Antibiotic Treatment

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Introduction

Digital ulceration is common and often recurs [1]. Recent data from the Digital Ulcers Outcome Registry reported that bacterial infection remains as one of the major concerns affecting 36% and 61% of patients with recurrent and chronic DU in SSc [2]. Factors that increase the risk of infection may be disease specific, and these may either be systemic or local to the infected tissue. Systemic factors would include severe gastrointestinal disease and malnutrition, immunosuppressive agents including steroids, duration of disease and ulcer, smoking and coexisting macrovascular disease in addition to other comorbidities including diabetes, while local factors that contribute to infection include history of soft tissue infections, presence of calcinosis, contractures and exposed underlying structures [2–6]. The prolonged healing time of DUs associated with the persistence and chronicity of ulcer in SSc itself also increases the risk of infection.

Features suggestive of an underlying infection include erythema and/or heat at the edge of ulcer, increasing pain and tenderness, presence of discharge, foul odour and breakdown of ulcer (Fig. 22.1). Although concurrent local joint deformity, calcinosis and contractures may cloud assessment, patients are advised to be vigilant of these warning signs and to seek medical review. Infectious complications are particularly detrimental and often contribute to the significant comorbidities with tissue gangrene and amputations (Fig. 22.2) [7]. A global approach including local and systemic treatment with pain management and vasoactive drugs is mandatory, and antibiotic treatment is central to the management of patients with infective DU.

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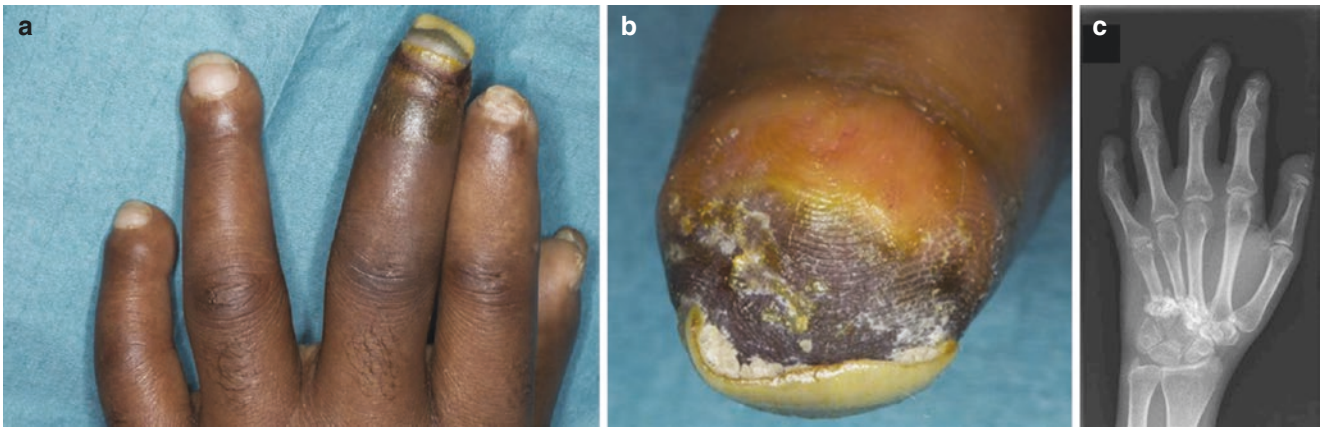

Fig. 22.1 Infected digital tip ulcer. (**a**) Ulcer at the tip of left middle finger with increased swelling and discolouration extending to the proximal interphalangeal joint. Inset (**b**) shows the fingertip ulcer with indistinct ulcer border. (**c**) Radiograph showed acro-osteolysis affecting all distal phalanges of the left five digits with exuberant calcinosis over the carpal bones with no clear loss of soft tissue over the middle finger tip

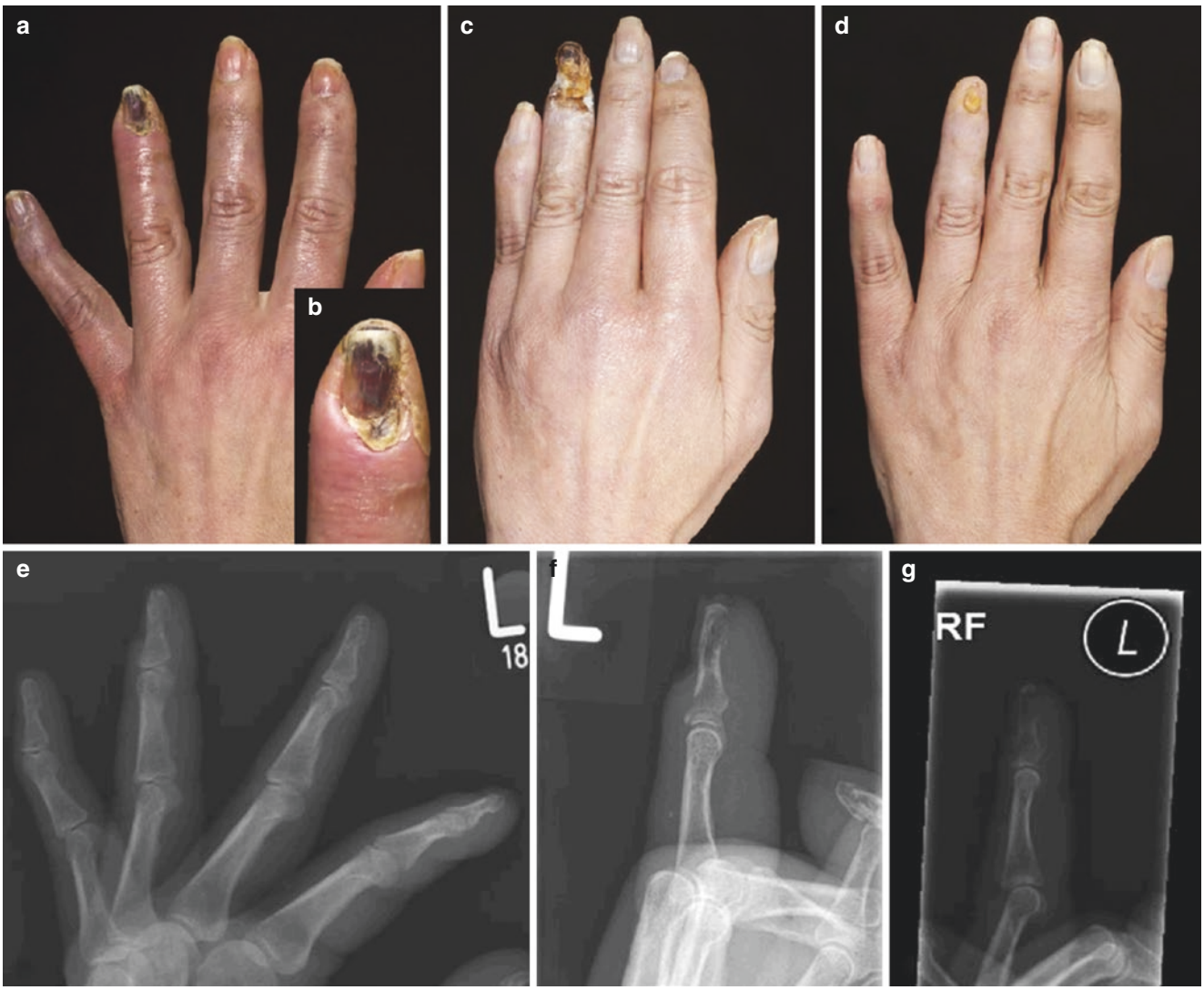

Fig. 22.2 Consequence of severe digital vasculopathy with tissue gangrene and autoamputation. (**a**–**d**) (with inset **b**): Serial panels showed progressive tissue loss with dry gangrene resulting in autoamputation of the left ring fingertip. (**e**–**g**) Serial radiographs showed worsening focal area of lucency with cortical erosive irregularity of the distal phalangeal head of the left finger consistent with osteomyelitis

Investigations

All digital ulcers with suspected infection should be evaluated by microbiologic examinations. Wound swabs should be taken routinely. Other potential sources of infections should be excluded in particular indwelling catheters or percutaneous endoscopic gastrostomies/jejunostomies feeding sites. Ideally this should precede the use of systemic antibiotics so that sensitivities can be determined. Empirical treatment can be given once wound swabs have been taken.

Culture of biopsy tissue has been advocated to allow more infections to be identified and to overcome the challenge of overgrowth of commensal or colonising bacteria.

Imaging can be useful to determine the presence of soft tissue infection, extension to involve underlying bone, joint or soft tissue structures. The presence of more invasive infection will necessitate much more intensive antibiotic therapy.

Plain X-ray can be useful, but the impact of acro-osteolysis and calcinosis can make this difficult together with the longer-term effect of bone loss secondary to severe digital ischaemia (Fig. 22.3). In the absence of clear clinical signs of infection, serial plain X-rays may be helpful to monitor evidence of infection. Rapidly progressive osteolysis as evident on serial X-rays may be indicative of osteomyelitis (Fig. 22.4). MR imaging is useful to identify bone marrow oedema that

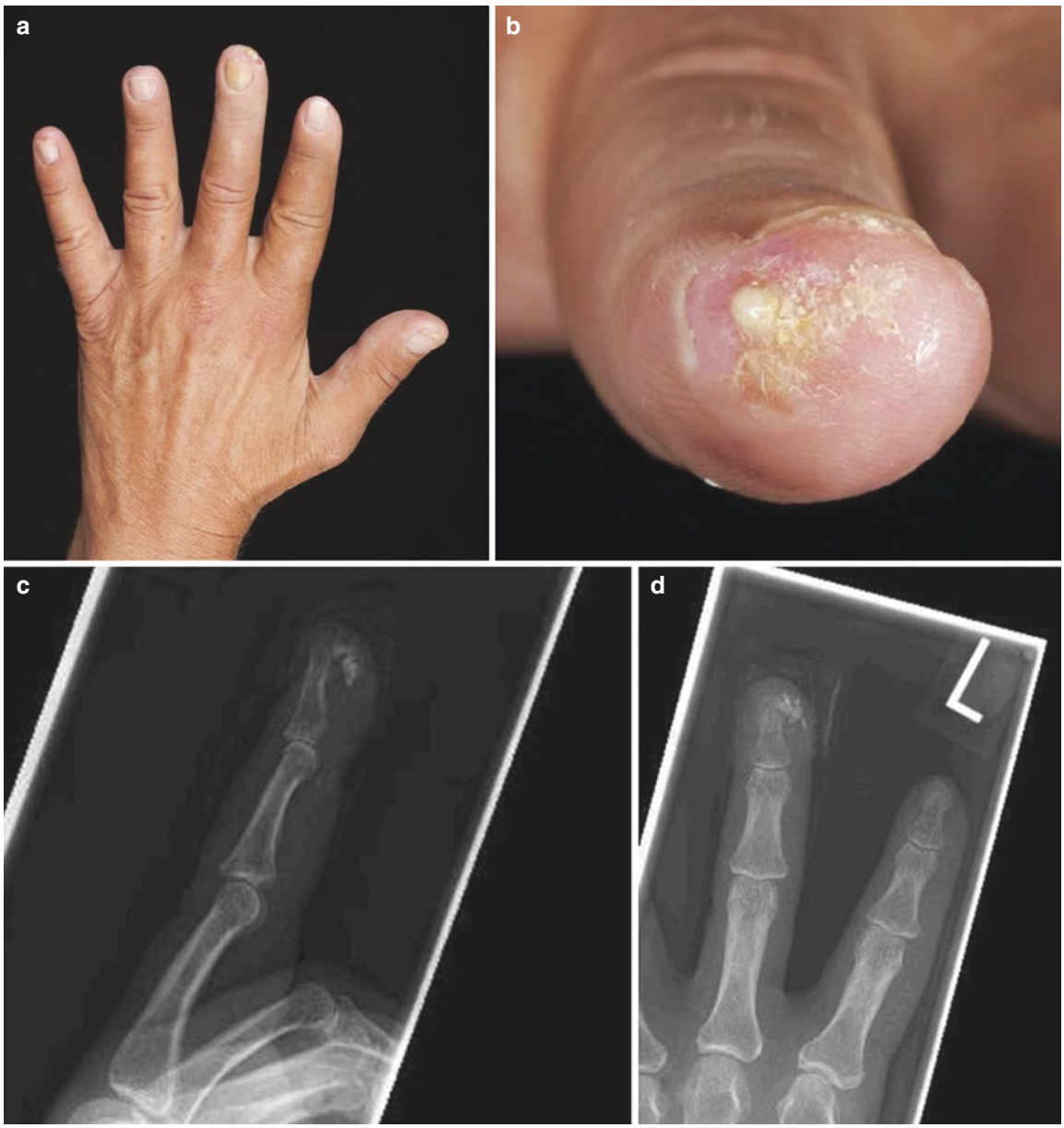

Fig. 22.3 Panel illustrates ulcer at the tip of middle finger associated with calcinosis. (**a**) Left middle finger with digital ulcer at its tip with soft tissue loss. (**b**) The underlying calcinotic nidus at the radial aspect of the digital pulp. (**c**, **d**) Lateral and anterior views of the ulcer with overlying dressing. Multiple calcific foci are shown along the distal tuft of distal phalanx with some associated soft tissue loss with no radiological evidence of osteomyelitis

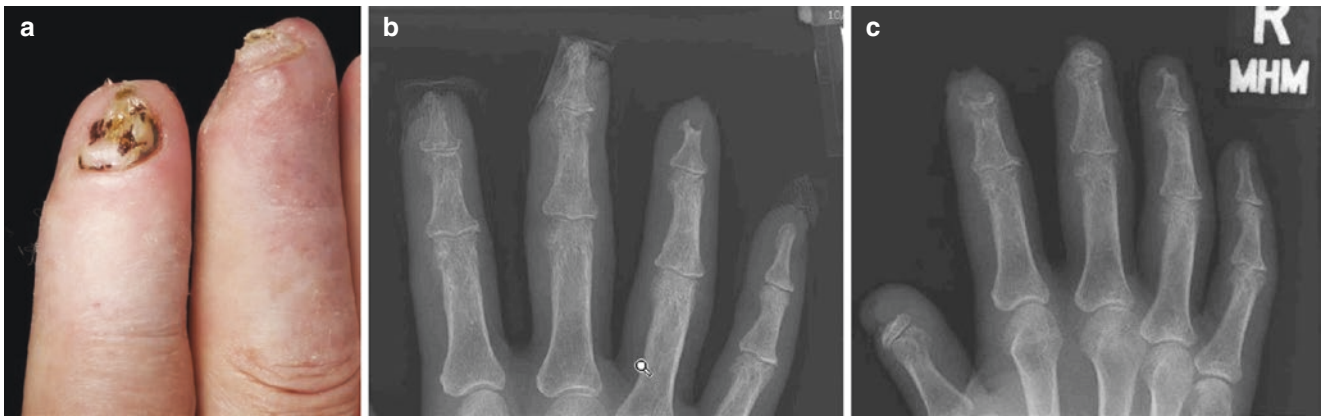

Fig. 22.4 Progressive digital resorption as a consequence of digital vasculopathy. Ulceration of right index and middle digits is shown in panel (**a**). (**b**, **c**) Serial radiographs showed progressive resorption of the affected distal phalanges over a month with irregular and ill-defined cortical erosion suspicious of osteomyelitis over the distal phalanx of the right index finger in panel C. Note the amputation of the distal phalanx of the right thumb as part of the digital vasculopathy in panel C

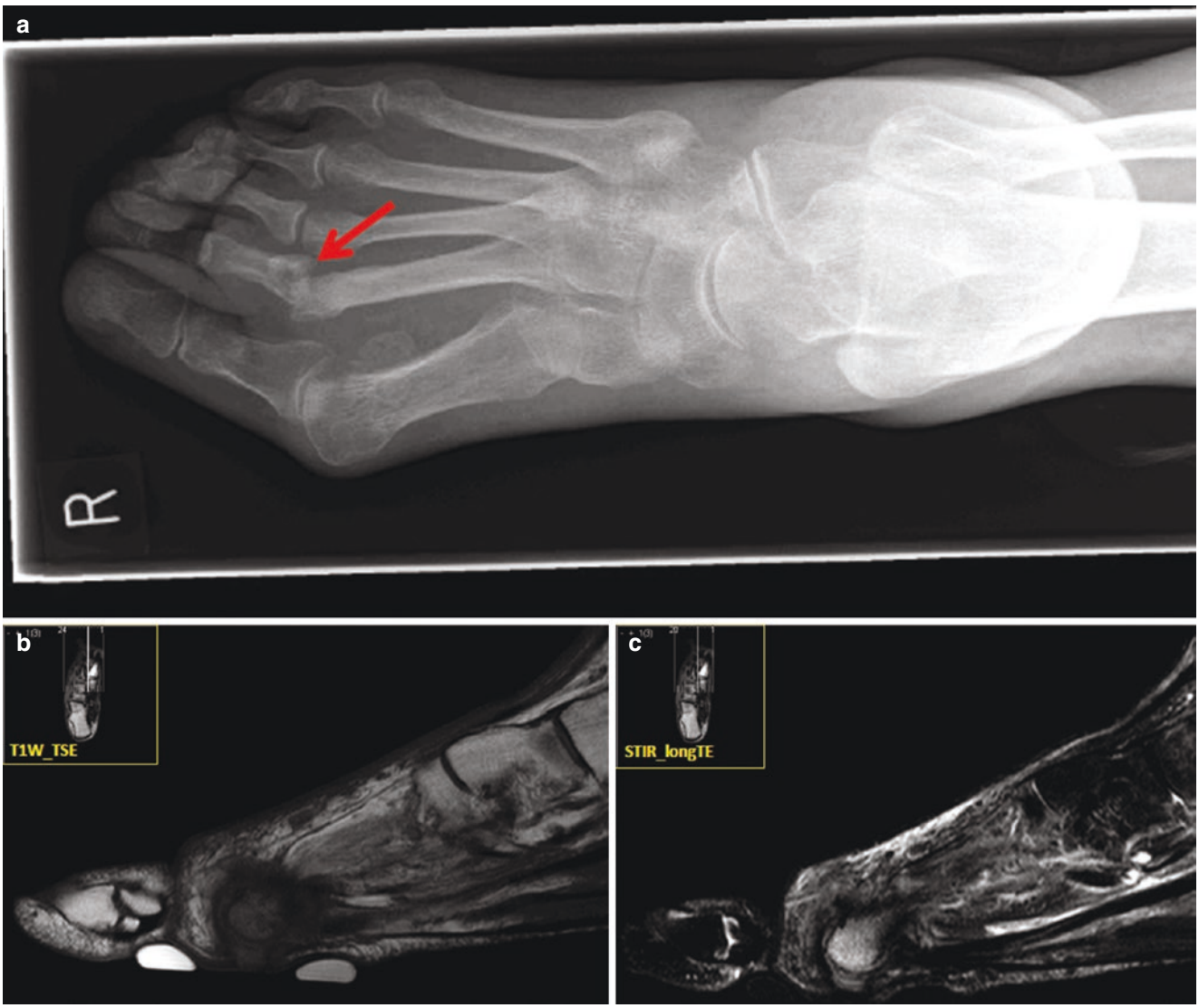

Fig. 22.5 Radiological evidence of osteomyelitis. This patient had an ulcer on the plantar aspect of the right forefoot underlying the head of the second metatarsal. Panel (**a**) showed subluxation of the right second metatarsophalangeal joint in addition to hallux valgus. There is sclerosis and destruction at this point (red arrow) suspicious of osteomyelitis. Panels (**b**, **c**) showed marked bone marrow oedema within the second metatarsal head extending to involve the distal half of the second metatarsal with cortical destruction of the metatarsal head

may suggest or confirm the presence of osteomyelitis (Fig. 22.5).

Local Treatment

Debridement can be very helpful to remove necrotic tissue to prepare the wound bed to heal. However, this largely depends on local expertise and nature of the DUs. A variety of approaches have been described, and these can be mechanical with either curettage or scalpel under local anaesthetic or chemical or biological techniques with enzymatic agents (including topical D-alpha-tocopheryl acetate) or maggot therapies [8].

Systemic Treatment

Early institution of systemic antibiotics forms the cornerstone of management of infected DU. Up to 50% of patients were reported from various studies to receive systemic antibiotics for soft tissue infections involving digital ulcers [1, 9, 10]. This is most easily administered orally, and the general principle is that higher dose may be required over a prolonged duration due to poor tissue perfusion. This is especially important in ischaemic fingertip invasive ulcers associated with severe secondary Raynaud's. Associated calcinosis can also impact on treatment and makes eradication of associated infection particularly challenging. Intravenous antibiotics are generally used for more severe infections and in association with cellulitis, osteomyelitis or septic arthritis. Choice of antibiotic is governed by results of culture informed by local microbiological expertise.

Supportive Treatment

Other factors to consider include optimal treatment of Raynaud's with vasodilators including advanced therapy with PDE5 inhibitors and endothelin receptor antagonists (ERA). Management is generally in line with the UKSSG management best practice pathway [11, 12].

Concept of Antibiotic Use in Infected Digital Ulcers in SSc

Contamination and colonisation with patients' endogenous flora from the skin, mucous membranes and gastrointestinal tract should be considered carefully as chronic wounds such as SSc are susceptible to colonisation, in the interpretation of swab results in SSc-associated DUs.

The host and local factors related to SSc in particular the immunocompromised state of the individual may predispose these chronic ulcers to be colonised by bacteria. The term critical colonisation describes the clinical state in which bacteria are able to induce the failure of wound healing with formation of biofilm. In fact, there is emerging evidence that biofilm formation is an important virulence factor in contributing to the bacterial persistence and chronicity [13]. As a consequence, these bacteria are difficult to be eradicated. On the other hand, there are also concerns regarding significant excess use of antibiotics in various non-healing ulcers which could contribute to the emergence of antibiotic resistance [14].

The initial choice of antibiotics may be empirical based on local prevalence of the pathogens and should be tailored to the specific needs of each population and institution. The cultures of swab are frequently negative or show mixed growth of microbes; however with cultures demonstrating a predominant bacteria, the choice of antibiotics should be targeted towards that organism depending on the sensitivity of the culture. Further advice from microbiologist on the appropriate antibiotic and the route of administration would be useful.

For mild superficial infection or for prevention of infection, topical antibiotics can be used but with caution as certain topical treatment such as Neosporin and bacitracin can incite irritant contact dermatitis to the already compromised soft tissue. Mupirocin 2% ointment (Bactroban) is a favourable choice instead as it rarely causes dermatitis and protects against MRSA [15]. Antiseptics should also be avoided due to its cytotoxic effects on cells [16].

Intravenous antibiotics should be considered in patients with multiple digital ulcers in particular in those who failed oral therapies. Other circumstances in which intravenous antibiotics may be preferred over oral route include complications of DUs with deep-seated infection and poor tolerability due to comorbidities, for example, gastrointestinal tolerance.

Pathogens Encountered in Infected Digital Ulcers in SSc

Similar to the pathogens identified from common chronic ulcers, digital ulcers in patients with SSc frequently isolate *Staphylococcus aureus* which is found around 50% among the pathogens [6, 10]. In one study involving 42 SSc patients, interestingly intestinal bacteria such as *Escherichia coli* and *Enterococcus faecalis* were detected in 26% from the cultures taken and were the second most common pathogens identified following *Staph aureus* [17]. It is believed that the patient's hand hygiene is often inadequate and the presence of digital ulcers further compromises this after defecation.

Hence the importance of effective hand hygiene should be emphasised among patients, relatives and health workers dealing with the ulcers. Other pathogens isolated were *Pseudomonas aeruginosa* (12%) and less frequently *Proteus mirabilis*, *Streptococcus agalactiae*, *Citrobacter koseri* and *Stenotrophomonas maltophilia.*

The prevalence of osteomyelitis was invariably found (42%) in the setting of infected SSc digital ulcers in a follow-up study [18]. The most frequently isolated pathogens from the digital ulcers complicated with osteomyelitis were *Staph aureus* and Gram-negative enterofaecal bacteria. Other less commonly identified microorganisms were *Pseudomonas aeruginosa*, *Streptococcus agalactiae*, *Staphylococcus epidermidis*, *Enterobacter aerogenes*, *Stenotrophomonas maltophilia*, *Proteus mirabilis* and *Serratia marcescens.* Standard radiographic examinations in chronic infected SSc digital ulcers is important to exclude osteomyelitis as the treatment offered would be variable in terms of the choice, route of administration and duration of antibiotics.

The predominant clinical manifestation of *S. aureus* is colonisation, rather than infection. Both methicillin-sensitive *S. aureus* (MSSA) and methicillin-resistant *S. aureus* (MRSA) infections are directly or indirectly caused by skin colonisation by these microbes. The difficult challenge faced by clinicians treating the infected digital ulcers is infection caused by drug-resistant *Staphylococcus aureus*, particularly MRSA. In the USA, MRSA was seen in 59% out of 320 patients with staphylococcal infection in a study of patients with skin and soft tissue infection attending the emergency departments [19]. Inappropriate use of antibiotics contributes to the emergence of antibiotic resistance in the community resulting in difficulty and complexity in treating this condition. The presence of MRSA infection can occur in soft tissue infection alone or together with osteomyelitis in the setting of digital ulcer.

Choice of Antibiotic

The choice of antibiotic needs consideration of several factors, even though it depends primarily on culture growth and sensitivity. Factors need to be considered include drug tolerability and adverse effects (existing scleroderma-related gastrointestinal symptoms may dictate choice of antibiotics), complications in particular osteomyelitis, drug interaction, predicted duration of therapy, route of administration, cost, toxicity and monitoring and soft tissue and bone penetration profile. SSc patients most often will need prolonged length of antibiotic course due to diminished vascular supply and immunocompromised state. In complex soft tissue infection, 1–4-week length of treatment is recommended, while for cases of osteomyelitis, the predicted treatment course would be from 6 to 12 weeks. The length of treatment is variable between individuals even though similar pathogen is encountered. Therefore, clinical response is the best measure of treatment success. Regular review and monitoring of the ulcer would be necessary to assess the response. Besides antibiotics, debridement of non-viable tissue and drainage of accompanying abscess, if any, for example, would facilitate the resolution of an infection.

It is advisable for the GP and health practitioner to start the patient on a course of oral antibiotics when infection of the digital ulcer is suspected, while swab cultures are taken. The likely pathogen for most digital ulcer-associated infection is *Staph aureus*. It is important to recognise that normal skin flora, e.g. *Pseudomonas* species, is often detected on wound swab and clinical correlation is critical. Subject to local microbiological practice, the recommended antibiotic during initial review of an infected digital ulcer is oral flucloxacillin 500 mg four times daily for a minimum of 2 weeks. Another option would be oral co-amoxiclav 625 mg three times daily. If allergic to penicillin, alternatives such as macrolides, erythromycin or clarythromycin may be considered. Cephalexins and doxycycline are also suitable for this indication [20]. In cases of chronic non-healing, persistently recurring infections, prolonged and/or rotating courses and parenteral administration may be required. Multidisciplinary approach with an expert advice of a microbiologist and infectious disease physician with local wound care and dressings is essential.

As discussed earlier, MRSA is an emerging problem and difficult to treat infection. Both bactericidal and bacteriostatic agents have been effective in the treatment of MRSA. A number of antibiotics, both oral and intravenous, are recommended in treating soft tissue and bone infected with MRSA and are outlined in Table 22.1. It has also been suggested that minocycline is an effective therapeutic option and provides rapid improvement and resolution of MRSA infection following prolonged and unsuccessful therapy with doxycy-

Table 22.1 Antibiotics recommended in treating soft tissue and bone infected with MRSA

Antibiotic	Route of administration	Main benefits	Main problems
Erythromycin (macrolide)	PO (main) and IV	Widespread experience of use	Comparatively poor oral absorption, GI side effects
Clindamycin (macrolide)	PO (main) and IV	Excellent bone penetration	Risk of *Clostridium difficile* diarrhoea
Linezolid (bacteriostatic)	PO (main) and IV	Excellent bioavailability and tissue penetration. Well tolerated; resistance rare	Reversible myelosuppression on prolonged courses; expensive
Daptomycin	IV	Once-daily administration Resistance rare	Skeletal muscle toxicity. Creatine kinase monitoring required
Vancomycin (glycopeptide)	IV	Widespread experience of use. Studies on bone penetration is less conclusive	Nephrotoxicity – monitoring required Increasing resistance concerns
Teicoplanin (glycopeptide)	IV	Less nephrotoxic than vancomycin Once-daily administration	Monitoring required Concerns regarding resistance
Doxycycline (tetracycline)	PO	Once-daily administration	Nausea ± vomiting, oesophageal irritation
Minocycline (tetracycline)	PO (main) and IV	Good safety profile and efficacy against MRSA; inexpensive	
Tigecycline (bacteriostatic)	IV	Use in polymicrobial infection	GI side effects
Rifampicin (bactericidal)	PO (main) and IV	Excellent tissue and bone penetration	Must be used in combination Extensive interactions Liver function monitoring
Fusidic acid	PO (main) and IV	Excellent tissue and bone penetration	Must be used in combination

PO per oral, *IV* intravenous, *GI* gastrointestinal, *MRSA* methicillin-resistant *staphylococcus aureus*
Adapted from Thompson and Townsend [22], with permission from Elsevier

cline, in cases of doxycycline-related MRSA resistance [21]. Choice of antibiotics under these circumstances should be guided by local standards of microbiological guidance and recommendations.

An important consideration in SSc-related digital ulceration is the presence of calcinosis that may contribute to the initiation and chronicity of ulceration and infection. Mannose-binding lectin levels and markers of oxidative stress, the advanced glycation/lipoperoxidation end products with their respective receptor, have been found to be upregulated in SSc patients with calcinosis [23, 24]. Recent mass spectrometric analysis on protein composition of calcinotic deposits from a small cohort of patients with SSc revealed a subset of immune-related components with neutrophils, immunoglobulins and complement system, thus supporting that immunoinflammatory response may underlie the aetiopathogenesis of dystrophic calcinosis [25].

There is evidence to suggest that tetracyclines including minocycline may have anti-inflammatory effects with suppression of key cytokines including tumour necrosis factor-alpha (TNF-α) and interleukins (IL-6 and IL-1β). Other potential mechanisms include downregulation of collagenolytic enzymes including matrix metalloproteinases, elastase and cathepsins with augmentation of antioxidant effects [26, 27]. In support of this, minocycline was reported to be effective in the treatment of calcinosis in a small case series of nine patients [28], and while its use has not been formally evaluated in a larger study, minocycline may be considered in selected patients with ulcers associated with calcinosis.

Observational Data from Royal Free Hospital (2014–2015)

Table 22.2 summarises recent data on our experience on the management of SSc-related infected digital ulcers with antibiotics in an unselected cohort of patients followed up in a specialist nurse-led digital ulcer clinic over a 12-month period. Consistent with the published literature, *Staph aureus* remains the most frequently isolated pathogen in our cohort. A majority of these pathogens were either MRSA or MSSA despite the routine practice of topical decolonisation of our patients. This highlights the complexity and challenge in the management of soft tissue infection in SSc given the chronicity of the disease, frequent hospitalisations with recurrent antibiotic use and associated use of immunosuppressive agents in this disease. The other pathogens encountered were *Pseudomonas aeruginosa*, *Enterobacter cloacae* and *Serratia marcescens.* On the other hand, normal skin flora was demonstrated in 25%, and the significance of this needs to be considered in the appropriate clinical context.

All patients had initial treatment with the penicillin group (flucloxacillin and co-amoxiclav). Subsequent courses of antibiotics were either macrolide (erythromycin or clarythromycin) or tetracycline synthetic (doxycycline). The patients received the antibiotics over 1–4 weeks. Prolonged antibiotic treatment was given to three patients who had digital ulcers complicated by osteomyelitis. All three patients received doxycycline; one patient received teicoplanin before switching to doxycycline. Patient 12 received prolonged 3-month course of doxycycline even though no osteomyelitis was detected and swab culture only demonstrated normal skin flora. The rationale for extended therapy was based on the anecdotal evidence of doxycycline on chronic inflammation associated with poor ulcer healing. Similarly, minocycline and pamidronate were continued for Patient 11 with underlying calcinosis complicating the ulcer. In addition to antibiotics, all 12 patients received concomitant treatment for Raynaud's and digital ulcers with prostacyclin analogue, vasodilators, endothelin receptor antagonist (bosentan) or PDE5 inhibitor (sildenafil), antiplatelets alone or in combination. All 12 patients showed good clinical response and improvement of their ulcers with negative wound swabs at the end of the observation period. An illustrative case with patient 2 is shown in Fig. 22.6.

Table 22.2 Observational data on antibiotics use in infected digital ulcers in 12 SSc patients at the Royal Free Hospital from 2014 to 2015

Patient	Antibiotics	Antibiotics duration	Swab culture and sensitivity	Therapies	Complications
1	Fluclox	4 weeks	*P. aeruginosa*	Ilo, sil, los	No OM
2	Fluclox, doxy	1 week, 12 weeks	MSSA (S: fluclox), MRSA (S: teic). Repeat swab (NG)	Ilo, sil, los, nif, clo	OM
3	Fluclox, doxy	4 weeks (Doxy)	*P. aeruginosa* (S: cipro, taz). Repeat swab (NG)	Sil, ena, asp	OM
4	Fluclox	1 week, 3 weeks	MSSA (S: fluclox)	Ilo, sil, IVIG, asp, los	No OM
5	Fluclox	2 weeks	Normal skin flora	Ilo, asp, fluox, dil, monopril	
6	Fluclox, claryth (total of 4 courses)	1–2 weeks each	MRSA (S: mupirocin)	Ilo, sil, asp, los, GTN patch	No OM
7	Aug; day 11 ceft (allergy), switched to teic and genta; doxy	2 weeks (augm), 3 days (teic and genta), 4 weeks (doxy)	MSSA (S: fluclox, eryth, claryth)	Ilo, sil, los, asp	OM
8	Aug, fluclox, doxy	4 weeks (fluclox), 4 weeks (doxy)	MSSA (S: fluclox, eryth, claryth)	Ilo	NA
9	Fluclox	2 weeks	*E. cloacae* (S: cipro) Possibility of colonising flora	Ilo, los, clo	NA
10	Fluclox, eryth	1 week each	*S. marcescens* (R: amp, aug, cephal) Possibility of colonising flora	Ilo, sil, amlo, ram, bosentan	NA
11	Fluclox, claryth	2 weeks each	MRSA (S: cipro, clinda, eryth, fucidin, teic)	Minocycline, pamidronate	Calcinosis
12	Fluclox, doxy	5 weeks, 12 weeks	Normal skin flora	Ilo	No OM

Fluclox flucloxacillin, *doxy* doxycycline, *claryth* clarythromycin, *eryth* erythromycin, *aug* aumentin, *teic* teicoplanin, *genta* gentamicin, *ceft* ceftriaxone, *cipro* ciprofloxacin, *taz* tazocin, *amp* ampicillin, *cephal* cephalexin, *clinda* clindamycin, *ilo* iloprost, *sil* sildanefil, *los* losartan, *nif* nifedipine, *clo* clopidogrel, *asp* aspirin, *ena* enalapril, *dil* diltiazem, *fluox* fluoxetine, *amlo* amlodipine, *ram* ramipril, *IVIG* intravenous immunoglobulin, *GTN* glyceryl trinitrate, *P. aeruginosa Pseudomonas aeruginosa*, *E. cloacae Enterobacter cloacae*, *S. marcescens Serratia marcescens*, *NG* no growth, *MSSA* methicillin-sensitive *Staphylococcus aureus*, *MRSA* methicillin-resistant *Staphylococcus aureus*, *OM* osteomyelitis, *S* sensitive, *R* resistant, *NA* not applicable

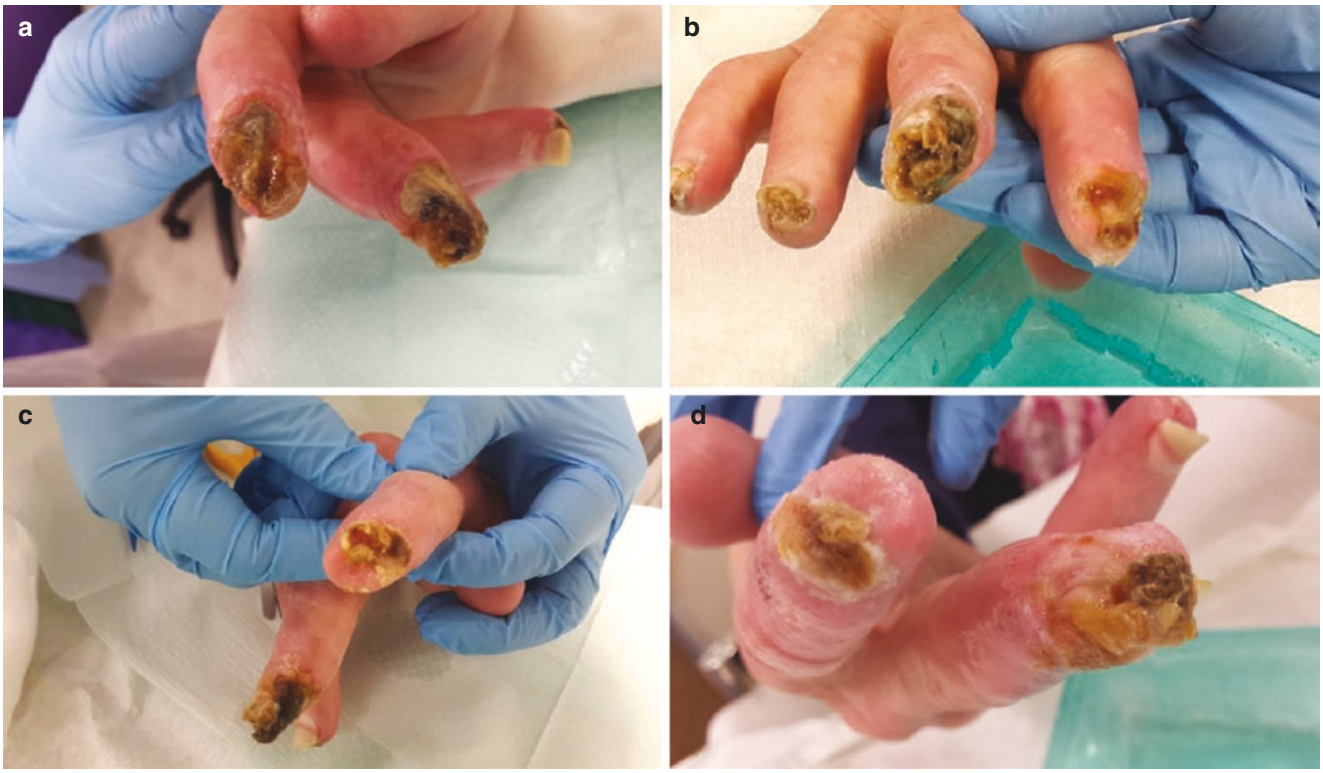

Fig. 22.6 The serial photographs ((**a**) baseline, (**b**) week 2, (**c**) week 6, (**d**) week 10)) demonstrate the temporal course of treatment response with prolonged course of doxycycline in a SSc patient with severe chronic non-healing digital ulcers predominantly right index and middle fingers complicated with MRSA osteomyelitis. Multidisciplinary approach with expert advice from microbiologist and close monitoring and regular wound care in a specialist nurse-led digital ulcer clinic was critical in managing this complex case

Conclusion

Infection should be considered in all DU, and management involves local and systemic therapy together with general management of SSc vasculopathy. Early and prompt recognition based on clinical signs and symptoms is critical. Patient education and awareness of this complication ideally within a dedicated SSc digital vascular clinic is pivotal for the prevention of digital ulcers and management of these patients. Early treatment with appropriate antibiotics and local wound care are crucial to prevent complications such as osteomyelitis and gangrene. Empirical choice of antibiotics and definitive treatments should be guided according to local practice. A multidisciplinary approach across all levels of medical and surgical teams is essential to guide diagnostic and therapeutic management.

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