Updates from EULAR 2026: Gastrointestinal Involvement in Systemic Sclerosis

Authors:	*Corrado Campochiaro,[1] Claudia Iannone[1,2] 1. Rheumatology, IRCCS Ospedale San Raffaele, Milan, Italy 2. ASST Gaetano Pini-CTO, Milan, Italy *Correspondence to campochiaro.corrado@hsr.it

Disclosure:	The authors have declared no conflicts of interest.
Keywords:	Autoantibodies, biomarkers, dysmotility, gastrointestinal tract, systemic sclerosis (SSc).
Citation:	EMJ Rheumatol. 2026;13[1]:34-37. https://doi.org/10.33590/emjrheumatol/54PB50N4

GASTROINTESTINAL (GI) involvement affects up to 90% of patients with systemic sclerosis (SSc) and ranks among the most disabling internal organ manifestations, contributing substantially to morbidity, malnutrition, and impaired quality of life. Unlike skin and lung, the GI tract has long been the underserved frontier of SSc research: clinically ubiquitous, mechanistically obscure, and short of validated biomarkers and effective therapies. The European Alliance of Associations for Rheumatology (EULAR) Congress 2026 in London, UK, suggested this is changing, with a body of work that, taken together, drew a new track: predicting GI disease early, dissecting its biology and biomarkers, measuring it objectively rather than by symptoms alone, and, for the first time, showing that a disease-modifying immunotherapy can improve gut dysfunctions.

PREDICTING GI DISEASE AND ITS PROGNOSTIC WEIGHT

Two large cohorts converged on early prediction. In the GENISOS cohort, Ayla et al.[1] followed 450 patients with early SSc (≤5 years from the first non-Raynaud's symptom) over a mean of 5.3 years. Baseline gastro-oesophageal reflux disease (GORD; hazard ratio [HR]: 4.15) and diarrhoea (HR: 2.25) independently predicted progression to significant GI involvement, and each additional baseline GI manifestation raised the hazard by 48%. The same symptoms carried prognostic weight for survival: peptic ulcer (HR: 1.89) and diarrhoea (HR: 1.66) independently predicted death. Approaching the question from the vascular and cutaneous side, Bonomi et al.[2] and European Scleroderma Trials and Research Group (EUSTAR) colleagues analysed 7,789 patients: among those GI-negative at baseline, 11.7% developed new-onset GI involvement over a median of 4.8 years, with highest incidence in the first 5 years. Puffy fingers and digital ulcers independently predicted GI onset, and, critically, incident GI involvement was independently associated with increased all-cause mortality (HR: 1.99). Together, these cohorts frame GI disease as an early, predictable, and prognostically weighty event.

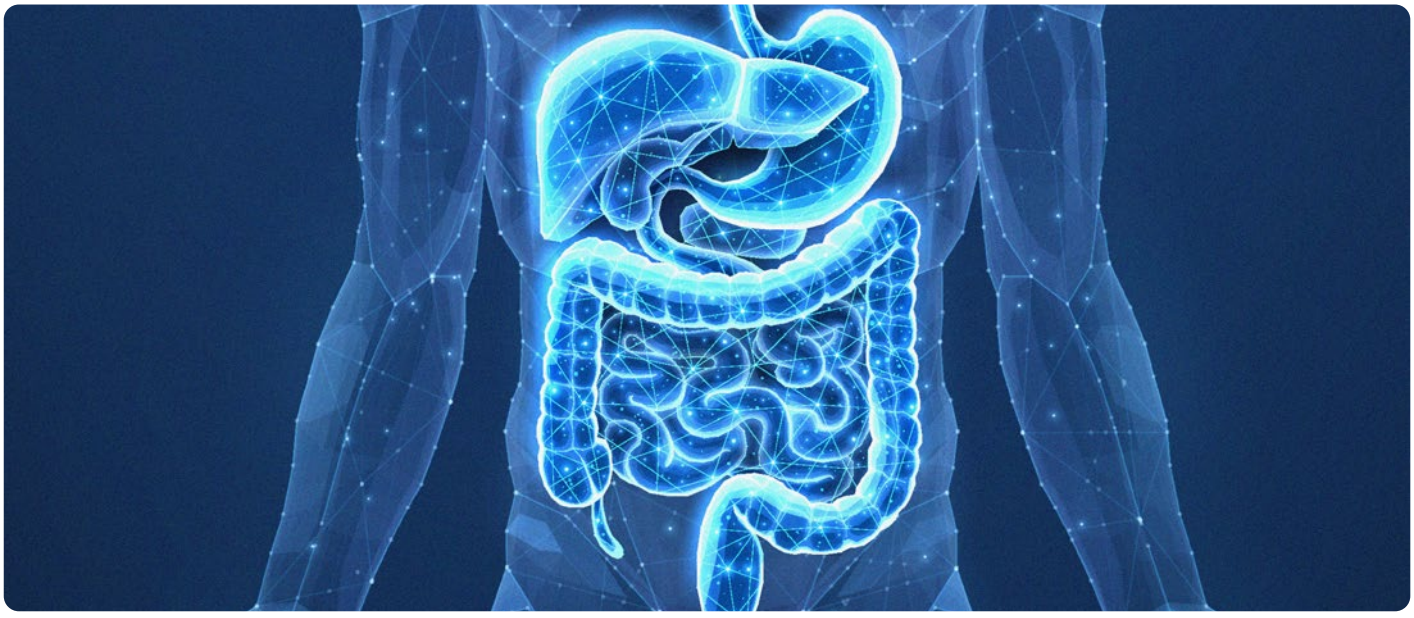
> **These cohorts frame GI disease as an early, predictable, and prognostically weighty event**

BIOLOGY AND BIOMARKERS

The most mechanistically ambitious contribution came from McMahan et al.,[3] who identified two enteric nervous system-relevant autoantibodies defining clinically distinct GI phenotypes. Antibodies to Argonaute (AGO) proteins (anti-AGO1/2), present in 9–14% of patients and absent in controls, marked severe lower-GI dysmotility and constipation, with dual positivity producing a particularly severe phenotype and titres tracking symptom severity. Antibodies to dihydrolipoamide branched-chain transacylase (DBT) instead marked an upper-GI signature of impaired oesophageal transit. Mechanistically, AGO proteins localised to myenteric ganglia and were enriched in neurone-derived extracellular vesicles, implicating disrupted vesicle-mediated RNA signalling, while DBT was concentrated in mesoderm-derived enteric neurones. Complementing this antigen-based work, Makol et al.[4] applied targeted serum proteomics to 84 patients, defining a signature of GI symptom severity in which inflammatory and tissue-remodelling proteins (hepatocyte Growth Factor [HGF], extracellular newly identified receptor for advanced glycation end-products-binding protein [EN-RAGE], oncostatin M [OSM], TGF-α) were elevated in moderate-to-severe disease. A third strand came from the gut itself: Spinella et al.[5] used full-length 16S metagenomic sequencing in 25 patients and 25 controls to show reduced microbial richness and a dysbiotic profile that tracked with symptom severity. It was a preliminary single-centre study, but a reminder that the microbiome remains an under-explored axis. Together, these antigen-, protein-, and microbe-level readouts point toward circulating biomarkers and candidate therapeutic targets.

MEASURING IT OBJECTIVES

The year's richest seam was objective measurement, which repeatedly exposed the limits of symptom scores. Bonomi et al.[6] applied high-resolution manometry across 109 patients including very early (Very Early Diagnosis of Systemic Sclerosis [VEDOSS]) cases: fatigue worsened stepwise with oesophageal motor severity (manometric dysmotility independently associated with lower Functional Assessment of Chronic Illness Therapy – Fatigue [FACIT-F]; $\beta=-3.87$), and University of California Los Angeles (UCLA) Gastrointestinal Tract 2.0 (GIT 2.0) burden did not differ across manometric patterns, emphasising that patient-reported symptoms can miss underlying motor dysfunction. Moving to the lower gut, Alcala-González et al.[7] used high-resolution jejunal manometry in 46 patients, finding overt small-bowel dysmotility in 67%. Severe hypocontractility defined a high-risk subgroup characterised by diffuse disease, active microangiopathy, exclusive anti-Ro positivity, greater



symptom burden, and progression to intestinal pseudo-obstruction. The same drive toward physiology ran through studies of objectively-defined GORD phenotypes, which dissociated acid from non-acid reflux and argued for assessment beyond empiric acid suppression (Felix-Tellez et al.),[8] magnetic resonance-enterography quantifying small-bowel motility heterogeneity (Minerba et al.),[9] and ultrasound of hyoid excursion as an early, and potentially modifiable, marker of dysphagia detectable already in VEDOSS (Peretti et al.).[10]

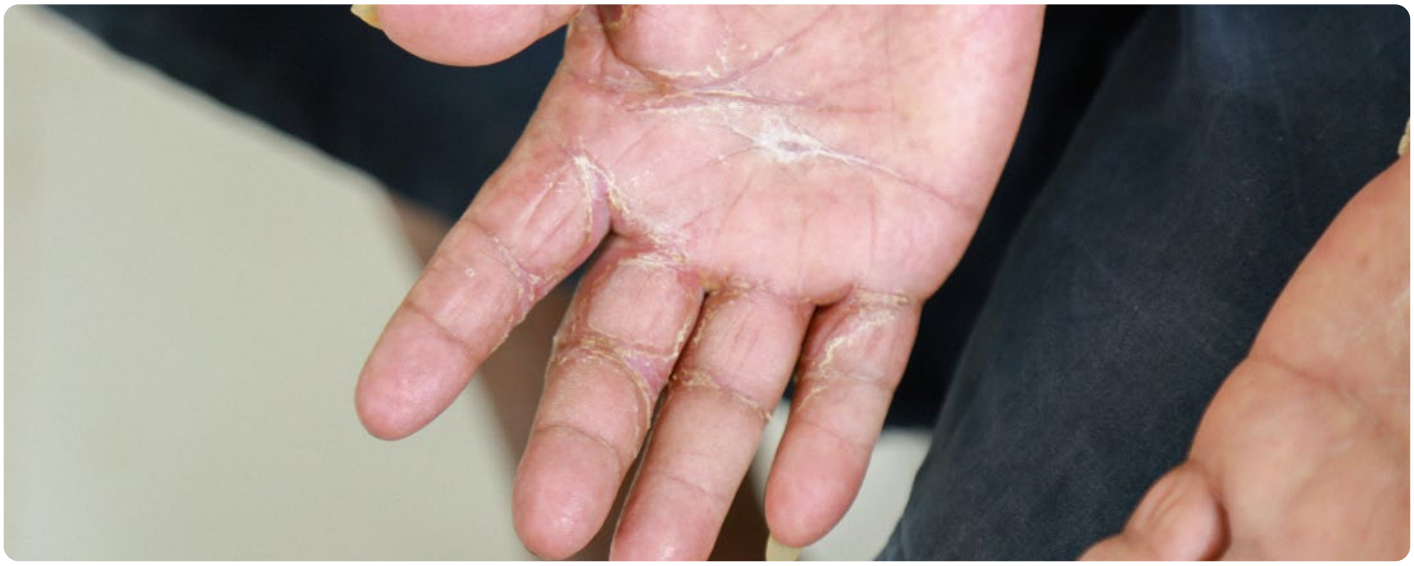
THE FIRST THERAPEUTIC SIGNAL IN THE GUT

Perhaps the most striking translational result linked the year's headline therapy to GI disease. Auth et al.,[11] from Erlangen, Germany, studied eight patients with progressive diffuse cutaneous SSc treated with cluster of differentiation 19 (CD19)-targeting CAR-T cells within the CASTLE study, all with baseline GI involvement. UCLA GIT 2.0 scores improved significantly by 3 months, exceeding the minimally important difference, with the clearest gains in distention/bloating and, by 6 months, in constipation and social functioning with reflux being the most refractory domain. Critically, oesophageal gallium-68-labeled fibroblast activation protein Inhibitor (68Ga-FAPI)-PET uptake, a marker of fibroblast activation, declined progressively (median standardised uptake value mean reductions of −0.747 at 6 months and −1.222 at 12 months). This is among the first evidence that deep B cell depletion can modify not only skin and lung, but also the fibrotic and functional GI compartment, although the eight-patient sample warrants cautious interpretation.

> **Deep B cell depletion can modify not only skin and lung, but also the fibrotic and functional GI compartment**

FROM BENCH TO BEDSIDE: DIFFICULT-TO-TREAT MANIFESTATIONS

The clinical counterpoint came in the dedicated 'Challenges in Clinical Practice' session, 'Difficult-to-treat GI manifestations in SSc',[12] chaired by Alain Lescoat, Institut National de la Santé et de la Recherche Médicale, Paris, France; and Muriel Elhai, Department of Rheumatology, University Hospital Zurich, Switzerland. Structured around two of the most demanding scenarios: gastric antral vascular ectasia (presented by Artur Ejsmont, and discussed by Otylia Kowal-Bielecka, Department of Rheumatology and Internal Medicine, Medical University of Białystok, Poland) and small intestinal bacterial



overgrowth (presented by Marco Minerba, Rheumatology and Clinical Immunology, Department of Medicine, University of Rome Campus Bio-Medico, School of Medicine, Rome, Italy, and discussed by Francesco Del Galdo, Leeds Raynaud's and Scleroderma Program, NIHR Biomedical Research Centre Leeds, UK). It underscored a practical reality: even as measurement and prediction advance, management of refractory gastric antral vascular ectasia and recurrent small intestinal bacterial overgrowth remains largely empirical. For gastric antral vascular ectasia, the take-home message was simple: any unexplained anaemia or iron deficiency in a patient with SSc should prompt gastroscopy, as the lesion is often subclinical. Argon plasma coagulation, together with iron and transfusion support, should be first-line therapy. In the index case, it achieved complete endoscopic resolution over 18 months, alongside immunosuppression. For small intestinal bacterial overgrowth (pooled prevalence ~35%, roughly ten-fold the general population), cyclical rifaximin remained the mainstay, outperforming rotating antibiotics for eradication (77.8% versus 44.8%) and working best with an added probiotic. The discussion reframed it not as an isolated infection but as one facet of a heterogeneous dysmotility syndrome, with magnetic resonance-enterography and bowel ultrasound phenotyping, notably segmental small-bowel volume loss, offering a way to explain antimicrobial failure and, in future, to target motility-directed therapy. The unifying caution was that disease-modifying treatments can themselves trigger or worsen GI symptoms, reinforcing the case for multidisciplinary management and controlled trials with GI-specific endpoints.

CONCLUSION

EULAR 2026 marked a quiet inflection point for GI involvement in SSc. The conversation is shifting from documenting a near-universal problem to predicting it early from clinical and symptom profiles, dissecting its biology through antigen-specific autoantibodies and serum proteomics, measuring it objectively where symptoms fall short, and, for the first time, showing that a disease-modifying immunotherapy may reach the gut. The outstanding gap remains therapeutic: these maturing biomarkers and endpoints must now be harnessed in interventional trials so that this long-neglected domain finally receives treatments matched to its clinical weight. On the evidence from London, the foundations for that next step are being laid.

References

1. Ayla A et al. Early gastrointestinal manifestations predict outcomes in patients with systemic sclerosis. Abstract POS0533. EULAR Congress, 3-6 June, 2026.
2. Bonomi F et al. Incidence, timing, and predictors of new-onset gastrointestinal involvement in systemic sclerosis: a longitudinal cohort study from the EUSTAR database. Abstract POS0562. EULAR Congress, 3-6 June, 2026.
3. McMahan Z et al. Autoimmune targeting of enteric neurons and extracellular vesicles defines distinct gastrointestinal phenotypes in systemic sclerosis. Abstract POS0542. EULAR Congress, 3-6 June, 2026.
4. Makol A et al. Distinct serum proteomic signatures associated with gastrointestinal symptom severity in systemic sclerosis. Abstract POS0577. EULAR Congress, 3-6 June, 2026.
5. Spinella A et al. Evaluation of gastrointestinal microbiome in patients with systemic sclerosis: our experience and emerging research. Abstract POS1090. EULAR Congress, 3-6 June, 2026.
6. Bonomi F et al. Fatigue severity relates to esophageal manometric patterns beyond gastrointestinal symptoms in systemic sclerosis. Abstract POS0539. EULAR Congress, 3-6 June, 2026.
7. Alcala-González LG et al. Objective assessment of small bowel involvement identifies high-risk phenotypes in systemic sclerosis. Abstract POS0560. EULAR Congress, 3-6 June, 2026.
8. Felix-Tellez FA et al. Objective physiological assessment across the GERD spectrum in systemic sclerosis: a multicenter international study. Abstract POS0576. EULAR Congress, 3-6 June, 2026.
9. Minerba M et al. Marked heterogeneity of small bowel motility in systemic sclerosis with gastrointestinal involvement: a pilot MR enterography study. Abstract POS1083. EULAR Congress, 3-6 June, 2026.
10. Peretti S et al. Hyoid dysfunction as an overlooked mechanism of dysphagia in systemic sclerosis from the early disease stages. Abstract POS1091. EULAR Congress, 3-6 June, 2026.
11. Auth J et al. Analysis of esophageal 68Ga-FAPI-uptake and gastrointestinal symptoms in patients with diffuse cutaneous systemic sclerosis upon CD19-targeting CAR T cell therapy. Abstract POS0505. EULAR Congress, 3-6 June, 2026.
12. Difficult-to-treat gastrointestinal manifestations in systemic sclerosis. Presentation Sesion 8. EULAR Congress, 3-6 June, 2026.