Methotrexate was associated with a modest skin improvement in small studies. Mycophenolate mofetil treatment was associated with improved skin induration in uncontrolled studies and was generally well tolerated. Small studies support the use of rituximab in SSc patients with skin involvement and ILD. The use of cyclosporine, azathioprine, extracorporeal photopheresis, thalidomide, rapamycin, imatinib, and IV immunoglobulin is currently not well supported by the literature. Intensive immune ablation using a conditioning regimen of high-dose chemotherapy with or without irradiation, followed by autologous stem cell reconstitution, has resulted in durable disease remission in some cases and is undergoing evaluation in randomized clinical trials. In light of its potential morbidity and mortality, as well as significant cost, autologous stem cell transplantation in SSc is still considered experimental.

**Antifibrotic Therapy** Because widespread tissue fibrosis in SSc causes progressive organ damage, drugs that interfere with the fibrotic process represent a rational therapeutic approach. D-Penicillamine has been extensively used as an antifibrotic agent. In retrospective studies, D-penicillamine stabilized and improved skin induration, prevented new internal organ involvement, and improved survival. However, a randomized controlled clinical trial in early active SSc found no difference in the extent of skin involvement between patients treated with standard-dose (750 mg/d) or very low-dose (125 mg every other day) D-penicillamine. Recent clinical trials show benefit of pirfenidone and of nintedanib in patients with idiopathic pulmonary fibrosis, with significant slowing of the loss of lung function. Whether these two new drugs will have comparable efficacy in the treatment of SSc-associated lung disease is still under investigation.

**Vascular Therapy** The goal of therapy is to control Raynaud's phenomenon, prevent the development and enhance the healing of ischemic complications, and slow the progression of obliterative vasculopathy. Patients should dress warmly, minimize cold exposure or stress, and avoid drugs that precipitate or exacerbate vasospastic episodes. Some patients with Raynaud's may respond to biofeedback therapy. Extended-release dihydropyridine calcium channel blockers such as nifedipine, amlodipine, or diltiazem can ameliorate Raynaud's phenomenon, but their use is often limited by side effects (palpitations, dependent edema, worsening gastroesophageal reflux). While ACE inhibitors do not reduce the frequency or severity of episodes, angiotensin II receptor blockers such as losartan are effective and generally well tolerated. Patients with Raynaud's phenomenon unresponsive to these therapies may require the addition of $\alpha_1$-adrenergic receptor blockers (e.g., prazosin), 5-phosphodiesterase inhibitors (e.g., sildenafil), serotonin reuptake inhibitors (e.g., fluoxetine), topical nitroglycerine, and intermittent infusions of IV prostaglandins. Low-dose aspirin and dipyridamole prevent platelet aggregation and may have a role as adjunctive agents. In patients with ischemic ulcers, the endothelin-1 receptor antagonist bosentan reduces the risk of new ulcers. Digital sympathectomy and local injections of botulinum type A (Botox) into the digits are options in patients with severe ischemia and impending loss of the digits. Empirical long-term therapy with statins and antioxidants may retard the progression of vascular damage and obliteration. Vasodilators such as ACE inhibitors, calcium channel blockers, and endothelin receptor blockers may also improve myocardial perfusion and left ventricular function.

**TREATMENT OF GASTROINTESTINAL COMPLICATIONS** Because oral problems including decreased oral aperture, decreased saliva production, gum recession and periodontal disease leading to teeth loss are common, regular dental care is recommended. Gastroesophageal reflux is very common and may occur in the absence of symptoms; therefore all patients with SSc should be treated. Patients should be instructed to elevate the head of the bed, eat frequent small meals, and avoid oral intake before bedtime. Proton pump inhibitors reduce acid reflux and may need to be given in relatively high doses. Prokinetic agents such as domperidone may be helpful, especially if delayed gastric emptying is present. Episodic gastrointestinal bleeding from gastric antral vascular ectasia (watermelon stomach) may be amenable to treatment with endoscopic laser photocoagulation, although recurrence can occur. Bacterial overgrowth due to small-bowel dysmotility causes abdominal bloating and diarrhea and may lead to malabsorption and severe malnutrition. Treatment with short courses of rotating broad-spectrum antibiotics such as metronidazole, erythromycin, and tetracycline can eradicate bacterial overgrowth. Parenteral hyperalimentation is indicated if malnutrition develops. Chronic hypomotility of the small bowel may respond to octreotide, but pseudo-obstruction is difficult to treat. Fecal incontinence, a frequently underreported complication of SSc, may respond to anti-diarrheal medication and biofeedback therapy.

**TREATMENT OF PULMONARY ARTERIAL HYPERTENSION (PAH)** In patients with SSc, PAH carries an extremely poor prognosis and accounts for 30% of deaths. Because PAH is asymptomatic until advanced, patients with SSc should be screened for its presence at initial evaluation, and on a yearly basis thereafter. Treatment is generally started with an oral endothelin-1 receptor antagonist such as bosentan or a phosphodiesterase type 5 inhibitor such as sildenafil. Patients may also require diuretics and digoxin when appropriate. If hypoxemia is documented, supplemental oxygen should be prescribed in order to avoid hypoxia-induced secondary pulmonary vasoconstriction. Prostacyclin analogues such as epoprostenol or treprostinil can be given by continuous IV or SC infusion, or via intermittent nebulized inhalations. Combination therapy with different classes of agents, such as an endothelin-1 antagonist and a phosphodiesterase inhibitor, is often necessary. Lung transplantation remains an option for selected patients who fail medical therapy.

**TREATMENT OF RENAL CRISIS** Scleroderma renal crisis is a medical emergency. Since the outcome is largely determined by the extent of renal damage present at the time that aggressive therapy is initiated, prompt recognition of impending or early scleroderma renal crisis is essential, and efforts should be made to avoid its occurrence. High-risk SSc patients with early disease, extensive and progressive skin involvement, tendon friction rubs, and anti-RNA polymerase III antibodies should be instructed to monitor their blood pressure daily and report significant alterations immediately. Potentially nephrotoxic drugs should be avoided, and glucocorticoids should be used only when absolutely necessary and at low doses. Patients presenting with scleroderma renal crisis should be immediately hospitalized. Once other causes of renal disease are excluded, treatment should be started promptly with titration of short-acting ACE inhibitors, with the goal of achieving rapid normalization of the blood pressure. In patients with hypertension persisting despite ACE inhibitor therapy, addition of angiotensin II receptor blockers, calcium channel blockers, and direct renin inhibitors should be considered. Anecdotal evidence indicates responses to endothelin-1 receptor blockers and prostacyclins. Up to two-thirds of patients with scleroderma renal crisis go on to dialysis. The outcome of scleroderma renal crisis is worse in patients with antibodies to topoisomerase I compared to those with antibodies to RNA polymerase III. Substantial renal recovery can occur following scleroderma renal crisis, and dialysis can be discontinued, in 30–50% of the patients. Kidney transplantation is appropriate for those unable to discontinue dialysis after 2 years. Survival of transplanted SSc patients is comparable to that of patients with other connective tissue diseases, and recurrence of renal crisis is rare.

**SKIN CARE** Because skin involvement in SSc is never life-threatening and because it stabilizes and may even regress spontaneously, over time, the management of SSc should not be dictated by its cutaneous manifestations. The inflammatory symptoms of early skin involvement can be controlled with antihistamines and cautious short-term use of low-dose glucocorticoids (<5 mg/d of prednisone). Retrospective studies have shown that D-penicillamine