Digital ulcer management in patients with systemic sclerosis
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Abstract
Introduction
Digital ulcers (DUs) are a major clinical problem for patients with systemic sclerosis (SSc). Almost half of SSc patients experience at least one acral DU during the course of the disease. Patients with DUs may suffer from severe pain and often undergo a limitation of daily life activities, thus resulting in a functional impairment with a significant impact on the patient’s health-related quality of life. Prevention of further complications and lesions is possible if the initial evaluation is performed early and correctly and if a treatment is started promptly. Pharmacologic treatment is important, but it is not the only possible approach to patients with DUs. This review provides an overview of the available different treatment options for DUs together with a proposal of a diagnostic-therapeutic approach aimed at a better definition and treatment of patients with SSc and DUs.

Discussion
A correct approach to the patient with DUs begins with a careful examination and evaluation of risk factors and comorbidities in order to cure and prevent complications and further lesions. Then also a correct local treatment of the DU provides a better milieu to foster healing and prevent complications such as infection or gangrene. Each drug with different mechanisms of action are to date available for the treatment and prevention of DUs in SSc, but it will be swiftly effective only if in combination with good information of the patient and a thorough local treatment of the ulcers.

Conclusion
A correct therapeutic approach can be based only on a correct education and information of the patient.

Introduction
Digital ulcers (DUs) are a major clinical problem for patients with limited or diffuse systemic sclerosis (SSc) and a recurrent challenge for rheumatologists. About half of patients with SSc experience at least one acral DU during the course of the disease.1 Patients with DUs may suffer from severe pain and often undergo a limitation of daily life activities, thus resulting in a functional impairment with a significant impact on the patient’s health-related quality of life (HRQoL)2. The aim of this review is to provide the reader with an overview of the currently available approaches for the management of DUs in SSc and to propose a step-by-step diagnostic and therapeutic flow-chart, based on updated evidence and the personal experience of our team.

Characteristics and terminology
Pure DUs are usually punctiform, very painful, they develop mainly in the fingers or toes, usually on the tips, but they may also involve skin creases, over the proximal interphalangeal (PIP) joints3.

The definition of DU has been a problem for a long time, until a very recent consensus approach has attempted to find a more precise classification4 for use in observational studies or randomized clinical trials (RCTs). Based on this classification, a DU is a lesion with loss of continuity of epithelial coverage, which can be denuded, with discernible and measurable depth or covered by a scab or crust (i.e. a hardened covering of dried secretions such as blood, plasma or pus) or necrotic tissue (i.e. a black or dark brown remnant of normal tissue that has become necrotic because of the ischemia of that area)3. Following this classification, only DUs at or distal to PIP joints and without bone infection or calcinosis are to be assessed. DUs do not include fissures, paronychia, extrusion of calcium, ulcers over calcium nor ulcers over the metacarpophalangeal joints or elbows5. DUs at or distal to PIP joints may be traumatic and the actual contribution of SSc vasculopathy is still to be determined, thus it is up to the designers of the trials to decide whether to include these DUs in the trial or not4.

Active ulcers are those in which denudation is clearly visible at any part of the base and de-epithelialization can be observed. Indeterminate ulcers are those in which the examiner is not able to evaluate the presence of a de-epithelialized base. Healed ulcers are those with a complete re-epithelialization, also in the form of an atrophic hypopigmented area.

Possible complications of DUs are infections, osteomyelitis, gangrene or amputation as shown in figure 1. Gangrene occurs more frequently in diffuse SSc, possibly related to a major vascular involvement4. Gangrenous lesions at the fingertip that may be dry.

Figure 1: Multiple digital ulcers of the fingers with associated gangrene and bone exposure leading to auto-amputation.
Etiopathogenesis

DUs are a manifestation of the underlying vasculopathy and fibrosis that characterize SSc. They are almost always associated with Raynaud’s phenomenon (RP), a vasospasm in response to cold or emotion resulting in impaired oxygenation of the distal extremities (Figure 3)\(^2\). The underlying pathogenetic mechanisms of DUs in SSc are multiple, such as microtrauma, sclerodactylly and dry skin, but the vasculopathy that characterizes SSc is believed to play a pivotal role. Although the triggering factors are still unknown\(^2\), the initial endothelial injury is accompanied by an increase in the levels of endothelin-1 (ET-1), a peptide with vasoconstrictor effects mediated by endothelin type A (ETA) receptors present on vascular smooth muscle cells (SMCs) causing vasoconstriction and vascular remodelling effects, and by means of endothelin type B (ETB) receptors, present on endothelial cells and SMCs with vasodilating effects\(^2,5\).

Alternatively, endothelial cells may be injured by the presence of endothelial cell antibodies, which would imply platelet activation with release of thromboxane and eventually intraluminal thrombosis\(^5\). The subsequent migration of SMCs into the intimal layer of the microvasculature and differentiation into myofibroblasts producing collagen and other extracellular matrix are responsible for the intimal proliferation with fibrosis, thus leading to a fixed narrowing of the intravascular lumen and causing chronic tissue ischemia\(^2,5,6\).

Discussion

The authors have referenced some of their own studies in this review. These referenced studies have been conducted in accordance with the Declaration of Helsinki (1964) and the protocols of these studies have been approved by the relevant ethics committees related to the institution in which they were performed. All human subjects, in these referenced studies, gave informed consent to participate in these studies.

Evaluation

As shown in figure 1, the evaluation of a patient with DUs should start from the patient’s history, which should be aimed at finding risk factors which may favour the development of DUs such as thrombophilia, dislipidemia, hypercholesterolemia, dehydration, traumas, neoplasias, autoimmune pathology, smoke, drugs that may favour vasoconstriction. Physical examination should evaluate localization, depth, boundaries, presence of fibrin, debris, granulation.
Clinicians should start helping patients in managing pain, which has considerable impact on HRQoL and further triggers vasospasm. Secondary prevention, i.e. prevention of further lesions, by minimizing the occurrence of minor trauma as well as prevention of complications is very important. It is important to restore hand function, improve digital circulation, prevent infection and promote healing.

Whenever a macrovascular disease underlying or contributing to the ischemic digital process is suspected, an ultrasonographic Doppler study of the vessels or an angiography should be performed.

**Primary prevention and lifestyle changes**

Avoidance of cold temperatures by means of proper garments and gloves, hats, heavy socks, should be sought not only during cold seasons, but in all the cases required by a cold external temperature (e.g. refrigerators in a supermarket; cold temperature in hot seasons due to sudden weather changes, etc.). Stress is another trigger for vasospasm in RP. Although there are not enough data to support the use of techniques such as conditioning, biofeedback and relaxation techniques in SSc patients, the high prevalence of anxiety and depression in these patients requires careful examination of the psychologic conditions of the patients with SSc and, if necessary, the use of anti-depressants or anxiolytics. Patients should also be taught to use topical hydrating creams in order to maintain skin moist.

Whenever possible, trauma to the digits should be avoided, such as working in a cold environment (e.g. fridge aisle, etc) or repetitive hand working (e.g. typing). Smoking should be avoided even if there is a lack of univocal data regarding its pathogenic role in Raynaud’s triggering.

**Supportive care and local treatment**

Pain control should not be overlooked by physicians, not only for improvement of their HRQoL, but also in order to avoid further vasospasm generated by the adreno-receptors that may worsen the ischemic condition. Pain management should be started quickly and adjusted on the patient needs. Acetaminophen and opiates should be preferred. If infection is suspected, a specific antibiotic should be started, based on antibiogram. If osteomyelitis is suspected, prompt treatment with i.v. antibiotics should be started.

**Therapeutic approach**

The treatment of DUs must parallel the treatment of RP with or without ischemic complications. A possible approach to treat patients with DUs and/or RP is shown in figure 4. It is pivotal to have a good skin care in order to promote healing, basing the choice of the dressings depending on the presence or absence of infection and other factors (Table 1). To foster DU healing, surgical debridement is often required. The presence of fibrin, oedema or inflammation, necrosis, eschars or gangrene delays significantly the time to healing. Ischaemia involving the whole distal phalanx needs hospitalizations for aggressive treatment.

Figure 4: The flow-chart shows the proposed approach to digital ulcers in systemic sclerosis (AB: antibiotic therapy, DU: digital ulcer; ERA: endothelin receptor antagonist; i.v.: intravenous).

Patients with systemic sclerosis and digital ulcers

<table>
<thead>
<tr>
<th>Is the patient taking calcium channel blockers? If no, add in:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Check for any coexisting pathology (large vessel disease, vasculitis, coagulopathy) or infection:</td>
</tr>
<tr>
<td>Infection: Add AB</td>
</tr>
<tr>
<td>Swab and antibiogram:</td>
</tr>
<tr>
<td>Osteomyelitis: Add i.v. AB</td>
</tr>
<tr>
<td>Macrocirculatory involvement:</td>
</tr>
<tr>
<td>&gt;4 DUs?</td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>Consider short-term anticoagulation or antiplatelet therapy:</td>
</tr>
<tr>
<td>Consider surgical intervention as appropriate:</td>
</tr>
<tr>
<td>Continuing severe symptoms or progression of critical ischaemia/gangrene:</td>
</tr>
</tbody>
</table>

Table 1 shows the most common used wound dressings and their different indications. Antiseptics should be avoided because of the known cytotoxic effects on cells and local antibiotics may induce the emergence of resistance to the entire class of antibiotics used topically. Ulcers must be cleaned with physiologic water. The use of systemic antibiotics should be reserved only for clinically infected ulcers and not for bacterial colonization. Debridement is important because the removal of necrotic tissue and sloughs have been demonstrated to be effective in accelerating wound healing.
Debridement can be mechanical via curette or scalpel, or chemical, via enzyme-debrid ing agents such as collagenase, papain, trypsin. D-alpha-tocopheryl acetate (acetic ester of alpha-tocopherol) gel on DU s of SSc patients treated twice a week was shown to induce a faster healing of DUs, with a faster resolution of pain and a lower cost of medications in respect to controls with a lower number of medications.

### Pharmacological therapy

Despite the substantial impact that DUs have on function and HRQoL, currently there is no widely accepted therapeutic algorithm.

#### Prostacyclin analogues

In Europe, cyclic use of i.v. iloprost is the standard of care for the treatment of ischemically threatened digits and severe SSc DUs. The most robust study supporting the use of iloprost is a multicenter trial in patients with SSc and RP. After three weeks, 14.6% more patients receiving i.v. 6-hour infusion of iloprost (dose 0.5-2 ng/kg/minute) for five days had 50% or more lesions healed compared with those given placebo. A trend was also observed towards prevention or reduction of the formation of new DUs (25% of the patients had new lesions after iloprost compared with 33% of the patients receiving placebo). A Cochrane review also concluded that i.v. iloprost is effective in the treatment of RP secondary to SSc at decreasing the frequency and severity of the attacks and in preventing or healing DUs. The effect seems to be prolonged after the intravenous infusion is given. Oral prostanoids may have minimal or no efficacy for the treatment of RP secondary to SSc. Other prostacycline analogues such as epoprostenol and beraprost demonstrated no efficacy in DU healing, although trends towards a decrease in the number of new DUs were observed with both drugs. By contrast, subcutaneous treprostinil showed efficacy in both healing and preventing DUs, but its use is limited by the acute injection site pain. An ongoing phase II double blinded multicenter RCT of oral treprostinil in SSc DUs is currently recruiting.

#### Calcium channel blockers (CCBs)

CCBs act on vascular SMCs to cause arterial vasodilatation. A small RCT compared oral nifedipine at 30 to 60 mg dosage, with i.v. iloprost in patients with SSc and RP, who were severely affected by skin lesions (ulcers, fissures or paronychias), demonstrating a decrease in the mean number of digital lesions. The limitations of this study are the small number of patients, the lack of clear baseline number of DUs per patient and the use of different skin lesions apart from ulcers as outcome measure.

#### Endothelin receptor antagonists (ERAs)

Bosentan was initially developed for pulmonary hypertension and was found to be useful in the prevention of the onset of new lesions in SSc patients who had already experienced DUs but seems to have no effect in healing the existing ulcers. The RAPIDS-2 study confirmed bosentan effects on prevention of new DUs in SSc patients, particularly in those with multiple DUs (at least four as suggested by the Authors) not receiving i.v. prostacyclin analogues or phosphodiesterase-5 (PDE-5) inhibitors in the previous three months, but also confirmed the absence of efficacy in the healing of pre-existing DUs. Therefore, the use of bosentan is indicated as secondary prevention in those patients presenting with multiple DUs. The incidence of liver aminotransferase elevation requires tight monitoring of blood tests.

#### PDE-5 inhibitors (PDE5I)

PDE5I induce vasodilation by increasing the levels of endogenous nitric oxide (NO). Case reports, case series and a meta-analysis indicate a benefit of sildenafil on SSc-DUs. In an open-label study on 19 patients with 49 DUs present at baseline, the number of DUs decreased to 17 after a 6-month therapy with sildenafil, although a total of 9 patients developed 12 new DUs during sildenafil treatment. The effects of tadalafil on DUs were shown in a study on 25 SSc patients. Although the patients were receiving also other therapies for RP and the healing and prevention of DUs were secondary outcomes, the results were promising: all the 24 digital lesions healed during tadalafil therapy as compared with 3 on 13 during the placebo treatment. One new DU was reported during tadalafil therapy vs 13 during placebo therapy. Significant adverse events are headache, myalgia, priapism, allergic reactions, chest pain and others.

### Table 1: Wound care dressings and their main indications.

<table>
<thead>
<tr>
<th>Type of dressing</th>
<th>Healing stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocolloids</td>
<td>Mildly exuding ulcer</td>
</tr>
<tr>
<td>Alginites</td>
<td>Debridement</td>
</tr>
<tr>
<td>Hydrogels</td>
<td>Necrotic ulcer, dry ulcer</td>
</tr>
<tr>
<td>Hydrofibers</td>
<td>Infected ulcer, heavily exuding ulcer (debridement stage)</td>
</tr>
<tr>
<td>Impregnated or coated meshes</td>
<td>Mildly exuding ulcers, alters peripheral wound skin</td>
</tr>
<tr>
<td>Foam dressings</td>
<td>Heavily exuding ulcers, granulating ulcers, altered peripheral wound skin</td>
</tr>
<tr>
<td>Hyaluronic acid-based dressings</td>
<td>Mildly exuding ulcer</td>
</tr>
<tr>
<td>Charcoal dressings</td>
<td>Foul-smelling ulcer</td>
</tr>
<tr>
<td>Silver-coated dressings</td>
<td>Infected ulcer, foul-smelling ulcer</td>
</tr>
<tr>
<td>Protease-modulating dressings</td>
<td>Hard-to-heal ulcer</td>
</tr>
</tbody>
</table>

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**Table 1: Wound care dressings and their main indications.**

**Critical review**
Other drugs

There is a lack of evidence for the efficacy of other drugs such as N-acetylcysteine, angiotensin converting enzyme inhibitors, angiotensin II receptor blocking agents, nitrates and statins. A Cochrane review of prazosin demonstrated efficacy versus placebo, but the efficacy is modest and side effects limit its use. While there is no evidence that aspirin may accelerate DU healing, beneficial effects of low molecular weight heparin were observed in severe RP patients.30

The role of the surgeon for DUs

A surgical consult may be necessary in the case of failure of the medical approaches and thus it is a pivotal intervention not only in the case of macrovascular disease. To foster DU healing, surgical debridement may be required. As shown in figure 1, a surgical opinion should be sought whenever a macrovascular involvement is suspected and, if necessary, also arteriography could be performed, both with diagnostic and therapeutic aims. For patients who do not respond to the above mentioned interventions, a surgical approach in order to inhibit vasoconstriction and to improve blood flow to the fingertips (sympathectomy) should be considered.

Conclusion

Management of DUs in SSc must be based on a complex approach which comprehends the treatment of blood flow reduction, vascopathy, possible thrombosis of the vessels involved, antibiotic therapy if necessary and local treatment of DUs. Prevention should not be left behind: patients should be taught to refer to their rheumatologist as soon as signs or symptoms of critical digital ischemia present, as well as in case of DU appearance and to lifestyle and hygienic rules that patients should follow even in the case of a mute history for digital ischemia or DUs. A correct therapeutic approach can be based only on a correct education and information of the patient.

References

20. Vayssairat M. Preventive effect of an oral prostacyclin analog, beraprost sodium, on digital necrosis in systemic