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Systemic Sclerosis – A Diagnostic Challenge or a Clinically Controllable Disease?

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Abstract
Systemic sclerosis is a complex and heterogeneous autoimmune condition in which skin and internal organ involvement progresses through interrelated processes of vasculopathy, immune activation, and fibrosis. Although considered an uncommon disease, its impact is disproportionate due to delayed diagnosis and potential for multiorgan complications. This review aims to synthesize current knowledge on the underlying mechanisms, clinical spectrum, and management strategies of systemic sclerosis, with particular attention to validated classification criteria and therapeutic recommendations. The paper emphasizes the role of early clinical suspicion, specific serologic and capillaroscopic findings, and the significance of evolving immunomodulatory and antifibrotic therapies. An individualized and multidisciplinary approach remains essential in improving patient outcomes and quality of life.
Review Methods
The literature used in this review was obtained through a narrative search of PubMed and Google Scholar. Publications from 1997 to 2025 were considered. Preference was given to articles focused on autoimmune mechanisms, vascular abnormalities, fibrosis, and current recommendations for the diagnosis and treatment of systemic sclerosis.

Keywords
systemic sclerosis, scleroderma, autoimmunity, vasculopathy, fibrosis, EULAR recommendations

Introduction

Systemic sclerosis (SSc) is a rare autoimmune disorder of connective tissue, marked by immune dysregulation, vascular dysfunction, and progressive fibrosis involving the skin and internal organs (Allanore et al., 2015; Volkmann et al., 2023). These processes lead to widespread skin thickening (scleroderma of the skin) and dysfunction of involved organs (e.g. lungs, heart, kidneys, gastrointestinal tract). SSc is associated with significant morbidity and has one of the highest mortality rates among rheumatic diseases (Allanore et al., 2015). The leading causes of death are pulmonary complications (interstitial lung disease and pulmonary hypertension), cardiac complications, and scleroderma renal crisis (Elhai et al., 2017; Mouthon et al., 2014). The disease affects women more frequently – women are estimated to be affected about 4–5 times more often than men – and peak onset is in the 4th to 6th decades of life (Volkmann et al., 2023). SSc has a heterogeneous course; for example, the limited cutaneous and diffuse cutaneous subtypes differ in the extent of skin involvement and the profile of organ manifestations (discussed below). Despite its rarity, SSc can be severe – it leads to chronic multi-organ failure, substantially reducing quality of life and life expectancy (Allanore et al., 2015; Elhai et al., 2017).

Early diagnosis of systemic sclerosis is a major clinical challenge, as initial symptoms (e.g. Raynaud's phenomenon) are non-specific. However, prompt recognition is crucial for improving prognosis (Steen & Medsger, 2000). In aggressive diffuse SSc, severe organ involvement (e.g. lung or kidney) may develop within the first few years of disease, before the diagnosis is fully established (Steen & Medsger, 2000). Diagnostic difficulties also arise

from the varied clinical presentation and overlap with features of other autoimmune disorders. In recent years, there has been significant progress in understanding SSc pathogenesis and the development of new classification criteria, which facilitate identification of the disease at an early stage (van den Hoogen et al., 2013; Avouac et al., 2011). In parallel, therapeutic options have expanded – systemic sclerosis, once considered untreatable and therapy-resistant, can now be partially controlled with new drugs and treatment strategies (Volkmann et al., 2023). The aim of this article is to present the current state of knowledge on systemic sclerosis, with particular emphasis on its pathogenesis, clinical features, diagnostic principles, and contemporary treatment strategies. We highlight the importance of early disease detection and intervention, which translate into improved patient outcomes.

Pathogenesis

Despite growing understanding, the mechanisms underlying systemic sclerosis remain incompletely defined due to the disease's multifaceted nature. It is thought that three interrelated processes play key roles: immune system dysfunction (autoimmunity), small-vessel damage (vasculopathy), and excessive fibroblast activation leading to extracellular matrix deposition (fibrosis) (Varga & Abraham, 2007; Allanore et al., 2015). In the early stage of disease, there is injury to endothelial cells in the microcirculation of the skin and internal organs, accompanied by activation of innate and adaptive immunity – with T- and B-lymphocyte infiltrates in tissues and circulating immune complexes and antinuclear antibodies (ANA) detectable (Allanore et al., 2015). The damaged endothelium releases vasoconstrictive (e.g. endothelin-1) and pro-fibrotic factors, resulting in persistent vasospasm and tissue ischemia. Clinically this manifests as, among others, worsening of Raynaud's phenomenon and characteristic nailfold capillaroscopic changes (areas of avascularity and enlarged, deformed "mega-capillaries") (Koenig et al., 2008; Cutolo et al., 2013). Simultaneously, there is aberrant activation of fibroblasts and transformation of epithelial and endothelial cells into myofibroblasts, which overproduce collagen and other matrix components, leading to progressive fibrosis of skin and organs (Varga & Abraham, 2007). An important mediator of this process is transforming growth factor-beta (TGF-β) and other pro-fibrotic cytokines – their levels are elevated in SSc, stimulating pro-collagen gene expression in fibroblasts (Varga & Abraham, 2007).

Genetic and environmental factors also play significant roles in SSc pathogenesis. Certain HLA haplotypes (e.g. HLA-DQB1) and polymorphisms in genes regulating immune responses and fibrosis may predispose individuals to the disease (Volkmann et al., 2023). There is also evidence that environmental exposures can trigger SSc. Potential triggers include silica dust, organic solvents, vinyl chloride, and certain drugs (e.g. bleomycin), which may initiate endothelial damage and an autoimmune reaction (Allanore et al., 2015). In summary, the fundamental pathology of SSc involves autoimmune injury to the microvasculature and excessive fibrosis, wherein tissue ischemia exacerbates inflammation, which in turn stimulates further fibrosis – leading to a self-perpetuating cycle of ischemia, inflammation, and fibrosis. Understanding these mechanisms has been reflected in new therapeutic approaches: in addition to classic immunosuppressants, targeted therapies against pro-inflammatory pathways (e.g. IL-6 inhibition, B-cell depletion) and anti-fibrotic agents (e.g. nintedanib, which inhibits tyrosine kinases involved in TGF-β signaling) have been introduced (Khanna et al., 2020; Distler et al., 2019). Nonetheless, completely arresting the disease process remains a challenge.

Clinical Features

The clinical presentation of systemic sclerosis is highly variable – in both the severity of changes and the range of organs involved. Based on the extent of skin involvement, two main SSc subtypes are classically distinguished (van den Hoogen et al., 2013):

Limited cutaneous systemic sclerosis (lcSSc): Characterized by a long-standing period of isolated Raynaud's phenomenon followed by slow development of skin sclerosis that involves primarily the distal extremities (fingers, hands, forearms, lower legs) and the face. Skin changes are less widespread, and internal organs are affected later and to a lesser degree than in the diffuse form. A hallmark of the limited form is the presence of the CREST syndrome (Calcinosis, Raynaud's phenomenon, Esophageal dysmotility, Sclerodactyly, Telangiectasia). Patients with lcSSc more often have anticentromere antibodies (ACA), and after a disease duration of many years they may develop pulmonary arterial hypertension as a leading complication (van den Hoogen et al., 2013; Volkmann et al., 2023).

Diffuse cutaneous systemic sclerosis (dcSSc): Defined by a rapid progression of skin thickening, which within a few months of disease onset involves not only the fingers and hands but also more proximal parts of the limbs (upper arms, forearms, thighs) and the trunk (van den Hoogen et al., 2013). In this subtype, major internal organs – lungs, heart, kidneys, gastrointestinal tract – become involved early in the disease course (often within the first 5 years), leading to a worse prognosis. Patients with dcSSc more frequently have anti-topoisomerase I antibodies (anti-Scl-70) or anti-RNA polymerase III antibodies, which are associated with higher risk of interstitial lung disease and scleroderma renal crisis, respectively (Stochmal et al., 2020; Nihtyanova et al., 2020). Overall, the diffuse form has a more aggressive course – rapidly progressive extensive skin fibrosis (causing joint contractures and reduced mobility) and early organ complications contribute to increased mortality in this group of patients (Steen & Medsger, 2000; Elhai et al., 2017).

In addition to the above, there are rarer variants such as systemic sclerosis sine scleroderma, in which typical internal organ manifestations (e.g. lung fibrosis, pulmonary hypertension, renal crisis) and immunological markers of SSc are present, but skin thickening is absent. This is an uncommon subset, posing a diagnostic challenge and described mainly in case reports (Kucharz & Kopeć-Mędrek, 2017). Another category is overlap syndromes – features of scleroderma coexisting with other connective tissue diseases (e.g. polymyositis, rheumatoid arthritis, or systemic lupus erythematosus). An example is an overlap of SSc with polymyositis (scleroderma/PM overlap) or mixed connective tissue disease (MCTD) with features of scleroderma.

Systemic sclerosis can affect virtually every organ system. Key clinical manifestations include:

Skin changes: Skin thickening (sclerosis) typically begins in the fingers (sclerodactyly) – initially with puffy swelling of the fingers, followed by induration of the skin leading to flexion contractures of the fingers. The skin becomes tight, shiny, and less elastic; on the face this causes a characteristic "mask-like" facies. Hyperpigmentation and depigmentation often occur in a mottled pattern ("salt-and-pepper" skin changes), and telangiectasias (dilated superficial blood vessels) are commonly seen, especially on the face, lips, and hands (Allanore et al., 2015). In the CREST syndrome, calcinosis (calcium deposits in subcutaneous tissues, especially on the fingers) is characteristic. Long-standing sclerosis of the fingers and hands leads to distal tissue atrophy and a claw-like appearance of the hands (flexion contractures of the fingers). Patients often report skin tightness and pruritus in the early inflammatory phase of the disease, and in the chronic phase – painful digital ulcers and poorly healing fingertip wounds.

Vascular system: In the majority of patients, Raynaud's phenomenon appears first and may predate other manifestations by months or even years (Pauling et al., 2019). This episodic

vasospasm in the fingers (and less often toes, nose, ears) is triggered by cold or stress and results in a triphasic color change of the digits (pallor, cyanosis, then redness) accompanied by pain. In the course of SSc, Raynaud's phenomenon tends to worsen over time – structural damage to capillaries (visible on capillaroscopy) and chronic ischemia of the fingers ensue. Consequences include difficult-to-heal ischemic ulcers (mainly on fingertip pads and over distal interphalangeal joints) and gangrene of distal tissues, which can lead to autoamputation of phalanges (Herrick, 2011). Chronic ischemia of the hands causes pain and impaired hand function and predisposes to infection of ulcers. Other signs of microvascular involvement are cutaneous telangiectasias and damage to the pulmonary vasculature resulting in pulmonary arterial hypertension (discussed below).

Musculoskeletal system: Some patients experience joint and muscle pain and morning stiffness of the small joints of the hands. An inflammatory arthritis can develop, resembling rheumatoid arthritis (though erosive changes are rare). A characteristic finding is tendon friction rubs – on examination, the patient has a grating sensation on movement of certain joints (especially wrists, elbows, knees) due to fibrosis of tendon sheaths. Secondary joint contractures may occur as a result of sclerodactyly and skin tightening. In about 10–20% of patients, myositis (primary or as part of an overlap syndrome) develops, manifesting as proximal muscle weakness with elevated muscle enzyme levels (Lefebvre et al., 2021). Chronic inflammation and reduced mobility also contribute to osteoporosis.

Lungs: Lung involvement occurs in over half of SSc patients and primarily takes two forms. The first is interstitial lung disease (ILD) – a progressive pulmonary fibrosis, particularly common in the diffuse subset of SSc and in those with anti-Scl-70 antibodies. ILD presents with chronic cough, progressive exertional dyspnea, and reduced exercise tolerance. High-resolution CT (HRCT) of the chest shows changes typical of fibrosis – most often a pattern of non-specific interstitial pneumonia (NSIP) with reticular markings and volume loss in the lung bases. Untreated SSc-ILD leads to respiratory failure and is one of the leading causes of SSc-related mortality (Elhai et al., 2017). The second pulmonary manifestation is pulmonary arterial hypertension (PAH) resulting from vascular changes in the pulmonary circulation. PAH occurs more often in long-standing limited cutaneous SSc (with anticentromere antibodies), sometimes after a disease duration of one or two decades (Volkmann et al., 2023). Clinically it causes progressive exertional dyspnea, syncope, and signs of right-heart failure (peripheral edema, jugular venous distension) – it is also a complication with high mortality (Chung et al., 2014). Some patients have both lung fibrosis and pulmonary hypertension simultaneously, further worsening the prognosis (Elhai et al., 2017).

Heart: SSc can affect the heart both primarily (fibrosing cardiomyopathy due to SSc itself) and secondarily as a consequence of vascular (right ventricular strain from PAH) or renal complications (malignant hypertension in renal crisis). Primary cardiac changes include myocardial fibrosis (leading to restrictive cardiomyopathy or arrhythmias), fibrosis of the cardiac conduction system (heart blocks, arrhythmias), pericardial effusion or pericarditis, and microangiopathy of coronary vessels (Bruni & Ross, 2021). Clinically, patients may experience palpitations, chest pain, or syncope. Cardiac arrhythmias are common – ranging from premature beats to dangerous ventricular arrhythmias that can cause sudden cardiac death (Bruni & Ross, 2021). An ECG may show conduction blocks (e.g. right bundle branch block) or low-voltage QRS complexes in the presence of a large pericardial effusion. Echocardiography can reveal diastolic dysfunction, right ventricular enlargement (with PAH), or pericardial fluid. Cardiac involvement significantly worsens prognosis – arrhythmias and heart failure are among the leading causes of death in SSc (Elhai et al., 2017).

Kidneys: A characteristic, though fortunately relatively rare (5–10% of patients), complication of SSc is scleroderma renal crisis (SRC) (Mouthon et al., 2014). SRC presents with abrupt onset of malignant hypertension and acute kidney injury (rapidly rising creatinine), often accompanied by microangiopathic hemolytic anemia and retinopathy on fundoscopic exam. Renal crisis occurs mainly in diffuse SSc, usually within the first 4 years of disease. Risk factors include the presence of anti-RNA polymerase III antibodies and the use of high-dose glucocorticoids (Mouthon et al., 2014; Hudson et al., 2014). Untreated SRC follows a fulminant course – within days to weeks it can cause hypertensive encephalopathy, acute left ventricular failure, and death. In the era before ACE inhibitors, the 1-year mortality of SRC exceeded 50% (Penn et al., 2007). Today, with early recognition and aggressive treatment (described in the Treatment section), most patients survive a renal crisis, though many require chronic dialysis (Cole et al., 2023).

Gastrointestinal tract: GI involvement occurs in about 90% of SSc patients, most often affecting the esophagus and intestines (McMahan, 2019). Fibrosis of smooth muscle and autonomic neuropathy in the GI tract lead to dysmotility. In the esophagus this manifests as weakened peristalsis and lower esophageal sphincter incompetence, resulting in gastroesophageal reflux with chronic heartburn, mucosal inflammation, and risk of strictures. In the stomach and small intestine, impaired motility and bacterial overgrowth cause malabsorption (symptoms include bloating, diarrhea, weight loss) (McMahan, 2019). Sometimes intestinal muscle fibrosis leads to a serious complication: chronic intestinal pseudo-obstruction – presenting as acute bowel obstruction without a mechanical blockage, requiring hospitalization (Dein et al., 2019). In the colon, constipation is common, and even fecal incontinence can occur if the rectum and sphincters are affected (Garros et al., 2017). A characteristic stomach lesion, particularly in lcSSc, is gastric antral vascular ectasia (GAVE, "watermelon stomach"), which can cause GI bleeding (Ghrénassia et al., 2014). Gastrointestinal symptoms significantly impair patients' quality of life – chronic reflux, dysphagia, abdominal pain, and alternating diarrhea and constipation are frequent. Uncontrolled severe reflux can lead to aspiration pneumonia, and severe bowel involvement can result in malnutrition.

The above manifestations illustrate the multi-organ nature of systemic sclerosis. Given this broad spectrum of symptoms, standardized criteria and appropriate ancillary tests are essential for diagnosing SSc and assessing disease activity. Moreover, the clinical picture (including the titers and specificities of autoantibodies) allows some prediction of disease course – for example, patients with anticentromere antibodies usually have a more indolent course and later complications (though a higher risk of isolated pulmonary hypertension), whereas the presence of anti-topoisomerase I antibodies is associated with early lung fibrosis and more severe disease (Nihtyanova et al., 2020). Individualized patient management therefore requires a comprehensive clinical and immunologic assessment.

The clinical course of systemic sclerosis follows characteristic stages in which different symptoms and organ complications predominate. Table 1 outlines a typical timeline of disease progression, including dominant clinical symptoms, common organ manifestations, and key diagnostic/therapeutic recommendations at each stage.

Table 1. Clinical progression of systemic sclerosis – typical timeline

Time Since Symptom Onset	Dominant Clinical Features	Typical Organ Changes	Clinical Notes / Recommendations

0–1 year	Raynaud's phenomenon (cold, cyanotic fingers), numbness, paresthesia	No significant organ abnormalities on imaging or labs	Differentiation between primary and secondary Raynaud's is often difficult at this stage (Koenig et al., 2008).
1–3 years	Swollen fingers ("sausage digits"), onset of skin thickening on hands and face	Esophageal dysmotility, early skin and peripheral vessel changes	Key period for diagnosing SSc; capillaroscopy and autoantibody testing recommended (Koenig et al., 2008).
3–5 years	Progressing skin changes (sclerodactyly, mask-like face), fatigue	Interstitial lung disease (NSIP), arrhythmias, reduced exercise tolerance	Perform HRCT, ECG, and echocardiography; consider starting immunosuppressive therapy (Nihtyanova et al., 2020).
5–10 years	Systemic symptoms: dyspnea, reflux, arrhythmias, hypertension	Pulmonary hypertension (PAH), renal crisis, heart failure, advanced lung fibrosis	High-risk stage for complications and hospitalization – regular organ function monitoring is essential (Steen et al., 1997).
>10 years	Multiorgan failure, cachexia, chronic pain	Generalized fibrosis, chronic respiratory failure, cardiomyopathy	Palliative care and multidisciplinary support (pulmonologist, cardiologist, rheumatologist) recommended.

Source: Adapted from Koenig et al. (2008), Steen et al. (1997), and Nihtyanova et al. (2020).

Diagnosis

The diagnosis of SSc is based on a characteristic clinical picture, immunological findings, and exclusion of other conditions with similar features. In clinical practice, the ACR/EULAR 2013 classification criteria are utilized, which have standardized the diagnosis of SSc and allow earlier identification of the disease (van den Hoogen et al., 2013). According to these criteria, a patient can be classified as having SSc once a score of ≥9 points is reached based on the features present. The single most important criterion is skin thickening of the fingers extending proximal to the metacarpophalangeal joints (i.e. on the hands and forearms) – this finding alone is scored with 9 points and fulfills the classification threshold for systemic sclerosis (van den Hoogen et al., 2013). In the absence of such extensive skin changes, points are summed for other clinical features, for example:

Sclerodactyly (skin thickening of the fingers extending up to the metacarpophalangeal joints) – 4 points (van den Hoogen et al., 2013).

Fingertip ulcers or pitted scars (depressed scars on finger pads) – 2 points.

Telangiectasias – 2 points.

Abnormal nailfold capillaries (characteristic "scleroderma" pattern of capillaroscopy) – 2 points.

Raynaud's phenomenon – 3 points.

SSc-specific autoantibodies (anticentromere, anti–Scl-70, or anti–RNA polymerase III) – 3 points.

When the total score reaches 9 or more points, the diagnosis of systemic sclerosis can be formally established. While these criteria were initially intended for use in research settings, they have also proven helpful in guiding clinical evaluation. The key diagnostic features are the typical pattern of skin sclerosis with appropriate distribution and course, and the presence of characteristic autoantibodies. If a patient presents with sclerodactyly along with Raynaud's phenomenon and a positive ANA (especially with a characteristic fluorescence pattern, such as centromere or nucleolar), early systemic sclerosis should be strongly suspected – even if extensive proximal skin thickening has not yet developed beyond the wrists (van den Hoogen et al., 2013).
Table 2 presents a simplified diagnostic algorithm for patients with suspected very early systemic sclerosis, focusing on Raynaud's phenomenon, ANA status, and capillaroscopy findings.

Table 2. Diagnostic algorithm for suspected early systemic sclerosis

Diagnostic Step	Examination	Interpretation	Clinical Action
History – Raynaud's phenomenon	Presence of episodes of finger cyanosis	Common in SSc and other conditions	Proceed with diagnostics (Koenig et al., 2008).
ANA testing	Indirect immunofluorescence or ELISA	Positive – risk of autoimmune disease	Order capillaroscopy (Walker et al., 2019).
Nailfold capillaroscopy	Capillaroscopy microscope	SSc pattern: megacapillaries, avascular areas	High SSc risk (Cutolo et al., 2013).
Specific autoantibodies	Anti-Scl-70, ACA, RNA polymerase III	Presence confirms SSc diagnosis	Confirm disease and assess severity (Nihtyanova et al., 2020).
Organ assessment (HRCT, ECHO, EMG etc.)	Imaging and lab work-up	Evaluate lungs, heart, kidneys, muscles	Start therapy and monitoring (Steen et al., 1997).

Source: Adapted from Koenig et al. (2008), Cutolo et al. (2013), Nihtyanova et al. (2020), Steen et al. (1997).

In 2011, a EULAR (EUSTAR) expert group also proposed criteria for very early systemic sclerosis (VEDOSS) to identify patients at a stage when they do not yet fulfill the full criteria but are at high risk of developing the disease (Avouac et al., 2011). The proposed very-early SSc criteria include the combination of Raynaud's phenomenon, presence of SSc-specific ANA, and scleroderma-pattern capillaroscopic changes (Avouac et al., 2011). A prospective study by Koenig et al. (2008) showed that in patients with idiopathic (primary) Raynaud's phenomenon, the simultaneous presence of antinuclear antibodies (especially anticentromere or anti–Scl-70) and characteristic capillaroscopic abnormalities was associated with a very high risk of progression to full-blown scleroderma in subsequent years – the proposed criteria had 79% sensitivity and 99% specificity for predicting SSc. In practice, therefore, a person with primary Raynaud's should always undergo nailfold capillaroscopy and ANA testing – if both tests show findings typical of SSc, the patient requires close rheumatologic surveillance, even in the absence of skin sclerosis. Capillaroscopy is a simple, noninvasive examination in

which capillaries at the nailbed are viewed under magnification. A “scleroderma pattern” consists of areas devoid of capillaries (avascular areas), the presence of enlarged (giant) capillaries, and pericapillary hemorrhages – such changes are highly suggestive of secondary Raynaud’s due to scleroderma or related connective tissue diseases, in contrast to benign primary Raynaud’s which shows a normal capillaroscopic picture (Cutolo et al., 2013).

Immunologic tests play a key role in diagnosing SSc. Over 90% of patients have a positive ANA by indirect immunofluorescence (Hamaguchi & Takehara, 2018). Among these, about 80–90% have autoantibodies specific to scleroderma, and usually one main antibody specificity predominates in a given patient (these specificities are generally mutually exclusive). The most important include:

Anticentromere antibodies (ACA): Present in ~20–40% of patients, especially in the limited cutaneous subtype. They produce a characteristic centromere speckled ANA pattern in interphase nuclei. ACA are associated with the CREST syndrome and a higher risk of developing PAH, while they are less often linked to severe lung fibrosis or renal crisis (Stochmal et al., 2020). Prognostically, they are considered a relatively favorable marker (disease tends to progress more slowly and involve organs later).

Anti-topoisomerase I antibodies (anti-Scl-70): Found in ~20–30% of patients, mainly in diffuse cutaneous SSc. They target DNA topoisomerase I and usually produce a nucleolar or fine speckled ANA pattern. These antibodies are associated with a more severe course – more extensive lung fibrosis, early widespread skin involvement, and overall worse prognosis (Stochmal et al., 2020). Patients with anti-Scl-70 require vigilant pulmonary function monitoring from the early stages of disease.

Anti-RNA polymerase III antibodies: Present in ~5–10% of patients, almost exclusively in diffuse SSc. They are not detected by standard ANA immunofluorescence (requiring immunoprecipitation or ELISA for detection). Their presence strongly predisposes to scleroderma renal crisis and rapidly progressive skin thickening (Steen & Medsger, 2000; Stochmal et al., 2020). Some studies have also noted a higher incidence of cancer in patients with anti-RNA Pol III (it is hypothesized that an occult malignancy may trigger the autoimmune response to this antigen) (Stochmal et al., 2020).

Other autoantibodies: Less common but also diagnostically helpful. These include, for example, anti-U3 RNP (anti-fibrillarin) – seen more often in younger patients and those of African ancestry, associated with cardiac involvement and PAH; anti-Th/To antibodies – found in limited SSc with early PAH; and PM-Scl antibodies – typical of overlap syndromes (scleroderma with myositis) (Hamaguchi & Takehara, 2018; Stochmal et al., 2020). In laboratory diagnosis of SSc, immunoblot or ELISA panels that detect many of these specific antibodies concurrently are used. It should be noted that a negative ANA essentially excludes the diagnosis of scleroderma – seronegative cases are exceedingly rare.

In addition to immunologic tests and capillaroscopy, imaging and functional studies assessing internal organs are critical in scleroderma diagnostics. When evaluating a patient for SSc, other conditions that cause skin hardening or similar symptoms must also be excluded (differential diagnosis is discussed later). Below is a summary of the key elements of organ assessment in a newly diagnosed SSc patient:

Lung evaluation: Every SSc patient should undergo assessment of lung function – typically spirometry with measurement of forced vital capacity (FVC) and diffusion capacity (DLCO). A reduced DLCO can be an early indicator of pulmonary involvement, especially developing pulmonary hypertension or incipient fibrosis (Volkmann et al., 2023). If spirometry or DLCO are abnormal (or if these parameters worsen over time), high-resolution CT of the lungs is indicated to detect interstitial fibrotic changes. In SSc, HRCT typically shows subpleural

reticular changes in the lower lobes, ground-glass opacities, or, in advanced fibrosis, honeycombing (Solomon et al., 2013). Multiple studies suggest that regular monitoring of FVC and DLCO and periodic HRCT (for example, every 6–12 months in the first years of disease) allows early detection of ILD progression and timely initiation of immunosuppressive therapy (Hoffmann-Vold et al., 2015). SSc patients should also undergo periodic plain chest X-rays (though in early fibrosis these may be normal) and a 6-minute walk test to assess exercise tolerance.

Heart and pulmonary circulation: The primary screening test for PAH is transthoracic echocardiography with estimation of the systolic pulmonary artery pressure (PASP) and assessment of right ventricular function. Echocardiography is performed at least annually in SSc patients, especially those with limited SSc of >3–5 years' duration, in line with expert recommendations (Bruni et al., 2020). If PAH is suspected (e.g. PASP >40–50 mmHg or other echocardiographic signs such as right atrial enlargement), the patient should be referred for confirmatory invasive hemodynamic measurement by right heart catheterization, the gold standard for PAH diagnosis. For earlier detection of PAH, risk score algorithms (such as the DETECT algorithm) have been developed, incorporating parameters like DLCO, NT-proBNP level, and clinical features – these help identify which patients should undergo catheterization (Young et al., 2021). In addition to echocardiography, every SSc patient should have periodic resting ECGs (to screen for arrhythmias or conduction blocks). If arrhythmia is suspected clinically, 24-hour Holter monitoring is recommended. Cardiac MRI is sometimes performed to evaluate myocardial fibrosis (late gadolinium enhancement can detect even subclinical myocardial involvement) (Bruni & Ross, 2021). In an acute disease course with suspected myocarditis, an endomyocardial biopsy may be considered.

Renal evaluation: Blood pressure should be monitored in every SSc patient – ideally daily by the patient at home. A sudden increase in blood pressure may signal the onset of renal crisis. Regular blood chemistry (creatinine, estimated GFR) and urinalysis are also recommended – new-onset proteinuria or hematuria can be early signs of SRC. If there is uncertainty about the cause of renal dysfunction, a kidney biopsy can be performed, although in a classic renal crisis scenario biopsy is usually avoided due to the risk of complications under severely elevated blood pressure (Mouthon et al., 2014). Measurement of plasma renin activity can be helpful – a dramatic rise in renin accompanies renal crisis (reflecting renal ischemia and activation of the renin-angiotensin system), providing an additional diagnostic clue (Mouthon et al., 2014).

Gastrointestinal evaluation: Diagnosis of GI involvement is mainly clinical (symptoms of dysphagia, reflux, abdominal pain, bowel movement disturbances). In cases of severe reflux symptoms, an upper endoscopy is performed, which often shows findings such as reflux esophagitis, ulcers, or strictures. Endoscopy can also identify GAVE lesions (fragile dilated vessels in the antrum). To evaluate esophageal motility disorders, manometry is useful – in SSc it typically shows greatly diminished peristalsis and hypotonia of the lower esophageal sphincter (McMahan, 2019). Intestinal transit can be assessed with a barium swallow study or, more modernly, a wireless motility capsule. If small intestinal bacterial overgrowth is suspected, hydrogen breath tests (e.g. lactulose breath test) are done. In cases of recurrent pseudo-obstruction episodes, prompt imaging (plain abdominal X-ray, CT of the abdomen) is advised to differentiate functional obstruction from mechanical causes.

Differential diagnosis: In evaluating SSc, one must exclude other conditions that cause skin hardening or similar features. Localized scleroderma (morphea) affects only the skin (no Raynaud's or internal organ involvement). Generalized idiopathic fibrosing disorders (sometimes termed MPOPS in Polish literature) or eosinophilic fasciitis (Shulman's syndrome)

also present with skin induration but without systemic features. Raynaud's phenomenon occurs in other connective tissue diseases (e.g. lupus, MCTD), but those lack sclerodactyly and the specific SSc autoantibodies. Generalized edema and skin induration can appear in a scleroderma-like drug reaction (e.g. from bleomycin or pentazocine) or as a paraneoplastic syndrome – therefore, in patients with an atypical SSc course (e.g. very rapid skin changes with negative ANA), an underlying malignancy should be considered (Stochmal et al., 2020). Disease-specific autoantibodies aid in the differential – their presence strongly supports an SSc diagnosis.

In summary, diagnosing systemic sclerosis requires correlating the clinical picture (characteristic skin changes, Raynaud's phenomenon, organ manifestations) with results of investigations (ANA and SSc-specific antibodies, capillaroscopy). Applying the 2013 ACR/EULAR criteria allows formal confirmation of the diagnosis even in the absence of full-blown disease (thanks to the point system that incorporates early features). Furthermore, assessment of organ involvement (lungs, heart, kidneys) at the initial diagnostic stage is crucial for planning appropriate therapy and determining prognosis.

Treatment

Management of systemic sclerosis is very challenging because the disease has a complex pathophysiology and diverse clinical manifestations. To date, no therapy can eliminate the underlying cause of SSc – treatment is largely symptomatic and disease-modifying, aimed at slowing fibrosis progression and preventing organ complications. Effective management requires a multidisciplinary approach involving a rheumatologist and relevant organ specialists (dermatologist, pulmonologist, cardiologist, nephrologist, gastroenterologist) depending on dominant manifestations (Volkmann et al., 2023). Patient education is also key, including avoidance of factors that exacerbate symptoms (e.g. cold exposure in Raynaud's), smoking cessation, and engagement in rehabilitation (exercises to improve joint mobility, pulmonary physiotherapy for lung involvement, etc.).

The treatment regimen is tailored to the disease subtype and the organs involved. In 2017, EULAR published recommendations for SSc treatment, and the latest update in 2023 (published in 2025) incorporates new targeted therapies and organizes management into 8 clinical domains (Raynaud's phenomenon, digital ulcers, pulmonary hypertension, skin fibrosis, lung disease, musculoskeletal involvement, gastrointestinal involvement, and renal crisis) (Del Galdo et al., 2025). The main therapeutic strategies are discussed below.

Immunosuppressive and Systemic Therapies

Because SSc involves immune dysregulation and an inflammatory process that drives fibrosis, immunosuppressive drugs are used to modify the disease course. They are particularly indicated in diffuse SSc with rapidly progressive skin changes and in patients with active internal organ involvement (lung, heart, muscle). The most commonly used agents include:

Cyclophosphamide (CYC): A classic alkylating agent. Its efficacy in scleroderma lung fibrosis was demonstrated in the randomized Scleroderma Lung Study I – one year of oral cyclophosphamide slowed the decline in lung capacity and modestly improved dyspnea compared to placebo (Tashkin et al., 2006). CYC is recommended for active interstitial lung disease with rapid progression, especially in patients with early diffuse SSc (Kowal-Bielecka et al., 2009). It is most often given intravenously in monthly pulses (e.g. 0.5–0.75 g/m² IV every 4 weeks for 6–12 months) to reduce cumulative toxicity compared to continuous oral dosing. In addition to its effects on lung function, cyclophosphamide has shown modest benefit in reducing skin thickening in patients with early, rapidly progressive diffuse cutaneous systemic sclerosis, as reflected by improvements in the modified Rodnan skin score (Tashkin et al., 2006). Its use is limited by side effects (myelosuppression, infections,

gonadotoxicity, hemorrhagic cystitis, secondary malignancy risk), so after disease stabilization it is often switched to a maintenance therapy with another agent (most commonly mycophenolate).

Mycophenolate mofetil (MMF): An inhibitor of purine synthesis that inhibits lymphocyte proliferation, with documented efficacy in SSc-ILD. The Scleroderma Lung Study II showed that 2 years of MMF (2–3 g/day) provided lung function improvement comparable to cyclophosphamide, with better tolerability (Tashkin et al., 2016). MMF has now become a first-line drug in many centers for scleroderma-associated pulmonary fibrosis. In addition, numerous reports indicate that mycophenolate also improves cutaneous symptoms (reduces skin thickening) – it is therefore recommended for progressive skin sclerosis as well (Del Galdo et al., 2025). The usual dose is about 2 g per day (divided into two doses). MMF has a more favorable safety profile than cyclophosphamide (its main side effects are gastrointestinal upset and leukopenia; serious opportunistic infections are less frequent). According to the newest 2024 EULAR recommendations, mycophenolate mofetil should be considered as a first-line treatment for both lung involvement and progressive skin disease in SSc patients (Del Galdo et al., 2025).

Methotrexate (MTX): An antimetabolite that is primarily used to treat skin manifestations in scleroderma. Randomized trials have shown moderate efficacy of MTX in improving skin thickening in patients with early diffuse SSc (Kowal-Bielecka et al., 2009). At weekly doses of 15–25 mg (orally or subcutaneously), MTX can slow progression of skin fibrosis. It is especially recommended for patients with prominent skin and joint involvement (inflammatory arthritis or tendon friction rubs) (Kowal-Bielecka et al., 2009). Its impact on internal organ involvement is limited, so in cases of significant lung fibrosis, MTX is generally second-line to MMF or CYC. Given its well-known safety profile (need for folic acid supplementation and monitoring of blood counts and liver enzymes), MTX is a valuable option in milder disease.

Glucocorticoids: The role of corticosteroids in scleroderma treatment is limited. Low doses may be used short-term in diffuse SSc (e.g. prednisone ≤10 mg daily) to alleviate inflammatory symptoms such as arthralgias, myalgias, or tendon friction pain (Kowal-Bielecka et al., 2009). However, long-term use of high-dose steroids (>15–20 mg prednisone daily) should be avoided due to the strong association with precipitating renal crisis – the mechanism is not fully understood but steroids likely increase sensitivity to angiotensin II and may mask early signs of rising blood pressure (Mouthon et al., 2014). Therefore, steroids are used with great caution, usually in combination with other immunosuppressants, and in more severe SSc it is preferable to use other immunosuppressive agents rather than high-dose glucocorticoids.

Biologic (Targeted) Therapies

In recent years, evidence has emerged for the efficacy of certain biologic agents in SSc, which has been reflected in new guidelines. In particular, rituximab (an anti-CD20 monoclonal antibody causing B-cell depletion) has shown in observational studies to improve both skin thickening and lung function in scleroderma. Meta-analyses suggest that rituximab may slow the decline in FVC and improve skin scores (mRSS), especially when therapy is started early in the disease course (Tang et al., 2020). The 2024 EULAR recommendations endorse rituximab as a treatment option for skin and lung fibrosis when standard therapy (MMF, CYC) is inadequate or contraindicated (Del Galdo et al., 2025). Rituximab dosing in SSc is similar to rheumatoid arthritis (e.g. 2 × 1000 mg IV infusions given 2 weeks apart, repeated every 6–12 months). Another biologic is tocilizumab – an anti-IL-6 receptor antibody. In a Phase 3 trial (the focuSSced trial) in patients with early, aggressive diffuse SSc, tocilizumab slowed

the decline of lung vital capacity (FVC) compared to placebo, although it did not meet the primary endpoint of significantly improving skin fibrosis (Khanna et al., 2020). s a result, tocilizumab became the first biologic agent approved specifically for systemic sclerosis with associated interstitial lung disease (Khanna et al., 2020). Guidelines suggest tocilizumab can be considered in patients with active inflammatory lung disease, especially if other therapies are insufficient (Del Galdo et al., 2025). The typical dose of tocilizumab in SSc is 162 mg subcutaneously once weekly. Additionally, studies are ongoing for other targets – e.g. co-stimulation blockade (abatacept, investigated for SSc arthritis), JAK inhibitors (like tofacitinib), and anti-TGFβ therapies (e.g. fresolimumab) – but these are not yet part of routine SSc care (Volkmann et al., 2023).

Antifibrotic Therapies

A breakthrough in recent years has been the use of nintedanib – a small-molecule tyrosine kinase inhibitor originally used in idiopathic pulmonary fibrosis. In the SENSCIS trial (2019), SSc-ILD patients treated with nintedanib had a significantly reduced rate of decline in FVC (by 44% relative to placebo, equating to ~41 mL less annual FVC loss) (Distler et al., 2019). Although nintedanib did not improve subjective symptoms or quality of life, its antifibrotic effect led to the drug's approval for treating SSc-associated lung fibrosis. Current guidelines recommend considering nintedanib in addition to immunosuppression for patients with progressive pulmonary fibrosis, especially if lung function worsens despite immunotherapy (Del Galdo et al., 2025). Nintedanib is given orally at 150 mg twice daily; its main side effects are diarrhea and an increased risk of bleeding. In treating skin fibrosis, antifibrotics have not yet found an established role, although trials are ongoing (e.g. therapies targeting the TGF-β pathway).

Autologous Stem Cell Transplantation (HSCT)

In very severe, rapidly progressive diffuse SSc, intensive immunosuppression with myeloablation and autologous hematopoietic stem cell transplantation (HSCT) has been utilized. Two large randomized trials (ASTIS and SCOT) showed that this approach leads to significant improvements in event-free and overall survival compared to standard cyclophosphamide therapy (van Laar et al., 2014; Sullivan et al., 2018). In the SCOT study, 54% of patients undergoing HSCT (with cyclophosphamide + radiation conditioning followed by autologous CD34+ stem cell transplant) were alive without disease progression at 72 months, versus 27% of those treated with cyclophosphamide alone (Sullivan et al., 2018). Some transplant patients even experienced regression of skin fibrosis and stabilization of lung function. However, this therapy carries substantial risk – the treatment-related mortality was around 5–10%, and some patients developed severe complications (infections, organ damage) (Sullivan et al., 2018). The latest guidelines specify that HSCT should be considered for carefully selected patients with early, aggressive diffuse SSc and poor prognosis who have not improved with induction therapy (e.g. cyclophosphamide) (Del Galdo et al., 2025). Possible indications include rapidly progressive skin involvement (rising mRSS) and significant organ involvement (lung, heart) within <3 years of disease onset, in the absence of contraindications (e.g. advanced lung, heart, or kidney damage precluding conditioning). HSCT offers a chance for long-term disease remission, but requires an individualized risk–benefit assessment for each patient.

Other Therapies

For skin involvement, phototherapy modalities have been tried – extracorporeal photopheresis (ECP) and UVA1 phototherapy. Some reports suggest that prolonged photopheresis (e.g. for 12 months) may modestly improve skin induration and inflammatory markers in some patients with diffuse SSc, but data are inconclusive (Knobler et al., 2014). UVA1

phototherapy (wavelength 340–400 nm) penetrates into deeper skin layers; small studies showed it can reduce skin thickness in localized scleroderma (morphea) and possibly provide some improvement in SSc acral sclerosis (Kreuter et al., 2004). These methods can be considered as adjuncts in selected patients with prominent skin disease, though they are not standard care. In cases of calcinosis (calcific deposits) – especially painful calcium nodules in the fingers – there is no highly effective pharmacotherapy; calcium channel blockers (e.g. diltiazem) or minocycline have been tried, but evidence of benefit is weak (Hsu et al., 2019). Large, troublesome calcific deposits sometimes require surgical removal, particularly if they cause chronic ulcers or recurrent infections.

Management of Raynaud's Phenomenon and Digital Ulcers

Controlling Raynaud's phenomenon and preventing ischemic digital ulcers is a crucial aspect of therapy that improves patients' comfort and reduces complications. Non-pharmacologic measures include avoiding cold exposure, smoking cessation (nicotine exacerbates vasospasm), keeping the hands warm (gloves, hand warmers), and avoiding stress and vasoconstrictive substances (e.g. caffeine, sympathomimetics) (Herrick, 2011). Pharmacologic treatment first-line is dihydropyridine calcium channel blockers – most commonly amlodipine or long-acting nifedipine. Nifedipine 30–60 mg/day reduces the frequency and severity of Raynaud's attacks in about two-thirds of patients (Herrick, 2011). Side effects (headache, hypotension, edema) can limit use, but overall these drugs are well tolerated. If a calcium channel blocker alone is insufficient, a phosphodiesterase type 5 (PDE-5) inhibitor is added – e.g. sildenafil (20 mg three times daily) or tadalafil (5–20 mg once daily). Studies have shown that sildenafil reduces the frequency of Raynaud's attacks and promotes healing of digital ulcers (Pauling et al., 2019). PDE-5 inhibitors improve digital blood flow and are useful in treating active ulcers by accelerating healing. An alternative or additional option is a prostacyclin analog – in severe Raynaud's with ulcers, intravenous iloprost infusions are used (e.g. 5–20 ng/kg/min over 6 hours daily for 5 consecutive days, repeated every 4–8 weeks) (Herrick, 2011). Iloprost has been shown to reduce pain and expedite healing of existing ulcers, and also to prevent new ulcers from forming. Drawbacks include the need for frequent infusions and side effects (headache, flushing, hypotension). To prevent ulcer recurrence, bosentan, an oral endothelin-1 receptor antagonist, has proven highly effective: in the RAPIDS-2 trial, bosentan reduced the number of new digital ulcers by about 50% compared to placebo over 6 months (Korn et al., 2004). Bosentan did not significantly accelerate healing of existing ulcers (for which prostanoids are better), but it is the only medication shown to effectively prevent ulcer recurrence. Bosentan is recommended for patients with recurrent, multiple digital ulcers despite standard therapy (calcium channel blockers, PDE-5 inhibitors, iloprost) (Kowal-Bielecka et al., 2009). The usual dosing is 62.5 mg twice daily for 4 weeks, then 125 mg twice daily, with mandatory liver enzyme monitoring (due to risk of hepatotoxicity). Other medications used in refractory Raynaud's include losartan (an angiotensin II receptor blocker – can modestly alleviate symptoms, especially in hypertensive patients) and SSRIs like fluoxetine – some data suggest a benefit in Raynaud's severity, though the mechanism is unclear (Pauling et al., 2019).

In cases of digital ischemic necrosis, conservative measures may be insufficient – procedural interventions can be necessary. Sympathectomy is used, for example periarterial digital sympathectomy or cervicothoracic sympathectomy, to achieve lasting vasodilation in the distal extremities. This can provide relief in the most refractory cases, though the effect may be temporary and complications (sensory loss, infection) can occur. Alternatively, sympathetic nerve blocks (e.g. stellate ganglion blocks) with local anesthetics can produce a few weeks of improved perfusion. If frank gangrene develops, unfortunately amputation of necrotic

fingertips may be required. In summary, aggressive management of vasospasm – using calcium channel blockers, PDE-5 inhibitors, prostacyclins, and bosentan – is standard in SSc, as it not only improves quality of life but also reduces complication rates (fewer bone and soft tissue infections from ulcers, fewer amputations).

Management of Pulmonary Arterial Hypertension (PAH)

SSc-related PAH (SSc-PAH) requires specialized therapy, analogous to idiopathic PAH, though the prognosis in SSc-PAH is worse than idiopathic PAH, so early and intensive treatment is indicated (Chung et al., 2014). The cornerstone of therapy is vasodilators and agents that inhibit vascular remodeling. Three main classes of drugs are used, often in combination:

Endothelin receptor antagonists (ERAs): bosentan, ambrisentan, macitentan. These block the effects of endothelin-1 (a potent vasoconstrictor). They improve exercise capacity and hemodynamics; additionally, bosentan – as noted – helps prevent digital ulcers. In SSc-PAH, ERAs are often first-line therapy (e.g. macitentan 10 mg daily). Liver monitoring is required (especially with bosentan). ERAs have been shown to improve exercise tolerance (6-minute walk test distance) and delay PAH progression in SSc (Chung et al., 2014).

PDE-5 inhibitors and sGC stimulators: Sildenafil and tadalafil (PDE-5 inhibitors) increase NO availability in pulmonary vessels, causing vasodilation. They improve exercise capacity and quality of life in PAH. Riociguat (a soluble guanylate cyclase stimulator) also targets the NO pathway via direct sGC activation. In practice, therapy is often initiated with a combination of an ERA + a PDE-5 inhibitor (so-called upfront combination therapy), which studies (e.g. the AMBITION trial) have shown yields better outcomes than monotherapy in patients with moderate-to-severe PAH (Galie et al., 2015). The latest guidelines advocate early use of combination therapy in SSc-PAH due to the aggressive disease course (Del Galdo et al., 2025).

Prostacyclin analogs and IP receptor agonists: Epoprostenol (continuous IV infusion), treprostinil (IV, subcutaneous infusion or inhaled), iloprost (inhaled), and the newer oral IP receptor agonist selexipag. These drugs strongly dilate pulmonary vessels and inhibit platelet aggregation. IV epoprostenol significantly prolongs survival in idiopathic PAH and is the gold standard for NYHA class III–IV disease. In SSc-PAH, epoprostenol is also used, though it can be harder to tolerate (risks from indwelling catheter, hypotension). Often in SSc-PAH a prostacyclin is added if oral ERA + PDE-5i therapy does not adequately control the disease, or if the patient presents in advanced functional class (Chung et al., 2014).

Management of PAH also includes general measures: pulmonary rehabilitation, supplemental oxygen for hypoxemia, and diuretics for right heart failure. Unlike idiopathic PAH, long-term anticoagulation is not routinely recommended in SSc-PAH – studies have not shown clear benefit, and SSc patients have an elevated bleeding risk (e.g. from GI telangiectasias and GAVE lesions) (Del Galdo et al., 2025). If PAH progresses to end-stage despite medical therapy, lung transplantation may be the only option – however, listing SSc patients for transplant is complicated by co-morbid issues (e.g. renal, cardiac involvement, severe reflux that can damage the transplanted lungs).

Management of Interstitial Lung Disease (ILD)

The approach to SSc-ILD overlaps with the immunosuppressive treatments discussed above. The primary goal is to halt progression of lung fibrosis and preserve pulmonary function.

Immunosuppression: As noted, mycophenolate mofetil is now often first-line for slower-progressing SSc-ILD, while cyclophosphamide is used in severe or rapidly progressive cases (e.g. marked FVC decline over a short period) (Tashkin et al., 2006; Distler et al., 2019).

Frequently, patients are induced with cyclophosphamide and then transitioned to long-term maintenance therapy with MMF. Low-dose corticosteroids can be used as an adjunct in ILD, but by themselves they do not stop fibrosis, and doses above 15 mg/day are risky (renal crisis), so they are used cautiously. In refractory cases or if CYC/MMF are contraindicated, rituximab is an option – retrospective studies have shown it can improve pulmonary function (FVC) in SSc-ILD (Tang et al., 2020).

Nintedanib: This is added for patients with progressive fibrosis despite immunosuppressive therapy, and is also being considered earlier in those with active fibrotic changes on HRCT at therapy initiation. In practice, many patients with SSc-ILD now receive combination therapy – an immunosuppressant (e.g. MMF) plus nintedanib – which provides complementary actions (simultaneous anti-inflammatory and anti-fibrotic effects) (Distler et al., 2019).

Tocilizumab: In cases where there is an "inflammatory" ILD phenotype (elevated CRP, features of alveolitis) and a rapid decline in DLCO, tocilizumab may be considered. In the focuSSced trial, patients on tocilizumab had less FVC loss than placebo, especially if baseline inflammatory markers were high (Khanna et al., 2020). Therefore, tocilizumab can be an option in early (<5 years) SSc with an inflammatory ILD profile, even though regulatory approval is for SSc-ILD in general. The dose in SSc-ILD is usually 162 mg subcutaneously weekly.

Oxygen and rehabilitation: For advanced fibrosis with hypoxemia, home oxygen therapy is indicated (e.g. if resting PaO_2 <55 mmHg). Pulmonary rehabilitation (exercise training) is recommended to improve endurance. Adjunctive treatments such as mucolytics (e.g. N-acetylcysteine) can be given if the patient has difficulty clearing secretions.

Lung transplantation: In select patients with end-stage lung disease (severe respiratory failure) and no major contraindications (e.g. no severe cardiac or renal involvement), referral for lung transplant evaluation can be considered. Five-year survival after lung transplantation for SSc-ILD is approximately 50%, which can significantly extend life for some patients (Miele et al., 2016). However, eligibility is often a challenge in SSc due to issues like renal impairment or severe GERD that can complicate post-transplant outcomes.

Management of Scleroderma Renal Crisis

Scleroderma renal crisis is a medical emergency requiring intensive inpatient management. The treatment of choice is angiotensin-converting enzyme (ACE) inhibitors – classically captopril, which has a rapid onset and short duration (facilitating dose titration). Captopril is started at 12.5–25 mg every 8 hours, with dose escalation every 1–2 days as needed if blood pressure remains high (Mouthon et al., 2014). The goal is to achieve control of blood pressure as quickly as possible (<140/90 mmHg), often requiring high doses (captopril >150 mg/24h). The introduction of ACE inhibitors in the 1980s dramatically improved outcomes – their use in SRC raised one-year survival from ~15% to >75% (Mouthon et al., 2014). ACE inhibitors work by dilating renal arterioles, reducing glomerular hyperfiltration, and interrupting the angiotensin II–norepinephrine cycle in the crisis. If ACE inhibitors are not tolerated or sufficient, an angiotensin II receptor blocker (ARB) or another antihypertensive (e.g. IV sodium nitroprusside in hypertensive emergencies) can be added. Loop diuretics are generally avoided at the outset (they may further activate the renin-angiotensin system), and beta-blockers are avoided as they might worsen peripheral perfusion. About 50% of patients with SRC require dialysis support during the acute kidney injury (Penn et al., 2007). Remarkably, in ~20–40% of SRC patients on dialysis, renal function recovers after several months – a unique phenomenon (in idiopathic malignant hypertension such spontaneous renal recovery is not seen) (Penn et al., 2007). Therefore, in SRC, ACE inhibitors are continued even if dialysis is needed, in hopes of later renal improvement and cessation of dialysis. However, if after 1–2

years the kidneys have not regained function, renal transplantation is considered – outcomes after kidney transplant are relatively good in SSc, although there is a small risk of SRC recurrence in the allograft (Cole et al., 2023). Preventing renal crisis mainly involves avoiding high-dose corticosteroids in SSc patients and closely monitoring blood pressure. Prophylactic ACE inhibitor use before SRC is not recommended, as studies suggest it does not prevent the crisis and may delay its recognition by masking rising blood pressure (and possibly exacerbating renin activation) (Mouthon et al., 2014).

Management of Gastrointestinal Involvement

Treatment of gastrointestinal manifestations in SSc is symptomatic and focused on managing complications. Key measures include:

Gastroesophageal reflux: Proton pump inhibitors (PPIs) at high doses are the standard therapy. Often twice-daily dosing is necessary (e.g. omeprazole 20–40 mg b.i.d.). If symptoms are refractory, an H_2 blocker at night can be added. Lifestyle and dietary modifications are advised (avoiding lying down after meals, elevating the head of the bed, avoiding fatty foods, caffeine, alcohol). In cases of severe reflux with erosive esophagitis despite PPIs, anti-reflux surgery (fundoplication) may be considered – though outcomes can be less optimal in SSc due to underlying motility dysfunction. PPI therapy also serves to prevent aspiration pneumonia and progression of pulmonary fibrosis (by reducing chronic microaspiration).

Esophageal dysmotility: In addition to PPIs, prokinetic agents are used to improve peristalsis – such as metoclopramide (used cautiously due to extrapyramidal side effects), domperidone, or itopride. In severe aperistalsis of the esophagus, the efficacy of these drugs is limited. Nitrates or sildenafil may provide some improvement in esophageal emptying by relaxing the lower esophageal sphincter. In extreme dysphagia, enteral feeding via jejunostomy or a PEG tube may be needed.

Intestinal dysmotility and bacterial overgrowth: The cornerstone is antibiotic therapy for bacterial overgrowth – e.g. rifaximin, neomycin, or metronidazole – often rotated every few weeks to control small intestinal bacterial overgrowth (SIBO) (McMahan, 2019). Supportive use of prokinetics to enhance bowel motility includes metoclopramide, domperidone, and in refractory cases cisapride (available on a limited basis) or low-dose erythromycin (acts as a motilin agonist). Newer agents like prucalopride (a 5-HT4 agonist) can help severe constipation. Diet is important – a diet rich in soluble fiber is recommended, and a lactose-free diet may be needed for secondary lactose intolerance. In cases of malnutrition, nutritional supplementation is provided, and in extreme cases, total parenteral nutrition may be required. Pseudo-obstruction is managed conservatively with bowel decompression (nasogastric tube), IV fluids and electrolytes, and sometimes neostigmine infusions to stimulate colonic motility during acute episodes (Downes et al., 2018). Recurrent episodes may necessitate a surgical venting ostomy (e.g. an ileostomy) to relieve intestinal pressure.

Gastric antral vascular ectasia (GAVE): Recurrent bleeding from “watermelon stomach” lesions requires endoscopic therapy – most often laser or argon plasma coagulation (APC) of the dilated antral vessels. PPIs and hormonal therapy (estrogen-progesterone) have been tried, but endoscopic treatment is most effective (Ghrénassia et al., 2014).

Rectal involvement and incontinence: Anti-diarrheal medications (like loperamide) can help with stool frequency. Pelvic floor exercises and biofeedback may improve continence. In severe refractory fecal incontinence, sacral nerve stimulation or ultimately a diverting colostomy can be considered.

Nutrition: Diffuse SSc often causes weight loss due to increased energy expenditure and malabsorption. Nutritional status should be assessed and calories/vitamins supplemented (especially fat-soluble vitamins if malabsorption is present). Common deficiencies in SSc

include vitamin D, iron (from chronic occult GI bleeding), and vitamin B12 (consumed by bacterial overgrowth) – these should be corrected (Nguyen et al., 2022). It is worth noting that treating GI complications in SSc can be challenging – often multiple approaches must be combined and regular monitoring is needed (e.g. periodic endoscopies to dilate esophageal strictures or coagulate GAVE lesions). Nonetheless, appropriate gastroenterological care significantly improves the comfort and nutritional status of SSc patients.

Conclusions

Systemic sclerosis is a rare but severe autoimmune disease characterized by progressive fibrosis, vascular abnormalities, and immune-mediated organ damage. The condition continues to carry high morbidity and mortality, particularly due to pulmonary, renal, and cardiac complications (Allanore et al., 2015; Elhai et al., 2017). However, recent advances in diagnostic criteria and therapeutic strategies have significantly improved the clinical course and long-term outlook for many patients.

Early diagnosis is a cornerstone of effective disease management. The application of the ACR/EULAR 2013 classification criteria allows identification of systemic sclerosis even in its initial stages, particularly when features such as Raynaud's phenomenon, sclerodactyly, and autoantibody positivity are present (van den Hoogen et al., 2013). Moreover, the concept of very early diagnosis (VEDOSS) supports identification of patients at risk before overt systemic features develop (Avouac et al., 2011).

Optimal management requires a combination of systemic immunosuppressive therapy and organ-specific interventions. Mycophenolate mofetil has emerged as a first-line agent in both interstitial lung disease and progressive skin sclerosis due to its favorable efficacy and safety profile (Distler et al., 2019; Del Galdo et al., 2025). Cyclophosphamide remains a valid option in aggressive or advanced pulmonary involvement (Tashkin et al., 2006), while targeted therapies such as rituximab and tocilizumab offer alternatives for refractory or rapidly progressing cases (Del Galdo et al., 2025). Antifibrotic therapy with nintedanib has opened new prospects for slowing pulmonary fibrosis (Distler et al., 2019), and autologous stem cell transplantation provides a potential disease-modifying approach in selected patients with diffuse cutaneous forms (van Laar et al., 2014).

In addition to pharmacologic treatment, comprehensive care addressing vasculopathy, gastrointestinal symptoms, digital ulcers, and psychological support is critical to improving quality of life. Effective management of pulmonary hypertension, renal crisis, and gastrointestinal involvement further contributes to improved outcomes (Mouthon et al., 2014; Herrick, 2011; Chung et al., 2014). Patients benefit significantly from multidisciplinary follow-up that includes pulmonary, cardiology, rheumatology, and rehabilitation input.

Although systemic sclerosis remains incurable, the combination of early recognition, appropriate monitoring, and personalized therapy offers a realistic opportunity to slow disease progression, reduce organ damage, and enhance patients' functional status and survival. Ongoing research into disease mechanisms and the development of new biologic and antifibrotic treatments remain essential to further improve patient outcomes and bring therapeutic strategies closer to disease modification and remission.

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