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Review

Curing inflammatory bowel diseases: breaking the barriers of current therapies– emerging strategies for a definitive treatment

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Chronic intestinal inflammation in inflammatory bowel diseases (IBD) reflects the interplay of genetic predisposition, immune dysregulation, microbial imbalance, and epithelial barrier defects. Current therapies for IBD primarily focus on controlling inflammation necessitating lifelong treatment and face a 'therapeutic ceiling' due to primary and secondary loss of efficacy over time. Immune-mediated approaches do not address additional pathogenic mechanisms, such as impairment of epithelial barrier and gut microbial ecology. Thus, innovative strategies are required to foster the field closer to a definitive cure. This review discusses novel strategies to overcome current therapeutic limitations, including immune reset via hematopoietic stem cell transplantation and B cell–targeted therapies, antigen-specific interventions such as chimeric antigen receptor T cells and tolerogenic vaccines, and intestinal epithelial barrier restoration. We also explore microbiota-based strategies — ranging from fecal microbiota transplantation to engineered consortia and bacteriophages — and discuss the adjunctive role of diet. Together, we outline a potential research roadmap toward a potential cure for IBD.

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Introduction

Inflammatory bowel diseases (IBD), comprising Crohn's disease (CD) and ulcerative colitis (UC), are chronic immune-mediated disorders affecting the intestinal tract, often associated with systemic manifestations. Despite extensive research, their exact pathogenesis remains incompletely understood. Current evidence suggests that IBD-related inflammation originates from an aberrant activation of the mucosa-associated lymphoid tissue, triggered by environmental stimuli, notably gut-derived microbial antigens [1,2]. This dysregulated immune response leads to a massive infiltration of proinflammatory immune cells, the release of inflammatory mediators and proteolytic enzymes, and disruption of the extracellular matrix, and eventual tissue damage leading to fibrosis [3,4].

Epidemiological data show a consistent increase in IBD prevalence worldwide over the past three decades, primarily due to a compounding prevalence [5]. While the incidence of IBD seems to have reached a peak in industrialized nations of North America and Europe, it is steadily increasing in regions undergoing rapid industrialization and adopting Western lifestyles. This epidemiological shift underscores the role of environmental factors, including dietary habits, pollution, and antibiotic exposure, in disease pathogenesis [6].

The growing burden of IBD prevalence, its onset in late childhood/early adulthood, and its chronic nature — often affecting the ability to study or work — place a significant burden on individuals and health care systems alike. Moreover, the increasing direct and indirect costs pose serious challenges to national health resources, underscoring the urgent need for continued research, with the ultimate goal of finding a definitive cure for IBD patients and those at risk.

In the decades following the description of CD, the histopathological identification of granulomas led to the hypothesis that an atypical mycobacterium — *Mycobacterium avium* complex — might be the trigger, prompting clinical trials with antimycobacterial antibiotic therapies [7–9]. The identification of adherent-invasive *Escherichia coli* strains in

CD patients, along with immunological and clinical correlations, continues to raise questions about their role in CD pathogenesis [10,11]. More broadly, numerous studies have shown that the intestinal mucus-associated microbiota — including bacteria, viruses, and fungi — is profoundly altered in IBD patients [11]. Thus, fecal microbial transplantation (FMT) has been explored as a therapeutic approach, particularly in UC [12].

At the same time, the identification of *CARD15/NOD2* — the primary genetic susceptibility factor for CD, which encodes an intracellular receptor for components of Gram-negative bacteria — highlighted the significant role of host innate and adaptive immunity in IBD pathogenesis. This discovery led to the hypothesis that replacing immune cells might offer a long-term therapeutic solution [13–16]. Alternatively, other groups investigated whether expanding mucosal regulatory cell populations could serve as an effective therapeutic approach [17–19].

This review explores emerging strategies aimed at overcoming current therapeutic limitations in IBD, including immune reset, antigen-specific therapies, epithelial barrier restoration, microbiota-based approaches, and dietary interventions — proposing a research roadmap toward a potential cure.

Why a cure has not been found: limitations of current therapies

The need for maintenance therapy

Current international and national guidelines recommend maintenance treatment as therapy withdrawal is associated with an increased risk of flare-ups, complications, and the potential need for surgical intervention [20–22]. While corticosteroids are effective for inducing remission, they are not suitable for maintenance use due to adverse effects [23]. Immunomodulators, monoclonal antibodies, and small molecules are effective in inducing and maintaining remission; however, their long-term maintenance use requires careful monitoring due to potential loss of efficacy over time and potential safety concerns, such as opportunistic infections [24–26]. To date, effective advanced therapies include a wide range of therapeutics targeting cytokines (tumor necrosis factor [TNF], interleukin [IL]-12, IL-23), leukocyte trafficking (integrins α4β7, sphingosine-1-phosphate receptor modulator), and intracellular pathways (Janus Kinase inhibitors) (Table 1).

Table 1

Effective therapies approved for CD and/or UC.

Class	Therapy	Indication
Aminosalicylates	Sulfasalazine	UC only
	Mesalamine	UC only
Corticosteroids	Prednisone	UC & CD
	Prednisolone	UC & CD
	Methylprednisolone	UC & CD
	Budesonide	UC & CD
Immunomodulators — thiopurines	Azathioprine	UC & CD
	Mercaptopurine	CD only
Immunomodulators — folate antagonist	Methotrexate	CD only
Biologic therapies — anti-TNF	Infliximab	UC & CD
	Adalimumab	UC & CD
	Golimumab	UC only
	Certolizumab pegol	CD only
Biologic Therapies — anti-integrin	Vedolizumab	UC & CD
	Natalizumab	CD only
Biologic Therapies — anti-IL-12/-23 p40	Ustekinumab	UC & CD
Biologic Therapies — anti-IL-23p19	Risankizumab	CD only
	Mirikizumab	UC only
	Guselkumab	UC & CD
Small-molecule drugs — Janus kinase inhibitors	Tofacitinib	UC only
	Upadacitinib	UC & CD
	Filgotinib	UC only
Small-molecule drugs — sphingosine 1-phosphate (S1P) receptor modulators	Ozanimod	UC only
	Etrasimod	UC only

The concept of the therapeutic ceiling

A significant proportion of patients fail to achieve or sustain remission — a phenomenon referred to as the 'therapeutic ceiling'. This term describes the plateau in treatment efficacy observed across all approved therapies in immune-mediated disease, where introducing additional options yields little to no further benefit [27].

Several factors contribute to the therapeutic ceiling in IBD. One of the foremost challenges is primary and secondary loss of response [28,29]. This is well documented in therapies targeting TNF where combination with immunomodulators can mitigate loss of response associated with immunogenicity [30,31]. The redundancy of inflammatory pathways and the dynamic evolution of the immune response often lead to compensatory mechanisms that sustain inflammation. Adding to this complexity, IBD encompasses a spectrum of clinical phenotypes [32]. Together, these factors underscore the need for more personalized treatment strategies, ideally tailored to each patient's individual immune profile. Immune-centered therapies do not directly target other key pathophysiological mechanisms, such as dysbiosis or epithelial barrier dysfunction [33–35]. This underscores the need for alternative strategies that extend beyond immune modulation. We envision a research pathway that integrates personalized medicine, microbiome-targeted interventions, and regenerative therapies to move closer to a cure for IBD.

Paving the way to a cure: emerging research strategies

Reprogramming the immune system

The notion of immune reset, aimed at eliminating autoreactive immune cells and allowing immune

reconstitution, has emerged as a potential strategy for achieving drug-free long-term remission in IBD. Autologous hematopoietic stem cell transplantation (aHSCT) has been investigated for severe, treatment-refractory CD. However, clinical outcomes have been inconsistent. The ASTIC trial, an open-label multicenter randomized controlled trial evaluating aHSCT in active CD patients refractory to two or more classes of biological therapy, did not show significant long-term benefits over standard therapy, though subsequent analyses have reported benefits in some patients [14]. More recently, the ASTIClite trial, an open-label, multicenter, randomized controlled trial evaluating aHSCT in the same target population with an immune-ablative regimen of reduced intensity, led to clinical remission in 60% of patients at 1 year, compared to 20% in controls [15]. Nonetheless, the risks associated with aHSCT remain notable. The procedure itself carries substantial risks, including profound immunosuppression, exposing patients to severe infections and treatment-related mortality. These concerns have limited its application to highly selected cases in specialized centers.

Recent evidence indicates that the B cell compartment is altered in IBD. In UC, increased naïve B cells, IgG+ plasma cells, and gut-homing plasmablasts have been identified as correlating with disease activity [36]. UC is characterized by an IgG-skewed immune response, with an increase in IgG plasma cells, reduced somatic hypermutation, and autoreactive clones — some of which target integrin αvβ6- suggesting a role in autoimmunity. CXCL13-expressing T peripheral helper cells contribute to this dysregulation by promoting IgG class switching and driving B cell dysregulation, linking them to active inflammation. The overactivation of IgG-driven pathways also extends to macrophages, where IgG-activated macrophages contribute to severe disease progression and anti-TNF resistance. Circulating gut-homing plasmablasts, reflecting the ongoing immune response, correlate with disease severity and may serve as biomarkers for disease monitoring and prognosis. In CD, deep B cell receptor sequencing revealed CD-associated clones, enriched in class-switched IgA and IgG, populating gut mucosa, draining lymph nodes, and blood during active disease. In addition, plasmablasts of patients with active CD revealed global somatic hypermutation reduction, suggesting antigen-driven affinity maturation. Consistently, a CD-specific antibody profile was identified against *Klebsiella Pneumonia*, *Bacillus circulans*, *Lactobacillus species*, and *Enterococcus faecalis* [37]. The evolving understanding of pathogenic B-cell subsets directly informs the exploration of B-cell-targeted therapies, for which surface markers have been investigated in immune-mediated diseases. CD19, for instance, is a pan-B cell marker expressed from early B cell development through to some plasma cells. CD20, another B-cell marker, is notably absent on plasma cells, while B-cell maturation antigen (BCMA) is predominantly found on plasma cells [38]. These distinct expression profiles underscore that identifying the most appropriate target for an individual patient's specific disease context is therefore essential. This was recently highlighted in a case report where a patient with idiopathic inflammatory myositis re-infusion of CD19 chimeric antigen receptor (CAR)-T cells following disease relapse was ineffective but achieved drug-free remission with BCMA-CAR T-cell treatment [39].

Therapeutic strategies emerging from this understanding include also bispecific T cell engagers (BiTEs), by redirecting cytotoxic T cells to selectively deplete pathogenic B cells, which might offer a promising immune-reset strategy [40]. Unlike conventional B cell depletion therapies, which may incompletely eliminate disease-driving subsets, BiTEs provide a more precise and sustained immunomodulatory effect, potentially reducing autoreactive immune responses while preserving protective immune functions. While BiTEs have shown efficacy in other autoimmune diseases, their therapeutic potential in IBD remains an open avenue for investigation.

Tackling antigen-specific immune response

Antigen-driven therapy represents a rationale next step toward personalized medicine. Inspired by breakthroughs in oncology, where CAR-T cell therapies have successfully targeted disease-driving antigens, similar patient-specific strategies could potentially revolutionize IBD treatment. By precisely identifying and addressing the pathogenic antigens or immune cells driving disease in each patient, this approach could pave the way for more effective long-term therapies. Notably, CAR-T cell therapy has already shown promise beyond cancer therapy, as demonstrated in systemic lupus erythematosus, where anti-CD19 CAR-T treatment led to sustained remission [41], providing a robust blueprint for analogous developments in IBD.

Several microbial and host antigens have been implicated as significant immune targets in IBD. Flagellin, a major structural protein of bacterial flagella, has been identified as a potent immune-stimulatory antigen in CD. Similarly, Anti-Saccharomyces cerevisiae antibodies are notably more prevalent in CD patients compared to those with UC, indicating yeast mannans as potential antigenic targets. Peptidoglycan recognition proteins, which recognize bacterial peptidoglycans, are increasingly recognized as key players in innate immunity; mutations in these proteins have been associated with increased susceptibility to IBD, reinforcing bacterial peptidoglycans as potential targets for intervention. Recent research has identified anti-integrin αvβ6 autoantibodies as biomarkers preceding the onset of UC and colonic CD, highlighting another potential pathway for

antigen-specific therapeutic interventions [42]. These findings underscore the potential for targeted therapies aimed at yeast mannans, bacterial peptidoglycans, and integrin αvβ6 to precisely modulate immune responses in CD and related IBD. We could envision nanoparticles containing consortia of IBD-associated antigens encapsulated within or conjugated to adjuvants designed to shape the dendritic cells' maturation and antigen presentation toward tolerance induction [43,44]. In parallel, the exploration of pathogen-directed therapies has gained traction. A recent randomized, double-blind, placebo-controlled study demonstrated the efficacy of an antimicrobial therapy targeting *Mycobacterium avium subspecies paratuberculosis*, further supporting the role of microbial antigens in disease pathogenesis and treatment [45].

Emerging immunotherapeutic strategies are also advancing toward clinical translation. CAR-T regulatory cells designed to home to intestinal tissues and target antigens, such as flagellin and the Interleukin-23 receptor, have demonstrated efficacy *in vitro* or in preclinical mouse models [19,46]. Regarding polysaccharides, a CAR-T derived from an engineered banana lectin has been shown to recognize high-mannose glycans [47]. In addition, proof-of-concept clinical studies employing tolerogenic dendritic cell vaccines and *ex vivo* expanded regulatory T-cell therapies have also shown encouraging preliminary outcomes [17,18]. Furthermore, advances in mRNA-based therapeutic strategies could further revolutionize antigen-specific treatments by allowing for the precise modulation of immune responses [6]. The flexibility of this technology enables the development of personalized interventions tailored to individual disease-driving antigens, marking a shift toward precision medicine in IBD.

Restoring intestinal barrier function

The integrity of the intestinal epithelial barrier is increasingly recognized as central to IBD pathogenesis. Evidence in murine models and clinical observations in humans suggests that epithelial dysfunction often precedes pathological symptoms, positioning barrier integrity as a critical early target for intervention [48,49]. The ERIca trial, a cross-sectional diagnostic study in which a large cohort of IBD patients in clinical remission were closely monitored for more than 2 years, notably highlighted the prognostic significance of intestinal epithelial barrier healing, demonstrating that mucosal integrity correlates with improved clinical outcomes, thereby shifting therapeutic goals toward active barrier repair in addition to inflammation control.

Recent research has provided a breakthrough in our understanding of the Liver X Receptor (LXR) pathway as a critical adaptive response mechanism to intestinal damage. Historically, promoting epithelial regeneration raised significant concerns regarding uncontrolled cell proliferation and oncogenesis. However, recent findings demonstrate that activation of the LXR pathway in intestinal epithelial cells promotes tissue repair through amphiregulin, a ligand for the epidermal growth factor receptor, while simultaneously limiting tumorigenesis by enhancing adaptive immune responses [50]. The LXR pathway can be specifically activated either endogenously through oxysterols, which are generated from cholesterol by enzymes like CYP27A1 particularly upregulated in intestinal epithelial cells after damage, or synthetically using specific LXR agonists. This discovery underscores the therapeutic potential of targeting the LXR pathway in IBD, offering a dual benefit: promoting mucosal healing while mitigating the risk of tumorigenesis — an advancement that distinguishes LXR-targeted strategies from earlier regenerative approaches. Nonetheless, these findings have been validated exclusively in mouse models, and their translatability to human IBD remains to be determined.

Given the well-established role of epithelial barrier dysfunction as an early event in IBD pathogenesis, barrier-enhancing strategies could serve as pathogenesis-driven preventive measures. Implementing these targeted interventions in preclinical disease stages may alter delay or even prevent disease onset, offering a more precise alternative to general immunosuppressive approaches.

Reprogramming the gut microbiota

Alterations in gut microbiota have been described not only in individuals already diagnosed with IBD but also in those at risk, with specific microbial signatures detectable years before clinical onset [51]. This observation highlights the potential role of early microbiome-targeted interventions not only in disease prevention but also in adjunction to already approved immune-targeted treatments.

FMT has achieved promising results, notably in UC. The recent Second Rome Consensus Conference emphasized the need to standardize FMT protocols for UC to optimize therapeutic outcomes [52]. In addition to restoring microbial balance, combining FMT with dietary interventions — such as fiber-rich diets — can supply prebiotic substrates that promote the engraftment of beneficial bacteria, improving the overall stability of the transplanted microbiota [53]. This dual approach aims to enhance short-term efficacy, prolong remission, and reduce the frequency of relapses. The consensus document also highlights several critical aspects for optimizing FMT in UC management, including rigorous donor screening, fecal biomass characterization, and tailored administration routes. Furthermore, integrating supportive measures such as bowel preparation and antibiotic pretreatment may help

to reduce interpatient variability, improving overall treatment outcomes. These refinements are crucial not only for enhancing clinical efficacy but also for laying the groundwork for future, large-scale multicenter trials that could establish FMT as a standardized therapeutic option for UC patients.

Beyond conventional FMT, engineered microbial consortia are gaining traction as a next-generation therapeutic approach [54]. Innovative formulations such as lyophilized or encapsulated microbial consortia offer a standardized, reproducible approach. By identifying specific microbial deficiencies or overabundances observed in IBD, these formulations promise greater precision. Moreover, encapsulated or lyophilized formulations address logistical challenges associated with fresh or frozen stool preparations by improving stability, enabling precise dosing, and offering more patient-friendly delivery options. In clinical trial settings, such advancements are expected to facilitate uniformity in treatment administration and potentially increase patient adherence over the long term.

While the optimal microbial consortia are still being investigated, several specific species have emerged as promising candidates for therapeutic modulation in IBD due to their anti-inflammatory properties and role in maintaining gut homeostasis. These include butyrate-producing bacteria like *Faecalibacterium prausnitzii*, consistently depleted in IBD patients, *Roseburia spp*., and *Clostridium butyricum*, which are critical for gut barrier integrity and immune regulation. Additionally, *Akkermansia muciniphila* contributes to mucus layer maintenance, and *Bifidobacterium* and *Lactobacillus* strains are recognized for their immunomodulatory properties and ability to compete with pathogenic bacteria. The goal is to selectively enrich these beneficial species through interventions described so far to restore a balanced and resilient microbial ecosystem that can counteract dysbiosis and chronic inflammation [55].

Bacteriophage therapy offers another promising microbial-targeting approach. By specifically targeting pathogenic bacteria implicated in CD, such as adherent-invasive *Escherichia coli*, bacteriophage therapies effectively reduce bacterial load and inflammation in preclinical models without affecting commensal microbiota, offering a precision strategy that avoids broad-spectrum antibiotics [56].

Dietary interventions have also emerged as effective microbiome-modulating tools. Exclusive enteral nutrition, particularly effective in pediatric CD, has demonstrated substantial microbiome modifications and therapeutic efficacy. Dietary interventions, like the Mediterranean diet and Crohn's Disease Exclusion Diet, have shown potential to significantly alter microbial profiles to selectively enrich beneficial microbial species and improve clinical outcomes [57,58]. Furthermore, microbial metabolites, such as butyrate and tryptophan derivatives, are gaining attention as postbiotic interventions capable of replicating the therapeutic benefits of healthy microbiome without requiring live bacterial administration [59].

Future microbiome strategies are expected to evolve toward preventive applications. High-risk individuals, identified through microbiome profiling, might benefit from prophylactic interventions, including tailored probiotic formulations or dietary interventions aimed at reinforcing microbial resilience. Additionally, synthetic biology approaches that engineer microbes to sense and respond to inflammation or dysbiosis in situ represent a futuristic yet feasible therapeutic option.

Possibilities to cure monogenic and very early-onset inflammatory bowel diseases with stem cell transplantation

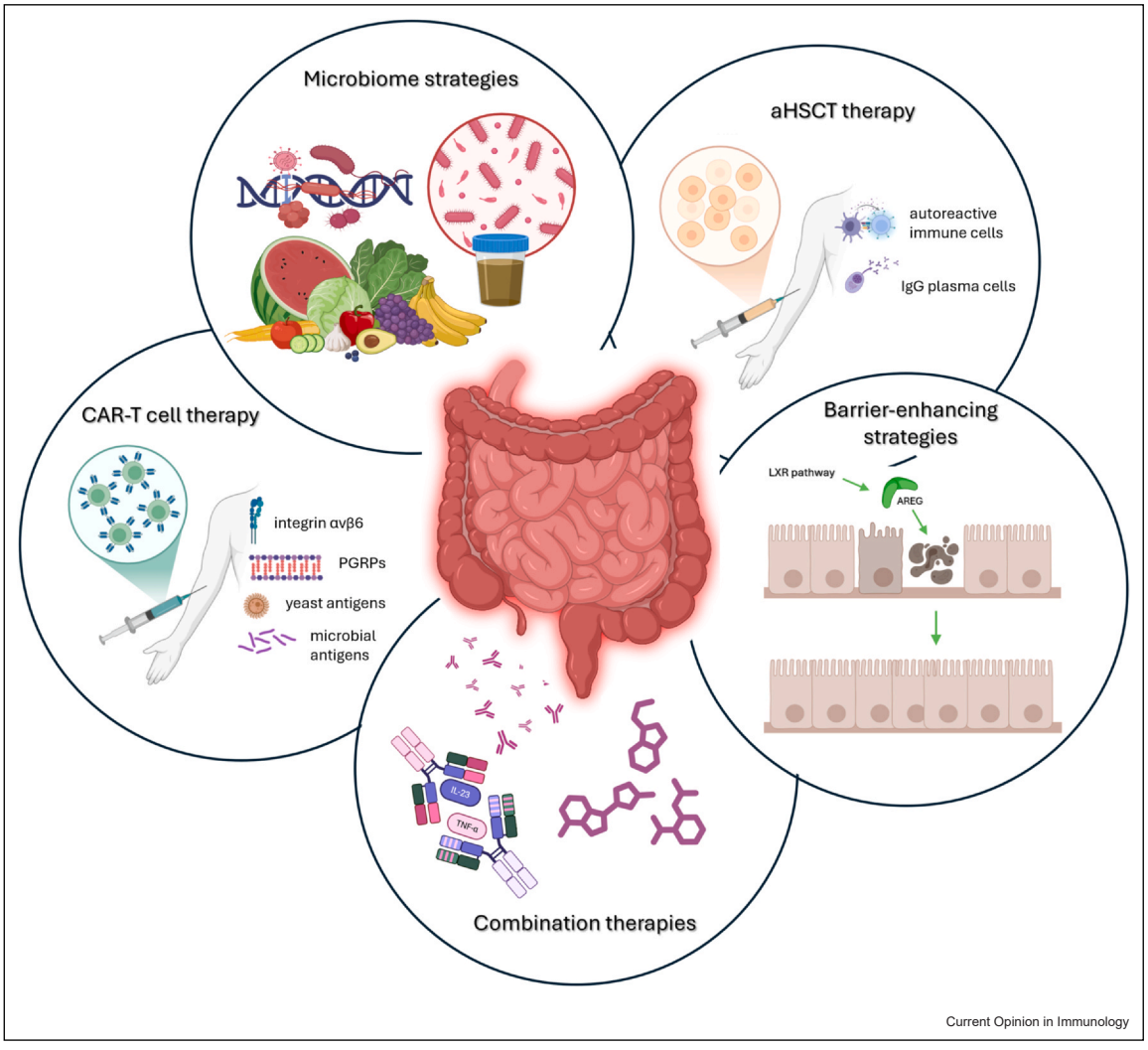
The use of HSCT as a curative approach in monogenic and very early-onset IBD (VEO-IBD), where a single gene mutation leads to profound immune dysfunction [60], has a strong biological rationale.

Monogenic IBD, which accounts for a subset of pediatric-onset IBD, is characterized by high-penetrance genetic defects affecting key pathways of immune regulation, epithelial barrier maintenance, or microbial sensing [61]. Unlike polygenic forms of IBD, which result from a complex interplay of multiple risk alleles and environmental triggers, monogenic IBD often presents within the first years of life, is highly refractory to approved therapy, and frequently requires escalation to aggressive immunosuppressive regimens or colectomy at a young age [62]. The identification of disease-causing mutations in genes such as *il10ra*, *il10rb*, *foxp3*, *ttc7a*, and *xiap* has revolutionized the management of these patients, shifting the focus from symptomatic control to targeted, potentially curative interventions [62,63].

Among these strategies, allogeneic HSCT continues to be a cornerstone treatment for patients with monogenic forms of IBD. In particular, patients with IL-10 receptor deficiencies exhibit severe and refractory colitis due to the inability to suppress excessive immune activation in the gut mucosa [61]. HSCT has been shown to induce long-term remission in these cases [64]. Similarly, individuals with *xiap* mutations, which impair NOD2 signaling and predispose to both Crohn's-like intestinal inflammation and hemophagocytic lymphohistiocytosis, have shown significant clinical improvement following HSCT [65,66].

Despite these promising outcomes, the decision to proceed with HSCT in monogenic IBD requires careful

Figure 1



Key emerging strategies aimed at achieving a definitive cure for IBD. The *microbiome strategies* circle represents interventions, such as FMT, engineered microbial consortia, and bacteriophage therapies, which seek to restore microbial balance and modulate gut inflammation. The CAR-T cell therapy circle highlights the potential of antigen-specific immune modulation, targeting pathways like integrin αvβ6, peptidoglycan recognition proteins (PGRPs), and microbial and yeast antigens. The *combination therapies* circle emphasizes the need for multitarget approaches, such as dual inhibition of TNF and IL-23, to overcome the limitations of single-agent therapies. The *barrier enhancing strategies* circle focuses on restoring intestinal epithelial integrity through innovative pathways like Liver X Receptor (LXR) signaling. Finally, the *aHSC therapies* circle represents immune reprogramming through aHSCT, offering a potential solution for refractory cases. Together, these strategies aim to modify the disease course, moving beyond symptom management toward long-term remission or a potential cure for IBD.

risk–benefit assessment. The procedure carries substantial risks, including graft-versus-host disease, treatment-related mortality, and prolonged immunosuppression, which predispose patients to life-threatening infections. Given these risks, HSCT is typically reserved for cases with life-threatening disease progression or complete therapy resistance [67]. The success of HSCT is also highly dependent on optimal donor selection and conditioning regimens, with recent advancements in reduced-intensity conditioning protocols aiming to minimize toxicity while ensuring engraftment [68].

As novel gene-editing technologies continue to advance, the future of monogenic IBD treatment may shift from traditional HSCT to more tailored, low-risk interventions, ultimately moving the field toward curative, personalized medicine.

Incoming therapies: the promise of combination strategies in inflammatory bowel disease treatment

The complex interplay of inflammatory pathways and disease heterogeneity have prompted a shift to

combination strategies, inspired by successes in other chronic diseases, such as human immunodeficiency virus, hepatitis C virus, and oncology. Combination therapy aims to break the efficacy ceiling reducing primary and secondary nonresponse [69].

Historically, combination therapy in IBD has primarily involved the concomitant use of immunomodulators with biologics, particularly anti-TNF agents. The landmark SONIC trial demonstrated superior efficacy with azathioprine plus infliximab compared to either agent alone [70]. Recently, the simultaneous blockade of TNF-α and IL-23 is currently being explored. The VEGA study, a phase 2 trial, suggested that combining guselkumab (an IL-23 inhibitor) and golimumab (a TNF-α inhibitor) led to higher rates of clinical and endoscopic remission compared to monotherapy in patients with moderate-to-severe UC [71]. Such an approach may reduce compensatory immune escape mechanisms [72]. Similarly, combinatorial approaches targeting leukocyte trafficking alongside cytokine inhibition may offer complementary benefits by simultaneously dampening systemic inflammation and limiting gut-specific immune cell infiltration [73]. However, it should be noted that a multidrug approach may present challenges in balancing efficacy with safety concerns or reimbursement considerations, as the cost of multiple high-priced biologics or small molecules may pose barriers to implementation [74,75].

Conclusions: a new era in inflammatory bowel disease treatment

Despite major advancements, a definitive cure for IBD remains elusive. Current therapies primarily control inflammation rather than addressing its root causes, necessitating lifelong treatment and exposing patients to potential therapy-related risks.

Future strategies aim to fundamentally modify disease course beyond immune-mediated inflammation. Immune reprogramming approaches, such as CAR-T cell therapy and B cell–targeted interventions, hold promise in the near future, while intestinal barrier restoration is emerging for both prevention and treatment. At the same time, microbiome-based interventions, including FMT, engineered microbial consortia, and bacteriophage therapy, could be a companion to immune modulation toward disease modification (Figure 1).

Emerging strategies are paving the way toward a new therapeutic era, bringing us ever closer to a potential cure for IBD.

Declaration of Competing Interest

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