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1 Raynaud's Phenomenon and Digital Ulcers in Systemic Sclerosis

2  
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32

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37 Sanofi-Aventis, Servier, in the area of systemic sclerosis.
- 38 • Lorinda Chung– Reata—Data Safety Monitoring Board Eicos—Steering Committee  
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47

48 Abstract

49 Raynaud’s phenomenon (RP) is a symptom complex related to impaired digital perfusion and  
50 can occur as a primary phenomenon or secondary to a wide range of underlying causes. RP  
51 occurs in virtually all patients with systemic sclerosis (SSc) and is often the earliest clinical  
52 manifestation in the natural history of the disease. Careful assessment is required in RP  
53 patients to avoid missing secondary causes of RP, including SSc. Digital ulcers (DUs) are a  
54 painful and disabling visible manifestation of the digital vascular injury. Significant progress  
55 has been made in the definition and assessment of DUs and understanding ulcer  
56 pathogenesis. There are a wide range of available treatments to both prevent and heal DUs;  
57 some of which are also used in RP management. The present review shall consider the  
58 assessment of patients with RP, including ‘red flags’ suggestive of SSc. We shall review the  
59 pathogenesis, definition and classification across the spectrum of SSc-DU disease, alongside  
60 a review on management approaches including drug therapies and surgery for SSc-RP and  
61 ulcers. We also highlight unmet needs and research priorities in SSc-RP and SSc-DUs and  
62 introduce the concept of a unified vascular phenotype in which vascular therapies may  
63 support disease modification strategies.

## 64 **Introduction**

65 Systemic sclerosis (SSc) is a complex connective tissue disease which is characterised by  
66 autoimmunity, progressive generalised obliterative vasculopathy and widespread aberrant  
67 tissue fibrosis.<sup>1,2</sup> Digital vascular disease (vasculopathy) occurs in virtually all patients with  
68 SSc, ranging from symptoms of Raynaud's phenomenon (RP) (Figure 1) to irreversible  
69 ischaemic tissue injury causing digital ulcers (DUs) (Figure 2) and sometimes gangrene.  
70 Although SSc is a very heterogenous disease, RP is experienced by the majority (>95%) of  
71 patients, and is the most common symptom and clinical sign of the disease.<sup>2,3</sup> Whereas, in  
72 primary RP tissue ischaemia is transient/reversible, in secondary RP (in particular SSc-RP)  
73 persistent tissue ischaemia can occur resulting in digital ulceration and/or gangrene.  
74 However, there are only limited to data to suggest an association between the severity of RP  
75 and DUs<sup>4</sup>, which likely reflects the complexity of vascular (and skin involvement) in SSc.

76  
77 The purpose of this review is to highlight 1) when to suspect SSc in the setting of RP, including  
78 how to assess the patient with Raynaud's to identify 'red flags' indicating potential SSc; 2) the  
79 spectrum of RP and DU disease in SSc encompassing relevant pathophysiology, diagnosis and  
80 classification, and management. We will also highlight current unmet needs and research  
81 priorities in RP and DU disease and discuss the concept of a unified vascular phenotype in  
82 which vascular therapy could be a disease modifying strategy.

## 83 84 **Epidemiology**

85 Endothelial injury is an important initiating event in SSc, often manifesting clinically as RP.  
86 Registry analyses suggest ~95% of patients with SSc experience RP.<sup>3</sup> The remaining 5% may  
87 not fulfil strict definitions of RP (often necessitating bi-phasic digital colour change) but digital  
88 microangiopathy is usually still evident by the presence of abnormal capillary morphology at  
89 the nailfold. In patients with limited cutaneous SSc, RP may predate the diagnosis of SSc by  
90 many years (sometimes decades).<sup>5</sup> Whereas, in patients with diffuse cutaneous SSc, RP  
91 typically develops in closer proximity to the onset of skin sclerosis.<sup>5</sup>

92  
93 DUs are common in patients with SSc and are a major cause of disease-related pain and  
94 morbidity.<sup>6</sup> Approximately half of patients with SSc experience DU with a point prevalence of  
95 5 to 10%.<sup>7-11</sup> In a study from the European Scleroderma Trials and Research cohort database,

96 the probability of developing DUs was 70% by the end of the 10-year observation period.<sup>12</sup>  
97 Several studies have reported that fingertip DUs have a higher prevalence than extensor  
98 ulcers.<sup>13–15</sup> In contrast, Ennis et al, reported that extensor ulcers had a similar prevalence (of  
99 6%) and were as similarly disabling as fingertip DUs.<sup>11</sup> Patients often develop ulcers affecting  
100 multiple digits simultaneously, including both fingertip and extensor-aspect DUs.<sup>15</sup> Despite  
101 the availability of a number of advanced therapies to prevent and treat DUs, around one third  
102 of patients with SSc may develop recurrent ulceration.<sup>16</sup>

### 104 **Clinical presentation**

105 RP is a highly variable symptom complex which results from aberrant digital perfusion. Digital  
106 colour changes (Figure 1) are the cardinal symptom of RP, although other body sites/vascular  
107 beds can be affected including the toes, lips, ears, nose and nipples<sup>17</sup> The stereotypical series  
108 of colour changes (physiological basis in parentheses) from attacks of RP consists of initial  
109 white/pallor (vasoconstriction/occlusion of pre-capillary arterioles), then blue/purple  
110 (cyanosis from deoxygenation of sequestered blood), and finally red (post-ischaemic  
111 hyperaemia).<sup>17</sup> Digital ischaemia results in significant pain and paraesthesias. In general, the  
112 majority of patients with primary RP will develop symptoms by 30 years of age, whereas, after  
113 40 it is almost always secondary. SSc patients can identify with distinct patterns of RP over  
114 time (that may reflect progression of vasculopathy) with established disease being associated  
115 with fewer 'stereotypical' attacks of RP, and more persistent features of tissue ischaemia.<sup>18</sup>  
116 Cold exposure is an important trigger for attacks of RP. However, most patients with SSc  
117 experience symptoms throughout the year, given a lower threshold for cold sensitivity in SSc  
118 patients.<sup>19</sup> Another important trigger of attacks is emotional stress, both in primary and  
119 secondary RP. A number of classification and diagnostic criteria for RP have been proposed.<sup>20–</sup>  
120 <sup>24</sup> In general, these are based on patient reported episodic digital colour changes in response  
121 to cold exposure, most of which have required at least two-colour changes in order to  
122 diagnose or classify RP.

123  
124 Approximately, 75% of patients with SSc will develop their first DU episode within 5 years of  
125 their first non-RP symptom<sup>7</sup>. Moreover, progressive vasculopathy in patients with SSc can  
126 progress to critical ischemia and gangrene, which may necessitate digital amputation, and can  
127 affect approximately 1.5% of patients per year.<sup>25</sup> SSc-DUs are associated with significant

128 pain<sup>11,26</sup> with higher analgesia requirements<sup>27</sup>, reduced health related quality of life<sup>28</sup> and  
129 hand-related disability including negative impact on occupation.<sup>8,26,29,30</sup> Data from the Digital  
130 Ulcers Outcome (DUO) registry identified that patients with ‘chronic’ and ‘recurrent’ DUs had  
131 greater rates of impairment in activity including occupation, and need for both paid and  
132 unpaid help.<sup>16</sup> In addition, these patients also had the greatest need for interventions  
133 including hospitalisation and analgesia.<sup>16</sup> The mean annual cost per patient in the European  
134 Union of SSc-DU has been estimated to be €23,619, was higher with complications (€27,309),  
135 and approximately 10% as a result of lost work productivity from patients and/or their care  
136 givers.<sup>31</sup> The availability of non-proprietary medications should see this cost fall in the future.  
137 SSc-DUs are typically very slow to heal. In an observational study which included 1,614 digital  
138 lesions, the mean (minimum and maximum) time to healing for ‘pure’ (ischaemic) DUs was  
139 76.2 (7 and 810) days, and for DU derived from calcinosis was 93.6 (30 and 388 days).<sup>14</sup> The  
140 DU characteristics associated with a significant delay in ulcer healing included the presence  
141 of fibrin, wet or dry necrosis, eschar, exposure of bone and tendon, and gangrene.

142

143 DU infection can be associated with delayed ulcer healing and osteomyelitis. The most  
144 common (approximately 50%) organism is *Staphylococcus aureus*.<sup>32,33</sup> Enteric organisms  
145 (*Escherichia coli* and *Enterococcus faecalis*) have also been reported in around 25% of patients  
146 with SSc-DUs, which highlights the need for patient education about the need for meticulous  
147 wound care.<sup>32</sup> Infection has been reported to be associated with greater perfusion (as  
148 assessed by laser speckle contrast imaging) to both the ulcer centre and surrounding area,  
149 and is highly (negatively) correlated with the time to healing.<sup>34</sup>

150

## 151 **Pathophysiology**

152 Primary RP (‘idiopathic’), is considered an isolated functional vasospastic condition. Whereas,  
153 the aetiopathogenesis of SSc-RP includes (amongst other factors) endothelial cell injury  
154 (possibly autoantibody mediated), an imbalance between vasoconstrictor and vasodilator  
155 factors (e.g. endothelin-1 and nitric oxide, respectively), structural microvascular changes  
156 from progressive microangiopathy, and intravascular factors leading to luminal occlusion and  
157 increased vasoconstriction (e.g. platelet activation and impaired fibrinolysis).<sup>2,35</sup>

158

159 In general, DUs which occur on the fingertips are considered to be ischaemic (Figure 3).  
160 Whereas, those which occur over the extensor aspects, in particular over the small joints of  
161 the hands, are also related to recurrent trauma at exposed sites, and potentially due to  
162 increased skin tension (Figure 3). Patients can also develop digital ulceration in relation to  
163 underlying subcutaneous calcinosis (Figure 3). The pathogenesis of calcinosis-associated  
164 ulceration may differ significantly (e.g. to ischaemic ulcers) and local mechanical and  
165 inflammatory phenomena may play a significant role.<sup>7</sup> Whether SSc-DU can be considered  
166 the consequence of 'severe Raynaud's' is debateable but DU are generally considered a  
167 manifestation of more advanced vasculopathy. Patient-reported RP severity has been noted  
168 to be higher in patients with active DU.<sup>4</sup> SSc-associated microangiopathy as assessed by  
169 capillaroscopy (namely capillary drop-out) is strongly associated with a number of clinical  
170 outcomes in SSc including the occurrence of new DU disease.<sup>36-39</sup> However, relatively little (if  
171 anything) is known about the pathophysiology of ulcers which occur at other sites of the  
172 hands which are less frequent including at the base of the nail and lateral aspect of the digits.  
173 Irrespective of the underlying cause, skin ulcers can result in significant irreversible tissue loss  
174 (Figure 3). Lower limb macrovascular involvement is well-recognised, in particular in patients  
175 with limited cutaneous SSc and positive anticentromere antibody.<sup>40,41</sup> Cutaneous ulceration  
176 of the lower limbs, in general, has not been as comprehensively studied as the fingers with  
177 respect to SSc-DU. The clinical appearances (Figure 4) and aetiopathogenic drivers of lower  
178 limb ulceration (e.g. arterial and venous macrovascular disease, lymphatic abnormalities) can  
179 be diverse and this is an area that warrants further study.<sup>42,43</sup>

180

## 181 **Assessment**

182 Early recognition of SSc-related RP is important to facilitate earlier diagnosis and  
183 management of SSc disease-related manifestations. Clinicians should be aware of a number  
184 of 'red flags' (Box 1) which are strongly suggestive of secondary causes such as SSc. Important  
185 red flags are included in the proposed 'very early diagnosis of SSc' [VEDOSS] criteria that  
186 includes RP, puffy fingers and positive antinuclear antibody<sup>44</sup> and further validation is  
187 ongoing. The identification of SSc-specific autoantibodies and/or the SSc pattern on nailfold  
188 capillaroscopy strengthens the likelihood of future SSc.<sup>44</sup> The second objective of assessment  
189 is to determine the impact of RP including the development of persistent tissue ischaemia  
190 (e.g. DUs).

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Key investigations in the assessment of patients with RP exhibiting any suspicion of secondary Raynaud's include the detection of autoantibodies and performing nailfold capillaroscopy, which are strong independent predictors of progression from isolated RP to SSc.<sup>45</sup> In a large prospective study of 586 RP patients who were followed up over 3,197 patient years, 12.6% developed definitive SSc.<sup>45</sup> Multivariate analysis revealed that predictors of progression to definitive SSc included positive antinuclear antibody (ANA) (Hazard ratio [HR] 5.67) and SSc-specific autoantibodies (HR 4.7), as well as the SSc pattern on nailfold capillaroscopy (HR 4.5), and all of which have a high negative predictive value.<sup>45</sup>

### **Clinical investigations**

A detailed examination of the hands should be performed including seeking evidence of SSc skin involvement (e.g. sclerodactyly), signs of persistent digital ischaemia (e.g. digital pitting scars and ulcers) and other stigmata of SSc (e.g. telangiectasia and calcinosis). The number, size and distribution of DUs should be assessed including signs of infection (e.g. discharge and erythema) and deeper progression (e.g. visualisation of underlying tendons and bone). Asymmetry in RP symptoms and/or DUs may indicate proximal (large) vessel involvement, which could be amenable to therapeutic intervention.

Routine investigations also include testing a full blood count, and ESR or CRP.<sup>46</sup> Routine biochemistry (e.g. renal and liver function) and thyroid function can suggest alternative secondary causes of RP.<sup>46</sup> Other investigations are guided by the clinical picture, including testing of creatine phosphokinase, complements C3 & C4, immunoglobulins with serum protein electrophoresis, fasting lipid profile (in patients at risk of atherosclerosis), and performing a chest radiograph to exclude (a bony) cervical rib.<sup>46</sup>

As previously described, autoantibodies can help to identify those patients who are at the greatest risk of developing autoimmune rheumatic diseases, including SSc. Therefore, testing for autoantibodies should be part of the initial assessment of patients with RP, including those with symptoms and/or signs of an underlying autoimmune connective tissue disease. The standard primary method for detecting ANA uses indirect immunofluorescence (IIF) and anti-centromere antibodies are often confirmed by the IIF staining pattern alone. SSc-specific



223 antigenic targets include anticentromere, anti-Scl-70 (which are commonly available), anti-  
224 RNA polymerase (I-III), U3-RNP, Th/To and EIF-2B (which are less frequently available  
225 specialist-/research-antibodies). Scleroderma overlap syndromes can occur with anti-  
226 RUVBL1/2, U1-RNP, anti-SS-A/Ro60, anti-Ro52, and anti-Ku and anti-PM/Scl.<sup>47</sup> SSc sometimes  
227 occurs in the presence of anti-synthetase antibodies such as anti-Jo-1, anti-PL7 and anti-  
228 PL12.<sup>48</sup> Commercially available solid phase assays to detect SSc-associated antibodies (e.g.  
229 line blots) can sometimes yield a false positive result and therefore a high index of suspicion  
230 should be maintained, and correlation with IIF staining patterns made where applicable (e.g.  
231 nucleolar staining for anti-U3 ribonucleoprotein and cytoplasmic staining for anti-synthetase  
232 antibodies) and further confirmatory testing requested (e.g. with protein  
233 immunoprecipitation) should be considered in patients with possible SSc.<sup>49</sup>

234

### 235 **Assessment of digital vascular structure and function**

236 A range of non-invasive methods can be used to assess digital vascular structure and function.  
237 Microvascular alterations are central to the early pathogenesis of SSc and many of the later  
238 disease complications, including DUs. There is also a strong need to assess the macrovascular  
239 system in patients with SSc. Some patients develop a disease-related SSc macroangiopathy,  
240 whereas, others develop macroangiopathy related to atherosclerosis<sup>50,51</sup> particularly when  
241 classical cardiovascular risk factors coexist. Furthermore, involvement of the ulnar artery has  
242 been reported to be strongly predictive of future DUs.<sup>52,53</sup>

243

### 244 ***Nailfold capillaroscopy***

245 Nailfold capillaroscopy is a non-invasive imaging technique which allows the microcirculation  
246 to be visualised in *situ* including examination of capillary morphology and architecture. The  
247 key importance of performing nailfold capillaroscopy is reflected by the inclusion of  
248 capillaroscopy in the 2013 American College of Rheumatology/European League Against  
249 Rheumatism classification criteria for SSc.<sup>54</sup> Nailfold capillary abnormalities have also been  
250 reported to be predictive of future DUs and other manifestations of SSc.<sup>36-38,55</sup>

251

252 Capillaroscopy is performed at the nailfold where the capillaries of the distal row lie parallel  
253 (compared to perpendicular) to the surface of the skin, and therefore allows them to be  
254 visualised in their entirety. Nailfold capillaroscopy can be performed using a wide range of

255 low- and high-magnification devices. Low-magnification devices<sup>56,57</sup> including the  
256 dermatoscope, stereomicroscope and ophthalmoscope allow for a global (wide-field)  
257 assessment of the nailfold area. Assessment at low-magnification allows the user to assess  
258 whether the nailfold capillaries and architecture are broadly normal or abnormal. In the  
259 future, the availability of low-cost, low-magnification USB-microscopes may broaden access  
260 to capillaroscopy. High-magnification (x200-600) videocapillaroscopy is considered the 'gold  
261 standard' and allows detailed examination of individual capillaries. Semi-quantitative  
262 assessment (e.g. measurement of capillary diameter and numbers) can also be performed  
263 and has been proposed as a promising future tool/biomarker to assess disease activity, and  
264 possibly as an outcome measure for therapeutic trials of SSc-vasculopathy.<sup>58</sup>

265  
266 Normal nailfold capillaries (Figure 5) have a homogeneous, 'hair-pin' like appearance with a  
267 regular distribution. In SSc-spectrum disorders the 'scleroderma' capillaroscopic pattern  
268 (Figure 5) includes enlarged (including 'giant' capillaries), capillary loss ('loop dropout') and  
269 microhaemorrhages. Characteristic microvascular alterations can also be identified in other  
270 connective tissue diseases, in particular, dermatomyositis (Figure 5). Cutolo proposed  
271 classification into the 'early', 'active' and 'late' scleroderma patterns.<sup>59</sup> Initially there are a  
272 few giant capillaries and microhaemorrhages ('early'), which subsequently increase in  
273 number, with moderate loss and mild disorganisation of capillaries ('active'). Finally, there is  
274 severe loss of capillaries with gross disorganisation of the capillary architecture with extensive  
275 avascular areas and marked evidence of aberrant neovascularization ('late' changes). The  
276 recently externally validated 'fast track' decision algorithm allows individuals with a range of  
277 prior capillaroscopic experience to successfully differentiate between abnormal (i.e.  
278 scleroderma patterns) from non-scleroderma patterns, with excellent reported reliability.<sup>60</sup>

279  
280 Microvascular structural abnormalities (as assessed by capillaroscopy) have been reported to  
281 be associated with functional microvascular disease (i.e. lower perfusion) in patients with  
282 SSc.<sup>61,62</sup> The agreement between objective non-invasive microvascular imaging and patient-  
283 reported assessment of digital vascular function is poor and explanations for such findings  
284 have not yet been fully elucidated.<sup>63</sup> Future research is indicated including to assess the  
285 potential benefit of combining assessment of microvascular structure and function for use as  
286 a combined outcome measure in future clinical trials of SSc-vasculopathy.

287

288 ***Laser-based techniques***

289 Laser Doppler imaging (LDI) has been widely used in research to investigate the  
290 pathophysiology of RP and SSc.<sup>64,65</sup> LDI and other laser Doppler-based techniques utilise the  
291 Doppler phenomenon, in which the wavelength of light changes from interaction with a  
292 moving object, which can be measured. Unlike laser Doppler flowmetry which measures  
293 perfusion at a single point, LDI measures blood flow over an area to build a global map of  
294 perfusion. LDI has also been used in a number of therapeutic trials to assess treatment  
295 response in a laboratory-based setting.<sup>66,67</sup> Laser speckle contrast imaging is an emerging  
296 imaging technique which allows constant measurement of perfusion over a large area, with  
297 higher spatial and temporal resolution than laser Doppler-based techniques.<sup>68</sup> Recent  
298 evidence suggests that laser speckle contrast imaging is a highly reliable method to assess  
299 peripheral blood perfusion in patients with SSc and healthy controls.<sup>68,69</sup> Laser speckle  
300 flowmetry measures perfusion at a single point and requires further research including to  
301 examine the discriminatory capacity (e.g. between primary and secondary RP) of the  
302 technique.<sup>70</sup>

303

304 ***Infrared thermography***

305 Infrared thermography uses a camera to measure skin surface temperature which is an  
306 indirect measure of tissue perfusion (from small and large blood vessels) (Figure 5).<sup>71</sup>  
307 Thermographic assessment has been reported to enable the successful distinction between  
308 primary and secondary RP.<sup>71</sup> Patients with RP (compared to healthy controls) often have  
309 cooler fingertips than the dorsal aspect of the hands. As below, some thermography protocols  
310 include a dynamic assessment including through a 'cold challenge' (Figure 5). The use of  
311 infrared thermography has been traditionally limited to specialist centres due to the historical  
312 high-cost of thermographic cameras and use of a temperature-controlled laboratory to  
313 perform provocation tests. However, the availability of relatively low-cost mobile phone-  
314 based thermographic imaging devices may facilitate wider access to infrared thermography  
315 used under ambient conditions.<sup>69</sup> In addition, there are significant differences in  
316 thermography imaging protocols between centres and internationally agreed  
317 protocols/consensus would help facilitate larger multi-centre studies of SSc-vasculopathy and  
318 potential future incorporation into routine clinical practice.

319

### 320 ***Dynamic assessment of microvascular function***

321 A number of previous studies have incorporated some form of local provocation (e.g. local  
322 cold exposure or iontophoresis of vasoactive substances), to distinguish between primary and  
323 secondary RP.<sup>63,72</sup> A subsequent 'rewarming' challenge during thermographic assessment has  
324 also been advocated. For example, Anderson et al<sup>73</sup> reported that a 'distal-dorsal difference'  
325 of >1°C at 30°C between the fingertips and the dorsum of the hand differentiated between  
326 primary and secondary RP.

327

### 328 ***Doppler ultrasound***

329 Doppler ultrasound is a useful tool which can identify significant macrovascular disease of the  
330 upper and lower limbs.<sup>74</sup> Doppler ultrasound is a relatively simple, non-invasive and  
331 reproducible test; however, it does require specialist training to make the necessary  
332 measurements.<sup>41,74</sup> The ankle brachial pressure index is an example of Doppler ultrasound  
333 and is calculated by the ratio of the systolic blood pressure in the upper and lower limbs,  
334 which can indicate the presence of significant lower limb ischaemia.<sup>74</sup> Abnormal colour and  
335 power Doppler sonography of the hand have been reported to be associated with past and  
336 new DUs in patients with SSc.<sup>75,76</sup>

337

### 338 ***Angiography***

339 Formal angiography is indicated in the presence of confirmed large vessel pathology including  
340 by Doppler ultrasound in order to define the anatomy of the causative vascular lesion/s.<sup>77</sup>  
341 Imaging techniques include digital subtraction angiography (DSA), computerised tomography  
342 (CT) angiography and magnetic resonance imaging (MRI) angiography. An advantage of CT  
343 and MRI angiography is that intra-arterial access is not required; however, endovascular  
344 procedures can be performed at the time of DSA.<sup>77</sup> Furthermore, a disadvantage of both CT  
345 and MRI angiography is poor visualisation of the distal limb vessels.<sup>77</sup>

346

### 347 **Definition and classification of digital ulcers**

348 This is hugely challenging and there is a key need to accurately define and classify SSc-DUs,  
349 not only for clinical practice to inform therapeutic decision making, but also to develop new  
350 treatments.<sup>67,8</sup> A number of previous studies have reported that the inter-rater reliability of

351 expert SSc clinicians is poor to moderate at best<sup>79-81</sup>, In particular, the inter (between) rater  
352 reliability has been very low.<sup>79-81</sup> This is a major concern in the design of multi-centre clinical  
353 trials and highlights the need for multiple ulcer assessments to be performed by the same  
354 rater. Furthermore, the agreement between individual patients and clinicians is very low,  
355 irrespective of the addition of 'real world' clinical contextual information (e.g. the severity of  
356 associated pain and the presence of discharge).<sup>80</sup> Different ulcer definitions have been used  
357 in recent multi-centre clinical trials of drug therapies for SSc-DU disease.<sup>82-86</sup> Recent initiatives  
358 to develop DU definitions have been undertaken by the auspices of the World Scleroderma  
359 Foundation (WSF) and the United Kingdom Scleroderma Study Group.<sup>81,87</sup> Both sets of  
360 definitions have included a 'loss of epithelium' and that if ulcer debridement was likely to  
361 confirm the presence of a DU, then it should be deemed an ulcer.<sup>81,87</sup> Although both  
362 definitions had high levels of intra-rater reliability (0.90 and 0.71, respectively), the inter-rater  
363 reliability was significantly higher for the WSF definitions (0.51 and 0.15, respectively)<sup>81,87</sup>,  
364 although no studies have compared reliability of different methods using the same image  
365 bank.

366

367 In general, the assessment of DUs in clinical practice and research relies upon the distinction  
368 between healed/non healed ulcers and clinician experience-based judgement.<sup>88</sup> The Digital  
369 Ulcer Clinical Assessment Score in Systemic Sclerosis (DUCAS) is a proposed clinical score  
370 which includes the number of DUs, new digital ulceration, the presence of gangrene, need for  
371 surgical approach (above standard of care), infection of the DU, unscheduled hospitalisation  
372 for DU, and analgesics needed to control DU pain.<sup>88</sup> Early data supports that the DUCAS has  
373 good levels of face, content validity and construct validity, and warrants further investigation  
374 for use in clinical practice.<sup>88</sup> In a recent DeSSciper/European Scleroderma Trials and  
375 Research group (EUSTAR) survey which included complete responses from 84 centres, three  
376 items were considered essential for DU evaluation.<sup>89</sup> These were the number of DU (which  
377 were defined as loss of tissue), recurrent DU, and the number of new DU.<sup>89</sup> Furthermore,  
378 similar to the previously described study from the DUO registry, 80% of the centres also  
379 favoured categorisation of DU into 'episodic', 'recurrent' and 'chronic'.<sup>89</sup>

380

381 Another potential approach to assessment could involve the use of ulcer photographs. A  
382 recent pilot study demonstrated that it was feasible for patients with SSc to 'monitor' their

own lesions by taking photographs with a smartphone camera over an extended period of weeks.<sup>90</sup> Furthermore, computer-assisted digital planimetry has been applied to SSc-DUs with excellent intra- and inter-rater reliability, either by fitting an eclipse to the shape of the ulcer, or by tracing the ulcer exterior by freehand.<sup>91</sup> Whereas, such an approach only measures ulcer surface dimensions, ultrasound also allows deeper measurement (e.g. of depth). Ultrasound has been used to assess SSc-skin ulcers, including objective measurement of ulcer morphology and extent, and could also provide novel insights into pathogenesis.<sup>92-94</sup> In a pilot study which examined high-frequency ultrasound to assess a range of (fingertip, extensor, and calcinosis-related) DUs, the average width and depth was 6mm and 1mm, respectively, which highlights the potential challenge of assessing ulcers by means of visual inspection alone.<sup>92</sup>

394

## 395 **Management**

### 396 **General approach**

397 Patient education is central to management of SSc-RP and DUs and should be delivered as  
398 part of a dedicated multi-disciplinary team, including specialist rheumatology nursing. Care  
399 should be taken by patients to avoid unnecessary trauma to the digits to prevent potential  
400 tissue ulceration, protection against the cold, and avoiding emotional stress. Patients should  
401 be counselled, and supported in their efforts, about the importance of smoking cessation  
402 because smoking promotes vasoconstriction.<sup>95,96</sup> Smoking has been reported to be associated  
403 with more severe digital vascular disease<sup>95</sup> including in relation to the intensity of  
404 smoking.<sup>95,96</sup> Patients should seek early medical advice about new and/or worsening ulcers,  
405 including potential signs of infection. The development of persistent digital ischaemia should  
406 prompt the patient to seek emergency medical advice. As previously described, DUs can be  
407 infected (Figure 2) and there should be a low threshold for prescribing appropriate antibiotic  
408 therapy. DUs can also be exceptionally painful and therefore sufficient analgesia is required  
409 and often requires the introduction of opioid-based analgesia.

410

### 411 **Differential diagnosis of critical digital ischaemia**

412 Critical digital ischaemia/gangrene (Figure 2) is a medical emergency which requires prompt  
413 assessment and introduction of treatment.<sup>97</sup> This can occur as a result of both SSc-related  
414 (e.g. non-inflammatory angiopathy) and non-SSc related causes (e.g. smoking)<sup>98</sup>. Thorough

415 investigation is required because some of these causes are potentially modifiable (e.g. large  
416 vessel disease and embolic disease).

417

### 418 **Non-pharmacological interventions**

419 Patients should be managed by an expert multi-disciplinary team including (but not limited  
420 to) rheumatology specialist nursing, physiotherapy and occupational therapy including  
421 education on lifestyle modification and functional adaptations (e.g. keeping warm and  
422 protecting the fingers to avoid traumatic ulcers).<sup>99,100</sup> Furthermore, meticulous wound care is  
423 mandatory for all ulcers to prevent infection and to minimise further tissue damage/loss.<sup>101</sup>  
424 The ulcer wound bed should be closely examined for signs of inflammation/infection, hyper-  
425 proliferation around the wound edges, evidence of exposure of the deeper structures (e.g.  
426 bone and tendon) and hydration status. For example, if the ulcer is 'wet' then appropriate  
427 dressings (e.g. with hydrogel and hydrocolloids) should be selected with an aim to reduce  
428 moisture/dry the wound, and vice versa for 'dry' wounds (with alginates and  
429 antimicrobials).<sup>46</sup> As previously described, clinicians should actively exclude proximal (large)  
430 vessel involvement early in the setting of digital ischaemia including ulcers, as this could  
431 potentially be amenable to therapeutic intervention. Non-surgical DU debridement is being  
432 performed by some clinicians in rheumatology and can be performed physically  
433 ('mechanical') with a scalpel or chemically (e.g. by using autolytic dressings). DU debridement  
434 removes non-viable (e.g. necrotic material) and can release pus, both of which can promote  
435 ulcer healing. Appropriate local analgesia is essential for successful DU debridement.<sup>102</sup>  
436 However, at present there is not strong evidence-base to support debridement in SSc at  
437 present, and requires further research. Furthermore, there is significant geographical  
438 variation in DU debridement. For example, in a survey which included responses from 137  
439 rheumatologists, the majority (80%) of North American and European responders reported  
440 that they never or rarely debrided DUs, compared to 37% of Europeans.<sup>103</sup> Work is currently  
441 underway to understand the barriers to DU debridement amongst clinicians in rheumatology.  
442 Other non-pharmacological interventions have been trialled include (but are not limited to)  
443 hyperbaric oxygen in patients with refractory DU disease.<sup>104,105</sup>

444

### 445 **Pharmacological interventions**

446 There a wide range of treatments to prevent and treat (heal) DUs; some of which are also  
447 used for RP (Figure 6). It is important to be aware how the pharmacological treatment of DU  
448 disease is potentially related to underlying RP. Primary RP usually requires no  
449 pharmacological treatment and is managed by general/lifestyle measures (e.g. cold  
450 avoidance and keeping warm).<sup>46</sup> Secondary RP is managed by relatively 'mild' oral  
451 vasodilatory drug therapies. Whereas, secondary RP and DU is managed with several different  
452 combinations including specific vasoactive therapies (e.g. bosentan). Drug treatments for DU  
453 disease should be tailored to the individual as there may be significant overlap/treatment  
454 benefit for other vascular-based complications (e.g. pulmonary arterial hypertension).  
455 Although a number of drug therapies have been explored (including but not limited to)  
456 statins, antioxidants, and anti-platelets/anticoagulation<sup>106–110</sup>, in this review we shall focus on  
457 the most commonly used drug therapies for SSc-DU disease (and RP).

458

### 459 ***Vasoactive therapies***

460 Vasoactive therapies attempt to address the underlying factors implicated in the  
461 pathogenesis of SSc-DUs (and SSc-RP). Calcium channel blockers (CCBs) are often used first  
462 line although, although clinicians are increasingly using phosphodiesterase type-5 (PDE5)  
463 inhibitors earlier in the treatment of SSc-associated digital vasculopathy, commonly in  
464 combination with CCBs. Vasodilatory side effects are not uncommon with vasoactive  
465 therapies (e.g. headaches and lower limb oedema) and are more common in patients in  
466 higher doses and potentially drug therapies in combination. Treatment with vasodilator  
467 therapy has been reported to be associated with a reduction in the development of DU.<sup>7</sup> In  
468 particular, there is some evidence that treatment with vasodilatory therapies (e.g. CCBs and  
469 PDE5 inhibitors) is associated with approximately 30% reduction in DU development.<sup>84,111</sup>  
470 There is also some evidence that PDE5 inhibitors can improve the healing of ulcers<sup>112</sup>;  
471 however, for example no difference was observed in a recent placebo-controlled trial of  
472 sildenafil (discussed later). Despite a strong therapeutic rationale (including vascular  
473 remodelling) for therapies which target the renin angiotensin system (e.g. ACE inhibitors and  
474 angiotensin receptor blockers)<sup>113</sup>, there is no convincing evidence for SSc-RP or SSc-DU  
475 disease. For example, in a multi-centre, randomised, placebo-controlled trial of quinapril  
476 which included 210 patients with limited cutaneous SSc or autoimmune RP (RP and a SSc-  
477 associated autoantibody), after 2 to 3 years of treatment there was no difference in DU



478 disease, or other vascular complications including RP and pulmonary artery pressure.<sup>83</sup>  
479 Bosentan, an endothelin-1 receptor antagonist which is licensed in Europe for DU disease,  
480 reduces the number of new DUs, but does not impact DU healing.<sup>82,114</sup> In a double-blind,  
481 placebo-controlled trial which included 188 patients with at least one DU, treatment with  
482 Bosentan for 20 weeks was associated with a 30% reduction in new DUs, but not DU healing.<sup>82</sup>  
483 In contrast, recent clinical trials of Macitentan did not reduce new DUs over 16 weeks<sup>85</sup>  
484 (possibly owing to differences in study populations, prior intervention and study design).<sup>115</sup>  
485 Intravenous prostanoids (given over 3 to 5 days) reduce the number of new DUs and fosters  
486 ulcer healing.<sup>116–118</sup> Prostanoids are also used in the context of critical digital ischaemia. There  
487 are no studies which have specifically assessed combination vasoactive therapies; however,  
488 the combination of PDE5 inhibition and endothelin receptor blockade has been reported to  
489 be a powerful treatment combination for digital vasculopathy.<sup>119,120</sup>

490

#### 491 **Other treatments**

492 Surgical intervention is indicated for severe RP and DU disease refractory to medical  
493 management.<sup>121</sup> Indications for surgery include (but are not limited to) severe pain (which  
494 suggests tissue necrosis), secondarily infected ulcers, and to remove underlying calcinotic  
495 material.<sup>121</sup> There is increasing worldwide experience in performing digital (periarterial)  
496 sympathectomy and earlier intervention may be beneficial in patients with severe Raynaud's  
497 and early digital ischaemia.<sup>122–125</sup> There is also increasing interest in botulinum toxin injection,  
498 which promote local arterial vasodilation.<sup>126,127</sup> However, at the present time, the evidence  
499 base is limited and further research is needed in this area. For example, in a recent double-  
500 blind, placebo-controlled, laboratory-based clinical trial, local injections of botulinum toxin  
501 did not significantly improve blood flow to the hands in patients with SSc-RP.<sup>128</sup> Furthermore,  
502 although there were improvements in a number of secondary clinical outcomes (e.g.  
503 Raynaud's Condition Score), these were of questionable clinical benefit. Autologous fat  
504 grafting and stem cell transplant is a novel treatment approach which has also been shown  
505 to benefit DU healing.<sup>129–132</sup>

506

#### 507 **Unmet needs**

508 There are a number of important unmet clinical needs and research priorities. Better  
509 approaches to the assessment and treatment of RP and DUs are urgently needed. Treatment

510 of Raynaud's is seldom fully effective<sup>133</sup> and approximately one third of patients with SSc have  
511 refractory DU disease, despite advanced vascular therapies. Treatments for RP and DUs can  
512 be poorly tolerated due to vasoactive side-effects, and well-tolerated, effective treatments  
513 are urgently needed. One approach could be to develop locally-acting vascular approaches to  
514 treatment which would likely be well tolerated from the lack of significant/absence of  
515 systemic vasodilation.

516

517 A major barrier to drug development programs relates to the suitability of existing outcome  
518 measures of efficacy. Significant concerns have been raised about our current methods to  
519 assess treatment efficacy in RP, including the Raynaud's Condition Score diary.<sup>134</sup> A key issue  
520 is that current outcome measures do not fully capture the complex, multi-faceted patient  
521 experience of either RP or DUs<sup>135,136</sup>. A recent multinational qualitative research study  
522 identified 7 inter-related themes (and subthemes) of the patient experience of SSc-RP that  
523 comprised physical symptoms, emotional impact, triggers and exacerbating factors, constant  
524 vigilance and self-management, impact on daily life, uncertainty, and adaptation.<sup>137</sup>  
525 International collaborative research is ongoing to develop novel patient reported outcome  
526 instruments for both RP and DUs.

527

528 It has been suggested that all DUs could have a potentially treatable ischaemic component  
529 and should all be included in DU clinical trials.<sup>138</sup> Recent clinical trials<sup>82,84,114,139</sup> of drug  
530 therapies for SSc-DUs have generally focussed on fingertip DUs, on the premise that such DUs  
531 are primarily driven by tissue ischaemia and more likely to benefit from vascular therapies.  
532 Recent studies have shown that both fingertip and extensor DUs have a relatively (compared  
533 to surrounding non-ulcerated skin) ischaemic core (as assessed by LDI) and with a reduction  
534 in ischaemia with ulcer healing.<sup>140,141</sup> In a double-blind, randomised, crossover, placebo-  
535 controlled study, the microvessels in the ischaemic DU centre were responsive to topical  
536 glyceryl trinitrate with an increase in perfusion, and with a similar effect observed for both  
537 fingertip and extensor DUs.<sup>142</sup> In addition, microangiopathic SSc-type capillary abnormalities  
538 (e.g. enlargement and neoangiogenesis) have been reported immediately adjacent to the skin  
539 surrounding both fingertip and extensor DUs, which could suggest that microangiopathy  
540 contributes to the pathogenesis of both.<sup>143</sup> Macrovascular involvement also likely reduces  
541 hand perfusion globally and could also promote the development of all types of SSc-DUs.<sup>53</sup>

542

543 Three major challenges complicating the design of RP clinical trials (and practice) are 1) the  
544 impact of the weather; 2) the lack of a robust 'target' akin to a 'treat to target' approach in  
545 inflammatory arthritis; and 3) the heterogeneity in the natural history of DU healing. In a  
546 recent randomised, placebo-controlled study, the time to DU healing which was the primary  
547 end point of the study (hazard ratio of 1.33 and 1.27, respectively) was not reached. The  
548 authors speculated that this could potentially be due to the unexpected high healing rate in  
549 the placebo group.<sup>84</sup> Furthermore, the contrasting findings of the within-class clinical trials of  
550 Bosentan and Macitentan<sup>115</sup>, and recent trials of promising treatments such as Selexipag (a  
551 non-prostanoid prostacyclin receptor agonist)<sup>144</sup> were disappointing.

552

553 Generalised vascular disease is a cardinal feature of SSc and likely to be responsible for the  
554 development of many of the organ-based complications associated with the disease.  
555 Biomarker studies support the presence of systemic vasculopathy, and autopsy studies have  
556 revealed silent lung and kidney vascular involvement.<sup>145</sup> For example, similar nailfold and  
557 pulmonary abnormalities, as well as progression of interstitial lung disease, have been  
558 reported in SSc.<sup>146,147</sup> DUs have also been reported to be associated with a worse disease  
559 course and prognosis including in patients with early disease.<sup>148</sup> In a study from the EUSTAR  
560 database, the use of CCBs was associated with a significant decrease in the prevalence (odds  
561 ratio of 0.41) of left ventricular ejection fraction <55%.<sup>149</sup> Therefore, confirmation of a unified  
562 (generalised) vascular phenotype in SSc could herald the use of vascular acting therapies as  
563 disease-modifying agents, in particular in patients with early SSc before the onset of  
564 significant skin fibrosis and organ dysfunction. A necessity to such an approach would be the  
565 successful case identification of patients with the earliest forms of SSc, likely using RP as the  
566 key entry symptom. Patients, including those with RP, are increasingly using mobile health  
567 technology to monitor their symptoms, and this can be a powerful method to encourage  
568 timely engagement with health care professionals.<sup>150,151</sup>

569

## 570 **Conclusions**

571 In conclusion, RP is a cardinal feature of SSc and is usually the first manifestation of the  
572 disease, thereby potentially allowing early diagnosis of SSc. Key investigations include the  
573 detection of autoantibodies and performing capillaroscopy. Structural and vascular imaging

574 plays a major role in both the diagnosis of disease and managing the peripheral vascular  
575 disease complications. DUs are a visible ischaemic manifestation of the SSc-disease process  
576 and represents secondary Raynaud's with digital vascular compromise. Digital ischaemia  
577 resulting in DUs and gangrene are serious complications which require prompt assessment  
578 and initiation of treatment. Patients should be managed by an expert multi-disciplinary team  
579 and first line treatment is non-pharmacological interventions including patient education.  
580 Although there are a range of vasodilator treatments to both prevent and treat DUs/RP, a  
581 number of patients experience refractory digital vascular disease. There are a number of  
582 unmet clinical and research needs relating to RP and DUs including establishing treatment  
583 efficacy in clinical trials. However, good progress is being made through international  
584 collaborative research. The concept of a unified vascular phenotype coupled with the early  
585 diagnosis of SSc, could potentially allow a paradigm shift in which vascular-acting therapies  
586 could be judiciously deployed as a means of disease-modification.

587

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- 1001
- 1002

1003 **Figure 1: Raynaud's phenomenon.** Mobile phone photographs taken of attacks of Raynaud's  
1004 in a patient with primary Raynaud's phenomenon and established peripheral nerve damage  
1005 from entrapment neuropathies. There is pallor (index, middle and little fingers) and cyanosis  
1006 (ring finger) with sparing of the thumb which is suggestive of primary Raynaud's  
1007 phenomenon.<sup>152</sup>

1008

1009 **Figure 2: Digital ulcers and complications in systemic sclerosis.** Ischaemic digital ulcers on  
1010 the fingertip (A) and volar aspect (B) of the digits. Digital ulcers on the extensor aspect (C) of  
1011 the hands overlying the small joints and calcinosis-related (D) digital ulceration. Infected  
1012 digital ulcer (E) and critical digital ischaemia (F).

1013

1014 **Figure 3: The pathogenesis of systemic sclerosis-related digital ulcers.** Proposed schematic  
1015 illustrating how the major factors could be potentially involved in both ulcer development  
1016 and healing. Focal ischaemia or trauma promotes loss of tissue integrity and ulceration. As  
1017 the digital ulcer develops the central core of tissue ischaemia progresses. There is often  
1018 inflammation/erythema of the surrounding the non-ulcerated skin and the  
1019 mechanism/implications of this is currently unknown. It could be postulated that this  
1020 represents increased blood flow from neoangiogenesis and promotes ulcer healing. However,  
1021 excessive blood flow could also result in a form of reperfusion injury and exacerbate further

1022 tissue injury. In addition, Infection is also associated with peri-ulcer inflammation. Over time  
1023 with ulcer healing the tissue is either restored to normal or there is evidence of persistent  
1024 digital ischaemic tissue loss. Digital pitting scars can also occur without prior ulceration.

1025

1026 Figure 4: The heterogeneity of lower limb cutaneous ulcer disease in SSc. A-D: significant  
1027 variation in appearance in ulcer appearance reflecting differences in aetiopathogenesis  
1028 including macrovascular arterial/venous involvement and other drivers (e.g. lymphatic  
1029 abnormalities). E&F: Evolution of lower limb refractory ischaemia/ulceration in a patient with  
1030 dcSSc (anti-Scl-70 antibody). E: cyanosis and small subungal ischaemic digital ulcer (2017). F:  
1031 ischaemic paronychia ulceration right great toe despite combination therapy with sildenafil,  
1032 bosentan and angiotensin II antagonist (2018).

1033

1034 **Figure 5: The utility of non-invasive digital microvascular structural and functional imaging**  
1035 **in the assessment of CTD-related digital vasculopathy.** A, Low-powered (50x) magnification  
1036 of the nailfold in primary Raynaud's; B, High-magnification (x200) of the same nailfold in A  
1037 revealed normal-appearance uniformly spaced and sized hairpin capillary loops; C, Low-  
1038 magnification appearance of nailfold in limited cutaneous systemic sclerosis with visible giant  
1039 capillaries; D, Corresponding high-magnification image of the same nailfold in C revealing  
1040 giant capillaries and capillary drop-out; E & F, Low and high-magnification nailfold  
1041 capillaroscopic images in dermatomyositis revealing characteristic ramified ('bushy')  
1042 capillaries; G, Thermal image of the hands of a patient with eosinophilic fasciitis 5 minutes  
1043 following local cold challenge revealing a healthy-looking preserved positive longitudinal  
1044 gradient in the early stages of re-warming not consistent with Raynaud's phenomenon; H,  
1045 Thermal image of the hands 5 minutes following local cold challenge in Raynaud's  
1046 phenomenon with a negative longitudinal gradient consistent with delayed re-perfusion

1047

1048 **Figure 6: Treatment of Raynaud's phenomenon and digital ulcers in systemic sclerosis.**  
1049 Adapted from the Consensus best practice pathway of the UK Scleroderma Study Group:  
1050 digital vasculopathy in systemic sclerosis.<sup>46</sup> A number of drug therapies are used for the  
1051 treatment of both RP and digital ulcers in SSc. The potential benefits vs. the risks of adjunctive  
1052 therapies must be considered on an individual patient basis. For example, anti-platelet  
1053 therapies and anticoagulation may be potentially hazardous in patients with SSc due to

1054 potential gastrointestinal bleeding from gastric antral vascular ectasia, and statins can have  
1055 adverse muscle effects in patients with SSc-myopathy.

1056

1057 **Box 1: Red flags in the setting of Raynaud’s phenomenon which suggest the presence of**  
1058 **systemic sclerosis.**

Cutaneous	Puffy fingers*
	Sclerodactyly and/or proximal skin thickening
	Digital ulcers
	Digital pitting scars
	Telangiectasia
Gastrointestinal	Gastro-oesophageal reflux disease*
	Abnormal oesophageal manometry
	Imaging evidence of gastrointestinal motility abnormalities
Immunological	Positive antinuclear antibody*
	SSc-specific autoantibodies
Vascular	Abnormal capillary morphology

1059

1060 \*These suggest the ‘very early diagnosis of systemic sclerosis’ and is confirmed by either the  
1061 presence of systemic sclerosis-specific autoantibodies and/or the scleroderma pattern on  
1062 nailfold capillaroscopy.<sup>44</sup>

1063

#### 1064 **Key points**

- 1065 • Vascular injury and Raynaud’s phenomenon are the earliest manifestations of  
1066 systemic sclerosis.
- 1067 • Patients with Raynaud’s phenomenon need careful assessment to identify secondary  
1068 causes including systemic sclerosis and key investigations include performing  
1069 capillaroscopy and the detection of autoantibodies.
- 1070 • Raynaud’s and ischaemic complications including digital ulcers are a major cause of  
1071 disease-related morbidity in systemic sclerosis.

- 1072 • The definition and assessment of digital ulcers can be very challenging and recent  
1073 efforts have made progress in this field.
- 1074 • There are a number of available treatments to both prevent and heal digital ulcers.
- 1075 • The concept of a unified vascular diagnosis could herald the onset of a potential  
1076 disease-modifying effect for vascular acting therapies in systemic sclerosis.
- 1077