

ORIGINAL RESEARCH

THE CHANGING DISEASE PARADIGM IN INFLAMMATORY BOWEL DISEASE: FROM SYMPTOM CONTROL TO DISEASE MODIFICATION

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ABSTRACT

Inflammatory bowel disease, comprising Crohn's disease and ulcerative colitis, is a chronic immune-mediated disorder of rising global prevalence and heterogeneous course. Management has historically been directed at relieving patient-reported symptoms, an approach that has not prevented the accumulation of irreversible bowel damage. Over the past decade the field has moved towards disease modification, in which therapy is guided by objective measures of inflammation and the goal is preservation of bowel function rather than short-term symptom suppression.

This narrative review examines that transition. Successive iterations of the Selecting Therapeutic Targets in Inflammatory Bowel Disease initiative have formalised a hierarchy of treat-to-target endpoints, from clinical response through biochemical and endoscopic remission towards histologic and transmural healing. The CALM trial established that biomarker-guided tight control improves endoscopic outcomes relative to symptom-driven escalation, and the PROFILE trial demonstrated that early combined immunosuppression at diagnosis substantially improves one-year outcomes in Crohn's disease, although the prognostic biomarker it tested did not show clinical utility. Transmural healing, assessed by magnetic resonance enterography or intestinal ultrasonography, has emerged as a candidate endpoint in Crohn's disease, and histologic remission and the aspirational concept of disease clearance are being explored in ulcerative colitis.

Substantial gaps remain. Standardised definitions of disease modification and of transmural healing are lacking, predictive biomarkers that reliably forecast therapeutic response are limited, and it has not been demonstrated that deeper endpoints confer prognostic value beyond endoscopic remission. Much of the supporting evidence for the deepest targets remains observational. The review synthesises current evidence on therapeutic endpoints, treat-to-target frameworks and precision medicine, and identifies what would be required to translate symptom control into validated disease modification.

Keywords: Inflammatory bowel disease; Crohn's disease; ulcerative colitis; disease modification; mucosal healing; transmural healing; treat-to-target; precision medicine.

Introduction

Inflammatory bowel disease is a chronic, immune-mediated disorder comprising Crohn's disease and ulcerative colitis. Prevalence now exceeds 0.3% in several Western populations and is rising steadily in newly industrialised nations, a pattern documented across population-based studies worldwide [1]. The disease follows a relapsing-remitting course of gastrointestinal inflammation producing diarrhoea, abdominal pain, rectal bleeding and weight loss, and a substantial minority of patients develop extraintestinal manifestations affecting the skin, eyes, joints and hepatobiliary system [2].

The disease remains incurable, and its heterogeneity in course, severity and treatment response poses a persistent obstacle to long-term management [3]. Conventional strategies have concentrated on reducing clinical symptoms, an approach that has not altered the progressive natural history of the disease [4]. Population-based cohorts show that a considerable proportion of patients with Crohn's disease progress from inflammatory to stricturing or penetrating behaviour over time,

with consequent hospitalisation, surgery and long-term disability [5]. In ulcerative colitis the corresponding concern is colectomy and, over the longer term, colorectal neoplasia [6].

The field is therefore moving from symptom suppression towards disease modification, defined by objective endoscopic, histologic and transmural endpoints [7]. This reflects a changed understanding of the disease: not an intermittent inflammatory event but a progressive condition in which mucosal inflammation may advance to permanent structural complications [8]. Because that transition typically takes years, the early inflammatory phase offers a window in which progression might be interrupted [9].

Precision medicine represents a further refinement, aiming to match therapy to the individual patient's molecular, genetic and microbial profile [3]. Integrating multi-omic with clinical data offers a route away from generalised algorithms and trial-and-error prescribing [10], with the prospect of improved efficacy and safety and reduced clinical and economic burden [11]. Whether that prospect can be realised is examined below.

Realising these aims requires the adoption of treat-to-target strategies in which objective measures of inflammation, rather than patient-reported outcomes alone, guide decisions [12,13]. Anchoring management in such benchmarks allows the disease course to be altered before irreversible damage accrues. The Selecting Therapeutic Targets in Inflammatory Bowel Disease initiative, first published in 2015 [13] and updated as STRIDE-II in 2021 [12], formalised this approach into a hierarchy of short-, intermediate- and long-term targets, and it is against that framework that the developments discussed here are best understood.

Scope and Literature Search

This is a narrative review. A structured but non-systematic literature search was undertaken in PubMed, Embase and the Cochrane Library for articles published between January 2015 and December 2025, using combinations of the terms “inflammatory bowel disease”, “Crohn's disease”, “ulcerative colitis”, “mucosal healing”, “histological remission”, “transmural healing”, “disease modification”, “treat-to-target” and “precision medicine”, together with the corresponding Medical Subject Headings. The window was chosen to span the interval from the original STRIDE consensus [13] to the most recent evidence, and reference lists of retrieved articles and relevant guidelines were hand-searched for additional sources. Randomised trials, longitudinal cohorts, systematic reviews and consensus statements reporting objective endoscopic, histologic or radiological endpoints in adults were prioritised; studies defining disease control solely by patient-reported outcomes were not included. Articles were selected by the authors on the basis of relevance to the themes developed here, and the review is reported with reference to the SANRA scale for narrative reviews [14].

From Symptom Control to Objective Targets

Management historically followed a step-up approach in which effective therapy was withheld until clinical deterioration or structural complications had already developed. Since symptoms correlate imperfectly with mucosal inflammation, this frequently permitted ongoing tissue injury in patients who felt reasonably well, and conversely exposed patients with functional symptoms to unnecessary escalation.

The STRIDE initiative reframed the problem. Its 2015 statement identified clinical remission together with endoscopic healing as the principal targets [13], and STRIDE-II extended this into a temporal hierarchy: clinical response as an immediate target, normalisation of C-reactive protein and faecal calprotectin as intermediate targets, and endoscopic healing with restored quality of life and absence of disability as long-term targets [12]. Histologic and transmural healing were considered but not adopted as formal targets, on the grounds that evidence for their independent prognostic value was then insufficient — a judgement that frames much of what follows (Figure 1).

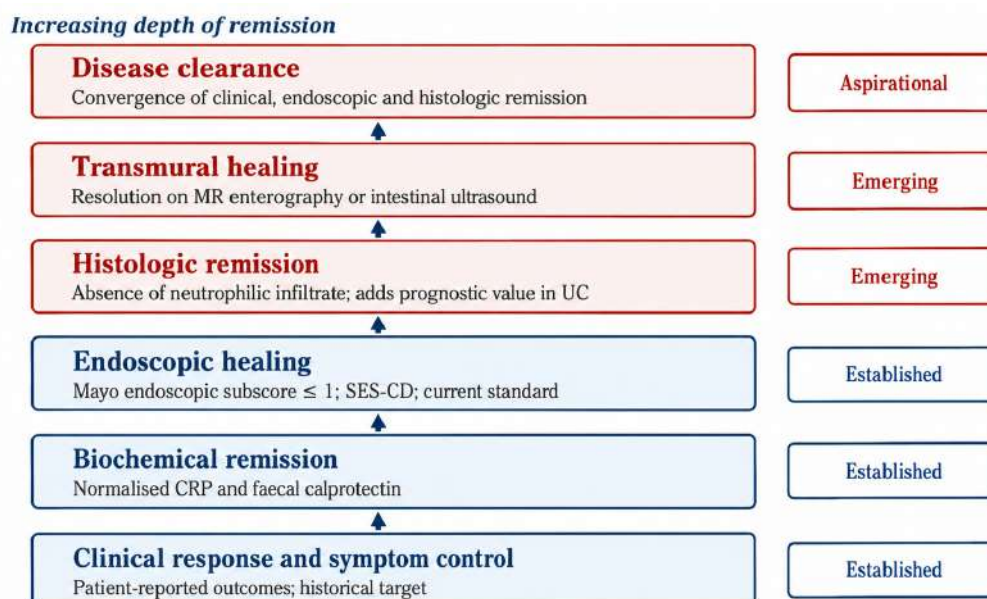


Figure 1. Hierarchy of therapeutic targets in inflammatory bowel disease, with the current status of each. Established targets are those adopted in STRIDE-II; emerging and aspirational targets remain under evaluation.

Two randomised trials have given this framework empirical support. CALM allocated 244 patients with moderate-to-severe Crohn's disease to escalation driven either by symptoms alone or by a tight-control algorithm incorporating C-reactive protein and faecal calprotectin; mucosal healing without deep ulceration at one year was achieved in 46% of the tight-control group against 30% of those managed on clinical criteria [15]. PROFILE subsequently randomised patients with newly diagnosed Crohn's disease to top-down combination therapy with infliximab and an immunomodulator or to accelerated step-up treatment, stratified by a blood-based transcriptional biomarker. Top-down treatment produced substantially better outcomes at one year, and the authors concluded that it should be considered standard of care for newly diagnosed active disease [16].

PROFILE also carries a cautionary finding that deserves emphasis in any discussion of precision medicine: the prognostic biomarker on which the trial was stratified did not demonstrate clinical utility. The benefit of early combination therapy was seen across biomarker strata rather than confined to a predicted high-risk subgroup. The trial therefore supports early intervention while simultaneously illustrating how far biomarker-guided therapy remains from clinical application [16].

Deeper Endpoints: Histologic and Transmural Healing

Endoscopic healing is now the accepted standard, but it does not exclude persistent microscopic inflammation. In ulcerative colitis, Bryant and colleagues followed a cohort for six years and found that histologic remission predicted corticosteroid requirement and hospitalisation better than endoscopic mucosal healing alone [17], and subsequent syntheses have supported histologic remission as an additional prognostic layer [18]. This has prompted interest in disease clearance, the convergence of clinical, endoscopic and histologic remission [19,20], although the supporting evidence remains largely observational and no randomised trial has yet demonstrated that treating to this target improves outcomes. It is notable that contemporary registration trials in ulcerative colitis, such as UNIFI, have incorporated histologic and endoscopic co-primary or secondary endpoints alongside clinical remission, which has improved the comparability of outcome reporting across agents [21].

In Crohn's disease, where inflammation is transmural, endoscopy assesses only the mucosal surface. Cross-sectional imaging by magnetic resonance enterography or intestinal ultrasonography can characterise the full thickness of the bowel wall, and transmural healing has accordingly been proposed as a more complete endpoint. A systematic review by Geyl and colleagues found transmural healing to be associated with better long-term outcomes than mucosal healing alone, while noting marked heterogeneity in how it was defined across studies [22]. Cohort data have supported this association [23], as have studies combining faecal calprotectin with intestinal ultrasonography [24] and sonographic assessment alone

[25]; the rationale and practical requirements for monitoring transmural activity have been reviewed in detail [26]. Neurath and Vieth have set out a taxonomy distinguishing mucosal, histological, transmural, barrier and complete healing, which usefully clarifies terms that are frequently conflated [7].

Enthusiasm should nonetheless be tempered. No consensus definition of transmural healing exists, thresholds for bowel wall thickness and vascularity differ between studies, and inter-observer reliability for intestinal ultrasonography depends heavily on operator training [27,28]. Most importantly, the association between transmural healing and favourable outcome does not by itself establish that treating to transmural healing changes outcome; that requires a trial in which the target is randomised, which has not yet been performed. The distinction between a prognostic marker and a therapeutic target is central and is not consistently observed in the current literature (Figure 2).

Target	Supporting evidence	Validated as disease-modifying?
Endoscopic healing	CALM; multiple cohorts	Yes — current standard
Histologic remission	Cohort and meta-analytic data in UC	Adds prognostic value; not yet shown to exceed endoscopy
Transmural healing	Systematic review; cohort studies	Promising; no standard definition
Disease clearance	Observational data only	Not established
Molecular signatures	Exploratory	Not established

Figure 2. Evidence status of candidate therapeutic targets. Association with favourable outcome is not equivalent to demonstrated benefit from treating to that target.

Precision Medicine and Its Present Limits

Precision medicine promises to match therapy to the individual, and considerable effort has been directed at prognostic and predictive biomarkers, pharmacogenomic markers of drug metabolism and immunogenicity, and multi-omic profiling [3,10,29]. The clinical reality is more modest. As Schreiber and colleagues observe, few candidate biomarkers have been prospectively validated, and fewer still have altered practice [10]. PROFILE provides the clearest illustration: a biomarker developed with strong biological rationale and retrospective support did not predict differential benefit when tested prospectively [16].

This does not diminish the case for early, effective intervention; it separates that case from the biomarker rationale originally advanced for it. On current evidence the argument for treating newly diagnosed Crohn's disease aggressively rests on trial data showing benefit across the population studied, not on the ability to identify in advance which patients will benefit. Honest presentation of this distinction matters, because overstating the maturity of biomarker-guided therapy risks a cycle of inflated expectation and subsequent disillusionment.

Implementation Challenges

Translating these targets into routine care presents practical difficulties. Repeated endoscopy is invasive, costly and poorly tolerated, which has driven interest in non-invasive monitoring. Intestinal ultrasonography is inexpensive, repeatable and well accepted by patients, but requires specific training and standardised reporting to achieve consistency between centres; European guidance has addressed both the diagnostic role of cross-sectional imaging [30] and the standardisation of reporting [28]. Magnetic resonance enterography provides reproducible assessment without ionising radiation but is resource-intensive and unevenly available.

There are also economic considerations. The Lancet Gastroenterology and Hepatology Commission on the cost of inflammatory bowel disease in high-income settings documented that expenditure has shifted substantially towards drug acquisition, and any strategy advocating earlier and more intensive therapy must be assessed against that background [11]. Whether earlier advanced therapy is cost-effective over a patient's lifetime, through avoided surgery and hospitalisation, remains an open question that the trials discussed here were not designed to answer.

Limitations of This Review

This is a narrative and not a systematic review. Articles were selected by the authors for relevance rather than by prespecified criteria applied independently, so selection bias cannot be excluded and no quantitative pooling was undertaken. Heterogeneity in the definition of transmural healing, histologic remission and disease modification limits direct comparison between studies. The search was confined to three databases and to English-language publications, and the focus on adult-onset disease limits applicability to paediatric populations. Because much of the evidence for the deepest endpoints is observational, associations reported here should not be read as demonstrating that treating to those endpoints alters outcome.

Conclusion

The management of inflammatory bowel disease is moving from reactive symptom control towards a strategy directed at preventing irreversible structural damage. That shift is now supported by randomised evidence: tight control guided by biomarkers improves endoscopic outcomes [15], and early combination therapy at diagnosis improves one-year outcomes in Crohn's disease [16]. Endoscopic healing is established as a therapeutic target, and STRIDE-II provides a workable framework for applying it [12].

Beyond that point the evidence is thinner than the enthusiasm. Histologic remission and transmural healing are consistently associated with better outcomes, but neither has been shown in a randomised comparison to confer benefit over endoscopic remission when adopted as the treatment target, and neither has an agreed definition. Disease clearance remains aspirational. Biomarker-guided selection of therapy has not yet been prospectively validated, as PROFILE demonstrated.

What is required is reasonably clear: consensus definitions of transmural healing and disease modification; randomised trials in which the depth of the treatment target is itself the randomised variable; prospective validation of predictive biomarkers in populations distinct from those in which they were derived; and health-economic evaluation of earlier intensive therapy. Until those are available, endoscopic healing supported by biochemical monitoring remains the defensible standard, with deeper endpoints best regarded as promising prognostic markers rather than established therapeutic goals.

Declarations

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