

Chapter 8

Critical Ischemia



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Critical ischemia is defined as the presence of ischemic symptoms at rest. It identifies patients with high risk of imminent tissue loss. Critical ischemia in SSc results from progressive microvascular insufficiency but occasionally it may result from macrovascular compromise by emboli, thrombosis or vasculitis. Outcome of critical ischemia is contingent on the duration of ischemia, presences of comorbidities, prompt institution of appropriate workup and therapy. Timely and comprehensive therapy is key to prevent loss of threatened tissues.

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Case Presentation

The following case presentation will be utilized to illustrate the practical application of the diagnostic and management strategies of critical ischemia.

A 60-year-old female presents to the rheumatology clinic from her primary care provider with a two-week history of worsening digital ulceration on the third and fourth digits of her right hand. Her past medical history includes limited cutaneous systemic sclerosis complicated by significant gastrointestinal involvement, and subcutaneous calcinosis. She is known to be anticentromere positive. Despite her efforts at primary prevention of ulceration (wearing protective clothing, warming her hands, limiting time outside, and taking her prescribed medications including CCB), she developed the digital ulcerations. Her primary care physician started her on a course of steroids, and when she did not improve, he sent a referral to rheumatology for the next available appointment.

Upon arrival to the rheumatology office 2 weeks later, the patient was in distress and her ulcerations had progressed despite the patient's strict adherence to her prescribed steroids. Her clinical exam was benign aside from digital gangrene (Fig. 8.1).

She was admitted to the hospital, and despite administration of prostacyclin analog and other therapy, she did not regain perfusion to any portion of the effected digits. Unfortunately, she lost one half of her third digit and the tip of her fourth by means of autoamputation.

Cases with this outcome prompt investigation into root cause as well as appropriate quality care measures. There is always the question of what could be done differently, and could this outcome have been avoided. This chapter aims to further prepare clinicians for similar clinical scenario.



FIGURE 8.1 Digital gangrene in patient with limited cutaneous systemic sclerosis

Definitions and Pathogenetic Pathways

Vascular features dominate the clinical presentation of systemic sclerosis (SSc). Raynaud's phenomenon (RP) is the most characteristic early and persistent vascular symptom [1]. A Raynaud-like vasoconstriction associated with decrease blood flow has been also described in the cardiac, pulmonary and renal circulations. A fibroproliferative remodeling of the vascular wall at the arteriolar level leads to fixed narrowing of lumina, and the subsequent rigidity of the vascular wall leading to vascular stiffness [2]. Ischemia of tissues eventually ensues and progressively intensifies leading to ischemic symptoms when blood supply does not meet tissue demand. Further progression of imbalanced supply and demand lead to ischemic symptoms at rest. This state is best described as

'critical ischemia'. Occasionally, a vasospastic attack in this setting may lead to total occlusion of the vessel and subsequent gangrene of surrounding tissue resulting in digital ulcers or renal crisis.

Microvascular endothelial cells (MVECs) exist as a continuous monolayer of cells attached tightly to the basal lamina, that are involved in important functional tasks such as regulation of coagulation and fibrinolysis, permeability, vaso-reactivity, cellular metabolism and nutrition [3]. MVECs have other functions that include fluid filtration, neutrophil recruitment and trafficking. Injury to the endothelium in SSc results in profound MVECs dysfunction that is prominent in the early stages of the disease and progressively worsens as the disease progresses. This dysfunction is manifested by increase vascular permeability and dysregulated control of vascular tone that is clinically best illustrated by the puffy hand stage and by RP. An imbalance in endothelial vascular signals with increased endothelin production and impaired nitric oxide as well as prostacyclin release mediates the vasospasm and contributes to the intimal proliferation, vascular fibrosis and stiffness of the vessel wall. Platelet activation and enhanced coagulation with reduced fibrinolysis may contribute to fibrin deposits and the evolution of the intimal fibroproliferative lesion resulting in luminal narrowing. Enhanced MVECs apoptosis and injury is proposed as a crucial initiating event leading to capillary breakdown, vascular remodeling, and ultimately to blood vessel occlusion. Attacks of RP leads to ischemia-reperfusion injury to the vessel wall and the activation of the NF-kB pathways leading to the generation of oxidative stress that add further insult to the endothelium. Immune activation and generation of autoantibodies and defective angio/vasculogenesis lead to impaired regeneration of blood vessels and restoration of adequate blood supply to affected tissues [4].

A distinct events and pathways are involved in the initiation and evolution of the critical ischemia that are inferred from the pathogenetic observations are listed (Table 8.1). The

TABLE 8.1 Potential targets for therapy

-
- Endothelial apoptosis
 - Immune activation and the generation of anti-endothelial antibodies and harmful cytokines
 - Oxidative injury
 - Adhesion molecule expression and endothelial activation
 - Enhanced cellular proliferation
 - Platelet activation
 - Hypercoagulation
 - Defective fibrinolysis
 - Impaired production of endothelial nitric oxide and prostacyclin
 - Enhanced endothelin production
 - Defective angiogenesis and vasculogenesis
 - Tissue hypoxia
-

observed pathways act consecutively or simultaneously and represent attractive targets for the prevention and treatment of critical ischemia.

Not all critical ischemia in SSc are entirely related microvascular disease. Macrovascular occlusion by thrombosis, emboli or vasculitis can occur and need to be promptly investigated. The key point is that digital ischemia and ulceration in SSc patient may be due to large vessel as well as to small vessel disease. The association of vasculitis and scleroderma is unusual but well documented in the literature. The most commonly observed vasculitis is anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis [5]. The presence of ANCA in the setting of SSc critical ischemia should raise the possibility of an associated vasculitis. Digital ischemia, similar to ones seen in SSc, is reported in patients with granulomatosis with polyangiitis (formerly termed Wegener's) [6].

Risk Factors for Developing Critical Ischemia

Risk factors associated with poor outcome and development of gangrenous lesions were proposed by analysis of the Digital Ulcer Outcomes (DUO) Registry (Table 8.2). This European prospective multicenter observational cohort enrolled 4944 patients with past or current DUs from April 2008 to November 2014 [7]. The data demonstrated that gangrene is a common event that occurred in 18% of patients with DUs. The data also can help to risk stratify patients with SSc-DUs and to assess preventive and management strategies. Anticentromere antibody positivity has been previously linked with the severity of vascular disease [8]. Thus, SSc patients with positive anticentromere antibody had increased risk of major peripheral vascular occlusive disease. Ischemia and digital loss were also reported in non-SSc patients with anti-centromere antibody, suggesting that the antibody may play a causal role in vascular damage [9].

Therapeutic Approaches

Approximately 11% of patients with systemic sclerosis will develop critical limb ischemia during the course of their disease, and 18% of all SSc patients have DUs [10]. Therapeutic

TABLE 8.2 Risk factors for developing gangrene

-
- Smoking status
 - Previous gangrene
 - Previous autoamputation
 - Previous soft tissue infection requiring systemic antibiotics
 - Previous osteomyelitis
 - Previous hospitalization(s) for DUs (at least 1 day)
 - Upper limb sympathectomy
-

interventions must be initiated quickly and imperatively. Rheumatologists experienced in the management of SSc complication should be responsible for initiating the diagnostic workup and for coordinating patient's care. Primary care physicians are not prepared to act fast or to choose the appropriate therapy as illustrated by the presented case. The treatment of critical ischemia should be individualized and must utilize a multidisciplinary approach. The stage, location, and comorbidities of the patient must be considered to achieve optimal outcome.

Interdisciplinary Team Care

Critical Ischemia in SSc requires a multidisciplinary management, since pharmacological therapy is indicated for some cases and complementary surgical management is better for others. A team of professionals representing different disciplines to assist in the evaluation and management of the patient with critical ischemia is essential for rational and timely care. The team typically include individuals who are skilled in in the management of critical ischemia (Table 8.3).

TABLE 8.3 Interdisciplinary team

-
- Vascular and orthopedic surgeons
 - Infectious disease specialists
 - Radiology and vascular imaging specialists
 - Physical medicine and rehabilitation clinicians
 - Physical and occupational therapists
 - Pain management specialists
 - Nutrition and dieticians
-

TABLE 8.4 Initial laboratory workup

-
- ANA titer and staining pattern
 - SSc specific autoantibodies: Centromere, Scl-70, and RNP polymerase III antibodies
 - Phospholipid antibodies and lupus anticoagulant
 - Cytoplasmic neutrophil cytoplasmic antibody ANCA,
 - Lupus serology: DNA, Smith, RNP antibodies.
 - Circulating immune complex levels, cryoglobulins, complement levels
 - Urinalysis, renal and hepatic function
 - Hepatitis serology
 - ESR and CRP
-

Initial approach—Hospital admission should be initiated immediately, patient should be stabilized and a central line need to be established. Pain management is important first step to reduce reflux vasospasm associated with pain. Laboratory workup including serologic testing of possible associated or overlapping disorders should be obtained (Table 8.4). Next, vascular imaging to detected possible large vessel disease should be completed as soon as feasible.

Pain management—Intense pain is associated with critical ischemia and can be quite punishing and exhausting. Pain management experts should be involved early after hospital admission to plan an individualized approach to achieve safe and effective analgesia by utilizing short and long acting analgesic agents. Opioids remain the principal agents, however, they should be used at the lowest effective doses to avoid short and long-term complications.

Vascular imaging—Duplex ultrasound, and non-invasive angiography with computerized tomography (CTA) or magnetic resonance (MRA), can demonstrate arterial obstruction. CTA requires iodinated contrast that may compromise kidney function. Non-contrast MRA is prone to artifact and concerns for nephrogenic systemic fibrosis from gadolinium

contrast limit the use of contrast MRA in patients with kidney disease. CTA and MRA can help localize disease targets and help plan the mode and approach to revascularization. Still, invasive angiography is often used to clarify the potential for revascularization and should be considered prior to any surgical intervention.

Wound care—The wound should be assessed for infection. Broad-spectrum systemic antibiotics should be instituted if infection is suspected. Careful debridement may be required if necrotic tissue develops, but should be done with extreme caution given the underlying vascular compromise that extends beyond the area of necrosis.

Detailed Treatment Approach

Treatment options with the most crucial therapies will be discussed first. While there are a number of surgical approaches and techniques, the overall focus will be on medical therapy both in this urgent setting as well as adjunctive therapies. The first step in therapy is to determine if the ischemia is related to macrovascular or microvascular disease since the two require distinct treatment strategies.

Macrovascular Ischemia

Critical ischemia secondary to larger vessel occlusion should be fully evaluated on initial presentation to search for reversible process like vasculitis, embolic, or thrombotic events. Arteriography is indicated in critical ischemia when macrovascular cause is suspected and the option of surgery is considered. There are obvious differences in the treatment of macro- and microvascular disease. From a macrovascular perspective, the American Heart Association guidelines for treatment of peripheral vascular disease dictate that inflow disease be treated first. This is either addressed by surgery or percutaneous intervention. At that point outflow disease would then be addressed [11]. The decision on whether to

pursue a bypass surgery rather than an angioplasty first approach depends on the complexity and location of the lesion. The gold standard for revascularization remains surgical bypass, but the endovascular first approach may be appropriate in those patients with significant comorbidities as a 2013 meta-analysis points out [12]. AHA guidelines also state that angioplasty should be offered first to patients with significant comorbidities who are not expected to live more than 2 years [13]. Upper extremity interventions for critical ischemia are generally successful with the rare need for immediate amputations [14]. However, despite efforts for limb salvaging surgery, approximately 25% of patients with chronic ischemia undergo amputation within 1 year. Those who are at higher risk of needing an amputation are those with pain in the limb at rest, septic complications, flexion contractures, and those who have necrosis of weight bearing parts of the feet [9, 11]. Recovering from any of the aforementioned procedures is complemented with aggressive wound care and physical therapy. Surveillance of bypass typically involves evaluation by a vascular specialist at least twice yearly for the first 2 years, ultrasound of the bypass, and measurements of ankle-brachial index when applicable (11). After surgery, the American College of Chest Physician's (ACCP) states that aspirin therapy should begin perioperatively and continue indefinitely. Clopidogrel can be used in those patients who cannot tolerate aspirin [15].

Microvascular Ischemia—The Acute Setting

Upon suspicion of microvascular critical ischemia, medical approaches in conjunction with surgical opinion are utilized for managing the microvascular insult. In the case of a critical digital ischemic event, patients will present with intense pain and debility which must be promptly and aggressively managed to preserve functionality. After confirming the diagnosis and mapping out vascular targets, the initial pain caused by vasospasm can be mitigated by local injection of lidocaine or

bupivacaine at the base of the digit [15, 16]. Once the initial pain had been managed, prompt administration of vasodilating agents should be provided. Short acting calcium channel blockers may be used, but in the case of rapidly progressing ischemia, IV prostacyclin analogs are the treatment of choice [15, 16]. Thrombotic events would prompt inhibition of platelet aggregation and evaluation for angioplasty or digital sympathectomy [16].

Sympathectomy—Clinical experience support sympathectomy early in course of critical ischemia. Chemical sympathectomy can be achieved by digital or regional administration of lidocaine or bupivacaine. Temporary cervical or lumbar sympathectomy may help for short period of time.

Digital sympathectomies/adventitial stripping are salvage procedures that should be considered only when more conservative therapies have been tried and failed or when there is a particular digit that appears to be imminently at risk for tissue loss. The procedure may improve blood flow in the digital arteries by interrupting the sympathetic vasoconstrictor supply to the superficial palmar arch, the common and main digital arteries of the fingers and stripping the periadventitial fibrotic tissues from around the arteries. The effect on blood flow can be immediate and long lasting. One study reported a mean follow-up period of 46 months with continues improvement in blood flow, healing of ulcers and rare recurrences of ulcers [17]. while, another study reported up to 26% of digits required surgical amputation on follow-up [18].

Pharmacologic therapy—Therapy is aimed at relieving symptoms and preventing further injury. Medications preferred for their vasodilatory effect include calcium channel blockers, cyclic guanosine monophosphate (cGMP) specific phosphodiesterase type 5 inhibitors, prostacyclin analogs, and alpha-1 blockers. Other therapies include, statins, botulinum toxin, and antioxidants.

Prostacyclin (PGI₂)—Prostacyclin is an arachidonic acid derivative that is generated by the vascular endothelium. PGI₂ is a potent vasodilator, it inhibits platelet aggregation and adhesion, and is a strong inhibitor of smooth muscle cells

proliferation. These biologic effects propose PGI₂ as a potent inhibitor of the fibroproliferative vasculopathy [15, 19, 20]. Furthermore, and relevant to SSc pathogenesis, PGI₂ is shown to facilitate angiogenesis and repair of injured endothelium [19]. PGI₂ effects are analogous to the effects of nitric oxide and it may offset the loss of NO in certain pathologic states. Accordingly, PGI₂ can maintain endothelial function when NO signaling is deficient [20]. Epoprostenol and iloprost are analogs of PGI₂ that are used clinically for the management of variety of vascular disorder and should be considered as first line therapy in SSc of critical ischemia. Both analogs are administered parenterally as a continuous intravenous infusion via a central venous catheter. Doses are escalated gradually to the maximal effective or tolerable dose. Duration of infusion is 72 hours in hospitalized patients and 6 hours per day in the outpatient setting that can be repeated 5 days in a row. Common side effects include flushing, cough, nausea, vomiting, jaw pain, insomnia, palpitations, muscle pain and headaches that increase transiently with dose escalation. Uncommon, but potentially severe adverse events include pulmonary edema, hypotension, syncope and hemoptysis [15, 16].

Epoprostenol was approved for use in the United States in 1995, the typical dose is 2 ng per kg body weight per minute. The dose can be increased every 15–30 min in increments of 1 to 2 ng/kg/min, up to 8 ng/kg/min based on clinical response and tolerance. Limited evidence supports the use of epoprostenol in SSc critical ischemia. The largest study reported acceptable safety and efficacy in the treatment of digital ischemia [21]. In that study, 29 out of 46 epoprostenol infusions had documented improvement in pain, increased perfusion of digits and reduction in the number and size of DUs.

Iloprost is a more stable and has a longer half-life than epoprostenol and is fourfold more potent. The starting dose is 0.5 ng/kg/min that is increased to a maximum of 2 ng/kg/min. A landmark study that popularized the use of Iloprost in therapy of SSc critical ischemia reported good efficacy and safety [22]. In this study 126 SSc patients completed 6-hour

intravenous infusions of iloprost (0.5 to 2.0 ng/kg per min) or placebo. Significant improvement in the number of Raynaud attacks, global Raynaud severity score and healing of DUs were all noted.

Calcium channel blockers are the most common first line treatment for RP. Primary RP is considered to be a self-limiting and benign pathology which is generally not associated with gangrene and digital ulcerations [23]. Calcium channel blockers are the first line medical treatment when conservative rewarming and protective measures are not adequate [15]. They act on vascular smooth muscle to cause arterial dilatation via action on L-type calcium channels thereby dampening vasoconstrictive response [15, 16]. Members of the dihydropyridine class (nifedipine and amlodipine) are the most commonly used agents. Dosing ranges for these medications are from 30-180 mg daily for nifedipine and 5-20 mg daily for amlodipine [16]. Other members of the calcium channel blocker class may be used, but there is no proven added benefit [16]. A 2017 Cochran review demonstrated that the dihydropyridine calcium channel blockers may be useful in reducing the frequency, duration, severity of attacks, and pain with an overall 1.72 fewer attacks per week (95% CI, 0.06–2.84) [24]. Side effects are generally mild and included headache, dizziness, nausea, palpitations, and ankle edema [15, 24].

Phosphodiesterase type 5 inhibitors are indicated should calcium channel blockers not be effective. Agents like sildenafil, tadalafil, vardenafil, pentoxifylline, and cilostazol have been used since 2003 when the first successful use of nightly sildenafil produced remarkable relief from RP in ten patients [15, 16, 25]. These medications act by inhibition of PDE-5 activity which allows cGMP to accumulate within the endothelial cells. This accumulation changes the cellular response to prostacyclin and nitric oxide whereby resulting in vascular smooth muscle relaxation resulting in increase perfusion to distal tissues [15, 16, 26]. These medications received a class A recommendation by the European League Against Rheumatism (EULAR), and a 2017 literature review noted that PDE-5

inhibitors improve healing of digital ulcers in patients with systemic sclerosis, and that they may prevent the development of new digital ulcerations [27]. Current dosing regimens include sildenafil 20 mg three times daily, tadalafil 5 mg–20 mg daily, and vardenafil 10 mg twice daily [15]. Common side effects of these medications include flushing, headache, and dizziness. Hypotension, arrhythmia, vision changes, and stroke have been observed but are less frequent [16].

Adjunctive Therapies

A lesser reviewed class of effective medication are the **alpha-adrenergic blockers**. These medications play a significant role in thermoregulation [16]. The most notable member of this class is prazosin the effects of which were studied in the 2000 Cochrane Review [28]. Here the 3 mg daily and the 4 mg daily regimens were studied, the data showed that it was more effective than placebo in the treatment of Raynaud's secondary to scleroderma, but there are no recommendations for its use in acute critical ischemia (28).

Glycerol trinitrate (GTN) has been studied using an intravenous approach but the effect was transient. GTN patches (0.2 mg/h) were also investigated however, the side effects, and in particular headaches, were intolerable. Unlike phosphodiesterase inhibitors which increase the availability of endogenous nitric oxide in smooth muscle, **topical nitroglycerin** preparations have been used for decades as a more direct way of inducing vasodilatation [29, 30]. There are several preparations of nitrates, and while the first preparation of IV nitrates was discontinued due to intolerable headaches, the process is more refined and suitable for treating ischemia [15, 29, 30]. This diversity of the modes of administration has made it more difficult to study all preparations in a standardized setting, and many of the patients evaluated were treated with MQX-503 which is a gel not currently approved by the FDA [29, 30]. The currently available forms have more systemic side effects, but when used in conjunction with calcium channel blockers, they are effective in restoring perfu-

sion [30, 31]. Dosing amounts and intervals will depend on the type of preparation used, but overall the side effect profile is the same. Headaches are the most common side effect, and larger doses are generally not well tolerated [15, 29–31]. Other side effects include hypotension, flushing, dizziness, tachycardia, and GERD. These agents should be used with caution or not at all in those with heart failure, use of a PDE inhibitor, or in dehydrated patients [30, 31].

Hyperbaric oxygen therapy has been used as an adjunctive treatment in critical ischemia for decades [32]. It is often utilized when CCB, vasodilators, and prostanoids fail, and for patients who need to avoid invasive treatments. The main mechanism is fairly straight forward and acts by increasing the amount of dissolved oxygen in the arterial supply whereby relieving the hypoxia of the skin and surrounding tissues [33]. This increased oxygen will also stimulate endothelial cell growth and promote neovascularization.

Botulinum toxin A has increasingly been investigated as a method to reduce pain from RP. When applied to supplying blood vessels, it improves surgical flap survival via oxygen delivery [34]. The toxin's main mechanism is inhibition of presynaptic acetylcholine release, but it may also block sympathetic vasoconstriction of the smooth muscle by inhibition of the norepinephrine vesicle release [35]. A pilot study demonstrated increase digital pulp temperature that persisted for up to 6 weeks after injection into the palmar arch [36]. A randomized double-blind placebo controlled clinical study of 40 patients was conducted wherein investigators injected one randomly chosen hand with botulinum toxin (50 units in 2.5 mL) and the contralateral hand with normal saline. The primary outcome was change in blood flow measured by laser Doppler imaging, but no significant benefits were noted at 4 months. However, clinical measures including cold sensitivity score, and pain on a visual analog scale improved briefly in the botulinum toxin treated hands [37]. Overall, this agent will benefit from further investigation especially in acute digital ischemia cases.

Angiotensin converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARBs) have been suggested

as therapies in ischemic events. Initial investigations of captopril in 1987 demonstrated improvement in cutaneous blood flow, but there was no difference in frequency or severity of ischemic attacks [16, 38]. Subsequent studies involving other agents from both of these classes has likewise yielded mixed results. The overall consensus is that these drugs are not recommended as first line or monotherapy for digital ischemia [15, 16].

Fluoxetine is a member of the selective serotonin reuptake inhibitor class (SSRI), and at a dose of 20 mg daily it was shown to reduce the severity and frequency of the attacks of RP in a prospective pilot study [39]. The effects of serotonin on vascular tone are complex, and both vasodilatation and vasoconstriction are mediated through separate serotonin channels [40]. There is limited available data, and the initial pilot study as well as recent criticisms have brought up the need for a randomized double-blind trial [39, 40]. SSRIs have found their niche in those patients in whom CCBs cannot be titrated upwards due to hypotension [16].

Statins have demonstrated efficacy in digital ulcer healing, but the data on their use in critical ischemia is lacking [16, 41, 42]. They are known to be vasoprotective as they decrease LDL and increase HDL. This change in turn decreased free radicals and coagulation [16]. Overall, they are generally added when everything else failed.

N-acetylcysteine (NAC) is the precursor of a major antioxidant, glutathione that may have beneficial effects in SSc ischemia due to its vasodilating properties and impact on platelet aggregation. A pilot study of intravenous NAC in 20 patients with SSc-DUs showed that more than half of the DUs present at baseline healed after 5-day infusion [43]. A prospective observational study of intravenous NAC dosed at 15 mg/kg/h for 5 hours every 14 days was recently reported [44]. The median treatment was 3 years, and the mean of ulcers/patient/year decreased significantly from 4.5 to 0.81 with minimal reported side effects. Although promising, this agent should be evaluated in a prospective, placebo controlled, randomized trials.

Revisiting the Case

At the beginning of the chapter, the case report discussed an unfortunate incidence of late diagnosis of critical ischemia. A long-term scleroderma patient with positive centromere presented to her PCP with digital ulcerations. At that point, initiating further workup including hospitalization and the chain of events illustrated in Fig. 8.2 would have been appropriate to do. Administering steroids in the absence of further diagnostic evaluation is not standard of care, and in this case led to delay in her care resulted in digital loss.

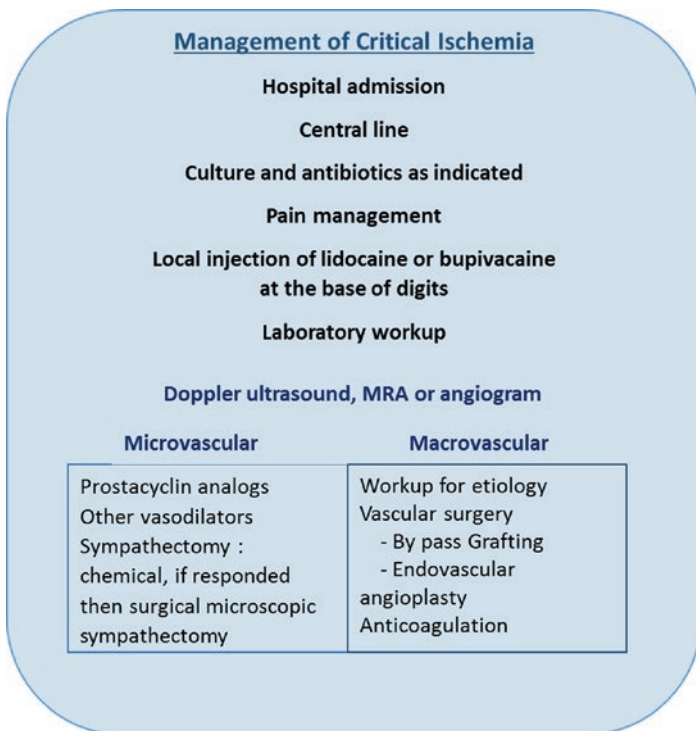


FIGURE 8.2 Evaluation and management algorithm for scleroderma patients with critical ischemia

References

1. Abraham DJ, Varga J. Scleroderma: from cell and molecular mechanisms to disease models. *Trends Immunol.* 2005;26(11):587–95.
2. Rajendran P, et al. The vascular endothelium and human diseases. *Int J Biol Sci.* 2013;9(10):1057–69.
3. Kahaleh B. The microvascular endothelium in scleroderma. *Rheumatology (Oxford).* 2008;47(5):14–5.
4. Distler JH, Gay S, Distler O. Angiogenesis and vasculogenesis in systemic sclerosis. *Rheumatology (Oxford).* 2008;47(2):234–5.
5. Rho YH, Choi SJ, Lee YH, Ji JD, Song GG. Scleroderma associated with ANCA associated vasculitis. *Rheumatol Int.* 2006;26(5):369–75.
6. La Civita L, Jeracitano G, Ferri C, et al. Wegener's granulomatosis of the elderly: a case report of uncommon severe gangrene of the feet. *Ann Rheum Dis.* 1995;54(4):328.
7. Yannick A, Denton C, Krieg T, Ornelisse P, Rosenberg D, Schwierin B, Matucci-Cerinic M. Clinical characteristics and predictors of gangrene in patients with systemic sclerosis and digital ulcers in the digital ulcer outcome registry: a prospective, observational cohort. *Ann Rheum Dis.* 2016;209481
8. Wigley FM, Wise RA, Miller R, Needleman BW, Spence RJ. Anticentromere antibody as a predictor of digital ischemic loss in patients with systemic sclerosis. *Arthritis Rheum.* 1992;35:688–93.
9. Takahashi M, Okada J, Kondo H. Six cases positive for anti-centromere antibodies with ulcer and gangrene in the extremities. *Br J Rheumatol.* 1997;36:889–93.
10. Hughes M, Herrick AL. Digital ulcers in systemic sclerosis. *Rheumatology.* 2017;56:4–25.
11. Hirsch AT, Haskal ZJ, Hertzler NR, et al. ACC/AHA 2005 practice guidelines for the Management of Patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic). *Circulation.* 2006;113:e463–654.
12. Antoniou GA, Chalmers N, Georgiadis GS, et al. A meta-analysis of endovascular versus surgical reconstruction of femoropopliteal arterial disease. *J Vasc Surg.* 2013;57:242–53.
13. Rooke TW, Hirsch AT, Hertzler NR, et al. ACCF/AHA focused update of the guideline for the Management of Patients with peripheral artery disease (updating the 2005 guideline) a report of the American College of Cardiology Foundation/American

- Heart Association task force on practice guidelines. *Circulation*. 2011;124(18):2020–4529.
14. Cheun T, Jayakumar L, Sheehan M, et al. Outcomes of upper extremity interventions for chronic critical ischemia. *J Vasc Surg*. 2019;69(1):120–8. e2
 15. Stringer T, Femia AN. Raynaud's phenomenon: current concepts. *Clin Dermatol*. 2018;36(4):498–507.
 16. McMahan ZH, Wigley FM. Raynaud's phenomenon and digital ischemia: a practical approach to risk stratification, diagnosis and management. *Int J Clin Rheumatol*. 2010;5(3):355–70.
 17. Ruch DS, Holden M, Smith B, Koman A. Periarterial sympathectomy in scleroderma patients: intermediate-term follow-up. *J Hand Surg*. 2002;27A:258–64.
 18. Tristain L, Hartzell E, Makhni C, Sampson C. Long-term results of Periarterial Sympathectomy. *J Hand Surg Am*. 2009;34(8):1454–60.
 19. Visalli E, Amato G, Di Gangi M, et al. Treatment with intravenous iloprost in patients with systemic sclerosis: a short review. *J Rare Dis Res Treat*. 2017;2(4):6–13.
 20. Fati R, Visalli E, Amato G, et al. Long-term clinical stabilization of scleroderma patients treated with a chronic and intensive IV iloprost regimen. *Rheumatol Int*. 2017;37:245–9.
 21. Law S, Simms RW, Farber HW. Use of intravenous Epoprostenol as a treatment for the digital vasculopathy associated with the scleroderma Spectrum of diseases [abstract]. *Arthritis Rheumatol*. 2016;68(suppl 10)
 22. Wigley FM, Wise RA, Seibold JR, et al. Intravenous iloprost infusion in patients with Raynaud phenomenon secondary to systemic sclerosis. A multicenter, placebo-controlled, double-blind study. *Ann Intern Med*. 1994;120(3):199–206.
 23. Rodriguez-Franco K, Miranda-Diaz A, Hoyes-Restrepo J, Melendez G. Systemic scleroderma: an approach from plastic surgery. *Rev Fac Med*. 2018;66(2):237–45.
 24. Rirash F, Tingey PC, Harding SE, Maxwell LJ, et al. Calcium channel blockers for primary and secondary Raynaud's phenomenon. *Cochrane Database Syst Rev*. 2017;(12):CD000467.
 25. Fries R, Shariat K, Wilmowsky H, Böhm M. Sildenafil in the treatment of Raynaud's phenomenon resistant to vasodilatory therapy. *Circulation*. 2005;112:2980–5.
 26. Andrigueti F, Ebbing P, Arismendi M, Kayser C. Evaluation of the effect of sildenafil on the microvascular blood flow in

- patients with systemic sclerosis: a randomized, double-blind, placebo- controlled study. *Clin Exp Rheumatol*. 2017;35:151–8.
27. Kowal-Bielecka O, Franssen J, Eustar AJ, et al. Update of EULAR recommendations for the treatment of systemic sclerosis. *Ann Rheum Dis*. 2017;76:1327–39.
 28. Harding SE, Tingey PC, Pope J, et al. Prazosin for Raynaud's phenomenon in progressive systemic sclerosis. *Cochrane Database Syst Rev*. 1998;(2):CD000956.
 29. Qiu O, Chan T, Luen M, et al. Use of nitroglycerin ointment to treat primary and secondary Raynaud's phenomenon: a systemic literature review. *Rheumatol Int*. 2018;38:2209–16.
 30. Chung L, Shapiro L, Fiorentino D, Baron M, et al. MQX-503, a novel formulation of nitroglycerin, improves the severity of Raynaud's phenomenon: a randomized, controlled trial. *Arthritis Rheum*. 2009;60:870–7.
 31. Khanna PP, Maranian P, Gregory J, et al. The minimally important difference and patient acceptable symptom state for the Raynaud's condition score in patients with Raynaud's phenomenon in a large randomized controlled clinical trial. *Ann Rheum Dis*. 2010;69:588–91.
 32. Dowling GB, Copeman PW, Ashfield R. Raynaud's phenomenon in scleroderma treated with hyperbaric oxygen. *Proc R Soc Med*. 1967;60(12):1268–9.
 33. Sato T, Arai K, Ichioka S. Hyperbaric oxygen therapy for digital ulcers due to Raynaud's disease. *Case Reports Plast Surg Hand Surg*. 2018;5(1):72–4.
 34. Schweizer D, Schweizer R, Zhang S, et al. Botulinum toxin a and B raise blood flow and increase survival of critically ischemic skin flaps. *J Surg Res*. 2013;184:1205–13.
 35. Berk-Krauss J, Christman MP, Franks A, Sicco KL, Liebman TN. Botulinum toxin for treatment of Raynaud phenomenon in CREST syndrome. *Dermatol Online J*. 2018;24(12)
 36. Jenkins S, Neyman K, Veledar E, et al. A pilot study evaluating the efficacy of botulinum toxin a in the treatment of Raynaud phenomenon. *J Am Acad Dermatol*. 2013;69:834–5.
 37. Bello R, Cooney C, Melamed E, et al. The therapeutic efficacy of botulinum toxin in treating scleroderma-associated Raynaud's phenomenon: a randomized, double-blind, placebo-controlled clinical trial. *Arthritis Rheumatol*. 2017;69:1661–9.
 38. Tosi S, Marchesoni A, Messina K, et al. Treatment of Raynaud's phenomenon with captopril. *Drugs Exp Clin Res*. 1987;13(1):37–42.

39. Coleiro B, Marshall SE, Denton CP, Howell K, Blann A, Welsh KI, et al. Treatment of Raynaud's phenomenon with the selective serotonin reuptake inhibitor fluoxetine. *Rheumatology*. 2001;40(9):1038–43.
40. Khouri C, Gailland T, Lepelley M, Roustit M, Cracowski JL. Fluoxetine and Raynaud's phenomenon: friend or foe? *Br J Clin Pharmacol*. 2017;83(10):2307–9.
41. Kuwana M, Okazaki Y, Kaburaki J. Long-term beneficial effects of statins on vascular manifestations in patients with systemic sclerosis. *Mod Rheumatol*. 2009;19:530–5.
42. Abou-Raya A, Abou-Raya S, Helmii M. Statins: potentially useful in therapy of systemic sclerosis-related Raynaud's phenomenon and digital ulcers. *J Rheumatol*. 2008;35:1801–8.
43. Sambo P, Amico D, Giacomelli R, et al. Intravenous N-acetylcysteine for treatment of Raynaud's phenomenon secondary to systemic sclerosis: a pilot study. *J Rheumatol*. 2001;28:2257–62.
44. Rosato E, Borghese F, Pisarri S, Salsano F. The treatment with N-acetylcysteine of Raynaud's phenomenon and ischemic ulcers therapy in sclerodermic patients: a prospective observational study of 50 patients. *Clin Rheumatol*. 2009;28:1379–84.