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Gastrointestinal Manifestations of Autoimmune Diseases: Diagnostic Implications for Frontline Clinicians

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Abstract

Systemic autoimmune diseases are a significant cause of morbidity and healthcare resource utilization and frequently present with nonspecific gastrointestinal (GI) manifestations such as abdominal pain, dyspepsia, nausea or vomiting, diarrhea, that hinder timely diagnosis. This narrative review synthesizes recent evidence on early GI symptoms and their value as an early "diagnostic window." We address key entities with digestive involvement—including systemic sclerosis, celiac disease within the autoimmune spectrum, autoimmune gastritis, autoimmune hepatitis, primary biliary cholangitis, primary sclerosing cholangitis, and autoimmune pancreatitis—emphasizing their presentation, initial evaluation, and early management. We also discuss shared pathophysiological mechanisms that account for clinical heterogeneity and support an integrative approach. Recognizing digestive "red flags" at the first point of contact enables shortening the diagnostic gap, initiating organ-directed and

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immunomodulatory treatments in a timely manner, and reducing complications. Finally, we identify gaps in the literature and the need for biomarkers and prospective cohorts to drive more precise diagnostic and therapeutic strategies.

Keywords

Autoimmune Diseases, Gastrointestinal Manifestations, Systemic Lupus Erythematosus, Systemic Sclerosis, Autoimmune Hepatitis

1. Introduction

Autoimmune diseases arise from a loss of immune tolerance and a dysregulated immune response that, in a pathological context, directs effector cells and autoantibodies against self-tissues. [1] The result is multi-organ damage with substantial clinical and economic burden on healthcare systems, accounting for a growing number of emergency and outpatient visits. [2] [3] Among the affected systems, the gastrointestinal (GI) tract may be involved along its entire length—from the esophagus to the rectum—as well as the liver, biliary tree, and pancreas. [1] [4] In systemic sclerosis, for example, GI involvement may occur in up to 90% of patients across disease stages, conferring high morbidity (Table 1). [5]

Initial manifestations are often nonspecific and, therefore, a source of diagnostic delay. [5] [6] Prominent features include refractory heartburn, dysphagia, chronic diarrhea, abdominal distension, and weight loss; in more severe scenarios, gastrointestinal bleeding, intestinal ischemia, or cholestatic jaundice may occur. [5] [7] The nonspecific nature of these symptoms requires a thorough clinical approach, particularly when systemic features coexist—such as Raynaud phenomenon, xerostomia/xerophthalmia, arthralgias, rashes, or personal/family history of autoimmunity. [1] [8]

Table 1. Gastrointestinal involvement in selected rheumatologic diseases: clinical, diagnostic, and therapeutic considerations.

Rheumatologic disease	Most affected GI segments	Main clinical manifestations	Useful initial studies	Immunologic clues/associations	Initial therapeutic pearls
Systemic sclerosis (SSc)	Esophagus, stomach, small intestine	Refractory GERD, dysphagia (dysmotility), strictures/Barrett's, gastroparesis, SIBO, pseudo-obstruction, GAVE, malabsorption, anemia	EGD + biopsies; high-resolution manometry; pH-impedance monitoring; breath tests (SIBO); gastric emptying scintigraphy	ANA; anti-centromere; anti-Scl-70; risk of microaspiration and ILD	Optimized PPIs; anti-reflux measures; selected prokinetics; non-absorbable/rotating antibiotics for SIBO; endoscopic ablation for GAVE; stricture dilation; partial fundoplication in selected cases
Systemic lupus erythematosus (SLE)	Small intestine/colon, peritoneum; less often liver/pancreas	Lupus enteritis (pain, diarrhea, "target sign" on CT), protein-losing enteropathy, pseudo-obstruction, peritonitis/ascites, pancreatitis, mild cholestasis	CBC, albumin, protein electrophoresis; contrast-enhanced CT; fecal α1-antitrypsin (PLE); EGD/colonoscopy as indicated	ANA, anti-dsDNA, ↓C3/↓C4; consider APS (anticardiolipin/β2GPI) if mesenteric ischemia	Systemic corticosteroids (± cyclophosphamide if severe); nutritional support; antibiotics if SIBO; anticoagulation if APS; manage infectious triggers

Continued

Primary Sjogren's syndrome (pSS)	Esophagus, stomach, small intestine; liver/biliary tract	Oropharyngeal dysphagia/GERD (xerostomia, dysmotility), chronic diarrhea (SIBO, bile acid malabsorption), associated celiac disease, autoimmune gastritis (pernicious anemia), PBC-related cholestasis, mild exocrine pancreatic insufficiency	EGD + biopsies (AIG/CD); celiac serology (anti-tTG IgA + total IgA); AMA and liver profile; breath tests (SIBO); fecal elastase if steatorrhea	Anti-Ro/SSA, Anti-La/SSB; AMA (if PBC); anti-parietal cell/anti-IF antibodies (AIG)	GERD management; antibiotics for SIBO; gluten-free diet if CD; B12/iron supplementation in AIG; UDCA for PBC; endoscopic surveillance if atrophy/metaplasia
IgG4-related disease (IgG4-RD)	Pancreas, biliary tract; occasionally stomach	Autoimmune pancreatitis type 1 (diffuse/focal mass, obstructive jaundice), IgG4-related cholangitis, weight loss, pseudotumoral lesions	Pancreatic CT/MRI, EUS-FNB; MRCP; serum IgG4; multiorgan evaluation (salivary glands, retroperitoneum, kidney)	Elevated serum IgG4; typical multiorgan pattern of IgG4-RD	Corticosteroids first-line; rituximab for relapsing/refractory cases; biliary stenting if obstructive cholestasis; long-term monitoring for relapse

Notes: GERD = gastroesophageal reflux disease; SIBO = small intestinal bacterial overgrowth; GAVE = gastric antral vascular ectasia; EGD = esophagogastroduodenoscopy; APS = antiphospholipid syndrome; PBC = primary biliary cholangitis; AIG = autoimmune gastritis; CD = celiac disease; IF = intrinsic factor; EPI = exocrine pancreatic insufficiency; MRCP = magnetic resonance cholangiopancreatography; EUS-FNB = endoscopic ultrasound-guided fine-needle biopsy.

Primary care physicians—the first point of contact—and internists play a decisive role in recognizing these warning signs and activating early diagnostic pathways. A reasoned initial approach includes a targeted history, complete physical examination, and basic laboratory testing, complemented by disease-specific serologies according to the working diagnosis, as well as endoscopy with biopsy when indicated. Early coordination among internal medicine, gastroenterology, and rheumatology enables the timely institution of organ-directed and immunomodulatory therapy, altering the natural history of disease and reducing complications.

2. Gastrointestinal Manifestations by System and Disease

2.1. Esophagus and Stomach

2.1.1. Dysphagia and Reflux in Systemic Sclerosis (SSc)

Esophageal involvement is frequent and often early in SSc. Smooth muscle atrophy and autonomic dysfunction reduce lower esophageal sphincter (LES) tone and peristalsis, leading to refractory heartburn, nocturnal regurgitation, and dysphagia to both solids and liquids. Chronic microaspiration is associated with worse interstitial lung disease. [5] [6] [9]

Upper endoscopy (EGD) documents esophagitis, strictures, and Barrett's esophagus while excluding structural causes. High-resolution manometry characterizes motility (ineffective peristalsis, absent contractility, hypotensive LES). pH-impedance monitoring quantifies both acid and non-acid reflux; gastric emptying studies should be considered in cases of early satiety, nausea, or vomiting. Suspect small intestinal bacterial overgrowth (SIBO) if there is bloating and diarrhea; breath testing or empiric therapy may be used. [5] [7] [10]

Optimization of proton pump inhibitors (PPIs) is the cornerstone of therapy; non-pharmacological measures include head-of-bed elevation, avoidance of late

or heavy meals, weight reduction, and limiting alcohol, caffeine, and peppermint. [11] Prokinetics such as metoclopramide or domperidone (depending on safety profile), 5-HT4 agonists, and baclofen (for predominant regurgitation, to reduce transient LES relaxations) may be considered. [6] [11] Treat SIBO with non-absorbable or cyclic antibiotics; provide nutritional support. Surgical anti-reflux procedures should be approached with caution, with partial fundoplication preferred. In selected cases, endoscopic dilation relieves peptic strictures, ideally combined with reflux control. [5] [6] [11]

Other gastric entities in SSc include gastroparesis, presenting with nausea and early satiety. Gastric antral vascular ectasia (GAVE) leads to iron deficiency or overt bleeding and is treated with endoscopic ablation and hematimetric monitoring. [5]

2.1.2. Autoimmune Gastritis (AIG) and Pernicious Anemia (PA)

AIG is an atrophic gastritis affecting the corpus and fundus, mediated by autoantibodies against parietal cells and/or intrinsic factor, associated with hypochlorhydria, hypergastrinemia, and enterochromaffin-like (ECL) cell hyperplasia. It frequently coexists with other autoimmune conditions such as Sjogren's syndrome, Hashimoto thyroiditis, and type 1 diabetes, and may present initially with iron deficiency or PA due to vitamin B12 deficiency. [12] [13]

The diagnostic approach includes basic laboratory tests such as complete blood count, iron studies, vitamin B12, anti-parietal cell and anti-intrinsic factor antibodies, serum gastrin, and pepsinogen I/II. [14] EGD with topographic biopsies following the Sydney protocol defines atrophy and metaplasia and can guide risk assessment for type I neuroendocrine tumors or, less commonly, adenocarcinoma. [14] [15] Treatment includes correction of B12 and iron deficiency, eradication of *Helicobacter pylori* if present, and endoscopic surveillance; screening for associated autoimmune diseases is also recommended. [14]

2.2. Small Intestine and Colon

2.2.1. Malabsorption and Celiac Disease Onset in the Context of Autoimmunity

Celiac disease (CD) often coexists with other autoimmune disorders and may present with chronic diarrhea, weight loss, or extraintestinal manifestations such as iron-deficiency anemia and elevated transaminases. [16] Initial screening includes anti-tissue transglutaminase IgA (tTG-IgA) antibodies along with total IgA; in IgA deficiency, tTG-IgG or deamidated gliadin peptide (DGP-IgG) should be used. [17] Multiple duodenal biopsies remain the confirmatory standard in adults; however, the 2023 ACG guidelines conditionally acknowledge a non-biopsy approach in cases with very high tTG-IgA titers, extrapolating ESPGHAN criteria, and reserve HLA-DQ2/DQ8 typing for complex diagnostic scenarios. Follow-up should document histological recovery and clinical response to a gluten-free diet. [16] [17]

2.2.2. Chronic Diarrhea in SLE and Sjogren's Syndrome

In systemic lupus erythematosus (SLE), the clinical spectrum includes lupus en-

teritis (mesenteric vasculitis), protein-losing enteropathy (PLE), and small intestinal bacterial overgrowth (SIBO). [18] Lupus enteritis typically presents with abdominal pain, nausea, and diarrhea; CT imaging may show the "target sign" due to bowel wall edema and mucosal enhancement, and it generally responds to systemic corticosteroids. [19] Lupus-associated PLE, although uncommon, may represent an initial manifestation, characterized by hypoalbuminemia with absent or minimal proteinuria; it requires immunosuppression targeting underlying lupus activity. [20] In Sjogren's syndrome, dysautonomia and dysmotility predispose to refractory diarrhea secondary to SIBO or bile acid malabsorption. Breath tests and non-absorbable antibiotics are useful diagnostic and therapeutic tools, alongside management of functional comorbidities. [21] [22]

2.2.3. Autoimmune Enteropathy (AIE)

Adult-onset AIE is rare but clinically relevant in cases of intractable chronic diarrhea with weight loss. Diagnostic criteria include villous atrophy with failure to respond to exclusion diets such as gluten-free regimens, with anti-enterocyte or anti-goblet cell autoantibodies often absent. [23] Histology may demonstrate crypt apoptosis and a graft-versus-host-like pattern. It is essential to exclude infectious causes, drug-induced injury (e.g., immune checkpoint inhibitors), collagenous sprue, and seronegative CD. [23]-[25] Treatment is based on induction with corticosteroids and steroid-sparing agents (azathioprine, tacrolimus/sirolimus) and, in refractory cases, biologics such as infliximab or vedolizumab, along with intensive nutritional support. Genetic characterization (e.g., immune regulatory defects) may guide targeted therapies in specific subgroups. [26] Early recognition is crucial to prevent recurrent hospitalizations and severe malnutrition. [26]

2.3. Liver and Biliary Tract

2.3.1. Autoimmune Hepatitis (AIH)

AIH may present with elevated ALT (sometimes with cholestatic features), asthenia, and arthralgias, along with hypergammaglobulinemia (IgG) and positive autoantibodies such as ANA and SMA, or anti-LKM/anti-SLA. [27] Liver biopsy is essential to confirm interface hepatitis and to exclude alternative diagnoses; scoring systems (IAIHG, simplified) help establish diagnostic probability. [28] The 2025 EASL and AASLD guidelines recommend prednisolone at 0.5 - 1 mg/kg/day or 40 - 60 mg/day as first-line therapy, combined with azathioprine at 1 - 2 mg/kg/day. Budesonide 9 mg/day is an option in non-cirrhotic patients without portal involvement. [27] [29] The therapeutic goal is a complete biochemical response (normal ALT/AST and IgG), with maintenance achieved using the steroid-sparing agent. Thiopurine methyltransferase activity should be assessed before initiating azathioprine, and adverse events must be monitored. [27]-[29]

2.3.2. Primary Biliary Cholangitis (PBC)

Diagnosis is typically established with elevated alkaline phosphatase (ALP) and

positive antimitochondrial antibodies (AMA-M2), without requiring liver biopsy unless there is diagnostic uncertainty or suspicion of overlap syndrome/steatohepatitis. [30] Ursodeoxycholic acid at 13 - 15 mg/kg/day indefinitely remains the therapeutic standard; biochemical response is evaluated at 12 months to stratify risk. In cases of insufficient response, a selective farnesoid X receptor agonist such as obeticholic acid may be considered, although it should be avoided in decompensated cirrhosis. Management should also address pruritus, osteoporosis surveillance, and cirrhosis-related complications. [30] [31]

2.3.3. Primary Sclerosing Cholangitis (PSC)

PSC follows a course of chronic cholestasis and is strongly associated with ulcerative colitis. Diagnosis is based on MRCP/ERCP showing characteristic multifocal strictures and dilatations in a "beaded" pattern; if imaging is normal but suspicion remains high, liver biopsy may demonstrate small-duct PSC. Serum IgG4 should be measured to exclude IgG4-related sclerosing cholangitis (IgG4-SC). Routine use of ursodeoxycholic acid is not recommended; management focuses on treating dominant strictures endoscopically, controlling bacterial cholangitis, and surveillance for cholangiocarcinoma and IBD (periodic colonoscopy). Liver transplantation should be considered in advanced disease. [32] [33]

2.4. Pancreas

Autoimmune Pancreatitis (AIP)

AIP is a fibroinflammatory form of pancreatitis that may present with obstructive jaundice, mild abdominal pain, or a pancreatic mass mimicking adenocarcinoma. [34] Two phenotypes are recognized: type 1, which represents the pancreatic manifestation of IgG4-related disease (IgG4-RD) and is typically multiorgan; and type 2, which is limited to the pancreas and lacks IgG4-RD features. Diagnosis is guided by the International Consensus Diagnostic Criteria (ICDC), which integrates five domains: pancreatic parenchymal/ductal imaging, serology, other organ involvement, histology, and steroid responsiveness (the latter being optional). [35]

First-line treatment consists of glucocorticoids—prednisone at 0.6 mg/kg/day for 2 - 4 weeks with gradual tapering. In many centers, low-dose maintenance (≈5 mg/day) for 6 - 24 months is considered to reduce relapse, which is more frequent in type 1 AIP and in the setting of proximal cholangiopathy. [36] In relapses or steroid intolerance, azathioprine or other steroid-sparing agents may be used; rituximab is effective for inducing and maintaining remission, particularly in IgG4-RD with biliary involvement. Endoscopic biliary decompression is reserved for cases with cholangitis or significant obstruction. [37]

In summary, AIP should be suspected in patients with obstructive jaundice or "idiopathic pancreatitis" with characteristic imaging findings, elevated serum IgG4, and/or multi-organ involvement. Clinical and radiologic resolution with corticosteroid therapy is a defining feature within the ICDC and aids in differentiating AIP from pancreatic neoplasia. [34] [36]

3. Common Pathophysiological Mechanisms

The digestive manifestations of systemic autoimmune diseases share a pathogenic core characterized by the loss of immune tolerance to gastrointestinal and hepatobiliary tissue antigens, the integration of systemic inflammation with fibrogenesis, and a close interaction with the gut microbiota. [1] [4] In the hepatobiliary system, for instance, the autoimmune cholangiopathy of primary biliary cholangitis arises from loss of tolerance to PDC-E2 in biliary epithelium, with the production of highly specific antimitochondrial antibodies (AMA) and chronic cholangiocyte injury. [6] [7]

In systemic sclerosis (SSc), gastrointestinal phenotypes derive from a triad of microvascular dysfunction, immune activation (both innate and adaptive), and excessive extracellular matrix deposition driven by profibrotic pathways such as TGF-β/SMAD, IL-13, and endothelin-1. This setting disrupts the motility of the esophagus, stomach, and small intestine, favoring malabsorption and small intestinal bacterial overgrowth (SIBO). [7] [9] [10]

The gut microbiota acts as a key modulator. In the early stages of SSc, dysbiosis has been described as depletion of butyrate-producing bacteria and reduced fecal butyrate levels, findings that may amplify mucosal inflammation and dysmotility. [38] [39]

In systemic lupus erythematosus (SLE), reduced microbial diversity, a decreased Firmicutes/Bacteroidetes ratio, and expansion of proinflammatory taxa have been documented. These changes may contribute to molecular mimicry and TH17 cell activation, promoting intestinal barrier disruption and systemic translocation of microbial products. [39] [40]

Taken together, these mechanisms—autoantigen-driven responses, dysregulated immunity, and gut microbiota dysbiosis—converge to produce fibrosis and vasculopathy. They also underpin clinical heterogeneity and overlap across entities, justifying integrative diagnostic strategies that combine serology, histology, functional imaging, and, increasingly, microbial and metabolic biomarkers to enable early, personalized diagnosis and treatment (**Table 2**). [1] [5] [40]

Table 2. Common pathophysiological mechanisms linking systemic autoimmunity and gastrointestinal/hepatobiliary disease.

Mechanistic axis	Molecular/immunologic drivers	Prototypical diseases	Predominant GI/hepatobiliary phenotypes	Helpful biomarkers /tests	Therapeutic implications
Loss of immune tolerance to tissue antigens	Breakdown of central/peripheral tolerance; autoreactive B/T cells; high-affinity autoantibodies against organ-specific antigens	Primary biliary cholangitis (PBC); Autoimmune hepatitis (AIH); Autoimmune gastritis; Celiac disease	Autoimmune cholangiopathy (cholestasis, pruritus), interface hepatitis, gastric atrophy/pernicious anemia, villous atrophy/malabsorption	AMA (anti-PDC-E2) in PBC; ANA/SMA/LKM/SLA in AIH; anti-parietal/anti-intrinsic factor; anti-tTG IgA (± EMA) in celiac disease; confirmatory histology	Antigen-directed immunomodulation (AIH: steroids ± azathioprine); UDCA in PBC; B12/iron replacement in AIG; gluten-free diet in celiac disease; endoscopic/histologic surveillance where appropriate
Innate/adaptive immune activation with cytokine amplification	Type I IFN signature; IL-6/IL-17/IL-23 axis; TH1/TH17 skewing; macrophage/NET activation	Systemic lupus erythematosus (SLE); Overlap syndromes (AIH-PBC/AIH-PSC)	Enteritis lúpica, protein-losing enteropathy, mesenteric vasculitis; mixed cholestatic-hepatitic patterns in overlaps	Low complement (C3/C4), anti-dsDNA (SLE); mixed autoantibody profiles; inflammatory markers	Systemic immunosuppression (glucocorticoids; steroid-sparing agents); targeted biologics per phenotype; anticoagulation when antiphospholipid coexists

Continued

Microvascular injury and vasculopathy	Endothelial dysfunction, oxidative stress; endothelin-1; ischemia-reperfusion microinjury	Systemic sclerosis (SSc)	Esophageal hypomotility/aperistalsis, gastroparesis, chronic intestinal pseudo-obstruction; GAVE; mucosal ischemia	High-resolution manometry; pH-impedance; gastric emptying studies; endoscopy (GAVE)	Aggressive reflux control (IBP), prokinetics; endoscopic therapy for GAVE; careful selection of antireflux surgery; nutritional optimization
Fibrogenesis and extracellular matrix deposition	TGF-β/SMAD pathway; IL-13; myofibroblast activation; ECM accumulation	SSc; PSC (periductal fibrosis); chronic AIH with fibrotic evolution	Progressive dysmotility; biliary strictures ("beading"); portal/periportal fibrosis	MRI/MRCP for biliary strictures; elastography; liver biopsy for stage	Antifibrotic-leaning strategies under study; treat upstream inflammation; endoscopic management of dominant strictures; transplant evaluation when advanced
Gut microbiota dysbiosis and barrier failure	Loss of butyrate-producing taxa; Firmicutes/Bacteroidetes ratio; increased pathobionts; impaired SCFA signaling; increased permeability	Early SSc; SLE; PSC with IBD	Dysmotility exacerbation, SIBO, low-grade mucosal inflammation; translocation of microbial products (LPS) driving systemic flares; PSC-IBD axis	Stool studies (dysbiosis research panels), breath tests for SIBO; fecal calprotectin (when IBD overlap suspected)	Non-absorbable antibiotics for SIBO; diet and nutritional therapy; emerging microbiome-targeted approaches (under investigation)
Autoantibody-mediated epithelial injury	AMA against mitochondrial antigens in cholangiocytes; anti-parietal/anti-intrinsic factor in stomach; anti-tTG at the brush border	PBC; Autoimmune gastritis; Celiac disease	Chronic cholestasis; achlorhydria → iron/B12 deficiency; villous atrophy → malabsorption	Specific autoantibody panels; targeted biopsies (Sydney system for stomach; duodenal mapping)	UDCA in PBC; micronutrient repletion; gluten withdrawal; endoscopic surveillance for atrophy/metaplasia or neuroendocrine tumors
Neuro-immune dysregulation of GI motility	Autonomic neuropathy; enteric neuronal dysfunction; cytokine/neuropeptide cross-talk	SSc; Sjogren syndrome	Oro-pharyngeal/esofágica dysphagia, reflux, delayed gastric emptying, small-bowel dysmotility	Manometry, scintigraphy, impedance; swallow studies	Prokinetics, baclofen for transient LES relaxations, aspiration prevention, multidisciplinary swallowing care
Immune-mediated biliary tract remodeling	Th1/Th17 responses; periductal "onion-skin" fibrosis; interaction with colonic inflammation	Primary sclerosing cholangitis (PSC) ± IBD	Multifocal biliary strictures, cholestasis, cholangitis; increased cholangiocarcinoma risk	MRCP (beading, strictures), IgG4 level to exclude IgG4-SC; colonoscopic IBD surveillance	Endoscopic dilation/stenting of dominant strictures; infection control; cancer surveillance; transplant consideration
IgG4-related fibro-inflammatory disease	IgG4-positive plasmacytic infiltrates; storiform fibrosis; obliterative phlebitis	IgG4-related cholangitis; Autoimmune pancreatitis type 1	Obstructive jaundice, pancreatic enlargement ("sausage-like"), biliary strictures	Serum IgG4 (supportive), EUS-FNB histology, multi-organ assessment	High steroid responsiveness; relapse prevention with steroid-sparing agents or rituximab; selective biliary drainage when indicated

4. Diagnostic Implications for the Primary Care Physician

The physician should interpret digestive symptoms within an autoimmune framework and order targeted tests from the first evaluation (Table 3). Particular attention should be paid to the following red flags:

1) Severe or refractory heartburn, dysphagia, and weight loss in patients with Raynaud's phenomenon or sclerodactyly, suggestive of systemic sclerosis (SSc) with dysmotility. Initial assessment should include upper endoscopy and high-resolution manometry, given the link between reflux and progression of interstitial lung disease (ILD) in SSc.

2) Chronic diarrhea, bloating, and weight loss in the setting of personal or family history of autoimmunity, which mandates exclusion of celiac disease (CD)

with anti-tTG IgA plus total IgA (using IgG-based tests in IgA deficiency). If positive or in high suspicion, multiple duodenal biopsies are indicated; a non-biopsy approach is reserved for specific scenarios.

3) Cholestasis associated with pruritus and fatigue, which suggests primary biliary cholangitis (PBC) when AMA is positive. MRCP/ERCP is the imaging modality of choice for primary sclerosing cholangitis (PSC), and serum IgG4 should be measured to exclude IgG4-related sclerosing cholangitis.

4) "Idiopathic" pancreatitis or obstructive jaundice with diffuse pancreatic enlargement on imaging and elevated serum IgG4, which raises suspicion for autoimmune pancreatitis (AIP). The ICDC (imaging, serology, other organ involvement, histology, and optional steroid responsiveness) should be applied to differentiate AIP from pancreatic neoplasia.

Table 3. Simplified initial algorithm (first consultation).

Step	Action	Indications/Scenarios	Objective and Practical Details
1	Basic laboratory panel	Any patient with digestive symptoms and a possible autoimmune background	CBC, ESR/CRP, liver profile (ALT/AST, ALP, GGT, bilirubin), albumin, ferritin/iron studies, vitamin B12/folate, TSH. Detect inflammation, cholestasis/cytolysis, malabsorption, and deficiencies
2	Targeted serology according to presentation	Select based on predominant symptom and personal/family history of autoimmunity	ANA; autoimmune liver panel (SMA, LKM, SLA); AMA; p-ANCA; anti-tTG IgA + total IgA (± EMA if uncertainty or high suspicion); total IgG and IgG4 when AIP or IgG4-related cholangiopathy is suspected
3	Endoscopy and biopsies	Refractory dysphagia/reflux; anemia/iron deficiency; chronic diarrhea or bleeding	EGD with biopsies (suspicion of AIG, CD, esophagitis/Barrett's/strictures). Colonoscopy if chronic diarrhea, bleeding, or suspicion of IBD/PLE. Obtain topographic samples following protocol
4	Functional and imaging studies	Dysmotility, cholestasis, pancreatic mass, or obstructive jaundice	Esophageal manometry and pH-impedance if refractory dysphagia/GERD. MRCP/MR cholangiography for cholestasis (PSC/strictures). Pancreatic CT/MRI and/or EUS if AIP or other lesion is suspected
5	Evaluation of SIBO	Bloating, diarrhea, malabsorption; SSc with symptoms and/or risk factors	Breath tests (lactulose or glucose). In selected contexts, an empirical trial with non-absorbable antibiotic and reassessment of clinical/nutritional status
6	Multidisciplinary discussion	Suggestive or discordant findings; need to integrate results	Joint evaluation with Internal Medicine, Rheumatology, and Gastroenterology/Hepatology to define differential diagnoses, prioritize further studies (e.g., liver/intestinal biopsy), and initiate timely organ-directed and immunomodulatory treatment

5. Conclusion

Systemic autoimmune diseases frequently involve the gastrointestinal tract, which may represent the first diagnostic clue. Early recognition of seemingly banal symptoms—refractory heartburn, dysphagia, chronic diarrhea, bloating, and weight loss—and their association with systemic features (Raynaud's phenomenon, xe-

rostomia/xerophthalmia, arthralgias, rashes) allows primary care physicians and internists to activate timely diagnostic pathways. A standardized approach integrating basic laboratory testing, targeted serologies, endoscopy with biopsy, and imaging/functional studies (manometry, pH-impedance, MRCP, EUS/CT) shortens diagnostic delays, differentiates key entities (CD, AIG, SIBO, AIH, PBC/PSC, AIP), and supports organ-directed and immunomodulatory therapy. The underlying pathophysiological heterogeneity—specific autoantibodies, inflammation-fibrosis axes, and dysbiosis—explains clinical variability and underscores the need for multidisciplinary evaluation with rheumatology and gastro-hepatology. Implementing screening algorithms, monitoring for complications (anemia, exocrine pancreatic insufficiency, cholangiopathies, associated neoplasia), and optimizing non-pharmacological measures improve quality of life and modify disease course. Finally, the development of serological, microbial, and imaging biomarkers, together with prospective cohorts, will drive precision medicine to enable earlier diagnosis, improved treatment, and reduced clinical and economic burden of these conditions.

6. Limitations of the Literature and Future Directions

Significant gaps remain in longitudinal studies describing the gastrointestinal onset of systemic autoimmune diseases (SADs), particularly in Latin America, where small case series and narrative reviews predominate. Further research is needed, incorporating serological biomarkers and imaging modalities capable of identifying early presentations, as well as noninvasive tools for assessing motility disorders.

Conflicts of Interest

The authors declare no relevant conflicts of interest related to this manuscript.

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