Cutting to the heart of digital ulcers – should debridement be a standard of care in systemic sclerosis?

Viewpoint

Michael Hughes PhD[1,2], Begonya Alcacer-Pitarch PhD[3,4], Yannick Allanore PhD[5], Murray Baron MD[6], Francesco Boin PhD[7], Cosimo Bruni MD[8], Lorinda Chung MD[9], Francesco Del Galdo PhD [3,4], Christopher P Denton PhD [10], Marco Matucci-Cerinic PhD[8]

Author affiliations

1. Department of Rheumatology, Royal Hallamshire Hospital, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK.
2. Centre for Musculoskeletal Research, Faculty of Biology, Medicine and Health, The University of Manchester, UK.
3. Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, UK.
4. NIHR Biomedical Research Centre, Leeds Teaching Hospital NHS Trust, Leeds. UK
5. Department of rheumatology, Cochin Hospital, AP-HP, Paris Descartes University, Paris, France.
6. Division of Rheumatology, Department of Medicine, McGill University, Montreal, Canada
7. Division of Rheumatology, Department of Medicine, University of California San Francisco, San Francisco, CA, USA.
8. Department of Experimental and Clinical Medicine, Division of Rheumatology, University of Florence, Florence, Italy.
9. Division of Immunology and Rheumatology, Department of Medicine, Stanford University School of Medicine and Palo Alto VA Health Care System, Palo Alto, CA
10. Department of Rheumatology, Royal Free Hospital, University College London, London, UK.

Corresponding Author:

Dr Michael Hughes BSc (Hons) MBBS MSc MRCP (UK) (Rheumatology) PhD
Consultant Rheumatologist
Department of Rheumatology, Royal Hallamshire Hospital, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, S10 2JF, UK.
Michael.hughes-6@postgrad.manchester.ac.uk
ORCID ID: 0000-0003-3361-4909 | Telephone: +44 (0)114 271 1900

Abstract

Digital ulcers (DUs) are a serious recurrent complication in patients with systemic sclerosis (SSc); often slow to heal and exquisitely painful. Local wound care is an essential component in the management of DU in SSc, including wound bed debridement. However, DU debridement is not currently a standard of care and there is significant international variation in the use of this approach. Using the TIME model, we discuss in this viewpoint the assessment of the wound bed as well as different methods that can be used to perform ulcer debridement. We highlight the current challenges and need for research in local wound care for DU with a potential roadmap to develop a standardised approach to support ulcer debridement in SSc. DU debridement may be the missing 'key' in achieving optimal management of DUs and we propose that ulcer debridement should be rigorously explored as standard of care in this common SSc complication.

Introduction

Digital ulcers (DUs) are a major cause of disease-associated morbidity in patients with systemic sclerosis (SSc) and often very challenging/refractory to treatment.[1] DUs are more common on the fingers than toes (Figure 1), with a prevalence of 50% and 20 %, respectively.[1,2] Over half of patients with SSc report a history of finger DUs with a point prevalence of 5-10%.[1,3–5] They commonly occur on the tips of the digits and over the extensor (dorsal) aspects, in particular, overlying the interphalangeal joints.[1,6] Several factors contribute to the development of DUs such as ischaemia, fibrosis and calcinosis.[1,6] DUs often occur early in the course of the disease (within the first 5 years) and are associated with a more severe disease course including internal organ involvement in patients with early disease.[1,7,8]

In general, SSc-DUs are believed to be driven by ischaemia, in particular those occurring on the fingertips, whereas, those overlying the extensor aspects are driven by recurrent microtrauma and increased skin tension.[1,6,9] However, recent research has questioned this dichotomy, with evidence which could suggest that also extensor DUs may have a potentially treatable ischaemic component.[10,11] For example, in a double-blind, randomised, crossover, placebo-controlled study, the capillaries at the centre of both fingertip and extensor SSc-DUs were responsive (i.e. demonstrating increased perfusion as assessed by laser Doppler imaging) from nitric oxide donation by topical application of glyceryl trinitrate.[12] Although lower limb skin ulcers can occur solely due to SSc-microangiopathy, it is critical to assess for potentially treatable large vessel disease from macrovascular arterial and/or venous involvement in SSc.[13]

DUs are often exquisitely painful including from the effect of recurrent trauma and/or superadded infection. DU disease significantly impacts negatively on hand function including domestic, work and social participation.[14–17] Patients report a constant level of vigilance to prevent the development of new DUs and/or infection of current ulcers. Furthermore, patients make many changes to their lives including utilisation of a range of coping strategies and adaptions to cope with their ulcer disease. Therefore, it is not surprising that SSc DU disease is associated with a significant personal and societal burden. For example, in a study from Italy, the mean cost for DU management was reported to be €20,032 per patient, and

the main driver of this was the number of admissions to the day hospital for intravenous vasodilator therapy.[18]

Against this background, the aim of our viewpoint is to explore the rationale and current role for debridement in SSc and to highlight the current challenges and need for research in local wound care for DU with a potential roadmap to develop a standardised approach for SSc-DU debridement.

Search strategy and selection criteria

To identify specific data related to DU debridement, we used the following search criteria (01/01/1970-21/10/2019) within the National Institutes of Health's National Library of Medicine (PubMed):

(Digital Ulcer* OR Ulcer* OR wound) AND (systemic sclerosis OR Scleroderma) AND (debridement OR healing OR local OR management OR treatment OR therapy OR scalpel OR autolytic OR curettage)

Due to the novelty and need to highlight the role of DU debridement to the broader rheumatology community, original research articles, case reports, and reviews were identified and examined for data relating to the major subheadings of this review. A grey search of manuscripts cited within these articles was also undertaken. Key legacy papers including seminal and influential work were also selected to illustrate the burden and treatment challenge of DU disease in SSc.

Overview of DU pharmacological and surgical management

In general, our current treatments to both prevent and/or heal SSc-DUs act via systemic vasodilation.[19,20] This is presumably based upon the assumption that DUs are driven by ischaemia, and therefore increasing ulcer perfusion is likely to benefit ulcer healing.[11] However, such treatments are often poorly tolerated by patients, thereby necessitating significant drug dose reduction and/or permanent drug discontinuation. Patients are commonly prescribed treatment with vasoactive therapies (e.g. calcium channel blockers and phosphodiesterase type-5 inhibitors) in the context of SSc-associated Raynaud’s

phenomenon[21], and these have been reported to be associated with a reduced burden of new DUs. Similarly, treatment with bosentan (an endothelin-1 receptor antagonist) has also been reported to be associated with a 30% reduction in new DU development.[22] Interestingly, in two more recent randomised controlled trials of macitentan (another endothelin receptor antagonist), there was no superiority over placebo, although the number of new ulcers was very small, suggesting limited potential to demonstrate treatment benefit, perhaps due to important differences in study design including the studied populations.[23] Intravenous prostanoids (e.g. iloprost) reduce the development of new DUs and are associated with improved DU healing.[24,25] Although approved in the EU and UK for the treatment of DU and severe RP, IV prostanoids are not yet approved for these indications in the US, but Phase III clinical trials are currently ongoing. There is some evidence that phosphodiesterase type-5 inhibitors may facilitate improved DU healing; however, the authors of a recent randomised, placebo-controlled trial of sildenafil found no difference (in part due to the unexpectedly high healing rate in the placebo arm).[26] Clinicians are increasingly using combination vasoactive therapies (phosphodiesterase type-5 inhibition and endothelin receptor blockade) in patients with refractory SSc-associated digital vascular disease.[27,28] An alternative treatment indicated for DUs which are not responsive to the previously described medical interventions is surgical debridement. This intervention is specifically indicated for tissue necrosis, abscess formation, infected ulcers including deeper bony infection (e.g. osteomyelitis), and to remove underlying subcutaneous calcinosis.[29] Furthermore, there is increasing experience in surgical digital (periarterial) sympathectomy and botulinum toxin injection, both of which promote increased digital perfusion.[30–32] Indeed, surgical debridement can be done concurrently with digital sympathectomy in the sterile surgical setting.

Ulcer assessment and local wound care

Ulcer local wound care is a cornerstone of DU management and is used in combination with systemic pharmacological management. Local DU wound care should be delivered by a dedicated specialist multidisciplinary team including (but not limited to) physicians in rheumatology and dermatology, rheumatology specialist nursing, and allied healthcare professionals (e.g. podiatry). A major challenge is that at present there is no strong SSc-specific evidence base for DU local wound care.[33] However, valuable guidance on the management of CTD/vasculitis-associated skin ulcers including local wound care have been

proposed.[34] In general, current management is largely based on expert opinion/experience and revolves around lessons learned from ulcer wound care in other common ulcer patient groups (e.g. diabetic and pressure ulcers). Furthermore, the lack of a standardised wound care protocol for SSc-DUs has important potential implications for the study design of randomised controlled trials of drug therapies for ulcers because differences in wound care could significantly influence DU healing.[35]

The acronym 'TIME' was developed by wound healing experts as a framework to help identify the key role and components of optimal wound bed preparation.[36] This acronym relates to tissue management, infection and inflammation, moisture control, and advancement of the wound edge/epidermal advancement.

Tissue management

Ulcer debridement is the essential first step of ulcer tissue management. Close attention is paid to the ulcer base (bed), edges and perilesional skin. Chronic DUs often have significant necrotic tissue/eschar present which is non-viable and significantly delays SSc-DU healing.[6] Such adverse ulcer features are additive. For example, in a study which included 785 DUs in patients with SSc, the presence of fibrin (compared to without) in a 'necrotic' DU was associated with a significant (mean) delay in healing (129.6 vs. 78.2 days, respectively).[6] 'Slough' is another type of devitalised tissue which can act as a potential reservoir for infective organisms and can vary widely in appearance from being dry and adherent to very liquid-like and loosely attached.

Devitalised tissue requires debridement (described later) in order to promote healthy wound tissue granulation. Other important barriers to DU healing include the presence of biofilm and the bioburden (e.g. the diversity and virulence of the microbial load) across the wound.[37] Biofilms are complex bacterial communities which are surrounded by a complex protective structure of sugars and proteins (glycocalyx).[37,38] Biofilms provide protection including (but not limited to) host immune responses and antimicrobial therapies.[38]

Infection and inflammation

Inflammation is a non-specific response and has a positive role in normal wound healing; however, when excessive, inflammation can damage tissue. DUs are often infected, in particular, by *Staphylococcus aureus*.[39] In addition, one study also identified that one-quarter of DUs were also infected by enteric organisms.[39] Clinicians should have a low threshold to consider prescribing antibiotic therapy if there is any concern about potential infection of DUs. As previously described, superficial DU infection can progress to bone infection (i.e. osteomyelitis). Of note, changes consistent with osteomyelitis are not evident on plain radiographs until late in the process, however, other imaging modalities (especially magnetic resonance imaging) may help to facilitate the early diagnosis of bone infection.[40] Different types of dressings (e.g. silver and iodine) can provide a vehicle for delivering locally-acting antimicrobial treatment. Furthermore, such dressings cannot be used for extended periods as they have negative effects on epithelial growth with long term use.

Moisture control

Optimal wound moisture (exudate) control is essential for ulcer healing. A moist wound bed stimulates epithelial growth, whereas, excess moisture exerts inhibitory effects related to the presence of pro-inflammatory cytokines.[37] High levels of exudate can also damage new (healthy) granulating tissue, cause maceration of perilesional skin, and can promote infection.[37] On another hand, excessive wound bed dryness can also delay ulcer healing. In the presence of excess exudate, the treatment objective is to absorb/control the exudate, while for an anhidrotic wound bed, the goal is to rehydrate. The choice of dressing (discussed later) can positively manipulate ulcer wound bed moisture.

Wound edge/epidermal advancement

The wound edge plays a key role in determining the outcome of the ulcer healing process. Failure of normal ulcer healing can result in hyperproliferation/rolling of the wound edge. The perilesional skin also plays a significant role in maintaining the integrity of wound edge and should be carefully examined when assessing the edge of ulcers (e.g. for signs of maceration and infection).

<u>Wound bed management</u>

Wound bed management is essential to enable ulcer debridement and involves removal of dressings, wound bed preparation, selection of suitable dressings and analgesia if required (e.g. for sharp debridement).

Any existing dressing must first be removed to allow debridement. If the dressing is adherent to the surface of the wound then warm solution (e.g. saline solution) can be applied to soften the bandage to allow removal. Lebedoff et al[35] highlight in their review that ulcer wound care (e.g. changing dressings and debridement) can be exceptionally painful for patients and can represent a major barrier to compliance for patients to engage with essential wound care. Local and systemic analgesia will be discussed later in the context of sharp debridement.

Detersion is performed by irrigating the wound with warm saline solution (NaCl 0.9%) through a needle and syringe (e.g. by using a 10ml syringe with an attached 19G needle). Mechanical agitation by detersion of the wound surface removes non-viable necrotic material as well as dirt and debris (including remnants of previous dressings), but without damaging healthy granulating tissue.

Ulcer debridement

Ulcer debridement is widely used in the management of ulcers to promote wound healing. Debridement can be used to remove necrotic material, eschar, devitalised and infected tissue, hyperkeratosis, slough, serocrusts, pus, haematomas, foreign bodies, debris and/or bone fragments. There are seven different methods (which are sometimes combined) to debride a wound: sharp, mechanical, autolytic and enzymatic, biosurgical debridement (i.e. larval/maggot), technical solutions (i.e. hydrosurgery, ultrasound, negative pressure), and surgical debridement.[41] Commonly used forms include 'sharp' (or 'mechanical') debridement which uses a scalpel or curette, whereas, 'chemical' (or 'autolytic') debridement uses different dressings to optimise endogenous tissue lysis. Sharp debridement is painful and therefore requires analgesia. Whereas, autolytic debridement is painless but is slower, as it relies upon endogenous processes to remove non-viable tissue.

Sharp debridement

An example of sharp DU debridement is provided in Figure 2. Sharp debridement is usually performed using a sterile scalpel (15 or 10 blade); however, other instruments can be used (e.g. courgettes and scissors) and is performed in a non-sterile environment (e.g. in the clinic or at the bedside). Calcinotic deposits can also be removed by sharp debridement. Careful debridement of the wound bed is required to avoid damaging granulating tissue, and with close attention to the perilesional skin.

Autolytic debridement

Autolytic debridement utilises naturally occurring endogenous proteolytic enzymes which break down necrotic material. This form of debridement relies upon the moist environment which occurs between the wound bed and dressing. Autolytic debridement is also often combined with other (e.g. sharp) debridement. Figure 3 depicts digital ulceration which has been treated with the combination of sharp and autolytic debridement. A key aspect of autolytic debridement is selecting an appropriate dressing which is based upon the amount of exudate and dryness of the wound.[37] Hydrogels and hydrocolloids are used for dry/necrotic wounds with low levels of exudate. For example, hydrogels help to regulate fluid exchange from the ulcer surface, and is often used in combination with sharp debridement.[37] Hydrocolloids are rarely used in patients with SSc due to significant associated pain and discomfort, and can potentially damage perilesional skin.[37,42]

Analgesia

Analgesia is required for sharp ulcer debridement and for painful dressing removal. Examples of analgesia include topical lidocaine hydrochloride (2%-4%) water compress solution or 2.5% lidocaine/2.5% prilocaine cream compress for 15 minutes.[37] Several authors have reported successful experience using local anaesthetic to facilitate ulcer debridement through significant reduction in peri-procedural (both during and after) DU debridement.[43,44] For example, Braschi et al[43], reported that after 15 minutes of topical lidocaine application, there was a significant reduction in mean pain (0-10, where 10 is most severe) compared to baseline (6.74) immediately after application of lidocaine (2.83) and after scalpel debridement (2.88). Furthermore, the authors used a dose escalation strategy, in which larger ulcers (diameter) were treated with a larger amount of local (topical) analgesia: 1ml on <0.5cm DU, 2ml on 0.5-1cm DU, and 3ml on >1cm DU.[43] Local analgesia is well tolerated by patients with only very

mild (e.g. with a sensation of itching and burning) and no systemic effects.[43] Combined local and systemic (including opioid-based analgesia) is often necessary for severe and/or infected SSc-DUs.[44]

Summary of ulcer debridement for common types of skin ulcers

Ulcer debridement is widely used in the wound care of patients with different types of common (e.g. diabetic and pressure) ulcers. As previously described, there are a number of different methods which can be used to perform ulcer debridement. However, at present, there is no robust evidence to endorse one method of debridement over another. Overall, there is a consensus from the wound literature that debridement aids wound healing.[36,41] However, the evidence base is limited and of low-quality. For example, the most recent Cochrane systematic reviews for diabetic foot ulcers[45] and venous ulcers[46] concluded that due to the low quality of the studies no conclusions could be made with regards to the effect of debridement on ulcer healing. Furthermore, the largest randomised controlled trial of venous leg ulcers comparing biosurgical debridement versus autolytic debridement showed no difference in time for ulcer healing between the two methods. In addition, the authors concluded that larvae were a more effective (and more painful) debriding agent than hydrogel. Taken together, although debridement is widely used in the management of chronic ulcers, the evidence-base to date is limited, and well-designed randomised controlled trials are required to confirm the efficacy of ulcer debridement.

Digital ulcer debridement in systemic sclerosis

At present, there is significant international variation in the use of DU debridement in routine clinical practice. An online survey of rheumatologists with an interest in SSc which included the responses from 137 individuals identified that over half (58%) never or rarely debrided DUs.[47] There was a notable difference between North American and European responders. The majority (85%) of North Americans rarely or never debrided DUs, whereas, only 37% of Europeans reported that they never or rarely debrided ulcers.[47] Out of all the responders, there was wide variation in the perceived benefit of debriding on ulcer healing. Two-thirds felt that debriding had either no effect on (30%) or delayed (29%) ulcer healing; whereas, around half (41%) felt debridement improved DU healing.[47]

Other than a few studies reporting personal experience with DU debridement in patients with SSc[42–44], no studies to date have specifically reported the effects of sharp debridement on DU healing. The majority have used sharp debridement in combination with autolytic debridement. However, there is no standardised DU debridement protocol in SSc. DU debridement is often associated with significant peri-procedural pain, in particular, for more severe and/or infected DUs. Topical anaesthetic (e.g. lignocaine) is often sufficient to allow ulcer debridement; however, systemic (e.g. opioid-based) analgesia is sometimes required to manage post-treatment pain or severe ulcer pain.[43,44] Autolytic debridement with hyaluronate-based products has been reported to be associated with significant ulcer inflammation and pain.[42] Ercengiz and Yazici Mutlu reported successful use of maggot debridement in a patient with SSc with refractory, infected DUs on the toes. The authors chose to use maggot debridement due to the severity of pain associated with the ulcers.[48]

Challenges and proposed roadmap to bring digital ulcer debridement into routine clinical practice

There is a clear need for high-quality research to explore DU debridement in patients with SSc. However, at present there are a number of important barriers to bring DU debridement into routine clinical practice. In Figure 4, we have proposed a possible roadmap which could guide research studies to provide evidence and expert consensus for future incorporation of ulcer debridement into the routine wound care for DUs in SSc. The initial steps are to further understand international variation in DU debridement including the perceived barriers to implementation (stages 1&2), and to understand those ulcers which clinicians would vs. would not debride (stage 3). A SSc-specific DU debridement protocol is urgently needed based upon international consensus opinion from key stakeholders including patient representatives (stage 4). This would include (but is not limited to) the indications and contraindications for DU debridement, timing (e.g. acute vs. chronic), periprocedural pain management, and subsequent wound care. This could also include the development of an 'atlas' containing pictures and other forms of multimedia (e.g. videos) to instruct the debridement process. Subsequently, well-designed randomised controlled trials are needed to confirm the safety and treatment benefit of ulcer debridement (stage 5). Such studies should also assess the perceived benefit/patient experience of DU debridement and health economics. In addition, studies will be required to directly compare the different possible

methods of ulcer debridement. Consensus must also be reached regarding formal training in debridement which is required for a basic level of competence for practitioners to safely perform DU debridement (stage 6).

Conclusion

Despite great advances in the pharmacological management of SSc-DUs, a number of patients have refractory DUs. Optimal wound care is essential for DU management in SSc; however, the use of ulcer debridement significantly varies internationally. At present, the evidence to support this intervention is lacking and we have proposed a roadmap to develop a standardized DU debridement protocol in SSc. Ulcer debridement could represent the missing 'key' in the optimal management of DUs and should be explored as part of standard wound care in patients with SSc. We call to arms the international community to advance the agenda for DU debridement in SSc, cutting to the core of ulcers to illuminate the optimal wound care for SSc-DUs.

Authors and contributors

The authors meet all four criteria for authorship as recommended by the International Committee of Medical Journal Editors (ICMJE).

Declaration of interests

Dr Chung reports ad board and steering committee from Eicos, ad board and consulting from Mitsubishi Tanabe, data safety monitoring board from Reata, ad board and consulting from Boehringer-Ingelheim, ad board and steering committee from Bristol-Myers Squibb, outside the submitted work. Professor Denton reports grants and personal fees from GSK, personal fees from Actelion, personal fees from Bayer, personal fees from Corbus, personal fees from Boehringer Ingelheim, grants from Servier, grants and personal fees from CSL Behring, personal fees from Sanofi, personal fees from Roche, grants and personal fees from Inventiva, outside the submitted work.

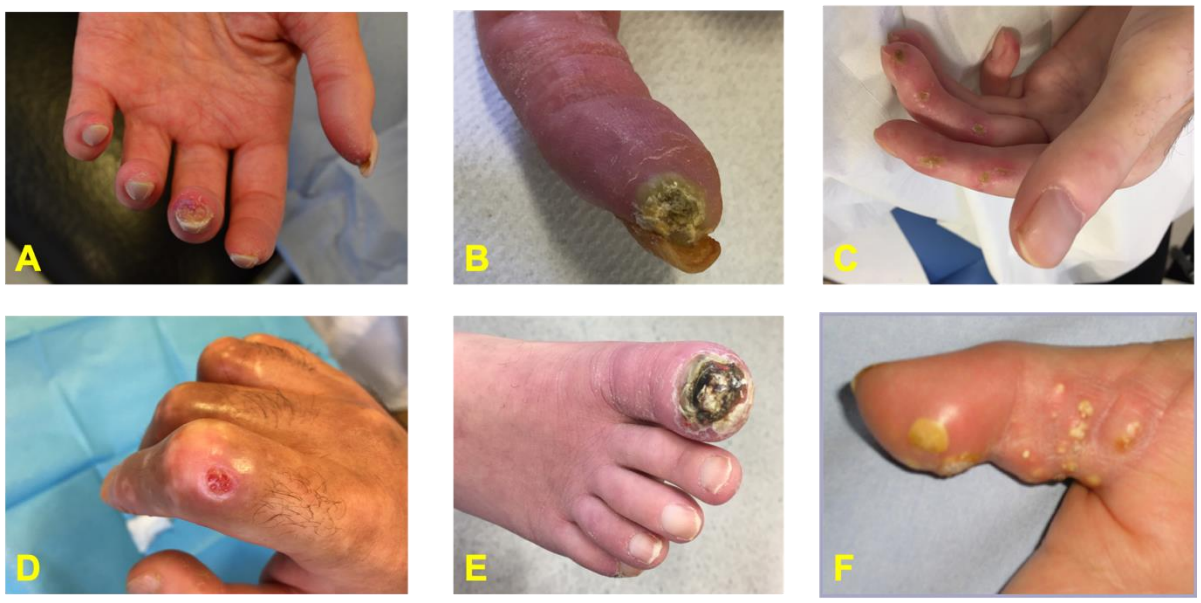

Figure 1: Spectrum of digital ulceration in systemic sclerosis. Ischaemic digital ulcers on the fingertips (A-C) and overlying the extensor/dorsal aspect of the hand (D). Toe digital ulceration (E) and systemic sclerosis-associated calcinosis which can ulcerate and discharge through the skin (F).

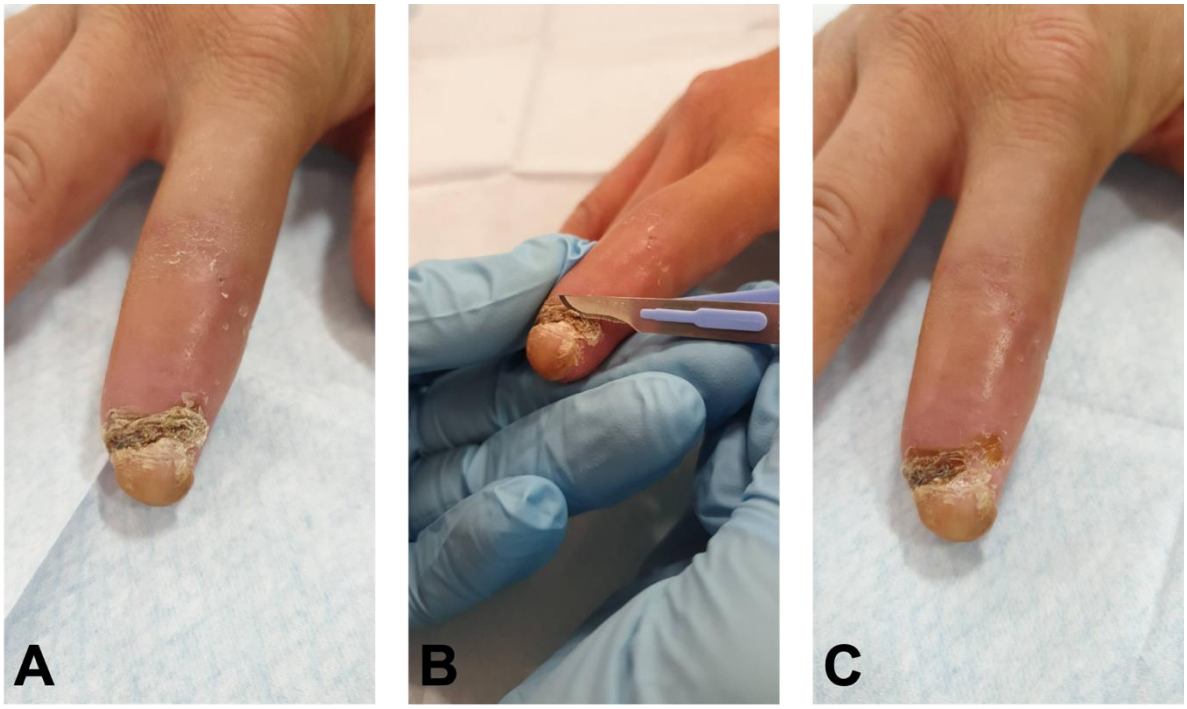

Figure 2: Sharp digital ulcer debridement. Images taken before (A), during (B) and after (C) DU debridement in a patient with systemic sclerosis. The ulcer was not fully debrided on this occasion as it was too painful for the patient. In future visits further debridement will be performed until the wound bed is fully exposed.

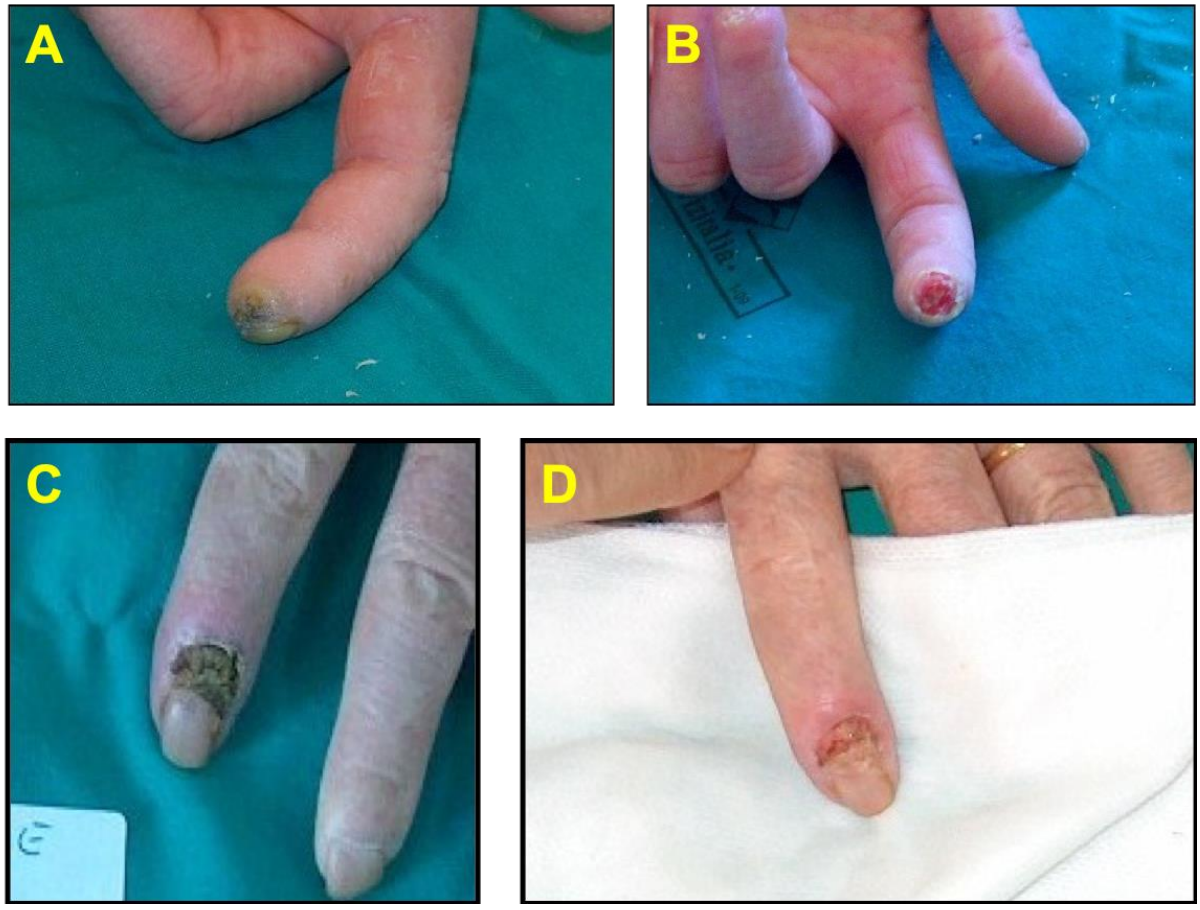

Figure 3: Digital ulcer debridement. Ulcer images at baseline (A&C) and during follow-up (B&D) following combined sharp debridement (with a scalpel) and autolytic debridement (from application of an autolytic dressing).

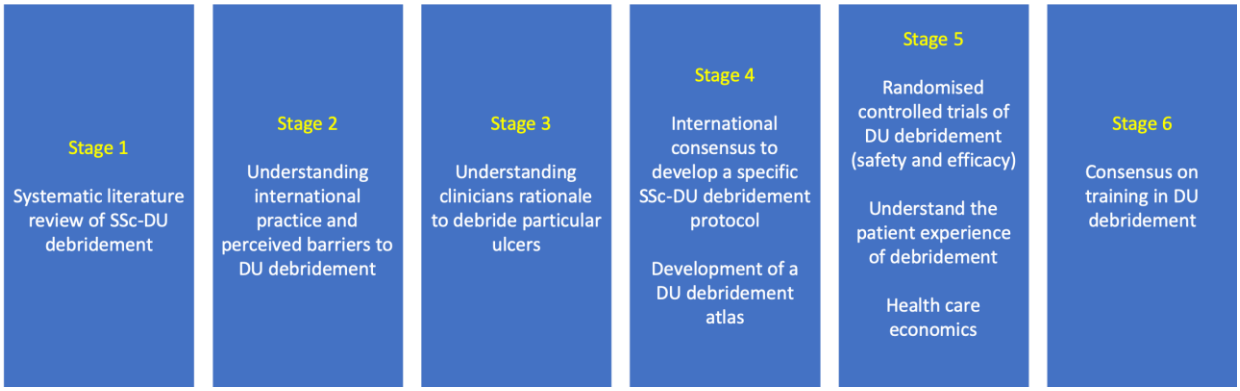

Figure 4: Proposed roadmap to develop a standardized debridement protocol for SSc-DUs. The stages are iterative and may need to be revised if consensus is not achieved and/or new research priorities are identified.

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