Raynaud phenomenon: a concise review with a focus on risk stratification and association with systemic sclerosis

Jesus MM[1], Rodrigues JR[2], Guerra M[2], Oliveira M[2]

[1] UCSP Belmonte, ULS Cova da Beira
[2] ULS Cova da Beira

Correspondence to

Miriam Massano Jesus

E-mail: miriam.massano@gmail.com

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Abstract

Raynaud phenomenon (RP) is a vasospastic disorder characterized by episodic constriction of small arteries and arterioles, most commonly affecting the extremities. The prevalence of RP in the general population is estimated to be approximately 5%, referring to Raynaud phenomenon overall rather than exclusively to primary Raynaud phenomenon (PRP). To date, there are no published epidemiological studies specifically addressing the prevalence of RP in Portugal. Some studies suggest that PRP may be more common, affecting 2–20% of women and 1–12% of men, and approximately half of patients report a family history, particularly females and those with early-onset disease.

RP may be primary (idiopathic) or secondary to underlying diseases, particularly connective tissue disorders, most notably systemic sclerosis (SSc). As such, it represents an important window of opportunity for early diagnosis. Despite its prevalence, the pathophysiology, diagnostic approach, and therapeutic strategies remain complex and heterogeneous.

Keywords: Raynaud Disease; Peripheral Vascular Diseases; Connective Tissue Diseases; Systemic Sclerosis; Capillaroscopy.

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Introduction

Raynaud's phenomenon (RP) is a condition marked by intermittent vasospasm, usually resulting in reduced blood flow to the fingers and toes following exposure to cold temperatures or emotional stress. Most cases (80–90%) are primary, meaning that they occur without an associated medical condition, known as primary Raynaud's phenomenon (PRP)[1]. Secondary Raynaud phenomenon (SRP), however, is linked to various medical conditions or medications. Raynaud phenomenon significantly diminishes quality of life and may lead to severe complications such as chronic digital ischemia, ulcers, and gangrene, particularly in secondary cases[1].

This review aims to discuss the epidemiology and pathogenesis of RP, outline its clinical features, and provide a comprehensive approach to its diagnosis and multifaceted management. Additionally, it seeks to identify patients with RP at risk of developing early systemic sclerosis, according to the modified LeRoy and Medsger criteria (2001)[8], and to guide the monitoring of patients with RP who cannot be clearly classified as primary but do not yet fulfil criteria for a defined connective tissue disease[26].

Furthermore, this review seeks to highlight the role of the general practitioner in the early recognition, initial diagnostic work-up, risk stratification, and longitudinal management of patients presenting with Raynaud's phenomenon.

Epidemiology

The prevalence of RP in the general population is approximately 5%[1],[19]. Some studies suggest that PRP may be more common, affecting 2–20% of women and 1–12% of men[19]. Approximately half of patients report a family history, particularly females and those with early-onset disease[1].

RP typically manifests before the age of 30, whereas onset after 40 years should raise suspicion for a secondary cause. In men, prevalence increases with age and is often associated with occupational exposure (e.g., vibratory tools) or atherosclerotic vascular disease[1].

To date, there are no published epidemiological studies specifically addressing the prevalence of Raynaud's phenomenon in Portugal, therefore, available data are derived from international cohorts.

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Classification

The classification of RP into primary and secondary helps differentiate between patients with a simple thermoregulatory defect (PRP) and those with an underlying disease (SRP) affecting vascular reactivity[1]. In the SRP, decreased arterial blood flow can lead to acute ischemia and, if prolonged, critical tissue damage[1]. Conditions like vasculitis, embolic events, or atherosclerosis can mimic RP through vasospasm but usually present asymmetrically and are not cold-dependent[1]. Among immune-mediated rheumatic causes, systemic sclerosis (SSc) is prominent, affecting at least 90% of individuals with the condition[1]. In these patients, Raynaud's phenomenon (RP) is a clinical manifestation of widespread microvascular damage and often precedes skin and visceral fibrosis by several years[1]. Proper management requires identifying any secondary causes to treat both the vascular reactivity and the underlying condition.

Pathogenesis

Mechanisms associated with primary Raynaud phenomenon

Raynaud's phenomenon is thought to be driven by neural and vascular mechanisms[2].

Recent research on the pathogenesis of Raynaud's phenomenon has highlighted significant genetic factors. Recent genetic studies have identified variants in ADRA2A and IRX1 as putative risk loci associated with RP[2]. ADRA2A encodes the α2A-adrenergic receptor, involved in adrenergic-mediated vasoconstriction, whereas IRX1 has been implicated in vascular regulation[2]. These findings suggest potential mechanisms related to exaggerated vasoconstriction and impaired vasodilation, although their clinical implications remain to be fully established[2]. Additionally, mitochondrial production of reactive oxygen species (ROS) in response to cold, initiating a redox signal that activates the Rho/Rho-kinase pathway and also playing a role in the condition, further elucidating the complex mechanisms behind Raynaud's phenomenon[3]. These insights offer new avenues for targeted therapies and better management strategies for affected individuals[3].

Acquired causes and diseases associated with secondary Raynaud phenomenon

A pilot study suggested that patients with RP (both primary and secondary) have chronically increased levels of oxidative stress and elevated free thiol following transient hypothermia-induced vasoconstriction[4]. Free thiol is thought to play a protective role against oxidative stress and appears to be functionally intact in these patients[4]. Vascular injury can result in platelet activation and the release from platelets of potent vasoconstrictors such as thromboxane and

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serotonin. Recent studies have also emphasized the role of platelet activation in the pathogenesis of SSc[4].

Systemic sclerosis (SSc) is one of the conditions in which Raynaud's phenomenon most frequently presents as an initial clinical manifestation. SSc involves immune system dysregulation, endothelial damage, and fibroblast activation, leading to fibrosis[5]. Raynaud phenomenon in SSc is primarily due to microvascular abnormalities and exaggerated vasoconstriction responses[5]. Factors like increased endothelin-1, reduced nitric oxide, and oxidative stress contribute to this pathogenesis[5].

Many other diseases can cause vascular damage or disrupt neurogenic regulation, leading to RP or similar vasospasms with tissue ischemia. These include vasculitis, cryoglobulinemia, cold agglutinin disease, carpal tunnel syndrome, antiphospholipid syndrome, embolic disease, paraproteinemia, frostbite, and chemotherapy drugs like bleomycin and cisplatin[4]. Metabolic disorders and medications, such as hypothyroidism, estrogen, non-selective beta-blockers, and vasoconstrictors like ergotamine, nicotine, and amphetamines, also affect vascular reactivity[4]. Conditions often confused with RP include chilblains, acrocyanosis, livedo reticularis, erythromelalgia, thoracic outlet syndrome, hypothenar hammer syndrome, complex regional pain syndrome, and migraine[4].

Hsu et *al.*[7], in their literature review, mention several potential pathogenic mechanisms, such as: tumor invasion of sympathetic nerves, hyperviscosity, hypercoagulability, vasoactive substances secreted by tumors, generalized vasospasm, and spontaneous platelet aggregation. Paraneoplastic Raynaud phenomenon differs from idiopathic forms, as it mainly affects older individuals, has a higher incidence in males, and is often associated with rapid progression. More than 80% of affected patients develop ischemic complications such as necrosis and gangrene[7]. RP may also present itself as a manifestation of malignancy such as in lung cancer (rare manifestation)[6] and paraneoplastic Raynaud phenomenon has also been reported in sarcoma, lymphoma, and leukemia[6].

Clinical Presentation

Raynaud's phenomenon is characterized by a typical sequence of color changes: pallor (white), followed by cyanosis (blue), and subsequently erythema (red)[3]. This triphasic pattern isn't always seen. According to the 2017 European Society for Vascular Medicine guidelines, blanching (pallor) is essential for diagnosing Raynaud's phenomenon, while cyanosis and erythema may or may not be present[14]. Both PRP and SRP usually spare the thumb; however,

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when present, thumb involvement is more suggestive of SRP[15]. Attacks are often painful due to sensory ischemia, with common complaints of tingling and increased sensitivity[1]. It commonly affects the fingers and toes but can also involve the ears, nose, and areolar tissue. Less commonly, RP-like vasospastic episodes have been reported in other sites, including the tongue and genital tissues[3]. Episodes can last from minutes to several hours[3].

RP as a predictor of SSc

The presence of RP scores 3 out of the 9 required points in the 2013 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) Classification Criteria for SSc[4]. Thus, in patients presenting with RP, the primary objective is to identify those at risk of developing systemic sclerosis (SSc) or another connective tissue disease (CTD)[4].

LeRoy and Medsger first proposed criteria for the identification of very early systemic sclerosis in patients presenting with RP, based on three parameters: Raynaud's phenomenon, the presence of SSc-specific autoantibodies, and a scleroderma pattern on nailfold capillaroscopy[8]. These criteria were subsequently validated by Koenig et al. in a 20-year prospective study, which demonstrated that autoantibodies and microvascular abnormalities were independent predictors of progression from RP to definite SSc[9]. The authors reported a negative predictive value (NPV) of 93%, a positive predictive value (PPV) of 79%, a specificity of 98%, and a sensitivity of 47%. Furthermore, a modified version of the criteria, requiring only RP plus either autoantibody positivity or capillaroscopic abnormalities, demonstrated a sensitivity of 89%, specificity of 85%, PPV of 47%, and NPV of 98%[9].

Building on these findings, Avouac et al. proposed preliminary criteria for the very early diagnosis of SSc through a Delphi consensus study from the EULAR Scleroderma Trials and Research group, supporting a structured approach based on RP, SSc-specific autoantibodies, puffy fingers, and nailfold capillaroscopic abnormalities[16].

Further evidence was provided by Pavlov-Dolijanovic et al., who followed 3029 patients initially classified as having primary RP over a mean period of 4.8 years and demonstrated that capillaroscopic abnormalities could identify patients at increased risk of developing connective tissue diseases[10]. At the end of follow-up, 54.8% remained classified as primary RP, 8.1% were considered to have suspected SRP, and 37.1% had developed a connective tissue disease, including SSc, systemic lupus erythematosus, rheumatoid arthritis, Sjögren's syndrome, mixed connective tissue disease, vasculitis, inflammatory myopathies, and overlap syndromes[10].

The VEDOSS initiative was subsequently evaluated in the EUSTAR multicentre study by Minier et al., which highlighted puffy fingers as a pivotal sign for suspicion of SSc and further supported the relevance of RP, autoantibody testing, and nailfold capillaroscopy in early SSc recognition[13].

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More recently, Bellando-Randone et al. analysed data from the multinational Very Early Diagnosis of Systemic Sclerosis (VEDOSS) registry in a five-year longitudinal study, confirming the predictive value of the VEDOSS approach for identifying patients at risk of progression from Raynaud's phenomenon to definite systemic sclerosis. The authors demonstrated that the combination of Raynaud's phenomenon, antinuclear antibody positivity, puffy fingers, and a scleroderma pattern on nailfold capillaroscopy identifies a subgroup of patients at particularly high risk of progression, reinforcing the importance of early recognition, risk stratification, and longitudinal follow-up of these patients[26].

Although robust predictive models are available for SSc, similar validated capillaroscopic predictors have not yet been established for most other connective tissue diseases[4]. Consequently, while nailfold capillaroscopy is a valuable tool for risk stratification in patients with RP, its predictive value outside the spectrum of SSc remains less clearly defined.

Establishing the diagnosis

There are currently no universally accepted diagnostic criteria for RP. Diagnosis is primarily clinical, based on characteristic history and symptomatology. However, classification criteria and risk stratification tools exist, particularly in the context of systemic sclerosis[8,9]. These include criteria such as those proposed by LeRoy and Medsger for early systemic sclerosis, which incorporate the presence of Raynaud's phenomenon, autoantibody positivity, and capillaroscopic abnormalities as key elements for identifying patients at risk[8].

A comprehensive clinical assessment is required in all patients with RP, with specific emphasis to the secondary causes of RP. It should always include a complete anamnesis and a full physical examination with a particular focus on the extremities and signs of systemic diseases associated with SRP including established digital ischemia (e.g. pitting scars and ulcers)[1].

The Table II offers guidelines in the first clinical assessment.

In the presence of episodes of Raynaud's phenomenon that are asymmetric/involving only one finger, altered peripheral pulses, asymmetry in blood pressure, and fixed color changes of the extremities not related to cold/stress, a vascular cause should be suspected[1].

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Investigations

Blood tests should always include Complete Blood Count with Differential, inflammatory parameters such as Erythrocyte Sedimentation Rate (ESR) and C - reactive protein (CRP), Creatinine, Urea, and Liver Transaminases, Antinuclear Antibodies (ANA) by Indirect Immunofluorescence and Specific Antibody Testing Based on ANA Results (titer and pattern)[1].

Autoantibody testing is particularly useful to help identify those patients who are at the greatest risk of developing a definitive connective tissue disease, including SSc[1]. Extractable nuclear antibody testing can determine the antigenic target of autoantibodies and are very helpful in identifying SSc (eg anticentromere and anti-Scl-70) and related connective tissue diseases (eg anti-Jo-1 in myositis) [1].

When clinically appropriate (eg., vascular thrombosis and/or pregnancy morbidity and mortality), testing for antiphospholipid syndrome (anticardiolipin and anti-b2-glycoprotein antibodies and lupus anticoagulant) can be performed[1].

Specialist Investigations:

Specialist investigations include assessment of microvascular structure using standardized nailfold capillaroscopy protocols and functional vascular imaging techniques, including infrared thermography, which provide complementary information regarding peripheral perfusion and microvascular function[1,23,24].

A nailfold videocapillaroscopy is performed to assess microcirculatory abnormalities, particularly those consistent with SSc (scleroderma pattern). It is performed using a videocapillaroscope with 200× magnification on the 2nd to 5th fingers bilaterally, capturing multiple images per nailfold[1]. It is a key non-invasive tool in the evaluation of patients with RP, allowing differentiation between primary and secondary forms, particularly in the context of SSc. Characteristic capillaroscopic patterns in SSc include the presence of giant capillaries, microhemorrhages, capillary loss, and disorganization of the microvascular architecture[20,23] (Figure 2).

Interpretation of nailfold capillaroscopy findings is essential for distinguishing primary from SRP, particularly in identifying a scleroderma pattern. A fast-track algorithm has been proposed to differentiate scleroderma from non-scleroderma patterns based on key capillaroscopic features[20].

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The presence of giant capillaries, often associated with microhemorrhages, and/or capillary loss is highly suggestive of a scleroderma pattern, whereas their absence and the presence of nonspecific findings such as mild capillary dilatation or tortuosity are more consistent with non-scleroderma patterns[20].

This structured approach provides a practical framework for the interpretation of capillaroscopic findings in patients with RP.

Infrared thermography represents a non-invasive method for assessing peripheral perfusion[24]. It may assist in distinguishing PRP from SRP, as patients with RP often have cooler fingertips compared with healthy individuals. However, its clinical use is limited by the lack of standardized protocols and variability in interpretation[1]. Some protocols include dynamic assessment (e.g., cold challenge) to further aid differentiation between PRP and SRP[1].

Patient-reported outcomes (PROs):

Patient-reported outcomes (PROs) are essential for assessing disease burden and treatment response in Raynaud's phenomenon. The Raynaud Condition Score (RCS) is the most widely used instrument, consisting of a patient-reported daily global severity score that reflects the overall impact of Raynaud's attacks[25].

In patients with systemic sclerosis (SSc), broader disease-specific PROs may also be used. The Scleroderma Health Assessment Questionnaire (SHAQ) evaluates functional disability and disease impact, while the ScleroID questionnaire is a patient-derived instrument specifically developed to assess health-related quality of life in SSc across multiple domains relevant to patients[21].

The ScleroID questionnaire is a disease-specific, patient-derived outcome measure developed to assess the impact of SSc on health-related quality of life across domains prioritized by patients[21]. It has undergone cross-cultural adaptation and validation in several countries, including a European Portuguese version[21,22]. However, data regarding the validation of PRO instruments specifically designed to assess Raynaud's phenomenon in Portuguese populations remain limited.

Management

Recent advances in the management of RP have focused on both pharmacological and non-pharmacological interventions, including drug therapies, surgical options, and lifestyle modifications[3]. Recent publications from ARP Rheumatology have further contributed to the

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understanding of RP management, particularly regarding therapeutic strategies and patient stratification[17,18], and are supported by a recent systematic literature review evaluating the efficacy and safety of these interventions[18].

Non-Pharmacological Treatments

Lifestyle Modifications

- Patients are advised to avoid cold exposure and stress, which are common triggers for Raynaud's attacks. Wearing warm gloves and socks, reducing caffeine intake, and quitting smoking can help mitigate symptoms[11].

Biofeedback and Stress Management

- Techniques like biofeedback, which help patients gain control over physiological functions, can reduce the frequency and severity of Raynaud attacks [12].

Pharmacological Treatments

Pharmacological management strategies are guided by disease severity and the presence of underlying connective tissue disease. According to recent Portuguese recommendations, calcium channel blockers remain the first-line treatment for RP, followed by phosphodiesterase-5 inhibitors in patients with inadequate response or more severe disease. Intravenous prostacyclin analogues and endothelin receptor antagonists may be considered in selected patients, particularly those with SSc-associated RP and digital ulcers [17,18]. A therapeutic algorithm summarizing the stepwise management of RP according to these recommendations is presented in Figure 2.

Calcium Channel Blockers

Nifedipine, a commonly used calcium channel blocker, remains a first-line treatment, effective in approximately 40–60% of patients. This medication promotes vasodilation and improves blood flow to the extremities[17,18].

Phosphodiesterase-5 Inhibitors (PDE5)

A meta-analysis of nine randomized trials demonstrated that PDE5 inhibitors could reduce the frequency and duration of Raynaud attacks, particularly in patients with systemic sclerosis (SSc) [11].

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Endothelin Receptor Antagonists and Prostacyclin Analogues

For severe cases, especially SRP, drugs like bosentan (an endothelin receptor antagonist) and iloprost (a prostacyclin analogue) are used to manage symptoms and prevent complications such as digital ulcers[12].

Other classes of medications

Includes angiotensin II receptor antagonists (e.g., losartan), angiotensin-converting enzyme inhibitors (ACE inhibitors), and selective serotonin reuptake inhibitors (e.g., fluoxetine), with the latter being particularly useful in patients who tend to experience significant vasodilator side effects [1].

Surgical Interventions

- Minimally Invasive Surgery
    - Recent studies have highlighted the efficacy of minimally invasive surgical techniques, such as digital sympathectomy, which can significantly reduce pain and the frequency of Raynaud attacks without major complications. This approach targets the nerves responsible for vasoconstriction in the extremities [11].

- Microscopic Digital Sympathectomy
    - This procedure has been effective in severe cases, showing significant improvements in the duration and severity of attacks, particularly for patients with refractory symptoms [11].

Patient Management and Follow-up:

1. Referral to General Rheumatology:

- Patients fulfilling the 2013 ACR/EULAR classification criteria for systemic sclerosis should be referred to a specialized SSc clinic, where they will receive structured and regular follow-up.
- Patients suspected of having another connective tissue disease (CTD), including undifferentiated connective tissue disease (UCTD), should be referred to a general rheumatology consultation for comprehensive evaluation and management.

2. Re-evaluation of Patients with Primary or Recently Onset Raynaud's Phenomenon (RP):

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- In cases where it is unclear whether RP is primary or secondary, or where baseline investigations are normal and RP onset is recent (less than 2 years), re-evaluation is recommended within 6 to 24 months, as shown in Figure 3.

Follow-up strategies should be individualized according to disease severity and risk stratification, in line with recent national recommendations and longitudinal evidence on progression to connective tissue diseases [16,17,18.]

During follow-up, patients considered to be at low risk of progression may continue to be monitored in primary care, provided that they fulfil all of the following VEDOSS-aligned criteria [13,16,17,18,26]:

- Raynaud's phenomenon remains clinically stable, without progression or the emergence of clinical signs suggestive of connective tissue disease (CTD), including puffy fingers, telangiectasia, or musculoskeletal manifestations.
- Nailfold capillaroscopy shows either a normal pattern or stable nonspecific findings over at least 12 months, with no evolution towards a scleroderma pattern (early, active, or late).
- Immunological studies demonstrate a low ANA titre (≤1:160) without the presence of systemic sclerosis-specific autoantibodies (e.g., anti-centromere, anti-Scl-70, anti-RNA polymerase III)

Conclusion

Raynaud phenomenon is a common clinical manifestation of connective tissue diseases, particularly systemic sclerosis, in which it frequently represents the earliest manifestation and may precede other disease features by several years. Understanding Raynaud phenomenon as a potential early indicator of systemic sclerosis allows for timely diagnosis and management, potentially improving patient outcomes. The interplay between these conditions underscores the importance of a comprehensive approach to patient assessment and care. By recognizing the early signs of Raynaud phenomenon and monitoring for the subsequent development of systemic sclerosis, healthcare providers can implement targeted interventions to mitigate disease progression and enhance quality of life. Continued research and clinical awareness are essential for advancing our understanding and treatment of these complex, interrelated conditions.

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Tables and Figures

Table I - Causes of Raynaud's Phenomenon

Causes of SRP	Conditions that mimic RP
Imune-mediated Systemic Sclerosis: 90% Mixed Connective Tissue Disease: 85% Sjögren's Syndrome: 35% Systemic Lupus Erythematosus: 10-45% Polymyositis/Dermatomyositis: 20% Rheumatoid Arthritis: 10-15%	**Occlusive Vascular conditions** Atherosclerosis Arteritis Microemboli Thromboangiitis obliterans Diabetic microangiopathy
Occupational Vibration exposure Cold injury Exposure to polyvinyl chloride	**Hematological/Hiperviscosity Syndrome** Polycythemia Paraproteinemia Cryoglobulinemia/Cryofibrinogenemia
Drug- Induced Anti-migraine medication Beta blockers Cytotoxic drugs Bromocriptine Sulfasalazine Minocycline Interferon alpha/beta Cocaine	**Other conditions that exacerbate the underlying risk factor:** Hypothyroidism Thoracic outlet syndrome Carpal tunnel syndrome Arteriovenous fistula
Infectious causes Chronic Hepatitis B/C Cytomegalovirus Parvovirus B19	
Others Complex Regional Pain Syndrome Carcinoid Syndrome	

(Table adapted from Haque et al., 2020; Herrick & Wigley, 2020; and Nawaz et al., 2022.)

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Table II - Guidelines for anamnesis and physical examination on the first clinical assessment

Anamnesis	**Physical Examination**
Characterize the raynaud phenomenon (phases, symmetry, precipitating factors, evolution time, clinical stability, raynaud condition score)	**Assess Blood Pressure and pulses:** - Measure blood pressure bilaterally. - Check the overall pulse and peripheral pulses.
Symptoms involving other organs: - Trophic skin changes - Upper digestive complaints (dysphagia, reflux) - Intestinal transit changes - Exertional dyspnea - Musculoskeletal complaints	**Evaluate Skin Surface:** - Conduct a comprehensive examination of the skin surface. - Pay special attention to the presence of telangiectasias (face/hands), subcutaneous calcinosis, and trophic changes at the fingertips.
Inquire about potential environmental / pharmacological factors causing RP.	Conduct a thorough assessment using the modified Rodnan skin score.
	Cardiac and Pulmonary Auscultation
	Joint Examination: - Count the number of tender/swollen joints

(Table adapted from Haque et al., 2020; Herrick & Wigley, 2020; and current EULAR recommendations on the assessment of Raynaud's phenomenon and connective tissue diseases.)

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Figure 1. Representative clinical photograph of Raynaud's phenomenon showing well-demarcated digital pallor of the fingers during a vasospastic episode. Image obtained from the authors' clinical practice.



(A) Normal capillaroscopic pattern.

(B) Nonspecific pattern showing microhemorrhages.

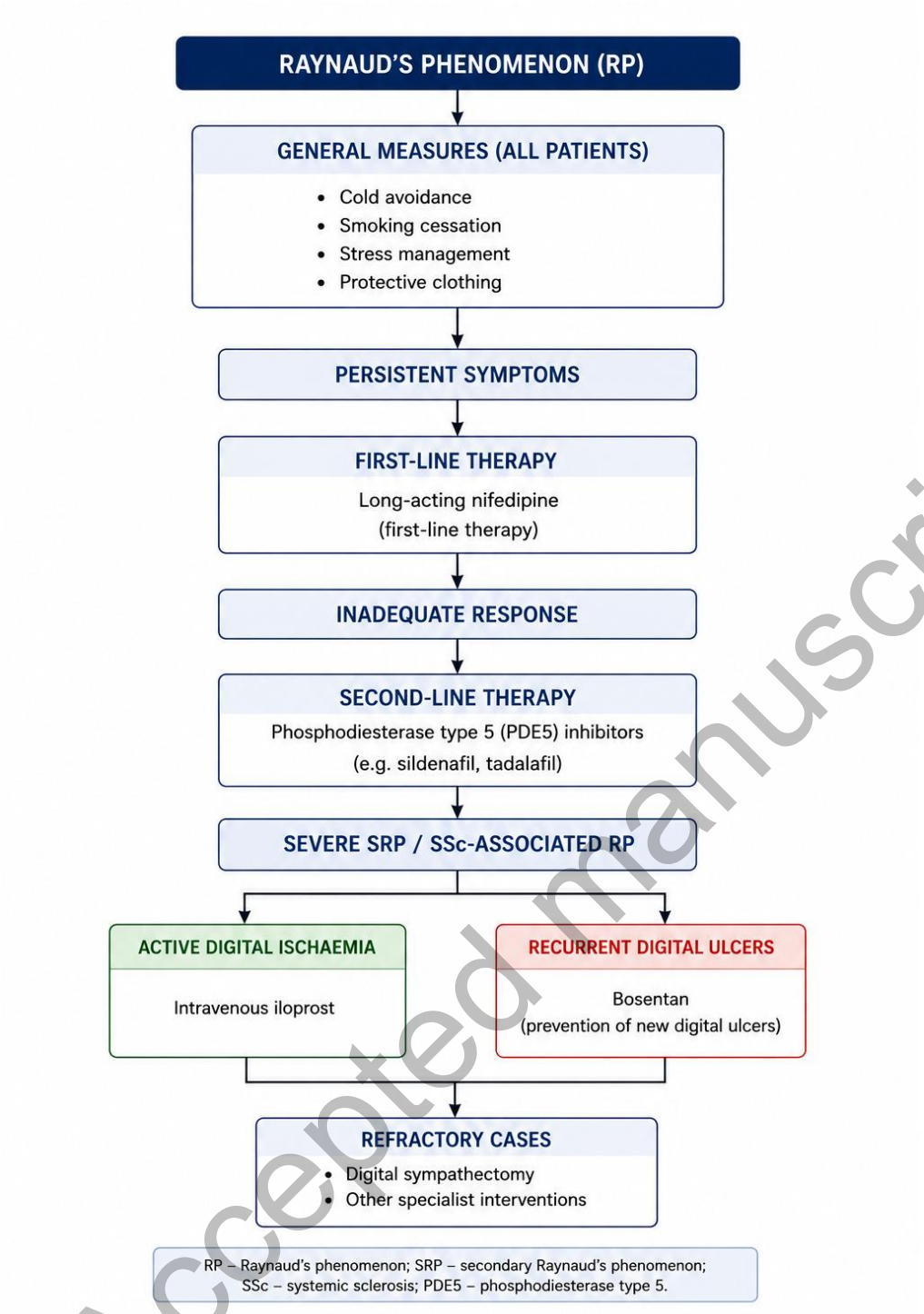
(C) Early scleroderma pattern characterized by the presence of giant capillaries without reduction in capillary density.

(D) Early scleroderma pattern with multiple giant capillaries and occasional microhemorrhage, without capillary loss.

(E) Active scleroderma pattern showing reduced capillary density, microhemorrhages, and giant capillaries.

Figure 2. Nailfold videocapillaroscopy patterns. Images obtained from the authors' clinical practice.

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Figure 3. Therapeutic algorithm for the management of Raynaud's phenomenon. Created by the authors and adapted from the Portuguese recommendations for the management of Raynaud's phenomenon and digital ulcers in systemic sclerosis and other connective tissue diseases[17,18].

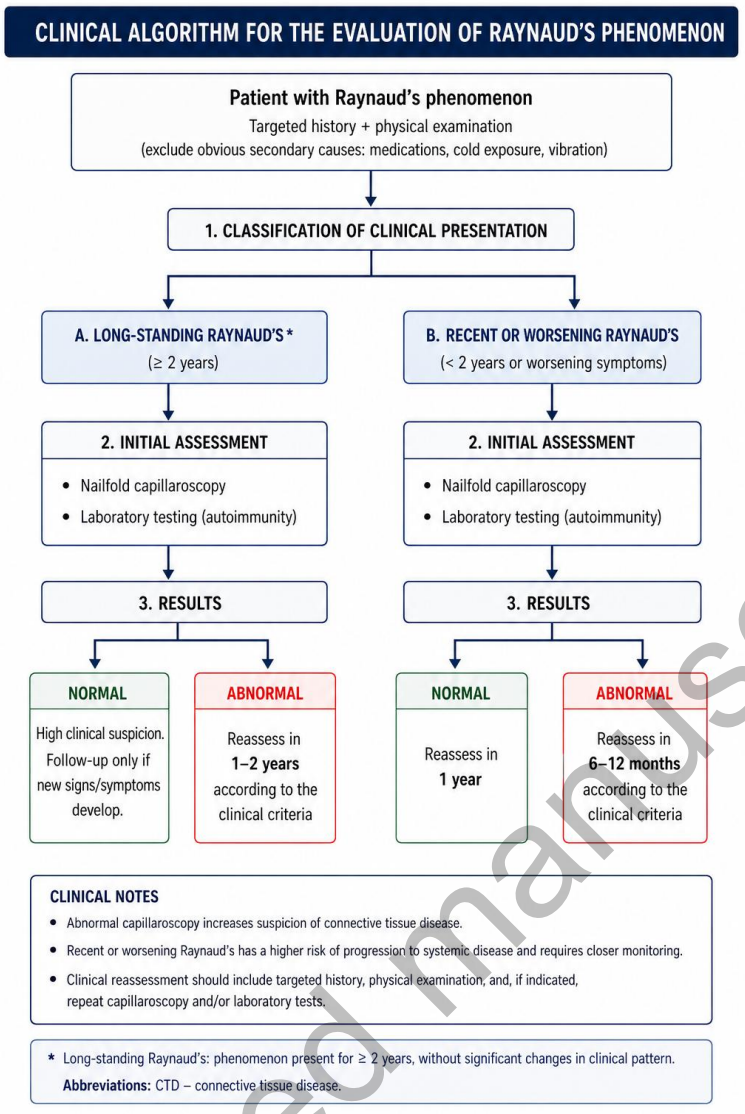


Figure 4 - Guidance for Patients Without a Definitive Diagnosis of Systemic Sclerosis (SSc) or Another Connective Tissue Disease (CTD). (Figure based on Haque A, Hughes M. Raynaud's phenomenon. Clin Med (Lond). 2020 Nov)

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