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A Practical Approach to the Management of Digital Ulcers in Patients With Systemic Sclerosis
A Narrative Review

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IMPORTANCE Digital ulcers (DUs) occurring on the fingers in patients with systemic sclerosis (SSc) are associated with substantial pain and disability and are often challenging to treat. However, careful clinical assessment and prompt intervention (wound bed management and systemic pharmacologic treatment) may modify the clinical course.

OBJECTIVES To provide a practical approach to the assessment and management of SSc-DUs and highlight unmet needs and research priorities.

EVIDENCE REVIEW A narrative review of the extant literature was undertaken to provide a broad overview of current knowledge and augmented by expert opinion.

FINDINGS Half of the patients with SSc have a history of DUs, and there is a point of prevalence of approximately 10%. Digital ulcers are often very painful and affect all aspects of physical, social, and family life as well as occupation. Digital ulcers are associated with a severe disease course. Systemic sclerosis DUs, particularly those occurring on the fingertips, represent a vascular ischemic complication, although other etiopathogenic factors play an important role. To guide management, a structured clinical approach is required, including DU definition, classification, and categorization. Digital ulcers require a multidisciplinary approach with close cooperation between physicians and specialist nursing and other allied health professionals to guarantee the appropriate treatment and provide patient education. Local wound bed management is necessary for all DUs and is combined with systemic (pharmacologic) treatments. When treating a DU, the clinician should actively review the therapeutic strategy to prevent further DUs, including the level of systemic disease control, and monitor closely for the development of DU complications, including infection and progression to gangrene. Despite a wide available therapeutic armory, a number of unmet needs and challenges remain that that require resolution to optimize DU management.

CONCLUSIONS AND RELEVANCE A practical approach to DU management, including local wound bed management and systemic treatments, is useful. Digital ulcers are of interest to a broad range of dermatologists, rheumatologists, and other physicians providing care for patients with SSc. Careful clinical assessment and prompt intervention can substantially modify the clinical course of DUs in SSc.

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Systemic sclerosis (SSc) is a heterogeneous disease characterized by prominent vascular alterations (often referred to as *vasculopathy*), skin sclerosis, and immune system (both innate and adaptive) dysfunction.[1,2] In SSc, digital vasculopathy is represented by Raynaud phenomenon, digital ulcers (DUs), and critical digital ischemia.

Half of patients with SSc have a history of DUs that often occur early within the course of the disease (within the first 5 years) and signal a severe disease, including internal organ involvement.[3-6] In SSc, DUs may lead to substantial tissue loss. Therefore, DUs require a multidisciplinary approach, including specialist nursing and patient education. The combination of careful clinical assessment and prompt intervention consisting of wound bed management and systemic treatment may be associated with benefits in the course of DUs. Moreover, DU complications (infection and gangrene) can reduce healing, and refractory DUs can require surgical intervention including digital amputation.

This review aims to provide a practical approach toward the assessment and management of SSc DUs of relevance to dermatologists, rheumatologists, and all other physicians treating patients with SSc. To support a practical approach to DU management, a narrative review of the extant literature was undertaken to provide a broad overview of current knowledge and augmented by expert opinion from clinicians involved in the SSc DUs management.

Literature Search

Articles (527 citations) published between January 1, 2000, and November 22, 2020, were identified within PubMed using the following broad search terms: *digital ulcer* and *systemic sclerosis* or *scleroderma* and *management* or *treatment* or *definition* or *classification* or *categorization* or *clinical trial*.

Articles were primarily included if they were published in the English language. Primary interest was the management of SSc DUs; ulcer epidemiologic factors, pathogenesis, and assessment (including definition, classification, and categorization), were of secondary interest. Cross-sectional studies, registry analyses, clinical trials, and case series/reports were included. The titles and abstracts from this search provided the mainstay of literature for this work, alongside gray searches of publications cited within these articles, and key legacy reports.

Clinical Spectrum and Outcome of DUs

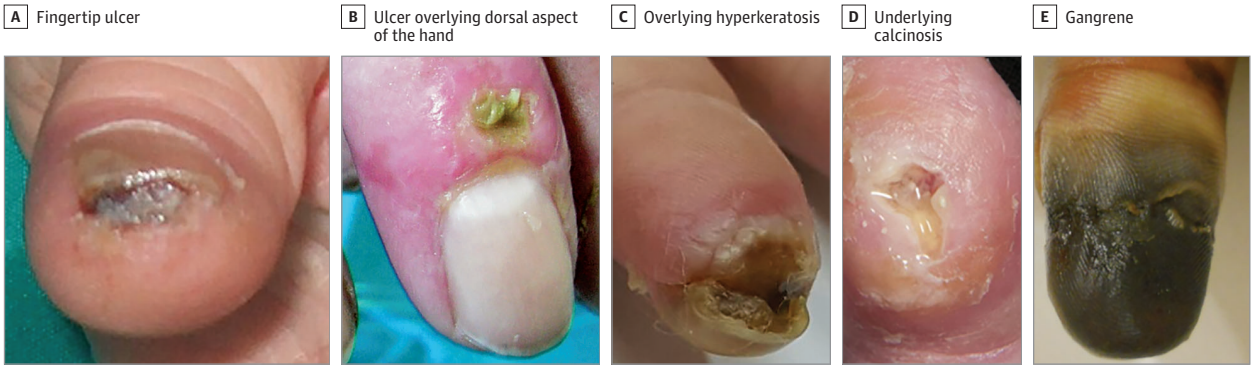
In SSc, DUs commonly occur on the fingertips and overlying the extensor (dorsal) aspect of the hands (**Figure 1**) but can also occur at other sites of the hands, including the base of the nail and the palmar and lateral aspects of the digits.[7] Digital ulcers can appear on all fingers and thumbs and on feet and toes[8] and are slow to heal in the presence of infection, gangrene/necrosis, and calcinosis.[7]

Digital ulcers may be painful, affecting all aspects of physical, social, and family life, including occupation.[9,10] Moreover, DUs are associated with substantial societal economic burden, which is largely associated with health care costs from the need for hospitalization and use of acute care services.[11] Furthermore, DUs are associated with deep and broad-ranging outcomes, including fear and embarrassment and the need for constant vigilance.[10,12] Patients use a wide range of coping strategies to mitigate, manage, and adapt to DUs. Patients often report residual symptoms at sites of previous DUs, including dysesthesia and paresthesia, which could indicate persistent nerve damage.[10] Some patients report that they can recognize when the emergence of a DU is imminent, describing pain like internal pressure, and physical skin signs (eg, white patches) that break down and ulcerate.[13]

DU Pathogenesis

In general, SSc DUs are considered a vascular ischemic complication, particularly those that occur on the fingertips.[14] The severity of microvascular disease as assessed by nailfold capillaroscopy has been reported to be associated with the development of SSc DUs.[15,16] It has been postulated that other types of ulcers in patients with SSc could share a potentially treatable ischemic pathogenesis that could be responsive to vascular therapy.[17,18] Sites of previous DUs, such as digital pitting scars, may represent ischemic foci particularly susceptible to future DUs.[7,13]

Figure 1. Spectrum of Digital Ulcers in Systemic Sclerosis



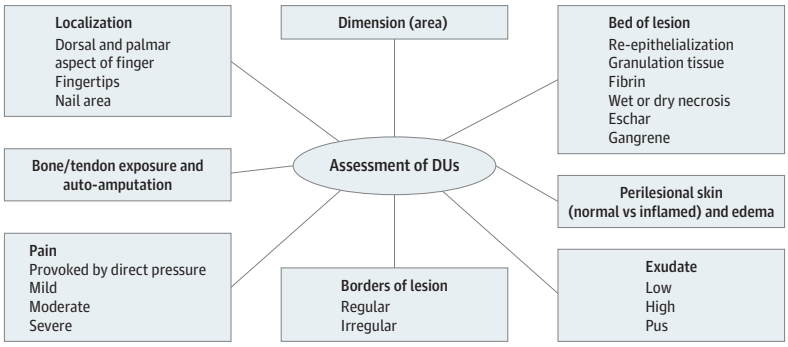
Fingertip ischemic digital ulcer (A) and ulcer overlying the extensor (dorsal) aspects of the hands (B), especially the small joints; digital ulcer with significant overlying hyperkeratosis (C) and relating to underlying calcinosis (D); and digital ulcer complicated by gangrene (E).

Table 1. Proposed DU Definitions Under the Auspices of the World Scleroderma Foundation and United Kingdom Scleroderma Study Group

Source	Definition
Suliman et al,[23] 2017; World Scleroderma Foundation	Loss of epidermal covering with a break in the basement membrane (which separates dermis from epidermis). It appears clinically as visible blood vessels, fibrin, granulation tissue, and/or underlying deeper structures (eg, muscle, ligament, fat) or as it would appear on debridement.
Hughes et al,[24] 2018; UK Scleroderma Study Group	A lesion on the finger or distal to the metacarpophalangeal joint with loss of surface epithelization and a visually discernible depth. The ulcer bed is often wet in appearance with surface slough. The perilesional skin surrounding DUs is not uncommonly erythematous and/or macerated, including in the absence of superadded infection. Patients often report pain, which may be severe, associated with DUs. Digital ulcers often have an overlying scab (eschar), and if there is a high index of suspicion of an underlying DU, the lesion should be classified as such. Common sites for DUs include the fingertips and over the extensor (dorsal) aspects of the hands and in relation to subcutaneous calcinosis. DUs may occur less frequently at other sites on the hands (eg, over the lateral aspects of the digits and at the base of the nail).

Abbreviation: DU, digital ulcer.

Figure 2. Assessment of Digital Ulcers (DUs)



Structured approach to understand the complexity and management of DUs. Adapted from Amanzi et al.[7]

Sometimes, DUs occur over the extensor (dorsal) aspect of the hands due to recurrent microtrauma on the skin overlying small joints and/or result from increased skin tension. The degree of skin thickening has also been associated with SSc DUs,[5,19,20] but DUs can develop from underlying tissue calcinosis (Figure 1).

The role of inflammation in the pathogenesis to date is unclear and requires investigation. For example, the presence of marked periulcer erythema is not an uncommon finding, even in the absence of clinically significant infection. Increased blood flow surrounding DUs, theoretically due to neoangiogenesis, could promote healing, but it could also result in reperfusion injury, thereby further exacerbating tissue loss.[4]

Table 2. TIME-Based Approach to Wound Bed Management[a]

TIME components	Approach
Tissue management	Clinically assess the ulcer base (bed), edges, and perilesional skin; perform sharp and/or autolytic debridement
Infection and inflammation	Monitor signs of ulcer inflammation (eg, erythema) and/or infection (eg, pus)
Moisture balance	Use appropriate dressing to absorb/control exudate or hydrate
Wound edge and epidermal advancement	Monitor healthy advancing wound edges; debride raised or rolled edges in chronic wounds; protect perilesional skin

Abbreviation: TIME, tissue management, infection and inflammation, moisture balance, and wound edge and epidermal advancement.

[a] Digital ulcers require a systematic approach to local wound bed management to identify the factors involved and interventions to facilitate ulcer healing.

Clinical Approach to DU Assessment

In routine clinical practice, a pragmatic approach is needed to identify DUs that may require and derive benefit from intervention, compared with those in which DU definition[9,21] is required only to homogenize the DU population for clinical trials.[22] A DU definition (**Table 1**) is available,[23,24] and the key aspect is that DUs are characterized by a loss of epithelium and, in particular, a break in the basal membrane, to distinguish an ulcer from an abrasion. When DUs are covered by scab (eschar), they should be treated accordingly.

The classification of DUs into subsets may help in prognosis and management: (1) DUs derived from digital pitting scars, (2) solely ischemic DUs, (3) DUs derived from underlying calcinosis, and (4) DUs derived from gangrene.[7] The DU categorization reflects the clinical burden of the patient and facilitates clinical research, and 4 categories based on DU recurrence have been proposed[25]: (1) none, (2) episodic, (3) recurrent, and (4) chronic. Among these categories, the dichotomy of recurrent and not recurrent DUs was considered preferable in practice.[8]

DU Clinical Assessment

Digital ulcers require a comprehensive clinical assessment (**Figure 2**), including history and physical examination. The duration (chronicity) of the lesion, level of associated pain, sleep disturbance, and presence of reported discharge/pus should be determined. Significant pain may suggest infection, necrosis/gangrene, and/or osteomyelitis. The acronym TIME (tissue management, infection and inflammation, moisture balance, and wound edge and epidermal advancement) (**Table 2**) is fundamental in wound healing to identify the key components involved in wound bed preparation.[26]

A key practical clinical point is to actively exclude proximal macrovascular arterial disease. Abnormalities of the peripheral pulses (eg, low volume and/or asymmetry) could suggest the presence of arterial disease that could be amenable to therapeutic intervention.[27] Distal flow can also be compromised due to problems at the cervical levels or to an axillary thrombosis.

The DU area can be measured by smartphone photographs over an extended period,[28] computer-assisted planimetry methods and ultrasonography,[21,29-31] and laser-based techniques that measure blood flow and response to treatment.[32,33] Nailfold capillaroscopy and thermography may estimate the future occurrence of DUs.[15,16,34] The composite DU clinical assessment score incorporates weighted items (number of DUs, new DUs, gangrene, surgical approach to DUs, ulcer infection, ulcers warranting unscheduled hospitalization, and analgesia for DU-associated pain) that can be useful in practice.[35]

Management of DUs

The management of SSc DUs (**Box**) reflects the clinical scenarios found more frequently in practice. A key point is that all DUs must be treated and that, when treating a DU, the clinician should actively evaluate the therapeutic strategy, including systemic disease control, to prevent DUs. Early treatment is needed to maintain function, preserve quality of life, and avoid evolution to gangrene, infection, and potential diffusion (septicemia). The following hierarchical principles should be addressed in DU management:

1. All other underlying diseases leading to DU-like ulcerations independent of SSc need to be excluded. The diagnosis of SSc DUs is typically made on clinical grounds alone. A skin biopsy usually is not required unless the presentation is atypical given poor vasculature and wound healing surrounding DUs.
2. The care of DUs should be delivered by a multidisciplinary team, and patients should be given education including the importance of early recognition and prompt use of health care for new ulcers, including the use of skin protection (gloves and creams), skin hydration, adequate nutrition, rehabilitation, and the importance of smoking cessation (smoking promotes vasoconstriction). Dedicated (eg, specialist nurse-led) clinics can improve access to essential DU care.[36]
3. Analgesic therapy may be used and should frequently be reviewed and optimized.[4,14] Regularly prescribed analgesia, often opioid-based, is needed to ameliorate nocturnal pain, and as-needed analgesia (eg, for exacerbation of ulcer pain and/or ulcer debridement) may be necessary.
4. Rehabilitation (ie, physiotherapy and occupational therapy) is part of the preventive strategy to maintain function and increase blood flow to the tissues.
5. Background vasodilation should be reviewed and optimized. Local wound bed management should be combined with systemic treatment.[37-39]
6. Macrovascular disease assessment is needed with ultrasonographic Doppler imaging in patients with recurrent DUs and/or when DUs occur in patients with diabetes or a history of myocardial infarction or stroke.

Box. Management of Systemic Sclerosis[a]

Mild DUs
- Patient education and adherence
- Multidisciplinary team approach, including nursing
- Prompt recognition and assessment
- Wound bed management including debridement
- Review of analgesic regimen
- Antibiotic therapy if clinically indicated
- Optimized oral vasodilator therapy
- Monitoring for progression, including complications

Severe DUs
- Intravenous prostanoid therapy
- Optimized analgesia
- Consideration of surgical intervention (eg, debridement, amputation)

DUs and the threatened digit or critical ischemic digit
- Early recognition and intervention
- Intravenous prostanoid therapy
- Surgical intervention, including digital amputation
- Excluding proximal (large) vessel disease

Complicated DUs
- High index of suspicion for DU complications (eg, osteomyelitis and necrosis/gangrene)
- Appropriate investigations (eg, magnetic resonance imaging for osteomyelitis)
- Surgical intervention

Recurrent DUs
- Intravenous prostanoid therapy, phosphodiesterase type 5 inhibitors and/or endothelin-receptor antagonists
- Consider combination therapy
- Consider surgical intervention (digital sympathectomy and botulinum toxin injection)

Refractory DUs
- Multidisciplinary approach
- Combination of phosphodiesterase type 5 inhibitors and endothelin-receptor antagonists
- Surgical intervention (digital sympathectomy and botulinum toxin injection)

DU indicates digital ulcers.

[a] These headings are arbitrary, and patients may move between them; therefore, regular reappraisal of the therapeutic strategy is required. The therapeutic behavior of mild DUs is also necessary for the management for severe DUs.

Wound Bed Management

The components of TIME are used to systematically identify the key factors involved in optimal wound bed management (Table 2). Tissue management relates to the DU bottom and edges and perilesional skin. The eschar or necrotic material, which delays ulcer healing, must be debrided,[7] including all other forms of devitalized tissue (eg, slough and pus), and foreign bodies. Thus, debridement is a key component of

wound bed management together with appropriate wound dressings.[39,40] Wound cleansing is also performed (eg, with warm NaCl, 0.9%, solution using a needle and syringe) to clean the surface without damaging the healthy granulating tissue. Debridement may be sharp (ie, mechanical) with a scalpel or curette to be performed by experienced personnel with periprocedural analgesia,[41] or autolytic, with dressings (eg, hydrogel) enhancing tissue lysis[39,42] that are chosen according to the amount of exudate and dryness of the wound bed.[39] In DUs, the balance between wet and dry is an "art" and needs to be determined by experienced personnel to be correctly managed.

Inflammation and infection are important factors to address in wound healing, and, in excess, can result in tissue damage.[4,39] Digital ulcers are often infected, especially by *Staphylococcus aureus*, and also by enteric organisms, which highlights the need for patients to adopt strict hand and wound hygiene measures.[14,43,44] The presence of DU infection can delay ulcer healing.[7,39] Moisture stimulates wound healing, but excessive moisture can damage healthy new granulating tissue and perilesional tissue (ie, maceration) and promote infection. An ulcer should not be allowed to dry but should be kept clean and in humid surroundings, which promotes granulation and epithelization. For dry DUs the goal is to rehydrate the tissue (eg, hydrogels and hydrocolloids) and, if the DU is excessively wet, the goal is to absorb and control the exudate (eg, alginates).[14,39] Care must be taken to protect the perilesional skin because wound edge and epidermal advancement are necessary events for DU healing. Therefore, the edges must be regularly cleaned to allow new granulation tissue to advance to cover the DU bottom.

Pharmacologic Therapies

In SSc, vasodilatory and vasoactive therapies may be used to prevent and/or heal DUs as well as to treat Raynaud phenomenon and pulmonary arterial hypertension. As vasodilatory therapies, calcium-channel blockers are the usual first-line treatment for Raynaud phenomenon.[37] Nifedipine reduced the mean number of DUs from 4.3 to 1.4 in a randomized trial during 16 weeks of treatment.[45] Phosphodiesterase-type 5 inhibitors may also be used for DU healing (relative risk, 3.28; 95% CI, 1.32-8.13) and DU improvement (relative risk, 4.29; 95% CI, 1.73-10.66).[46] The randomized, placebo-controlled SEDUCE trial showed a significant decrease in the number of DUs but not a significant healing with sildenafil.[47] Intravenous administration of the prostanoid agent iloprost is most commonly used for treatment of refractory Raynaud phenomenon and is associated with a significant reduction in the number of DUs and increased healing with different regimens.[48,49] Systemic adverse effects are common with vasodilatory drug therapies (eg, headache and hypotension). Prostanoids may have additional adverse effects (eg, myalgia, diarrhea, and stealing coronary effect), and should be carefully used in patients with SSc.[50] Selexipag and treprostinil have been recently proposed as treatments and await approval for the treatment of DUs.[51,52]

Endothelin-receptor 1 antagonists are used as vasoactive therapies. Bosentan significantly reduced the number of new DUs but not ulcer healing.[53,54] This outcome was not obtained with macicentan,[55] and ambrisentan was efficient only in healing DUs.[56] Despite positive experiences of DU healing associated with rituximab, tocilizumab, and cyclosporine, there is still insufficient evidence that immunosuppression may be beneficial for SSc DUs.[57-59]

To our knowledge, there are no specific data to inform the dosing of oral vasodilatory drug therapies for SSc DUs (eg, calcium-channel blockers or phosphodiesterase-type 5 inhibitors). Therefore, clinicians tend to use treatment regimens similar to those used for SSc Raynaud phenomenon. In general, drug therapies are started at low doses and gradually increased, balancing treatment efficacy vs the emergence and severity of adverse effects.

Local Therapies

There is a therapeutic rationale to developing local therapies for the treatment of SSc DUs, which would likely be well tolerated owing to the absence of systemic vasodilatory therapies.[40] Topical therapies, such as nitrates and vitamin E gel; phototherapy-based approaches; low-level light treatment (red, infrared, and violet); oral psoralen and UV-A therapy; amniotic membrane; platelet gels; and systemic therapies (erythropoietin, granulocyte-macrophage colony-stimulating factor, and hyperbaric chamber) have been suggested.[60-63] Autologous fat grafting has been proposed to be an efficacious option to foster DU healing.[64,65] Positive experience with locally, subcutaneously, and intramuscularly administered mesenchymal stem cell transplantation has been reported in case reports and small uncontrolled studies.[66-68] Also, intravenous mesenchymal cells have been used in one complicated case, but this treatment is still awaiting confirmatory trials.[69]

Clinical Scenarios

In practice, after careful DU assessment, the following main clinical scenarios may appear:

1. Mild DUs have limited size and tissue loss in the absence of complications (eg, infection and gangrene), no severe pain, and no involvement of the fascia and bone.
2. Severe DUs are large ulcers that produce substantial pain, which may indicate infection, requiring analgesia, and patients are at high risk of complications with involvement of the fascia and bone.[4,14] In these cases, intravenous prostanoid, antibiotic, and opioid therapy may be necessary.
3. Complicated DUs are of different sizes but with frequently nocturnal pain, which can suggest the presence of necrosis/gangrene, deeper bony involvement (ie, osteomyelitis),[70] and/or abscess development. Established abnormalities as assessed by plain radiography may be absent at baseline in osteomyelitis; however, early features (eg, bone marrow edema) can potentially be identified by magnetic resonance imaging. These cases are to be treated urgently, particularly in the presence of osteomyelitis. Amputation of the digit is sometimes required,[43] but early recognition of large-vessel disease could allow prompt revascularization.[71]
4. Digital ulcers and the threatened digit or critical ischemic digit present with a rapidly ischemic progression along the digit, sometimes involving the hand, and are often associated with severe, intractable pain. The finger is blue and cold and quickly converts to ischemic tissue. This development requires immediate assess-

ment and intervention with an intravenous prostanoid, selective sympathetic blockade, heparin and antiplatelet therapy, and botulinum injections. Amputation of the digit is sometimes needed because of uncontrollable pain, severe refractory infection with a risk of septicemia, and extensive necrosis.

5. Recurrent DUs may need intense intravenous prostanoid therapy, or treatment with phosphodiesterse-type inhibitors and/or endothelin-receptor 1 antagonists to avoid DU recurrence.[37,72,73]
6. Refractory DUs can provide significant challenges to clinicians. For this reason, the multidisciplinary team has a prominent role to discuss the alternative treatments, such as combined phosphodiesterase-type 5 inhibitors and endothelin-receptor 1 antagonists,[74,75] statins,[76,77] and antiplatelet and anticoagulant therapies.[78,79] There is increasing international experience with performing digital sympathectomy and botulinum toxin injection for refractory DUs.[80-84]

Conclusions

Digital ulcers are a sign of disease progression and evolution and a serious complication in patients with SSc and often are challenging to treat. Therefore, early careful DU assessment, wound bed management, and systemic treatment are necessary to modify the clinical course of DUs. Patient education is recommended, and a dedicated multidisciplinary team is needed to manage DUs; home-based therapy may be needed. Patients should be monitored for the development of ulcer complications.

We propose a practical approach to DU management (Box) including systemic and local wound bed management (Table 2). There are still many unmet needs and challenges, and international collaborative work may optimize the local and systemic strategy for the management of SSc DUs.

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