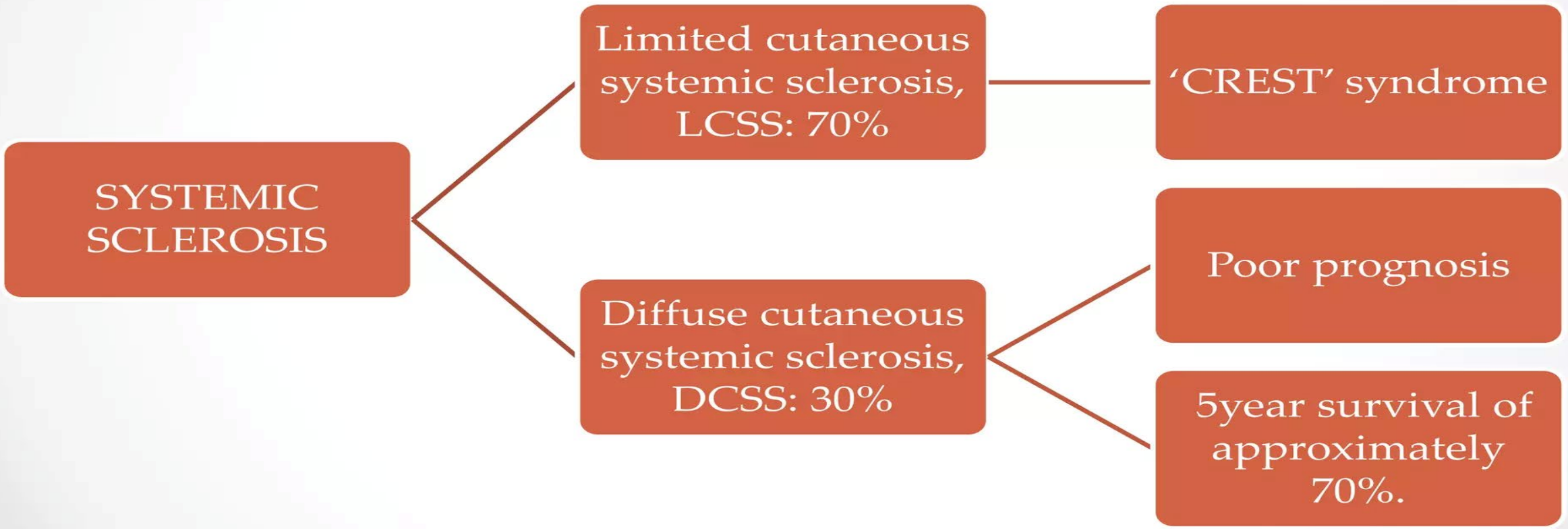
Gastrointestinal manifestations of systemic sclerosis

systemic sclerosis

- Introduction :

TYPE

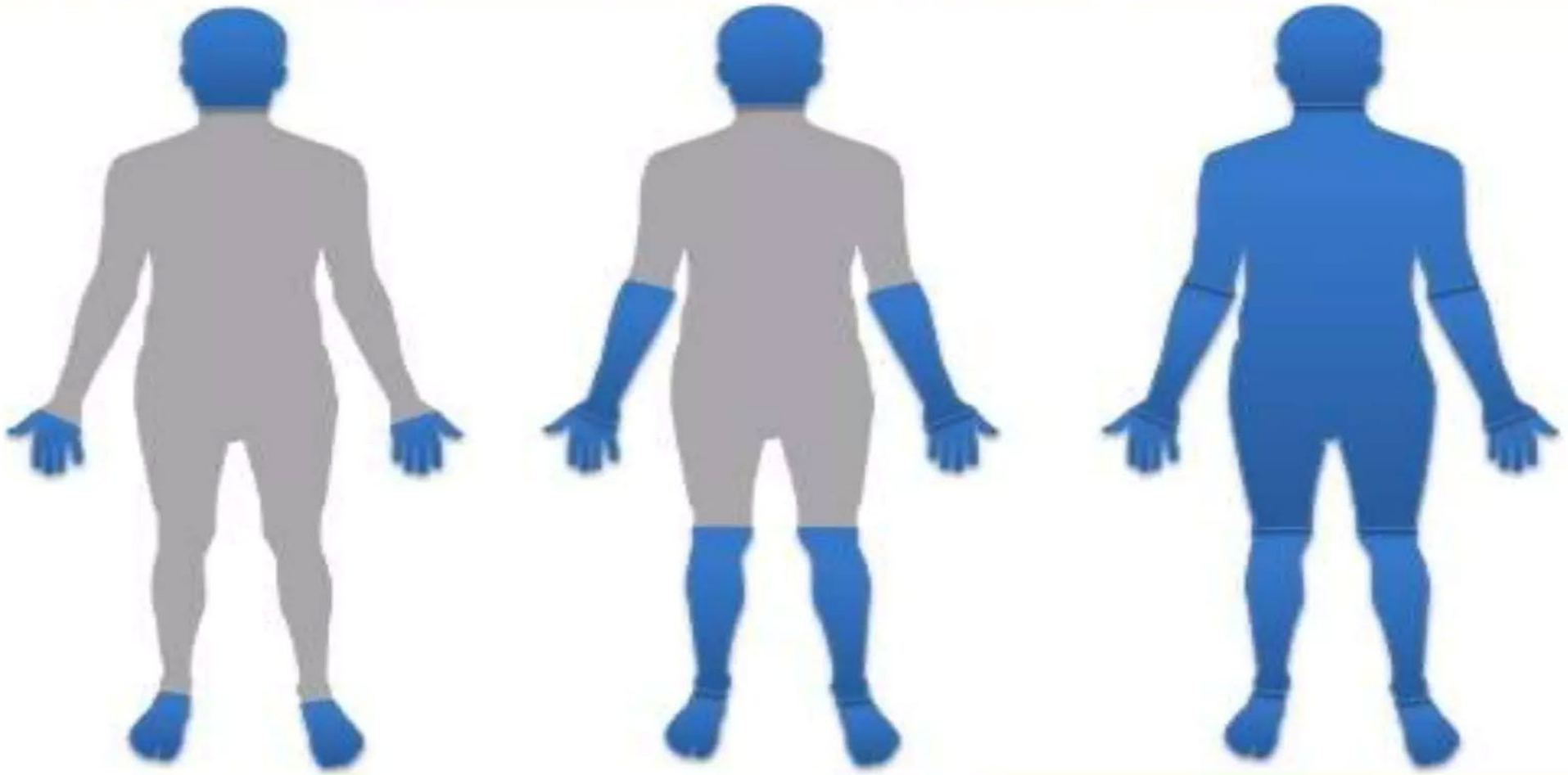

SYSTEMIC SCLEROSIS
Limited cutaneous systemic sclerosis, LCSS: 70%
'CREST' syndrome
Diffuse cutaneous systemic sclerosis, DCSS: 30%
Poor prognosis
5year survival of approximately 70%.

Diffuse vs Limited Scleroderma-- Definitions

- **Diffuse cutaneous scleroderma:**
  - Thick skin distal AND proximal to elbows and knees, with or without the face (widespread, or diffuse, skin thickening).

- **Limited cutaneous scleroderma:**
  - Thick skin distal, but NOT proximal, to elbows and knees, with or without the face (limited skin thickening)

Scleroderma: Classification and Clinical Subsets



Limited cutaneous/lcSSc

Diffuse cutaneous/dcSSc

distal

intermediate

Slide courtesy of Francesco Boin, MD

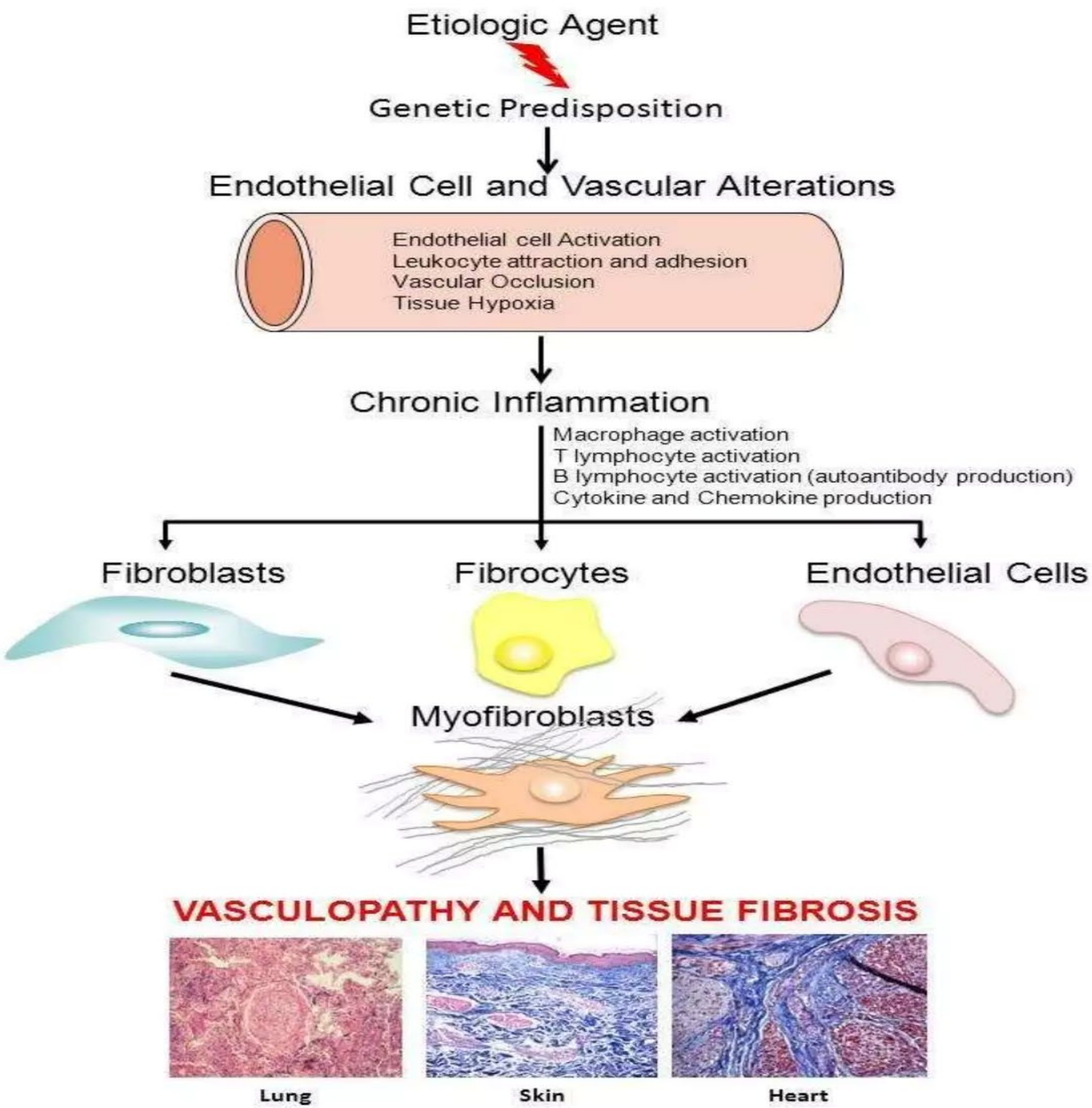
Diffuse vs Limited Scleroderma -Distinguishing Features-

Diffuse

- Lung fibrosis (severe in 15%)
- Heart (severe in 10%)
- Kidney (severe in 15-20%)
- Large joint contractures
- Disability, fatigue, MSK pains

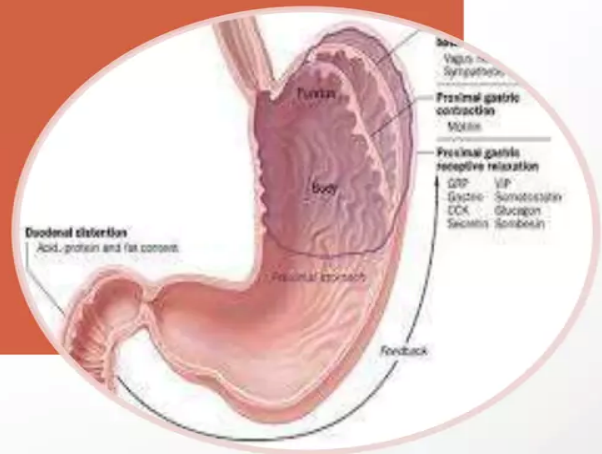
Limited

- Lung fibrosis (severe in 15%)
- Minimal heart
- Minimal kidney
- Late: Pulmonary hypertension (~15%)
- Late: Primary biliary cirrhosis (6-8%)


Etiologic Agent
Genetic Predisposition
Endothelial Cell and Vascular Alterations
Endothelial cell Activation
Leukocyte attraction and adhesion
Vascular Occlusion
Tissue Hypoxia
Chronic Inflammation
Macrophage activation
T lymphocyte activation
B lymphocyte activation (autoantibody production)
Cytokine and Chemokine production
Fibroblasts
Fibrocytes
Endothelial Cells
Myofibroblasts
VASCULOPATHY AND TISSUE FIBROSIS
Lung
Skin
Heart

Gastrointestinal involvement

- Smooth muscle atrophy and fibrosis in the lower two thirds of the oesophagus lead to reflux with erosive oesophagitis.
- Dysphagia and odynophagia may also occur.
- Involvement of the stomach causes early satiety and occasionally outlet obstruction.
- Recurrent occult upper gastrointestinal bleeding may indicate a 'watermelon' stomach (antral vascular ectasia), which occurs in up to 20% of patients.
- Small intestine involvement may lead to malabsorption due to bacterial overgrowth and intermittent bloating, pain or constipation.
- Dilatation of large or small bowel due to autonomic neuropathy may cause pseudo-obstruction with nausea, vomiting, abdominal discomfort and distension, often worse after food.

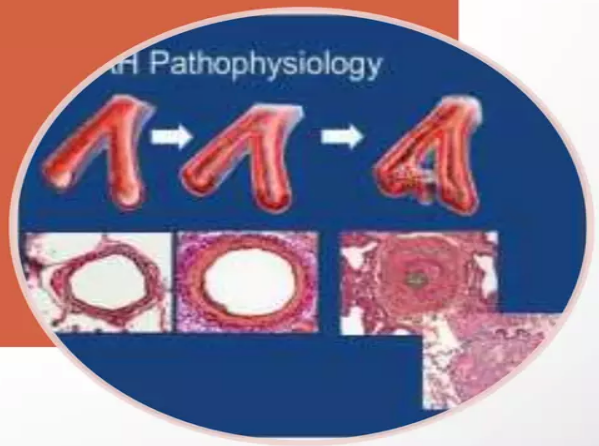


GASTROINTESTINAL INVOLVEMENT :

- The gastrointestinal tract (GI) is the second most affected organ system in individuals suffering from systemic/localized scleroderma (SSc) or localized scleroderma.
- SSc can affect any part of the GI, between the oral cavity and anorectum.
- Females are 5 times more likely than males to suffer from SSc. Morbidity and mortality rates associated with SSc are predominantly elevated among patients with GI manifestations.
- SSc patients may suffer from gastrointestinal complications that can negatively impact their quality of life on a daily basis.

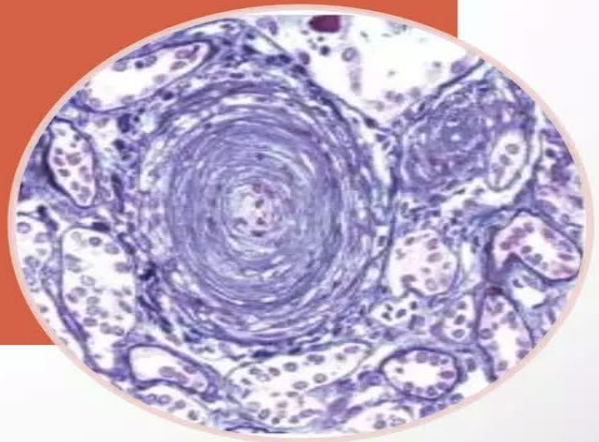
- Major cause of morbidity and mortality.
- Pulmonary hypertension complicates long-standing disease common in LCSS than in DCSS.
- It presents with rapidly progressive dyspnoea (more rapid than interstitial lung disease), right heart failure and angina, often in association with severe digital ischaemia.
- Fibrosing alveolitis mainly affects patients with dcss who have topoisomerase 1 antibodies

Pulmonary involvement



- Main causes of death is hypertensive renal crisis,
- Characterised by rapidly developing malignant hypertension and renal failure.
- Hypertensive renal crisis is much more likely to occur in DCSS than in LCSS, and in patients with topoisomerase 1 antibodies

Renal involvement



Clinical features

6. heart (10%)

1) pericarditis

2) heart failure

3) arrhythmia

4) myocardial fibrosis

small intestinal bacterial overgrowth (SIBO)

- gold standard relies on the microbial culture of jejunal aspirates.
- The diagnostic affirmation depends on the finding of $>10^3$ colony factor unit.
- The hydrogen (glucose or lactulose) and methane breath tests are largely utilized in clinical settings due to their noninvasive nature and easy availability.
- The positivity of the breath test relies on the hydrogen concentration of ≥ 20 parts per million during the 90 minutes glucose or lactulose challenge and an increase in methane levels to ≥ 10 parts per million.[65]
- The breath test's 60% sensitivity and 80% specificity make it a favorable diagnostic option for SIBO assessment.[66,67]
- The majority of the SSc patients exhibit nutritional deficiency, malnutrition, and weight loss, requiring evidence-based management via nutritional support and hydration.
-

CLINICAL FEATURES

- **Clinical presentation** — The majority of patients with SIBO present with bloating [21]. Other common symptoms include flatulence, abdominal discomfort, or chronic watery diarrhea. It is important to remember that traditional SIBO was associated with post-surgical anatomy such as blind loop syndrome. However, it is increasingly recognized that SIBO is a potential cause of irritable bowel syndrome (IBS), functional dyspepsia, gastroparesis, chronic pancreatitis, etc [22] and, in these cases, malabsorption is less common.

small intestinal bacterial overgrowth consequence :

- **Vitamin deficiency and excess –**
- Vitamin B12 deficiency in SIBO results from several different mechanisms. Although enteric bacteria synthesize cobalamin, they also successfully compete with the host for its absorption.
- In patients with severe SIBO, malabsorption of vitamin B12 results from mucosal damage to the ileal binding site. Only anaerobes can utilize vitamin B12 coupled to intrinsic factor. Thiamine and nicotinamide deficiency also result from bacterial utilization.
- In contrast, folate and vitamin K levels are elevated in SIBO due to bacterial synthesis. Increased intestinal permeability also contributes to increased vitamin K levels.

Organ involvement in scleroderma

- Most prominent are abnormalities of the circulation (most notably Raynaud phenomenon) and involvement of multiple organ systems,
- including the musculoskeletal
- , renal,
- pulmonary,
- cardiac,
- gastrointestinal (GI) systems, with fibrotic and/or vascular complications.

GI symptoms can cause significant morbidity .

-

EPIDEMIOLOGY

90 percent of patients with systemic sclerosis (SSc) have some degree of gastrointestinal (GI) involvement,

one-half are symptomatic .

Involvement of the gut occurs with equal frequency among patients with the diffuse and limited subtypes of SSc (dcSSc and lcSSc, respectively) . It is rare in localized scleroderma syndromes

GI involvement:

- The esophagus is the most frequently affected part of the GI tract, any part of the GI tract may be involved.
- The presence of malabsorption and esophageal dysfunction among patients with SSc is associated with an unfavorable prognosis because they can exacerbate other manifestations of the disease, notably lung fibrosis due to microaspiration and cardiac manifestations due to poor nutrition and electrolyte abnormalities
- Studies consistently identify GI involvement as a risk factor for early death in diffuse cutaneous SSc, particularly those with poor nutrition or severe midgut disease .

Which patient are prone to GI involvement

- As for other major complications of SSc, there are emerging associations with the hallmark diagnostic autoantibodies, especially anticentromere antibodies (ACA) and antibodies directed against ribonucleic acid (RNA) polymerase III (ARA) reactivity for higher GI symptom scores, which can help identify patients at higher risk early in the course of disease .

PATHOGENESIS Sjögren theory

- the disease begins with an initial neural disorder, progresses to muscle dysfunction, and ends with fibrosis. Early neural dysfunction may be a consequence of collagen deposits causing vascular derangement, compression of the nerves, or autoimmune-mediated injury
- The second stage of small bowel disease occurs with smooth muscle atrophy. Most patients present with symptoms at this stage. This is followed by the final stage of muscle fibrosis. At this point, the muscle is incapable of responding to stimuli and pharmacologic restoration of function is no longer possible.
- Interplay with the gut microbiome is also emerging as a potentially relevant factor, including evidence of dysbiosis early in the disease course [28], that may influence clinical impact, but the precise role in pathogenesis remains uncertain

- Another possible mechanism underlying GI disease in SSc is related to altered transforming growth factor (TGF)-beta signaling.

GI involvement :

- **Oropharyngeal dysphagia**
- Oropharyngeal dysphagia in SSc results from involvement of the oral and perioral tissues. Patients develop narrowing of the oral aperture, as well as rigidity and thinning of the soft palate, larynx, and oral mucosa (which may also become tender). Extrinsic pressure from skin changes may cause resorption of alveolar bone and malalignment of teeth.

ESOPHAGEAL INVOLVEMENT

- Esophageal dysfunction is present in 50 to 80 percent of patients with systemic sclerosis
- SSc leads to atrophy of the smooth muscle in the lower two-thirds of the tubular esophagus and the lower esophageal sphincter. On pathologic examination, the muscle of the lower esophagus may be partly replaced by fibrous tissue.
- However, esophageal muscle dysfunction in SSc may be secondary to a neuronal abnormality rather than excessive collagen deposition
- The incompetent lower esophageal sphincter leads to gastroesophageal reflux. Hypotensive peristaltic contractions in the esophagus are associated with ineffective esophageal transit and prolonged esophageal exposure to gastric acid. Acid reflux may result in reflux esophagitis and subsequent stricture formation. Patients with longstanding reflux may develop Barrett's esophagus; however, esophageal adenocarcinoma appears to be rare in SSc . The upper skeletal muscle portion of the esophagus is rarely involved, although thickening of the pharyngoesophageal muscles with collagenous tissue has been reported

Esophageal motility disorder and gastroesophageal reflux

- Abnormal esophageal motility as detected by esophageal manometry is present in 70 to 96 percent of patients of SSc. However, up to 30 percent of these patients are asymptomatic .
- Symptomatic patients may complain of heartburn, dysphagia or odynophagia. Patients with advanced dysphagia may regurgitate food and fluids.
- Dysphagia in SSc can result from reduced peristalsis, esophageal candidiasis, gastroesophageal reflux, or an esophageal stricture when the luminal diameter is ≤13 mm . Development of an esophageal stricture markedly decreases gastroesophageal reflux and the symptoms of heartburn. Esophagitis may be found in up to 60 percent of patients with scleroderma reflux, and Barrett's metaplasia is found in more than one-third of patients

Evaluation for esophageal involvement is guided by the patient's symptoms.

- Where symptoms are abolished or very well controlled with standard treatment such as proton pump inhibitor (PPI), then further evaluation may not be needed.
- However, upper endoscopy is indicated for evaluation in patients with refractory heartburn, dysphagia, or odynophagia and to screen for Barrett's esophagus in patients with risk factors.
- Direct measurement of esophageal motility with manometry is usually only necessary in patients with symptoms refractory to empiric trial of proton pump therapy.
- Do not routinely perform barium esophagram or esophageal scintigraphy to evaluate patients with SSc due to their low sensitivity and specificity, respectively. Our management is generally consistent with expert consensus guidelines

Findings of SSc on esophageal testing include:

- ●**Upper endoscopy** – Upper endoscopy findings in patients with SSc include reflux esophagitis, infectious esophagitis (eg, candidiasis), Barrett's esophagus, and esophageal stricture. In addition, upper endoscopy allows for mechanical dilatation of strictures or mucosal rings. (See "Endoscopic interventions for nonmalignant esophageal strictures in adults".)
- ●**Esophageal manometry** – Manometric findings in patients with SSc include a hypotensive lower esophageal sphincter with a low resting sphincter pressure (<10 mm Hg) and low-amplitude (<30 mmHg) contractions in the distal smooth muscle portion of the esophagus, or aperistalsis. Hypotensive peristaltic contractions are associated with ineffective esophageal transit. Patients with advanced disease may have diminished peristalsis in the upper skeletal muscle portion.
- ●Barium **esophagram** – Findings on barium esophagram in patients with SSc include an air-filled esophagus on plain radiograph, impaired or absent peristalsis with dilation of the esophagus, and a rapid flow of contrast medium in upright position ("waterfall esophagus") [42].
- ●**Esophageal transit scintigraphy** – Transit scintigraphy demonstrates prolonged esophageal clearance time in patients with SSc and is of little diagnostic value.

Upper endoscopy

–include

reflux esophagitis,

infectious esophagitis (eg, candidiasis),

Barrett's esophagus,

esophageal stricture.







GASTRIC INVOLVEMENT

- The most common gastric manifestation of systemic sclerosis (SSc) is gastroparesis Gastric antral venous ectasia (GAVE; "watermelon stomach") can also be seen in a small subset of patients.

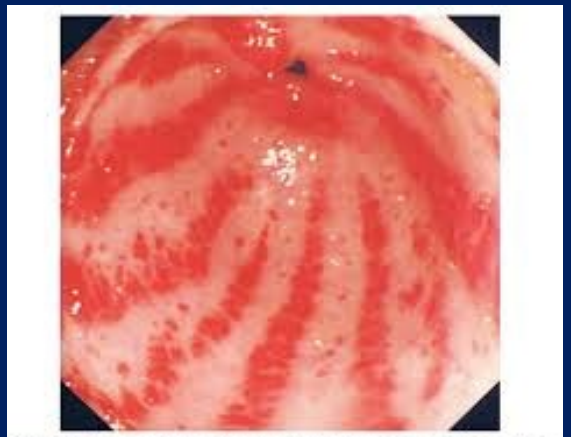


Figure 11.5 The classic appearance of gastric antral vascular ectasia (GAVE), which is often treated with argon plasma coagulation.

SMALL INTESTINAL INVOLVEMENT

- After the esophagus, the small intestine is the most common gastrointestinal (GI) target in systemic sclerosis (SSc) patients [Abnormal small bowel function has been reported in 20 to 60 percent of patients
- Severe GI problems, such as malabsorption and intestinal pseudo-obstruction, are much less common, affecting less than 10 percent of patients during the first nine years of illness

Pathophysiology

- — The major manifestations of small intestinal involvement are due to reduced peristalsis with resulting stasis and intestinal dilatation This results in abdominal distension and pain arising from dilated bowel loops. Small intestinal bacterial overgrowth (SIBO) subsequently emerges due to intestinal stasis and pooling. Impaired absorption of nutrients in SIBO results from either maldigestion in the intestinal lumen, or from malabsorption at the level of the intestinal microvillus membrane due to enterocyte damage. However, it is notable that malabsorption is usually seen in only severe cases of SIBO.

Small intestinal bacterial overgrowth

- — Approximately 10 to 30 percent of patients with SSc have evidence of SIBO
- The majority of patients with SIBO present with nonspecific symptoms of bloating, flatulence, or abdominal discomfort.
- Many patients diagnosed with severe SIBO have diarrhea.
- SIBO plays a major role in the pathogenesis of malabsorption and subsequent malnutrition
- The diagnosis of SIBO is made by a positive breath test or jejunal aspirate cultures.

Malnutrition

- The reported prevalence of malnutrition in SSc patients is approximately 15 to 20 percent, and it is a significant cause of morbidity and mortality
- Malnutrition in SSc patients may be due to loss of appetite, physical challenges of eating, oral symptoms, drug side effects, gastroparesis, and malabsorption secondary to bacterial overgrowth, and it is associated with higher disease activity rather than nutritional intake
- **Other** — Other rare complications include bleeding from small bowel telangiectasias, pneumatosis cystoides intestinalis, small bowel diverticula, and small bowel volvulus

COLON AND ANORECTAL INVOLVEMENT

- occurs in 10 to 50 percent of patients with systemic sclerosis (SSc), anorectum is the most frequently affected area
- In one study, the colon was almost as frequently involved as the esophagus; in addition, patients with abnormal esophageal manometry almost always had abnormal anorectal motility .
- Constipation and fecal incontinence are the common manifestations of colon and anorectal involvement of SSc and negatively impact quality of life among patients with SSc

Diarrhea and fecal incontinence

- Diarrhea is commonly reported in patients with SSc and many patients describe diarrhea that may alternate with constipation [2]. Diarrhea in SSc is often multifactorial and may be due to small intestinal bacterial overgrowth, pancreatic exocrine insufficiency, or overflow from constipation. Fecal incontinence may result from involvement of the anal sphincter, which is common in SSc and usually associated with atrophic change of both internal and external sphincters when assessed by endoanal ultrasound .Patients may also have an associated rectal prolapse. Diarrhea may also contribute to fecal incontinence in these patients.
- The most common manometric abnormality is an absent or diminished rectoanal inhibitory reflex and decrease in internal anal resting pressure

LIVER AND BILIARY TREE INVOLVEMENT

- **Primary biliary cholangitis overlap** —
- PBC occurs in 2 to 18 percent of patients with SSc [Most patients with both SSc and PBC have limited cutaneous SSc (lcSSc) or scleroderma overlap syndromes; diffuse skin involvement is much less common
- Patients with PBC and SSC are often positive for antimitochondrial antibodies (AMA) [
- SP100 has also been detected in AMA-negative PBC patients and is a useful marker for serological diagnosis of PBC].
- Anticentromere B autoantibodies (CENP-B) are strongly associated with PBC in SSc, while antitopoisomerase I and anti-RNA polymerase III antibodies are not

PANCREATIC INVOLVEMENT

- **Pancreatic exocrine insufficiency** — Advanced pancreatic exocrine insufficiency (PEI) results in maldigestion of fat and protein leading to steatorrhea and weight loss. Although subtle changes in exocrine function can be detected in patients with early pancreatic disease, overt steatorrhea does not occur until approximately 90 percent of glandular function has been lost.

Medication-associated colitis

- – Nonsteroidal anti-inflammatory drugs (NSAIDs) can cause chronic diarrhea and bleeding [Other drugs that may cause a similar clinical presentation include retinoic acid, checkpoint inhibitors, mycophenolate, and gold [The diagnosis is established by a history of medication use and the presence of nonspecific mucosal inflammation or mucosal erosions on biopsy that resemble ischemic changes