNPs associated with leg ulcer. It also showed that a cluster of genes in the MHC III region of chromosome 6 to be highly associated with leg ulcers [12]. A cross-sectional study identified that an SNP in IL-6, a pro-inflammatory cytokine, was associated with higher likelihood of leg ulcer and retinopathy [39].



**Figure 2.** Proposed simplified mechanism of sickle cell ulcer pathogenesis. Reproduced and modified with permission from Minniti et al. [2].

#### 4.7.3. Summary

Minniti and Kato proposed a stepwise, multifactorial model for SCD ulcer pathogenesis (see **Figure 2**) that depicts an interplay between poor nutrition, low BMI, skin injury, inflammation, thrombosis, hemolysis, vasculopathy, neuropathy, and poor socioeconomic status [2, 9, 16, 29, 33, 40].

## 5. Characteristics of ulceration

### 5.1. Mode and age of onset

Ulcer onset can be traumatic or spontaneous. Trauma accounts for approximately half the cases, which are incited by relatively insignificant physical damage such as scratches, abrasions, and animal or insect bites. In spontaneous ulcers, there is no history of trauma, but a lesion develops within the dermis often with surrounding induration and hyperpigmentation [7]. Initially, lesions may be covered by an intact epidermis, which then breaks down forming small, deep, and painful ulcers. Spontaneous ulcers are thought to originate from skin infarction. Ulcers occur initially in the second decade of life, around 18–20 years of age. The occurrence of a de novo ulcer in older patients is not common, unless the patient had an ulcer before.

### 5.2. Site

Leg ulcers most frequently affect the skin around the medial or lateral malleoli but can also occur on the anterior shin or dorsum of the foot [4] and occasionally in the digits [Minniti, personal observation]. The predilection for the malleoli is likely multifactorial due to marginal blood flow at the site, high venous pressure, less subcutaneous fat, thin skin, and lymphedema [12, 27]. This is similar to other hematologic conditions including hereditary spherocytosis,  $\beta$ -thalassemia intermedia, and Felty's syndrome. While medial involvement was more common in two studies [41, 42], there was no such difference found for the medial, lateral, left, or right legs in the CSSCD [6].

### 5.3. Size

In the CSSCD, ulcers ranged between 0.5, 5–10, 10–15, and >15 cm with equal frequency. Most Jamaican studies had ulcers <10 cm in size. However, large circumferential ulcers portend a poor prognosis due to inevitable damage to vessels and lymphatics [4]. Pain is not related to wound size, and often initial, small ulcers are extremely painful (see **Figure 3**). Purulence, poor granulation tissue, and nonhealing are frequently reported in ulcers >10 cm.

### 5.4. Appearance

Ulcers in individuals with sickle cell disease usually have a punched appearance with well-defined margins and slightly raised edges. The base comprises granulation tissue, often

covered by yellow slough. More than half of patients will have more than two ulcers that are present at the same time, and multiple small ulcers may then coalesce to form a large ulcer.

Histology of an early leg ulcer shows neovascularization, chronic inflammation, vasculopathy with blood vessel occlusion, fibrin deposition in the intima, and microthrombi [16] (see **Figure 1**). The epidermis adjacent to the ulcer reveals acanthosis, hyperkeratosis, and attenuated rete ridges. There is increased vascularity and inflammation in the dermis with a lymphoplasmacytic inflammatory infiltrate. Chronically inflamed granulation tissue with vasculopathic changes in small blood vessels is found subjacent to the ulcer bed [2, 4].

### 5.5. Staging and severity of leg ulcers

Ulcers may be staged according to their depth as follows [12]:

Stage 1: Nonblanchable erythema of intact skin, which may present as skin discoloration, warmth, edema, or induration in darker skinned patients.

Stage 2: Partial-thickness skin loss involving epidermis, dermis, or both, presenting as an abrasion, blister, or shallow crater.

Stage 3: Full-thickness skin loss involving damage to or necrosis of subcutaneous tissue that may extend down to, but not through, underlying fascia. The ulcer presents clinically as a deep crater with or without undermining of adjacent tissue.

Stage 4: Full-thickness skin loss with extensive tissue destruction or damage to muscle, bone, or supporting structures (tendon, joint capsule).



**Figure 3.** Large sickle cell leg ulcers associated with foot deformities (from author's personal collection).

## 5.6. Healing and recurrence

Leg ulcers can be classified as acute or chronic although there is no consensus as to a specific length of time to define chronicity. An acute ulcer usually heals in less than a month. Chronic ulcers usually persist for at least 6 months and may last for several years. As described above, ulcer healing is typically slow as the ulcer fills in with granulation tissue, and a bluish epithelium may be seen growing in from the ulcer margin. Healing rates of 3.3–8.1 mm<sup>2</sup>/d have been reported in SS disease [43, 44] compared with rates of 400 mm<sup>2</sup>/d in other types of leg ulcer [45]. Even after satisfactory healing, 25–52% recurred in the CSSCD [6]. It is generally accepted, and it is the author's experience that if an ulcer does not heal within 6 months, its chances of ever healing are slim.

Minniti et al. have proposed three patterns of leg ulcers in SCD [2]:

- *One-time ulcer*

One half of patients with SCDs will develop only one ulcer in their lifetime. It usually occurs in the second decade of life, heals within several months, and may recur during periods of stress. These patients often have infrequent pain crisis and have renal and pulmonary complications.

- *Stuttering ulcer*

Twenty-five percent of SCD patients develop small ulcers that recur every 6–12 months for several years.

- *Chronic, recurrent ulcer*

Approximately 1% SCD patients in the United States develop an ulcer that persists for years or even decades and/or ulcers that recur in the same or nearby sites. These patients experience the most disabling chronic pain, unemployment, and depression. Amputation may need to be considered in rare cases to improve quality of life [2, 46]. These patients are often tall, undernourished, and severely anemic with high hemolytic rate. They may have nephropathy, have rare vasoocclusive crisis, and often have trouble with employment, social interaction, and depression.

## 6. Diagnosis

### 6.1. History

Leg ulcer pain may be severe, excruciating, penetrating, sharp, and stinging. Patients often report a crescendo of localized pain just before new ulcers develop [2]. About 40–50% of patients recall prior trauma [15, 16], often trivial or pruritus that incites scratching and skin breakdown. The pain is often exacerbated by exposure to cold and to air. The size of the ulcer does not necessarily correlate with intensity of the pain, and very small ulcerations can be extremely painful as well. Most patients require opioids for pain control.

Patients should be specifically asked about history of ulcers, since many patients will report having leg ulcers at some point in their lifetime and may not volunteer the information themselves. History should also document prior ulcer therapies and other complications associated with leg ulcers in SCD including pulmonary hypertension, stroke, priapism, acute chest syndrome [38, 45], lower extremity venous thrombosis, and retinopathy [2].

## 6.2. Physical examination

Physical exam should assess the wound size with ruler measurement as well as digital photography for greater accuracy [47]. Surrounding skin hypo- or hyperpigmentation, edema, and muscle atrophy should be noted. Although serous discharge and fibrinous material are common, periwound erythema, purulent discharge, and worsening pain may be signs of acute infection. Inguinal lymph nodes are often enlarged, especially during ulcer exacerbations and do not necessarily signify infection. Pulse oximetry as well as blood pressure may be low. Attention should be paid to the nutritional status of patients as many are malnourished [2].

## 6.3. Lab testing and imaging

Sickle cell individuals with ulcers often have infrequent pain crises and may not have sought regular medical care prior to their presentation. Occasionally, this will be the first time a physician has evaluated them for end-organ diseases. Complete blood count and chemistry panel often reveal markers of severe chronic hemolysis. A significant increase in LDH may be seen [48]. Urinalysis may show microalbuminuria. Serum C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are often elevated. Patients may have low levels of antithrombin III, protein C or S, high level of factor VIII, or positive lupus anticoagulant. Wound cultures usually reveal only superficial colonizing bacteria and are rarely helpful. Nutritional status and exercise tolerance with 6-minute walk test (6MWT) should be recorded. When interpreting 6MWT, be aware that shorter distances secondary to physical impairment and pain can be caused by the ulcer. Echocardiography should be obtained to evaluate tricuspid regurgitant velocity to screen for pulmonary hypertension. Imaging studies of bones commonly show demineralization and bone infarcts. MRI should be obtained when osteomyelitis is suspected, but the gold standard for diagnosis remains bone biopsy. Osteomyelitis in the underlying bone is a rare occurrence, but if not diagnosed and treated appropriately will prevent healing [2]. A Doppler ultrasound of the lower extremities should be obtained to rule out the presence of a DVT.

## 7. Treatment

The management of leg ulcers in SCD involves a multipronged and multidisciplinary approach (see **Table 1**) with involvement of the primary hematologist, wound care specialist, nutritionist, surgeon, and social worker [2]. There remains a paucity of data from randomized controlled trials to guide treatment [49]. Current practice relies mostly on data from small case reports and case series along with expert opinion.

Local therapies	Systemic therapies
Topical antibiotics	Zinc sulfate
Skin grafts (autologous or bioengineered)	Pentoxifylline
RGD peptide matrix	L-Carnitine
Moist wound dressing	Arginine butyrate
Growth factors	Endothelin antagonists: bosentan
Medical honey	Hydroxyurea
Allogeneic keratinocytes	Red blood cell transfusions
Collagen matrix	Systemic antibiotics
Autologous or allogeneic platelet gel	Hyperbaric oxygen therapy
Synthetic heparan sulfate	
Topical sodium nitrite	
Energy-based modalities	
Negative-pressure wound therapy	
Leg compression and leg elevation	
Topical analgesics	
MIST™	
Transdermal oxygen	
Maggots	
Surgical debridement	

**Table 1.** Treatment modalities that have been used in patients with sickle cell disease and leg ulcers.

## 7.1. Topical treatment

### 7.1.1. Role of topical antibiotics

A randomized controlled trial of a topical antibiotic preparation (neomycin, bacitracin, and polymyxin B) in 30 patients with SS disease and chronic leg ulceration showed a significant reduction in ulcer size over a period of 8 weeks in the treatment group compared to the control group [50]. However, this trial had a high risk of bias, and the majority of the literature since 1987 questions the role of bacterial infections in wound pathogenesis [7, 51].

### 7.1.2. *Type of dressing*

La Grenade et al. conducted a randomized controlled trial, in 32 patients with SS disease, of Solcoseryl®, DuoDerm®, and conventional therapy, cleaning with Eusol® (a mild antiseptic) followed by wet dressing. Patients were randomized to one of three therapies and monitored for 12 weeks. DuoDerm® (ConvaTec, Greensboro, NC) hydrocolloid dressing was generally unacceptable, and two-thirds of the patients defaulted from this treatment. Solcoseryl®, a deproteinized extract from calf's blood that is meant to improve the tissue utilization of oxygen, increased ulcer healing compared to the controls, but the difference was not significant [52].

### 7.1.3. *RGD peptide matrix*

A 2014 Cochrane review described single trial that used an arginine-glycine-aspartic acid matrix (RGD peptide matrix) that achieved noticeable benefit in the treatment of leg ulcers in SCD. The RGD peptide matrix is believed to act as a synthetic extracellular matrix to promote cell migration, keratinocyte layer formation, and wound strengthening. Chronic ulcers treated with RGD peptide matrix had a statistically significant decrease in surface area; however, further studies are needed to corroborate these findings [51, 53].

### 7.1.4. *Moist wound-healing approach*

A small retrospective cohort study underscored the efficacy of simple moist wound-healing approach in patients with chronic leg ulcers in SCD who had failed to heal despite treatments such as debridement, split-thickness skin grafts, muscle flaps, wet-to-dry dressings, Unna boots, hydroxyurea, recombinant human erythropoietin, and arginine butyrate. Ultimately, all patients were treated with topical hydrocolloid dressing (DuoDerm CGF by ConvaTec). The eight patients who had not received surgical treatment healed completely within 2–16 months, with only one recurrence at 4 months. Of the ten patients who had previous surgical treatment, six healed without recurrence at 30 months, two experienced recurrence with resolution upon the reapplication of DuoDerm, and two did not heal though did not experience worsening of their ulcers [2, 54].

### 7.1.5. *Growth factors*

Several case reports have used topical growth factors as an approach to treating leg ulcers.

Granulocyte-macrophage colony-stimulating factor (GM-CSF) has been used topically and via intracutaneous injection [55, 56]. The cytokine activates macrophages and induces the proliferation of keratinocytes and differentiation of myofibroblasts. While it was shown to be beneficial in wound healing [55–58], high cost, severe vasoocclusive, and even fatal events have discouraged its use [58].

#### 7.1.6. *Use of skin substitutes*

There are several skin substitutes that are available commercially. One of them, Apligraf® (Organogenesis, Canton, MA), is a bi-layered bioengineered skin substitute that has been approved by the Food and Drug Administration (FDA) since 2000 for the treatment of diabetic foot ulcers and venous leg ulcers (VLUs) that have not responded within 4 weeks to standard of care (SOC) therapy [7]. Apligraf provides both cells and matrix for the nonhealing wound possibly via production of cytokines and growth factors similar to healthy human skin [59]. Several studies confirm the efficacy of Apligraf in treatment of VLUs, and the Society of Vascular Surgery approves the use of Apligraf for the treatment of VLUs [57, 60–62]. The optimal frequency of use is not known, and current clinical practice is for consideration of reapplication after at least 1–3 weeks of observation after initial application [7].

Gordon and Bui examined the efficacy of Apligraf in their study of sickle cell patients with chronic ulcers. Prior to application, they used a 4-week regimen of hydrogel, followed by 1 week of wet-to-dry dressings and 1 week of wet-to-dry dressings plus application of papain-urea debriding ointment (Accuzyme). After 6 weeks, the ulcer was sufficiently optimized for closure. The use of Apligraf resulted in complete healing, and the ulcer remained healed at the last follow-up (33 months) [63].

#### 7.1.7. *Allogeneic keratinocytes*

Allogeneic keratinocytes have been used to promote the migration of autologous keratinocytes from the peripheral wound bed. Sheets of cells applied twice per month successfully healed a chronic ulcer within 3 months, without recurrence at follow-up at 8 months [64].

#### 7.1.8. *Collagen matrix*

Two patients with chronic ulcers were treated with Collistat (collagen matrix) every 4 weeks and experienced complete healing by 10 and 12 weeks [65].

#### 7.1.9. *Autologous platelet gel*

A case series reported the use of an autologous platelet gel to treat leg ulcers in five SCD patients. Autologous platelet-enriched plasma was applied to the wound margins and fibrin matrix clot to the wound bed, before covering with moist saline gauze. A significant local release of platelet-derived growth factors (PDGFs), transforming growth factor- $\beta$  (TGF- $\beta$ ), and vascular endothelial growth factor (VEGF) was noted. Three of the patients showed a reduction of the leg ulcer area by 85.7–100% within 6–10 weeks. Two patients with ulcers threefold to tenfold larger experienced 20.5% and 35.2% decreases in the leg ulcer area. The authors concluded that the use of autologous platelet gel offers a promising and cost-effective adjuvant treatment for leg ulcers particularly in small ones [66].

#### 7.1.10. *Synthetic heparan sulfate*

A synthetic, bioengineered heparan sulfate solution, Caciqliq20, was used to treat a nonhealing leg ulcer. The solution is designed to function as a glycosaminoglycan mimetic, potentially restoring the extracellular matrix scaffold and enhancing growth factor recruitment to aid in collagen production and angiogenesis and to restore tissue homeostasis and protect the wound from further damage. The patient in this case report had failed to respond to several treatments, including moist wound therapy, grafting, and energy-based modalities. The patient experienced complete healing after 8 weeks of twice-weekly applications [67].

#### 7.1.11. *Topical nitrite therapy*

A phase 1 trial of escalating doses of topical sodium nitrite demonstrated a dose-dependent improvement in ulcer healing and decreasing pain at the ulcer site [68]. Application of topical sodium nitrite twice weekly for 4 weeks was associated with a significant increase in periwound cutaneous blood flow measured by laser speckle contrast imaging. It appeared to be well tolerated with no grade 3–4 adverse events. The authors concluded that topical sodium nitrite 2% cream is suitable for additional clinical trials in adults with sickle cell anemia to promote healing of leg ulcers.

#### 7.1.12. *Topical honey*

Topical honey has been utilized mostly in burns and postoperative wounds as a dressing providing a moist healing environment in addition to its natural anti-inflammatory, healing, and antibacterial properties [69]. Its use has also been described in the sickle cell literature for treatment of leg ulcers [15].

#### 7.1.13. *Energy-based modalities*

Low-frequency, noncontact ultrasound (e.g., MIST®) has been employed to accelerate healing of sickle cell ulcers. It is believed to act via effective removal of bacteria and biofilm along with reduction of chronic inflammation. It also appears to promote the release of NO and growth factors at the cellular level, thereby stimulating vasodilation, angiogenesis, and collagen deposition. This modality can also be used to optimally prepare the wound for grafting [70].

Low-level laser therapy has been reported to result in 80% reduction in the area of a leg ulcer after just five 10–15-minute sessions, leading to a marked improvement in the patient's quality of life [71]. Low-level laser therapy has previously been reported to modulate wound healing by increasing mitotic activity, fibroblast production, collagen synthesis, and angiogenesis and may have a role in the apoptotic processes of wound healing [72].

#### 7.1.14. *Negative-pressure wound therapy*

Paggiaro et al. examined the use of negative-pressure wound therapy (NPWT) in leg ulcers. Following surgical debridement and before grafting, three wounds were treated by different methods: a rayon and normal saline solution dressing, calcium alginate and gauze, and

negative-pressure therapy. Researchers found that the NPWT-treated wounds had a more homogenous surface with better vascularization in comparison with the other two groups. All three wounds received a split-thickness skin graft. While the other wounds experienced subsequent graft failure, the NPWT-treated wound did not, and the ulcers had not recurred by the time of follow-up (11 months) [73]. However, the painful nature of leg ulcers in SCD may be a limiting factor in the use of NPWT.

#### 7.1.15. *Role of leg compression*

Bed rest has been shown to promote ulcer healing. Patients who underwent 2–3 weeks of strict bed rest experienced complete closure of their wounds within 2–3 months. In addition to reducing venous back pressure and edema around the ankle, patients developed improvement in RBC deformability, possibly secondary to decreased plasma volume, which also aided healing [74]. However, this approach is not very practical.

The use of compression devices has been shown to be effective in reducing edema and improves healing in other types of ulcers. Although there are no prospective studies evaluating their role in sickle cell-related ulcers specifically, these were universally recommended in a survey of care providers treating these patients [75, 76]. The use of Unna boots is highly recommended by practitioners, as the zinc oxide-impregnated boots are useful in treating lower extremity lesions exacerbated by venous insufficiency. Multicomponent compression systems have been shown to be the most effective in reducing edema and improving venous reflux [20].

As venous insufficiency is often seen in SCD patients, the clinical practice guidelines of the Society for Vascular Surgery and the American Venous Forum are also applicable for treatment of leg ulcers in sickle cell with venous disease. The guidelines recommend compression therapy to increase VLU healing and to decrease the risk of ulcer recurrence. The use of multicomponent compression bandages is encouraged over single-component bandages [62].

#### 7.1.16. *Topical analgesics*

Topical opioids have been employed by dissolving oxycodone and meperidine tablets in water and applying them locally to provide topical analgesia. Total pain relief was reported likely because of modification of peripheral opioid receptors [77]. While this treatment is not commercially available, these findings warrant further research. Data in mice with SCD show that topical opioids such as morphine and fentanyl not only treat pain but also hasten healing [78]. Inhibition of neurogenic inflammation by topical opioids is advocated as the mechanism of action. A study of nitroglycerin applied above the ulcer demonstrated a significant reduction in ulcer-associated pain, with increased ability to be able to manipulate the ulcer. Pain in fact is often so intense that bedside debridement is not possible, thus ultimately delaying ulcer healing.

#### 7.1.17. Hyperbaric oxygen therapy

Hyperbaric oxygen therapy and its potential benefit in treatment of vasoocclusive crises and leg ulcers have been described in several case reports [76, 79, 80]. However, paucity of research, potential adverse side effects, lack of treatment protocols, limited availability, and economic factors restrict its use [7].

#### 7.1.18. Transdermal continuous oxygen therapy

A case report described the use of transdermal continuous oxygen therapy using a portable device that delivers oxygen directly to the wound site. Two LE wounds received treatment for 15 weeks, and the authors noted that both healed without recurrence in the 42-month follow-up. The authors urge further studies utilizing this form of therapy [81].

#### 7.1.19. Maggot therapy

Maggot therapy has had mixed results when studied in other types of ulcers. One study showed reduced time to debridement, but increased ulcer pain and no improvement in rate of healing [82]. In diabetic ulcers, maggot debridement provided outcomes equal to conventional surgical treatment [83]. At the NIH Clinical Center, Medical Maggots™ (disinfected *Phaenicia sericata* larvae; <http://www.monarchlabs.com>) has been utilized. Four patients with sickle cell disease received this therapy with mixed results. There was temporary improvement in ulcer appearance, quickly followed by relapse and unclear long-term benefit [7, 16]. Pain has also been a limiting factor for the use of medicinal maggots in this population, and an opioid PCA may be required. This modality is currently reserved only for patients who are poor candidates for surgical debridement [76].

### 7.2. Systemic treatment

#### 7.2.1. Zinc supplementation

Zinc supplementation has long been believed to promote healing in chronic wounds accompanied by serum zinc deficiency [84]. A placebo-controlled trial reported that 220 mg of zinc sulfate administered orally three times a day significantly improved the healing of leg ulcers in sickle cell patients [43]. However, no further studies have been undertaken to confirm these results, and the results are hard to interpret as neither the length of supplementation with oral zinc or statistical analysis was provided [7].

#### 7.2.2. Pentoxifylline

Pentoxifylline improves RBC and leukocyte deformability potentially decreasing blood viscosity, platelet aggregation, thrombus formation, and plasma fibrinogen levels [7]. This increases microcirculatory flow and tissue oxygenation making it a good modality for treatment of leg ulcers in sickle cell patients. One case report presented that 400 mg of oral pentoxifylline three times a day helped completely heal a leg ulcer in a sickle cell patient within 3 months [85]. In nine RCTs involving 572 patients, pentoxifylline combined with compression

bandages improved ulcer healing [86, 87]. The 2014 clinical practice guidelines of the Society for Vascular Surgery and the American Venous Forum recommend the use of pentoxifylline for treatment of long-standing or large VLU's [62]. As venous insufficiency is often present in SCD patients, pentoxifylline may be a good treatment option for them.

#### 7.2.3. *L-Carnitine*

Systemic therapy of leg ulcers in SCD with L-carnitine has been reported in only one randomized controlled trial and one case study. Data suggests that oral carnitine alters cellular chemistry to favor more efficient oxidative metabolism despite reduced levels of available tissue oxygen. The studies were limited by the fact that transfusion therapy was given concomitantly making it difficult to draw conclusions on the effect of L-carnitine alone [88, 89].

#### 7.2.4. *Arginine butyrate*

Arginine stimulates collagen production, improves immune function, and prevents vascular restenosis. Butyrate can stimulate PDGF production and downregulate inflammatory cytokines and enzymes that slow wound healing like TGF- $\beta$ , tumor necrosis factor-alpha (TNF- $\alpha$ ), and matrix metalloproteinases [90]. A phase II controlled trial showed significant improvement in ulcer healing in the treatment arm after 3 months (78% vs. 24% in controls,  $P < 0.001$ ). A limitation to this approach is the requirement of an IV catheter. Larger studies are needed to validate this potentially effective treatment modality.

#### 7.2.5. *Bosentan*

A case report described complete healing of a leg ulcer in a patient with concomitant pulmonary hypertension. The ulcer had previously failed multiple therapies. The researchers attributed the healing to the blockade of the endothelin-1 receptor and vasodilation in the patient with likely decreased NO availability [91]. However, concomitant transfusion therapy might have confounded the observations.

#### 7.2.6. *Hydroxyurea*

The role of hydroxyurea (HU) in the development or in the treatment of leg ulcers in sickle cell patients is not clear with conflicting data to date [92–97]. HU increases fetal hemoglobin levels, decreasing the intracellular polymerization of HbS, the incidence of painful crises, and the need for transfusions in SCD patients [98]. Moreover, HU is a known NO donor and decreases WBC counts [99]. These effects should theoretically decrease the incidence of leg ulcers. However, leg ulcers observed in patients with chronic myeloproliferative disorders on HU often resolved several months after the discontinuation of this medication [100–103]. A case report suggested that HU causes an acquired blood dyscrasia that increases the risk of ulceration [104]. Other multicenter studies have seen no evidence of an association between hydroxyurea and leg ulceration [76]. There are no prospective trials that specifically address the effects of HU use on leg ulcer healing in the sickle cell population, and therefore, we

discourage reflexively stopping HU in patients with leg ulcers who may be benefiting from it for other SCD complications like frequent pain crisis and acute chest syndrome.

#### *7.2.7. Blood transfusions*

There are no prospective RCTs addressing the role of blood transfusions for treatment of leg ulcers in sickle cell patients. Transfusions increase the oxygen delivery to tissues by increasing total hemoglobin and decreasing the HbS concentration [76]. Some authors suggest target hemoglobin of 10 g/dl for successful surgical treatment, although a level between 8 and 9 g/dl may be more realistic and adequate for wound healing [20]. However, transfusions come with their own risks including iron overload, alloimmunization, and risk of transfusion reactions and infections. In recent clinical trials and in our clinical practice, we note that there are patients with chronic wounds who are treated with chronic transfusions, either for other indications or because of the ulcer, with no apparent benefit in decreasing the length of ulceration. The author recommends supporting skin grafts with transfusions for a limited time period, 4–6 months, in order to maximize graft success and decrease SCD-related complications.

#### *7.2.8. Antibiotics*

As discussed above, bacterial colonization of leg ulcers appears to be common but of uncertain clinical significance. However, colonization may lead to infection or a chronic inflammation, and systemic antimicrobials with anti-inflammatory properties like doxycycline, clindamycin, and metronidazole may improve ulcer healing along with adequate debridement [20].

### **7.3. Surgical treatment**

Surgical treatments for leg ulcers often have high rates of failure and recurrence [7]. Scar tissue becomes denser and less vascular with each subsequent graft, shortening the ulcer-free interval between recurrences [7, 105]. Microsurgical free flap transfers are popular since they include their own blood supply, which is a favorable attribute in these poorly vascular regions [106]. However, they are often limited by complications like thrombi, microemboli, and infection ultimately requiring debridement and split-thickness skin grafts [7].

Aiming to reduce the incidence of graft failure, some experts recommend perioperative and even chronic lifelong transfusions to decrease HbS levels to <30% [106, 107]. Some surgeons support the use of anticoagulation with heparin and/or aspirin, antibiotics, and the rinsing of flaps with heparinized solution prior to attachment [106]. Larger RCTs are required to address these important issues.

## **8. Nutrition**

Nutrition is known to be important in the management of ulcers, and patients should be assessed for nutritional deficiencies and treated appropriately. Zinc deficiency has been shown

to be prevalent in SCD patients. The current recommendation is 220 mg of zinc sulfate thrice a day. Serum zinc levels should be remeasured 2 and 4 weeks after initiation of supplementation and therapy discontinued if levels normalize [7, 108]. Others and we have noted that the BMI of SCD patients with recurrent ulcers is lower than patients without leg ulcers [12, Ballas, unpublished data]. We have also noted that several of the most affected patients seem to be almost anorexic, and we speculate that the high state of inflammation that their ulcer causes could be responsible for the presence of TNF-alpha, similar to cancer patients.

## 9. Thrombosis

Assessment and treatment of occult deep venous thrombosis are essential. Anticoagulation may be necessary to treat known hypercoagulable disorder.

## 10. Pain control

The pain from leg ulcers in patients with sickle cell disease can be very severe and debilitating leading many patients to require therapy with chronic opioids. Moreover, severe pain may interfere with local therapies and further hinder healing. Nonsteroidal anti-inflammatory agents are often inadequate for optimal pain control. Currently, there are no guidelines recommending topical analgesics in this patient population, but provocative data in sickle cell mice suggest that the application of topical opioids can treat both the pain and increase healing rates [78] although they should be explored in future studies. Some experts recommend regional nerve blocks with good results in pain control and also for secondary vasodilation via reduction of stress-related catecholamine release. This approach is limited by the need for an indwelling catheter, the need for frequent clinic visit for pump refills, and the antecedent risks of infection [7].

## 11. Wound care

Leg ulcers in SCD are often resistant to treatment and have a high rate of recurrence, making optimizing the wound bed a cornerstone of therapy. The ulcer must be adequately debrided to remove biofilm and necrotic, nonviable tissue from the base and edge of the wound in order to begin the healing process [109]. Various types of debridement techniques may be used including autolytic, enzymatic, biological, mechanical, and sharp, depending on its suitability to the patient, the type of wound, its location, and the extent of debridement required [110]. Regular weekly chronic debridements may be needed for improved healing although the optimal frequency is not established [111]. Sharp debridement can be very painful and may only be possible with some form of analgesia, topical, injectable, or general anesthesia.

Although a multitude of dressings exist, the most important principle of wound care remains maintenance of a moist healing environment. Energy-based modalities like low-frequency,

noncontact ultrasound, electrical stimulation, and ultraviolet-C light are good adjuvant treatment options for wounds that fail to respond positively to standard of care methods [7].

The use of RGD peptide matrix, allogeneic keratinocytes, and autologous platelet gel are promising treatments for resistant ulcers, although more research is needed. These are not widely available as yet.

## 12. Venous insufficiency

Compression therapy is encouraged for the management and prevention of edema, especially if venous insufficiency is present. Compression stockings are useful for prevention, while multilayer compression bandaging is recommended for treatment. An alternative is using a self-applicable and adjustable short-stretch Velcro band [62].

The Society for Vascular Surgery and the American Venous Forum strongly advocate pentoxifylline for treatment of long-standing or large VLUs since venous insufficiency is frequently found in these patients. Apligraf is recommended for ulcers not responding to standard of care therapies within 4–6 weeks.

Minimally, invasive ablation of superficial axial and perforator vein reflux in patients with active venous insufficiency and patent deep venous system is a relatively safe procedure and leads to faster healing and decreased ulcer recurrence when combined with compression therapy [112]. This also underscores prompt referral to a vascular specialist for evaluation and management of leg ulcers in SCD.

## 13. Antibiotic therapy

The IDSA guidelines do not recommend treating an uninfected wound with antimicrobials since there is no evidence that this prevents infection or improves ulcer healing [113]. When there are clinical signs of infection, post-debridement deep soft tissue or bone biopsy should be sent for culture. Superficial wound cultures are less reliable than tissue biopsies and should be avoided [114]. Hospitalized patients with more severe infections and signs of cellulitis and/or osteomyelitis typically receive intravenous antibiotic therapy at least initially. Finally, topical antibiotics do not significantly affect leg ulcers healing [7]. Further studies are needed to explore the immunomodulatory and anti-inflammatory actions of tetracyclines on ulcer healing.

## 14. Prevention

A previous history of leg ulcer is the greatest predictor of developing another leg ulcer in patients with sickle cell disease, increasing the risk up to 23-fold in one study [84]. While

spontaneous ulcers are unpredictable, traumatic ulcers may be preventable. Encouraging patients to regularly check their skin for signs of early ulcers and preventing local trauma by wearing properly fitting shoes and protecting themselves from insect bites may decrease the risk of developing leg ulcers. Wearing appropriately sized above-the-knee compression stockings can reduce edema and prevent new and recurrent ulcers [16].

## 15. Complications

### 15.1. Association of leg ulcers to pulmonary hypertension in adults with SCD

Evidence suggests that SCD patients with hyper-hemolysis phenotype (characterized by severe anemia and markers of hemolysis like high LDH) are at risk for leg ulcers as well as pulmonary hypertension, priapism, and renal disease [115]. Studies have shown that leg ulcers are more common in SCD patients with pulmonary hypertension [12, 116, 117]. Experts recommend that patients with HbS with leg ulcers should be screened for pulmonary hypertension.

This epidemiological relationship between leg ulcers and pulmonary hypertension supports a common pathophysiologic mechanism. Sickle cell patients with leg ulcers have been shown to have higher rates of mortality than those without leg ulcers and are regarded as a marker of disease severity in sickle cell patients [9].

### 15.2. Local effects

Subcutaneous fibrosis impairing venous and lymphatic drainage may occur and can be severe enough to cause an equinus deformity [4] (**Figure 4**). Osteomyelitis is exceedingly rare but has



**Figure 4.** Leg ulcers of varying sizes (from author's personal collection).

been observed on occasion. Acute ankle arthritis complicates some cases of spontaneous leg ulceration, possibly as a result of associated ischemic synovial damage [118]. It resolves spontaneously with improvement of the leg ulcer.

15.3. Social and psychological effects

Leg ulcers can have a profound impact on patients’ psychological well-being. Patients often have social withdrawal at school and work places. They often suffer from depression, which may impair their ability to take care of their ulcers adequately and seek medical attention [4].

16. Summary

In summary, sickle cell leg ulcers are a disabling complication of sickle cell disease, and despite being widely described in the medical literature, there remains a paucity of large randomized controlled data pertaining to their treatment. Current recommendations include a multifaceted approach utilizing a combination of topical, systemic, and surgical techniques. We describe a simplified algorithm to aid management of these complex patients (Figure 5). While a multidisciplinary team is essential, it is important to retain primary responsibility of the patient as hematologists, optimizing the health of the patient and facilitating plans of care made by various specialties. As we begin to understand more about the complex pathophysiology of these chronic wounds, more research is needed targeting these identified pathways to improve ulcer healing and prevent recurrence.

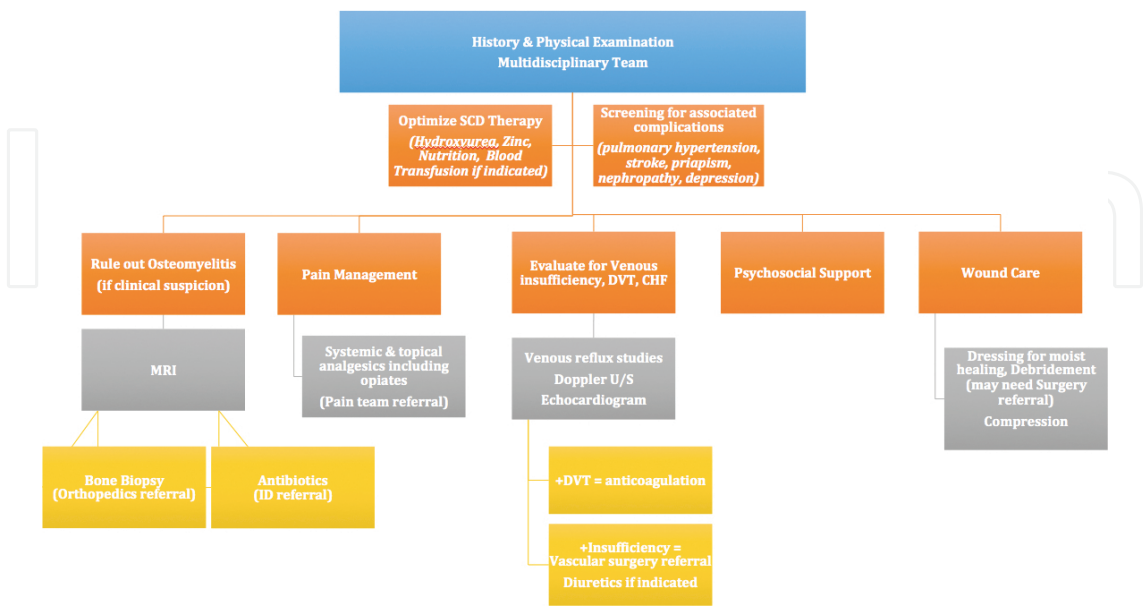


Figure 5. Approach to the management of patients with SCD and wounds.

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