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Epidemiology, pathogenesis, diagnosis, and treatment of inflammatory bowel disease: Insights from the past two years

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Abstract

Inflammatory bowel disease (IBD), including ulcerative colitis and Crohn's disease, is a chronic inflammation of the gastrointestinal tract with unknown etiology. The cause of IBD is widely considered multifactorial, with prevailing hypotheses suggesting that the microbiome and various environmental factors contribute to inappropriate activation of the mucosal immune system in genetically susceptible individuals. Although the incidence of IBD has stabilized in Western countries, it is rapidly increasing in newly industrialized countries, particularly China, making IBD a global disease. Significant changes in multiple biomarkers before IBD diagnosis during the preclinical phase provide opportunities for earlier diagnosis and intervention. Advances in technology have driven the development of telemonitoring tools, such as home-testing kits for fecal calprotectin, serum cytokines, and therapeutic drug concentrations, as well as wearable devices for testing sweat cytokines and heart rate variability. These tools enable real-time disease activity assessment and timely treatment strategy adjustments. A wide range of novel drugs for IBD, including interleukin-23 inhibitors (mirikizumab, risankizumab, and guselkumab) and small-molecule drugs (etrasimod and upadacitinib), have been introduced in the past few years. Despite these advancements, approximately one-third of patients remain primary non-responders to the initial treatment, and half eventually lose response over time. Precision medicine integrating multi-omics data, advanced combination therapy, and complementary approaches, including stem cell transplantation, psychological therapies, neuromodulation, and gut microbiome modulation therapy, may offer solutions to break through the therapeutic ceiling.

Keywords: Epidemiology; Pathogenesis; Diagnosis; Telemedicine; Treatment; Inflammatory bowel disease

Introduction

Inflammatory bowel disease (IBD), encompassing ulcerative colitis (UC) and Crohn's disease (CD), is a chronic, nonspecific inflammation of the intestine with an unknown etiology, characterized by a relapsing-remitting course.[1] IBD incidence is stable in Western countries but is rapidly increasing in newly industrialized countries, making it a global disease.[1–3] Advances in non-invasive and home-based technologies enable real-time assessment of disease activity and adjustment of treatment strategies. Despite considerable progress in IBD therapeutic agents, approximately one-third of patients are primary non-responders to initial treatment, and half eventually lose response over time.[4] Precision medicine and advanced combination therapies are promising for breaking through the therapeutic ceiling. This review highlights key advances over the past two years in the epidemiology, pathophysiology, diagnosis, assessment, and treatment of IBD.

Epidemiology

IBD's evolution is classified into four epidemiological stages: (1) Emergence, (2) Acceleration in incidence, (3) Compounding prevalence, and (4) Prevalence equilibrium.[2] Studies conducted in Western countries from 1990 to 2016 revealed that most regions are in the third stage, characterized by a stable or decreasing incidence and rapidly increasing IBD prevalence.[1,2] Recent data from Western countries confirm these trends. For instance, a population-based surveillance cohort from 2002 to 2014 in eight provinces of Canada forecasted the incidence and prevalence of IBD through 2035. IBD incidence is estimated to remain stable at approximately 30 per 100,000

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over the next decade, with a stable average annual percentage change of 0.36%.[5] However, IBD prevalence in Canada was estimated to be 843 per 100,000 in 2023 and is projected to increase to 1098 per 100,000 in 2035, surpassing 1.1% of the population within the next decade.[5] Similarly, a population-based study conducted in North Denmark also supported this trend, revealing a four-fold increase in IBD incidence from 11.5 in 1978 to 51.3 per 100,000 individuals in 2014, which then stabilized in 2020.[6] The prevalence of IBD more than doubled, rising from 424 to 872 cases per 100,000 persons from 2003 to 2020.[6] However, exceptions exist in Western countries. One notable exception is the Faroe Islands, where IBD incidence continued to increase significantly, from 8 to 70 per 100,000 in 1960–1979 and 2010–2020, respectively.[7] Despite the population's largely unchanged genetic homogeneity, the rapid increase in IBD incidence strongly points toward the influence of environmental risk factors.[7] Although the incidence of adult IBD is stable or decreasing in most Western countries, the incidence of pediatric or very early onset IBD continues to increase. In Canada, the incidence of pediatric-onset IBD is forecast to increase significantly from 14.4 to 18.5 per 100,000 between 2014 and 2035, respectively, with an average annual percentage change of 1.27%.[5] Similarly, the Global Disease Burden Study indicated a significant increase in the global incidence of pediatric-onset IBD from 0.92 to 0.99 per 100,000 population in 1990 and 2019, respectively, with a significant annual percentage change of 0.25%, particularly in countries with a high sociodemographic index where the incidence rate was notably elevated, reaching 6.3 per 100,000 person-years in 2019.[8] Moreover, an increasing incidence of elderly-onset IBD has been reported in several recent studies. According to a nationwide Danish population-based cohort study, the incidence of elderly-onset CD continues to rise, whereas that of elderly-onset UC may decrease.[9] A recent nationwide cohort study conducted in Finland revealed a notable increase in the crude annual incidence of IBD, from 28 to 48 per 100,000 person-years in 2000 and 2020, respectively, corresponding to an average annual increase in IBD incidence of 2.4%.[10] Notably, the increase was most pronounced in elderly-onset patients, with incidence rates increasing from 14 to 31 per 100,000 person-years in 2000 and 2020, respectively.[10] As the global population ages and the incidence of elderly-onset IBD rises, IBD prevalence among the elderly is also increasing. The increasing prevalence of IBD in this population will exert significant pressure on healthcare systems, as elderly patients are more susceptible to opportunistic infections, sepsis, comorbidities, and malignancies when undergoing immunosuppressive therapies.[11]

At the turn of the 21st century, globalization led to rapid economic development in newly industrialized and emerging regions, such as Africa, Asia, and Latin America. Economic growth, coupled with increasing westernization, urbanization, and industrialization, has been accompanied by a sharp increase in IBD incidence in these regions.[1] Currently, many newly industrialized countries in Asia and Latin America have entered the second stage.[2] China, the largest newly industrialized country, has experienced exponential increases in both national and personal income in recent years, accompanied by a shift toward a more Westernized lifestyle.[12] Over the past few decades, this change has been paralleled by an accelerated increase in IBD incidence.[13,14] Population-based studies on IBD incidence in China have primarily focused on specific cities. For example, the age-adjusted incidence of IBD was reported as 1.96 per 100,000 in 2010 in Wuhan of Hubei province,[15] 3.14 per 100,000 persons in 2011–2012 in Zhongshan of Guangdong province,[16] and 1.77 per 100,000 population in 2012–2013 in Daqing of Heilongjiang province.[17] A population-based study conducted across 13 countries and regions in the Asia-Pacific from 2011 to 2013 demonstrated that IBD incidence in 10 areas of China varied from 0.54 to 3.64 per 100,000.[18] Notably, a south-to-north disease gradient was observed with a higher incidence in Southern China. The incidence of IBD in Guangzhou (southern city) was the highest at 3.64 per 100,000, whereas that in Xi'an (northern city) was the lowest at 0.54 cases per 100,000.[18] Recently, the first nationwide population-based study in China, which included 0.51 billion urban-insured people in 23 provinces from 2012 to 2016, reported an IBD incidence of 10.04 per 100,000 person-years.[19] IBD incidence in China is higher than that in developing countries but lower than that in the Western world.[19] The ongoing accelerating urbanization and industrialization process in China are anticipated to exacerbate the IBD burden, posing substantial challenges for the country's healthcare system.[19] Addressing these challenges will require strategic planning and resources to mitigate the impact of IBD on the population.

Pathophysiology

The etiology of IBD is complex and not yet fully understood. Current evidence suggests multifactorial interactions, where environmental factors affect individuals with genetic susceptibility and, together with the involvement of the gut microbiota, trigger an inappropriate immune response in the gut, ultimately leading to persistent inflammation and tissue damage[12] [Figure 1].

Genetic susceptibility

Over the past 20 years, genome-wide association studies (GWAS) have advanced our understanding of IBD's genetic underpinnings.[20] Most data come from European populations; however, Liu *et al*[21] conducted the largest GWAS in East Asian populations, identifying 80 genetic loci associated with IBD in East Asian populations. Fifty-four genetic loci were reported for the first time in the East Asian populations, among which 38 had already been reported in European populations and 16 were new loci, such as *ADAP1* and *GIT2*. By combining data from over 30,000 European IBD cases with controls, the study identified 81 new IBD-related genetic loci, increasing the total to 320. Although the genetic impact of IBD is comparable across East Asian and European populations, CD exhibits a stronger heritability component than UC. In European populations, *NOD2* and *ATG16L1* are the primary susceptibility genes, whereas *TNFSF15* is predominant in East Asian populations. In addition, a polygenic risk score for IBD combining East Asian and European population data

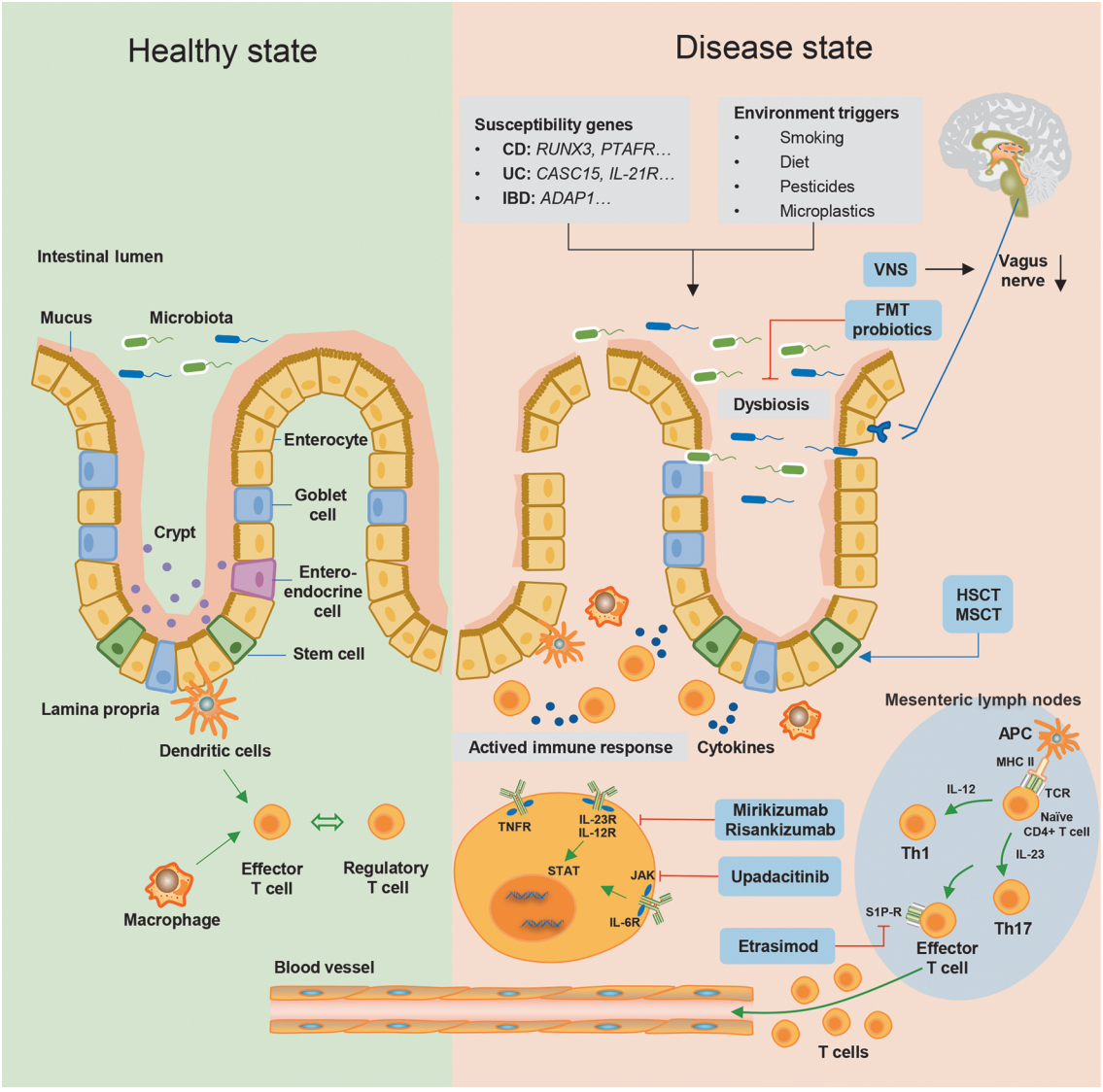

Figure 1: Overview of the pathophysiology and emerging therapeutic targets of IBD. IBD is characterized by genetically predisposed individuals exposed to environmental factors experiencing gut microbiota dysbiosis, leading to an increase in pathogenic organisms. This is accompanied by abnormal differentiation or exhaustion of intestinal stem cells, collectively impairing the intestinal mucosal barrier function. These changes trigger an imbalance between effector T cells and regulatory T cells. T cells differentiate into Th1 and Th17 cells via the JAK/STAT signaling pathway, releasing pro-inflammatory cytokines. These cells can also migrate into the vasculature and circulate to inflammatory sites through S1P receptor-mediated processes. Under physiological conditions, the vagus nerve mediates the cholinergic anti-inflammatory pathway to maintain intestinal immune homeostasis. However, IBD patients exhibit reduced vagal nerve activity, further exacerbating inflammation. Advances in understanding the pathogenesis of IBD have identified novel therapeutic targets. Recently, IL-23 inhibitors and JAK inhibitors have been approved for IBD treatment, offering new avenues for disease management. Furthermore, emerging therapeutic modalities such as FMT, probiotics, HSCT, MSCT, and VNS have shown promise in clinical and preclinical studies. APC: Antigen-presenting cell; CD: Crohn's disease; FMT: Fecal microbiota transplantation; HSCT: Hematopoietic stem cell transplantation; IBD: Inflammatory bowel disease; IL: Interleukin; JAK: Janus kinase; MHC: Major histocompatibility complex; MSCT: Mesenchymal stem cell transplantation; S1P: Sphingosine-1-phosphate; STAT: Signal transducer and activator of transcription; Th: T-helper cell; UC: Ulcerative colitis; VNS: Vagus nerve stimulation. Created using Figdraw (*www.figdraw.com*).

demonstrated a higher predictive accuracy than using data from a single population alone. Identifying new susceptibility genes enhances understanding of IBD pathogenesis and enables precise diagnosis and treatment. IBD susceptibility genes are associated with bacterial recognition, interleukin (IL)-23/Th17 pathway, autophagy, and epithelial barrier. A fine-mapping study of IBD-associated genes identified a long non-coding RNA, *CARINH*, linked to IBD within its risk locus. *CARINH* promotes IRF1 transcription in myeloid cells, forming a *CARINH*/IRF1 regulatory loop that maintains gut microbiota homeostasis and controls intestinal inflammation.[22] Recent studies have highlighted a gene desert on chromosome 21q22, identifying *ETS2* as a core regulator of human inflammatory macrophages and a key pathogenic factor in IBD. Furthermore, inhibitors targeting the mitogen-activated protein kinase pathway have shown potential in suppressing *ETS2*-mediated inflammatory effects, offering a new target for precision therapy in IBD and related inflammatory diseases.[23] Whole-genome methylation analysis of over 300 patient-derived intestinal epithelial organoids revealed a stable loss of DNA methylation in major histocompatibility complex (MHC) Class I molecules and *NLRC5* within the intestinal epithelium of CD patients. Increased MHC-I expression in the intestinal epithelial tissue of CD patients activates $CD8^+$ T cells, thereby promoting intestinal inflammation. Machine

learning approaches suggested that MHC-I methylation levels could serve as potential biomarkers for CD diagnosis and prognosis.[24]

Environmental factors

Environmental factors can exacerbate intestinal inflammation in genetically predisposed individuals. Earlier research indicated that smoking promoted CD development and may offer a protective effect against UC. However, recent prospective cohort studies have found that both current and former smokers exhibited a higher risk of developing CD and UC than non-smokers. Abnormal epigenetic modifications at the *DNMT3A*, *LTA/TNF*, and *AHRR* loci may mediate the impact of smoking on IBD pathogenesis.[25] Unhealthy dietary habits, especially a higher intake of ultra-processed foods, increase the risk of CD, with a 71% increased risk observed in individuals consuming more ultra-processed foods, though no significant link to UC was found.[26] Exposure to pesticides may also increase IBD risk by increasing systemic inflammation, disrupting the gut barrier function, and disturbing the microbiota. A study from the PREDICTS cohort observed that elevated serum concentrations of chemical mixtures 6–10 years before diagnosis were associated with an increased IBD risk; however, this association was not observed at other time points closer to diagnosis.[27] Microplastics are widely present in food and drinking water in modern society. Microplastic concentration in the stool of IBD patients is significantly higher than that in healthy individuals, and microplastic levels in the stool are positively correlated with IBD severity. Fifteen types of microplastics were identified, including polyethylene terephthalate and polyamide.[28] Prospective studies are required to explore the relationship between microplastics and IBD development and progression.

The gut microbiome plays a crucial role in the interaction between the external environment and intestinal mucosa. Research has revealed significant gut microbiota dysbiosis in IBD patients. However, whether this is a cause or consequence of intestinal inflammation remains unknown, as does which specific microbial strains are involved and how they influence disease progression and severity.[29] Patients with early-stage CD have been associated with a significant reduction in the gut microbiota, which produces short-chain fatty acids.[30] A large cohort study of healthy first-degree relatives of CD patients showed alterations in gut microbiota composition 5 years before CD onset, confirming for the first time a link between gut microbiota changes and future CD development. Researchers developed a microbiome risk score using machine learning models, identifying five key taxa, *Ruminococcus torques*, *Blautia*, *Colidextribacter*, *Oscillospiraceae*, and *Roseburia*, contributing to a score.[31] Furthermore, fecal microbiota transplantation from patients with a microbial composition close to CD into germ-free mice induced spontaneous colonic inflammation, reinforcing the causal role of specific microbial communities.[32] In addition, significantly increased fecal proteolytic and elastase activities in UC patients were observed before disease onset, negatively and positively correlating with the relative abundance of potentially beneficial bacteria (*Adlercreutzia*) and proteolytic bacterial groups (*Bacteroides vulgatus*), respectively.[33] These gut microbiota changes may serve as non-invasive biomarkers for monitoring the inflammatory status of individuals at IBD risk and may represent potential therapeutic targets.

Dysregulated immune responses

IBD is characterized by dysregulated innate immunity, abnormal activation of adaptive immunity, and an imbalance between anti-inflammatory and pro-inflammatory cytokines. Macrophages maintain intestinal homeostasis and drive the inflammatory response. In IBD, metabolic reprogramming is a key determinant of macrophage function and disease progression. IL-10 can switch macrophage metabolism from glycolysis to oxidative phosphorylation, thereby inducing an anti-inflammatory phenotype.[34] York *et al*[35] discovered that in the absence of IL-10 signaling, Toll-like receptor 2-activated macrophages exhibit increased metabolic flux through the sphingolipid synthesis pathway, abnormally activating downstream transcription factors, such as Rel of the NF-κB family. Innate lymphoid cells (ILCs) may also play a central role in IBD pathogenesis, with ILC3 serving as the major mediator of chronic intestinal inflammation. The expression of an immune regulatory checkpoint molecule—cytotoxic T-lymphocyte antigen 4 (CTLA-4) is significantly upregulated in ILC3s. Activated by gut microbiota and IL-23, this pathway suppresses inflammatory T-cell responses and promotes immune regulation. Human ILC3s also upregulate CTLA-4 in response to IL-23 or intestinal inflammation, which may be affected in IBD patients.[36] This study provides new insights into IL-23 as a driver of intestinal inflammation in IBD and suggests that ILC3 CTLA-4 could become a new marker and therapeutic target for intestinal health. Forkhead box protein 3 $(FOXP3)^+$ regulatory (Treg) cells maintain immune self-tolerance and modulate inflammatory signaling in many immune-mediated diseases. However, emerging evidence suggests alterations in function within the inflammatory environment. Single-cell sequencing technology revealed five unique pro-inflammatory $FOXP3^+$ Treg subpopulations in CD patients. Treatment with vorinostat specifically targeted these cells, restoring the suppressive capacity of tumor necrosis factor (TNF)-α-treated Treg cells.[37]

Unconventional T cells, including γδ T cells, invariant natural killer T cells (iNKT), and mucosal-associated invariant T cells (MAIT), recognize antigens independently of MHC class I or II molecules.[38] Research is increasingly focusing on the role of these atypical T-cells in IBD. A phenotypically distinct subpopulation of γδ T intestinal immune cells co-expressing the T cell receptor Vγ4 and the integrin CD103 promotes intestinal inflammation tissue repair and is maintained by butyrophilin-like gene. In IBD patients, this subpopulation is disproportionately reduced and dysregulated.[39] MAIT cells can sense bacterial metabolic pathways associated with gut inflammation and protect the host from intestinal inflammation by providing anti-inflammatory and tissue repair mediators.[40] iNKT cells derived from the colonic mucosa of CD patients can suppress $CD4^+$ T cell pathogenicity through IL-10 secretion. The abundance of iNKT cells is inversely

correlated with that of pro-inflammatory Th1 and Th17 cells, predicting a better clinical outcome.[41] Subsets of colonic $CD4^+$ and $CD8^+$ T lymphocytes with gene expression profiles similar to those of stem-like progenitors have been identified in colonic T cells isolated from UC patients and controls. T cell receptor sequence analysis revealed clonal associations between stem-like and pro-inflammatory T cells, suggesting their involvement in maintaining the effectors that drive inflammation.[42] These findings provide new perspectives on IBD treatment, highlighting the importance of unconventional T cells in maintaining gut homeostasis and preventing inflammation.

Diagnosis and Assessment

Preclinical phase in IBD

Most IBD patients already exhibit bowel damage at the time of diagnosis, making it essential to detect changes during the preclinical phase. A panel of 51 protein biomarkers was identified to predict CD development within 5 and 1 years with an area under the receiver operating characteristic curve (AUROC) of 0.76 and 0.87, respectively.[43] Analysis of these biomarkers indicated that imminent CD development was associated with significant alterations in several biological processes, including changes in the complement cascade, lysosomal activity, innate immune response, and glycosaminoglycan metabolism.[43] Although the exact events and processes occurring during the preclinical phase remain unknown, it is widely accepted that this phase likely precedes IBD diagnosis by approximately 1–5 years.[44] Interestingly, a recent study concluded that disease initiation, particularly in CD, may occur much earlier than previously believed. By analyzing 17 hematological and biochemical parameters collected up to 10 years before diagnosis in more than 20,000 IBD patients and population controls, Vestergaard *et al*[44] systematically characterized the preclinical phase of IBD, delineating widespread significant changes that occur in multiple biochemical and hematological parameters up to 8 and 3 years before CD and UC diagnosis, respectively. These changes in the pre-diagnostic phase revealed an opportunity for earlier intervention, especially in patients with CD. In addition, Rudbaek *et al*[45] conducted the first study to investigate the relationship between systemic inflammatory markers at birth and later IBD risk. This study measured cytokine concentrations a few days after birth in 464 individuals who later developed IBD and found that neonatal cytokine levels were not associated with pediatric IBD in the overall cohort.[45] However, decreased levels of IL-4 and increased levels of IL-17A were observed a few days after birth in patients who developed IBD before the age of 6 years.[45] This finding indicates that individuals with very early-onset IBD may present with systemic inflammatory changes at birth, providing essential evidence to advance our understanding of the mechanisms driving the onset and progression of IBD.

Assessment of disease activity in IBD

Early diagnosis and intervention are essential to improve the outcomes of patients with IBD. Equally important is the timely and accurate assessment of disease activity with adjustments to therapy. Endoscopic healing (EH) has consistently been associated with better short- and long-term IBD disease outcomes and is considered essential for modifying the natural IBD course.[46] Therefore, EH is recognized as a key long-term therapeutic target in the STRIDE (selecting therapeutic targets in inflammatory bowel disease)-II guidelines.[46] However, there is no universally accepted definition of EH, and considerable variation exists among definitions used for EH in clinical trials, particularly in CD.[46] The Modified Multiplier Simple Endoscopic Score for Crohn's Disease (MM-SES-CD), which places greater emphasis on specific features such as ulcer size, extent of ulceration, non-passable stenosis, and specific locations such as the ileum and rectum, has demonstrated significantly improved accuracy over the traditional SES-CD in predicting EH at week 52[47]; however, the definition of EH using the MM-SES-CD remains undetermined. Recently, Narula *et al*[48] demonstrated that achieving an MM-SES-CD score <22.5 in patients with ileocolonic or colonic CD is associated with a low risk of disease progression and may be a suitable target in EH clinical trials and practice. In UC, the endoscopic evaluation of mucosal injury remains the primary method for assessing disease severity and therapeutic efficacy. The Mayo Endoscopic Score (MES) reports the worst severity in the colon of UC patients. Advancements in artificial intelligence (AI) are transforming IBD assessment, offering revolutionary contributions to endoscopy field.[49] A prospective cohort study analyzed 11,472 endoscopic images from 110 clinically remittent UC patients and demonstrated that an AI-based MES diagnostic system during colonoscopy can stratify the risk of future clinical relapse in UC patients in clinical remission, enhancing the diagnostic capabilities of non-specialists, thereby improving patient treatment outcomes and quality of life.[50] However, MES does not account for variations in disease severity.[49] Stidham *et al*[49] used endoscopic videos from the UNIFI clinical trial, which compared ustekinumab and placebo for UC, to perform computer vision analysis. This analysis spatially mapped MES to generate a cumulative disease score.[49] The cumulative disease score demonstrated greater sensitivity and statistical power for detecting endoscopic changes than the MES and provided a higher resolution and more comprehensive depiction of UC activity, thereby enhancing the detailed assessment of treatment efficacy.[49]

Frequent endoscopies, though the gold standard for evaluating disease activity, can overburden patients. However, colonoscopy is less acceptable than non-invasive imaging techniques such as magnetic resonance enterography, computed tomography (CT) enterography, and intestinal ultrasound (IUS).[51] Although transmural healing in patients with CD is not routinely recommended in STRIDE II, it is linked to a lower risk of hospitalization, surgery, and slower bowel damage progression.[52] Buisson *et al*[52] developed and validated a reliable and easy-to-use magnetic resonance imaging scoring system to assess transmural response and healing in daily practice and clinical trials in patients with CD using three criteria: bowel thickness, the presence of ulcers, and enlarged lymph nodes. Obesity has also been identified as a factor

associated with IBD progression, higher surgery risk, and failure of biologics.[53] Specifically, visceral adiposity (calculated as the ratio of visceral adipose tissue to subcutaneous adipose tissue via CT measurements) might be a superior measure of obesity than body mass index (BMI).[53] Visceral adiposity was associated with a shorter time to IBD flares, whereas BMI was not.[53] IUS offers a non-invasive, radiation-free, accurate, well-tolerated, and cost-effective alternative to endoscopy, eliminating the need for fasting or bowel preparation.[51] Its global use in monitoring IBD has grown substantially in recent years.[54,55] Achieving ultrasound remission (bowel ultrasound score >3.52 by week 12) was associated with a higher risk of failure to achieve long-term endoscopic remission at 12 months.[56] IUS enables early and timely evaluation of disease activity and treatment response.[56] Fecal biomarkers are widely studied non-invasive methods for diagnosing and monitoring IBD. Neutrophil markers such as myeloperoxidase (MPO) and fecal calprotectin (FC) demonstrated high diagnostic capability (area under the curve [AUC] = 0.85) in differentiating patients with IBD from symptomatic patients without IBD.[57] In addition, MPO, FC, and human neutrophil lipocalin at diagnosis were associated with more aggressive UC disease course.[57] The Disease Severity Index (DSI) comprehensively measures IBD burden.[58] However, this relies on colonoscopy, an invasive and costly procedure, to assess gut inflammation levels. To reduce reliance on invasive procedures, Swaminathan *et al*[58] developed a non-invasive DSI using FC and fecal MPO, which showed comparable prognostic accuracy to the original DSI (FC: AUROC = 0.83, 95% confidence interval [CI] 0.77–0.89; MPO: AUROC = 0.80, 95% CI 0.73–0.87; $P_{difference}$ >0.05) without requiring endoscopic assessment.

Telemedicine in IBD

Traditional IBD monitoring and management rely on regular prescheduled face-to-face visits, with frequency determined by the treatment regimen. However, the chronic, lifelong, and incurable nature of IBD presents significant challenges for effective disease monitoring. Recently, particularly during the COVID-19 pandemic, telemedicine has been used to manage chronic conditions such as congestive heart failure and chronic obstructive pulmonary disease, enhancing care quality and optimizing resource use.[59]

Similarly, telemedicine has shown significant potential in enhancing IBD management. Telemonitoring enables rigorous and real-time disease surveillance and assessment [Figure 2], facilitating the early identification of disease

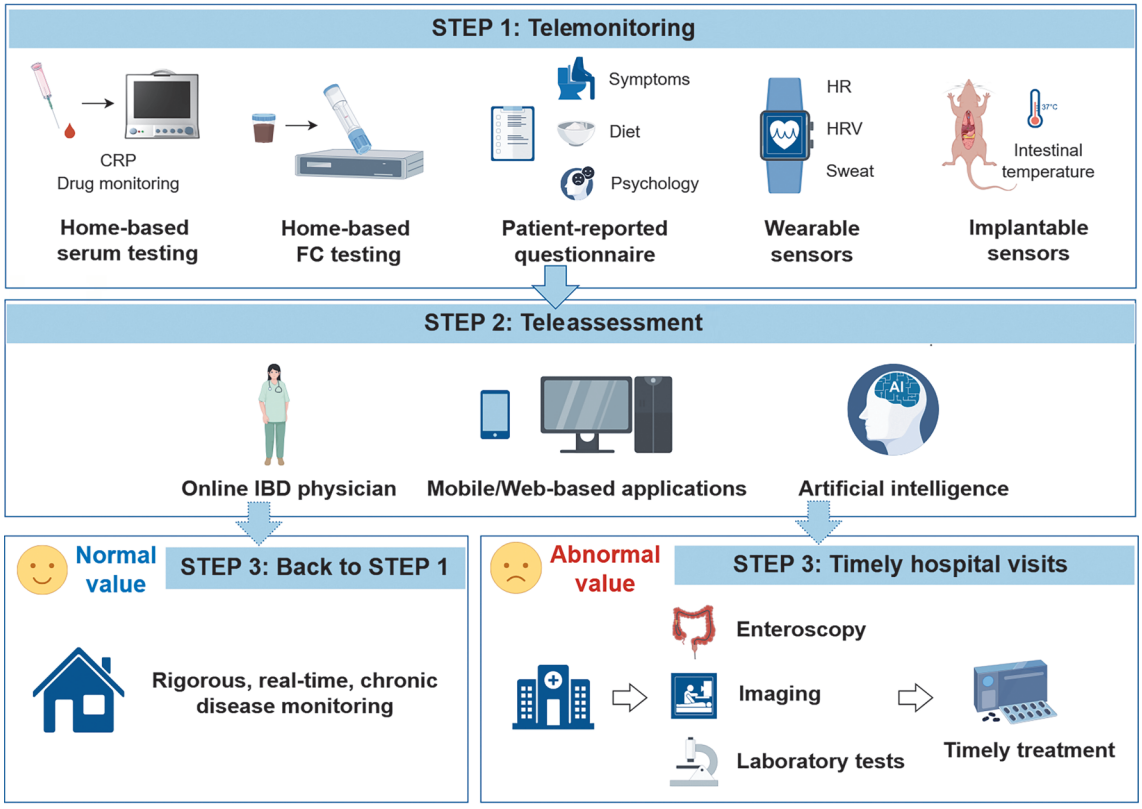

Figure 2: The telemedicine for the management of IBD. Step 1, telemonitoring: Patients can perform serum testing (CRP, drug monitoring including drug and antibody concentrations), FC, and patient-reported questionnaires (symptoms, diet, and psychology) at home. In addition, wearable sensors could perform real-time monitoring for HR, HRV, sweat CRP, IL-6, and calprotectin. Implantable sensors might be available in the future. Step 2, teleassessment: All the test results in step 1 are transferred to online IBD physicians, mobile/web-based applications, or artificial intelligence-based models for disease assessment and monitoring. Step 3: At this step, two possible situations may arise. If a patient's test results are all normal or the teleassessment from step 2 estimates that the patient is at a low risk for disease recurrence, then this patient will be moved back to step 1, which is to continue rigorous, real-time, chronic disease monitoring. If a patient's test results are abnormal or the teleassessment from step 2 estimates that the patient is at high risk for disease recurrence, the patient will be recommended to visit the hospital for further examinations including enteroscopy, imaging, and laboratory tests, or to modify or adjust the treatment. CRP: C-reactive protein; FC: Fecal calprotectin; HR: Heart rate; HRV: Heart rate variability; IBD: Inflammatory bowel disease.

flares before routine clinic visits, thereby offering new opportunities to prevent intestinal damage and improve long-term outcomes.[60] For instance, the telemedicine system myIBDcoach in the Netherlands has been shown to safely and effectively reduce outpatient visits (1.55 *vs*. 2.34, P <0.0001) and hospitalizations (0.05 *vs*. 0.10, $P = 0.046$) for patients with IBD.[59] This secure, web-based application, accessible via tablets or smartphones, includes monthly monitoring modules covering disease activity, medication use, treatment adherence, treatment satisfaction, potential side effects, and factors affecting patient-reported outcomes, such as quality of life and work productivity.[59] Another innovative tool is the patient-reported infections questionnaire (PRIQ), developed by Rezazadeh Ardabili *et al*[61] for the remote monitoring of infections in IBD patients. The PRIQ is a 7-item questionnaire covering 15 infection categories. In a prospective validation study conducted over one year involving 584 IBD patients, the PRIQ demonstrated a high level of agreement and diagnostic accuracy compared with an established gold standard.[61]

Advancements in technology have led to innovative methods for disease monitoring, aimed at alleviating the burden on patients and healthcare providers. Home testing kits for FC are now available, demonstrating comparable and acceptable agreement with companion enzyme-linked immunosorbent assay for FC levels below 500 mg/g, allowing patients to measure FC levels remotely.[60] A randomized controlled trial (RCT) demonstrated the effectiveness and positive reception of combining remote symptom monitoring with home-based FC testing.[62] This approach has the potential to reduce the need for face-to-face outpatient appointments without deteriorating symptoms or health-related quality of life.[62] Other remote monitoring tools, such as dried blood spot C-reactive protein (CRP) and fingerstick therapeutic drug monitoring, are feasible and equivalent to traditional serum sampling remote monitoring tools for disease activity in patients with rheumatic inflammatory diseases. Emerging biosensors integrated into wearable or implantable devices allow real-time monitoring of inflammation and environmental triggers.[63] These devices facilitate continuous remote monitoring to track flares before clinical symptom onset and achieve optimal disease interception and remission.[63] In particular, wearable devices are increasingly being used and accepted by patients with IBD. In a survey, 89.0% of respondents believed that wearable devices could provide important health information, and 93.8% were willing to use them to aid physician-led IBD management.[64]

Sweat, a biofluid containing analytes such as cytokines and inflammatory markers, is easily and non-invasively accessible.[65] Sweat and serum markers are similar in healthy individuals.[65] In a prospective cohort study, longitudinally collected IL-6 and CRP levels, measured in sweat using the IBD AWARE device, correlated with serum measurements in patients with IBD.[65] In another study, CRP, IL-6, and calprotectin levels during perspiration were measured using a novel wearable IBD AWARE device.[66] The strongest linear relationship was observed between perspiration and serum calprotectin levels ($R^2 = 0.7195$), followed by that between perspiration and serum CRP levels ($R^2 = 0.615$).[66] A moderate linear relationship was observed between perspiration and serum IL-6 levels ($R^2 = 0.5411$).[66] In addition, patients with active disease had higher levels of perspiration and serum calprotectin than those in remission.[66] Perspiration, as a non-invasive, continuous marker, can measure gut inflammation and distinguish between patients with active and inactive IBD.[66] In addition, sweat enables continuous monitoring of TNF-α level in patients with IBD over multiple days.[67] A moderate linear relationship was observed between serum and sweat TNF-α levels ($R^2 = 0.72$).[67] Patients with IBD exhibited significantly higher sweat TNF-α levels than healthy controls (mean 2.11 *vs*. 0.19 pg/mL, P <0.0001).[67] Furthermore, sweat TNF-α measurements differentiated patients with active IBD from healthy controls (AUC = 0.962, 95% CI 0.894–1.000).[67] These findings suggest that therapeutic drug monitoring and continuous inflammatory marker tracking at home may soon become feasible for IBD patients.[67]

Wearable devices can also provide a simple and longitudinal assessment of heart rate variability (HRV), an indicator of autonomic nervous system activity relevant to the enteric nervous system in the gastrointestinal tract. A pilot study involving 15 patients with UC measured HRV over 9 months using a remote patient-monitoring system, VitalPatch, and demonstrated that HRV was significantly associated with patient-reported stress, UC symptoms, and both CRP and FC levels.[68] Notably, HRV showed significant changes from baseline before any clinical or biochemical evidence of a flare, highlighting the potential of passive monitoring to predict disease activity in IBD patients.[68] In addition to wearable devices, implantable sensors have been developed for real-time monitoring. Madhvapathy *et al*[69] designed wireless, miniaturized, and implantable temperature sensors for real-time chronic monitoring of disease progression, which were tested for approximately four months to measure the local intestinal temperature in a CD-like ileitis mouse model. Ultradian rhythms developed approximately five weeks before the visual emergence of inflammatory skip lesions, correlating with variations in blood concentrations of stress hormones and inflammatory cytokines.[69] These miniaturized temperature sensors have the potential to facilitate early IBD treatment by enabling the detection of episodic flare-ups.[69] Advancements in remote and non-invasive monitoring technologies offer hope for improving IBD management. By enabling continuous real-time tracking of disease activity, these tools have the potential to revolutionize patient care, reduce reliance on invasive procedures, and support early intervention to prevent disease progression.

Treatment

New drugs in the past two years

A wide range of new drugs for IBD, mainly small molecules and biologics, has emerged in the past few years. The results of the phase III RCT for the major new drugs published in the last two years are shown in Table 1. In recent years, biological agents have continued to dominate IBD

Table 1: Results of phase III randomized controlled trials for the major new drugs published in the last two years.

First author, year	Patients	Drugs	Study groups	Outcomes
D'Haens, 2023[70]	LUCENT-1: 1281 UC LUCENT-2: 544 UC	Mirikizumab; IL-23	LUCENT-1: Mirikizumab: placebo = 3: 1 LUCENT-2: Mirikizumab: placebo = 2: 1	Clinical remission: LUCENT-1: Mirikizumab 24.2% *vs*. placebo 13.3% at 12 weeks, *P* <0.001 LUCENT-2: Mirikizumab 49.9% *vs*. placebo 25.1% at 52 weeks, *P* <0.001
Ferrante, 2024[72]	VIVID-1: 778 CD	Mirikizumab; IL-23	Mirikizumab: placebo = 3: 1	Patient-reported outcome clinical response at week 12 and endoscopic response at week 52: Mirikizumab 38.0% *vs*. placebo 9.0%, *P* <0.0001 Patient-reported outcome clinical response at week 12 and Crohn's Disease Activity Index clinical remission at week 52: Mirikizumab 45.4% *vs*. placebo 19.6%, *P* <0.0001
Louis, 2024[71]	INSPIRE: 975 UC COMMAND: 548 UC	Risankizumab; IL-23	INSPIRE: Risankizumab: placebo 2: 1 COMMAND: Risankizumab 180 mg: Risankizumab 360 mg: placebo = 1: 1: 1	Clinical remission: INSPIRE: Risankizumab 20.3% *vs*. placebo 6.2%, *P* <0.001 COMMAND: Risankizumab 180 mg 40.2% *vs*. Risankizumab 360 mg 37.6% *vs*. placebo 25.1%, *P* <0.01
Sandborn, 2023[76]	ELEVATE 12: 354 UC ELEVATE 52: 433 UC	Etrasimod; S1P1, S1P4 and S1P5	Etrasimod: placebo = 2: 1	Clinical remission: ELEVATE 12: Etrasimod 25% *vs*. placebo 15.0% at 12 weeks, *P* = 0.026 ELEVATE 52: Etrasimod 27% *vs*. placebo 7.0% at 12 weeks, *P* <0.0001 ELEVATE 52: Etrasimod 32% *vs*. placebo 7.0% at 52 weeks, *P* <0.0001
Loftus, 2023[79]	U-EXCEL: 526 CD U-EXCEED: 495 CD U-ENDURE: 502 CD	UPA; JAK1	U-EXCEL: UPA: placebo = 2: 1 U-EXCEED: UPA: placebo = 2: 1 U-ENDURE: UPA 15 mg: UPA 30 mg: placebo = 1: 1: 1	Clinical remission: U-EXCEL: UPA 49.5% *vs*. placebo 29.1% at 12 weeks, *P* <0.001 U-EXCEED: UPA 38.9% *vs*. placebo 21.1% at 12 weeks, *P* <0.001 U-ENDURE: UPA 30 mg 47.6% *vs*. UPA 15 mg 37.3% *vs*. placebo 15.1% at 52 weeks, *P* <0.0001

CD: Crohn's disease; IL: Interleukin; JAK: Janus kinase; S1P: Sphingosine-1-phosphate; UC: Ulcerative colitis; UPA: Upadacitinib.

treatment landscape, with notable advancements in therapies targeting IL-23 [Figure 1].

Formal results of two IL-23 inhibitors, including mirikizumab and risankizumab, for treating IBD patients have been published in the past two years.[70,71] In the LUCENT-1 induction trial, a significantly higher proportion of UC patients in the mirikizumab group achieved clinical remission at week 12 than those in the placebo group (24.2% *vs*. 13.3%, *P* <0.001). Similarly, in the LUCENT-2 maintenance trial, the clinical remission rates of UC patients at week 40 were significantly higher in the mirikizumab group (49.9% *vs*. 25.1%, *P* <0.001).[70] The VIVID-1 trial evaluated the efficacy and safety of mirikizumab in CD patients and demonstrated that the mirikizumab 900 mg group achieved significantly higher rates of the composite endpoint (patient-reported clinical response at week 12 and endoscopic response at week 52) than the placebo group (38.0% *vs*. 9.0%, *P* <0.0001).[72] Similarly, the mirikizumab group showed superior outcomes for another composite endpoint, patient-reported clinical response at week 12 and CD Activity Index clinical remission at week 52, when compared with placebo (45.4% *vs*. 19.6%, *P* <0.0001).[72] Two phase III RCTs evaluated the efficacy and safety of risankizumab in UC patients.[71] In the INSPIRE-induction trial, the clinical remission rates at week 12 were higher in the risankizumab 1200 mg group than in the placebo group (20.3% *vs*. 6.2%, *P* <0.001).[71] In the COMMAND-maintenance trial, the clinical remission rates at week 52 were higher in the risankizumab 180 mg group (40.2% *vs*. 25.1%, *P* <0.001) and risankizumab 360 mg group (37.6% *vs*. 25.1%, *P* = 0.002) than in the placebo group.[71] In addition, many phase II RCTs have explored new drugs that target different molecules. Olamkicept, a first-in-class selective inhibitor of the sIL-6R/IL-6 complex, demonstrated promising results in UC patients.[73] In a phase II RCT, UC patients in the olamkicept 600 mg group had a higher rate of achieving

a clinical response than patients in the placebo group (58.6% *vs*. 34.5%, $P = 0.03$) at week 12.[73] Guselkumab, a fully human immunoglobulin G1 lambda monoclonal antibody targeting the p19 subunit of human IL-23, has also shown efficacy in a phase IIb RCT study.[74] The clinical response rates at week 12 were significantly higher in the guselkumab 200 mg (61.4%) and guselkumab 400 mg (60.7%) groups than in the placebo group (27.6%; both $P < 0.001$).[74] Tulisokibart is a tumor necrosis factor-like cytokine 1A monoclonal antibody.[75] In a phase IIb RCT, clinical remission highly occurred in patients who received tulisokibart than in those who received a placebo (32% *vs*. 11%, $P = 0.02$).[75]

Unlike large-molecule biologics, small-molecule drugs can be administered orally and are not immunogenic, which is an issue associated with biologics. Etrasimod is an oral S1P receptor modulator that selectively activates S1P1, S1P4, and S1P5, and its efficacy was tested in two independent RCTs.[76] In the ELEVATE UC 52 trial, a significantly greater proportion of UC patients in the etrasimod group (2 mg once daily) achieved clinical remission than those in the placebo group at the completion of the 12-week induction period (27% *vs*. 7%, $P < 0.0001$) and week 52 (32% *vs*. 7%, $P < 0.0001$).[76] ELEVATE UC 12 study reached the same conclusion, indicating that the clinical remission rate in the etrasimod group was higher than that in the control group (25% *vs*. 15%; $P = 0.026$).[76] Similarly, in an induction trial evaluating the efficacy of etrasimod in Asian patients with moderately to severely active UC, a significantly higher proportion of patients in the etrasimod 2 mg group achieved clinical remission than those in the placebo group (25.0% *vs*. 5.4%, $P < 0.0001$).[77] In 2022, three RCT studies[78] confirmed that the selective JAK1 inhibitor upadacitinib was effective in UC patients. In 2023, the results of RCT evaluating the efficacy and safety of upadacitinib in patients with CD were published in the *NEJM*.[79] In two phase 3 induction trials, a significantly higher proportion of CD patients who received 45-mg upadacitinib had clinical remission than those who received a placebo in U-EXCEL (49.5% *vs*. 29.1%, $P < 0.001$) and U-EXCEED (38.9% *vs*. 21.1%, $P < 0.001$).[79] At week 52 in the U-ENDURE trial, a higher proportion of CD patients had clinical remission with 15-mg (37.3%) or 30-mg (47.6%) upadacitinib than with the placebo (15.1%) ($P < 0.001$ for all comparisons).[79]

Head-to-head study comparing the efficacy of different drugs

Despite the increasing number of small molecules and biologics available, determining the optimal positioning of various agents in therapeutic sequencing is an important clinical question that remains unanswered. A meta-analysis of 23 studies assessing induction therapy with either a biologic or small-molecule drug in UC patients demonstrated that upadacitinib was significantly superior to all other small molecules and biologics for clinical remission induction, but was the worst-performing agent in terms of adverse events.[80] Another meta-analysis of 31 studies assessing induction therapy with biologics in CD patients demonstrated that either infliximab with azathioprine or adalimumab might be preferred as first-line treatment, and adalimumab (after infliximab loss of response) or risankizumab as second-line therapy for clinical remission induction.[81] In addition, data from a cohort of 13,222 patients who received at least one biologic from the UK IBD BioResource revealed that vedolizumab demonstrated superior effectiveness as a first-line treatment over 5 years compared with anti-TNF agents, and was superior to both infliximab (IFX) and adalimumab (ADA) after ADA and IFX failure, respectively.[82] However, this study also demonstrated that non-anti-TNF biologics were superior to a second anti-TNF after first-line anti-TNF failure in CD,[82] which is contrary to the results of the aforementioned meta-analysis.[81]

However, these studies were limited by their indirect comparative observational designs, which provide low-level evidence that can guide clinical practice. Although head-to-head trials directly comparing agents have been conducted in patients with rheumatologic diseases, such trials in IBD patients are limited. In 2019, the first head-to-head study on biological therapies for UC (VARSITY) compared vedolizumab with adalimumab and demonstrated that patients in the vedolizumab group had a higher percentage of clinical remission than those in the adalimumab group at week 52 (31.3% *vs*. 22.5%, $P = 0.006$).[83] Subsequently, two additional head-to-head studies comparing the efficacy of etrolizumab, a gut-targeted anti-β7 integrin monoclonal antibody, with IFX and ADA were published in 2022.[84,85] In the phase III GARDENIA study, no significant difference was observed in the proportion of patients who achieved the primary endpoint of clinical response at week 10 or clinical remission at week 54 between the etrolizumab and IFX groups (18.6% *vs*. 19.7%, $P = 0.81$).[84] Similarly, pooled analyses of the HIBISCUS I and II trials showed that etrolizumab was not superior to adalimumab in terms of remission induction, endoscopic improvement, clinical response, histological remission, and endoscopic remission at week 10.[85] Furthermore, several head-to-head studies have also compared the efficacy of different biologics in patients with CD. In the phase 3b SEAVUE trial, there was no significant difference in clinical remission between the ustekinumab (UST) group and ADA groups (65% *vs*. 61%, $P = 0.42$) at week 52 in biologic-naive patients with moderately to severely active CD.[86] Interestingly, in other immune-mediated inflammatory conditions, such as psoriasis, selective IL-23 inhibition is superior to IL12/23 inhibition.[87] This has propelled the development of several IL-23p19 antibodies, such as risankizumab, mirikizumab, and guselkumab, for IBD treatment and prompted the initiation of comparative efficacy studies between IL-23p19 antibodies and UST.[87] In the phase 3b SEQUENCE study, risankizumab was non-inferior to UST with respect to clinical remission at week 24 (58.6% *vs*. 39.5%) but was superior to UST with respect to endoscopic remission at week 48 (31.8% *vs*. 16.2%, $P < 0.001$).[88] In phase 3 VIVID-1 study, no significant differences were observed between the mirikizumab and ustekinumab groups in terms of clinical remission (54.1% *vs*. 48.4%) or endoscopic response (48.4% *vs*. 46.3%, $P = 0.51$) at week 52 in CD patients.[72] Formal results of comparative efficacy studies between UST and Guselkumab are still awaited.[87]

Advanced combination therapy

Therapeutic strategies using a single agent for IBD have reached a plateau, with an overall clinical remission rate of approximately 50%. Therefore, the advanced combination therapy (ACT) strategy, which involves using two different targeted therapies, biological or small molecules, has become a new treatment approach for IBD, with the primary goal of breaking the therapeutic ceiling in IBD treatment. Clinical response and remission rates for ACT in IBD patients range from approximately 40%–80%.[89] The first RCT assessing the safety and efficacy of ACT found that CD patients receiving a combination therapy of natalizumab and IFX showed a trend toward higher rates of clinical remission over a 32-week follow-up period than those receiving IFX monotherapy.[90] However, the difference was not statistically significant.[90] Recently, the VEGA study evaluating the efficacy of combination induction therapy using guselkumab and anti-TNF golimumab compared with guselkumab or golimumab monotherapy in patients with moderately to severely active UC was published.[91] At week 12, 83% of the patients in the combination therapy group achieved a clinical response, compared with 61% ($P = 0.0032$) and 75% (nominal $P = 0.2155$) in the golimumab and guselkumab monotherapy groups, respectively.[91] Combination therapy with guselkumab and golimumab may be more effective for UC than therapy with either drug alone.[91] Whether ACT can break the therapeutic ceiling in IBD remains unknown for the following reasons: (1) in real-world studies, patients have already experienced a loss of response or no response to one or more agents used in ACT, or ACT is primarily used to treat extraintestinal manifestations rather than active IBD; and (2) data from RCTs evaluating ACT remain limited.

Precision medicine in IBD

The selection of the optimal treatment for individual IBD patient remains unresolved. Precision medicine, a strategy successfully implemented in fields such as oncology, might be another promising approach to break the therapeutic ceiling in IBD. Precision medicine aims to improve patient stratification and timing of healthcare by using bioinformatics and biomarkers and to ensure that the right treatment is given to the right patient at the right time.[92] Although numerous biomarkers and algorithms claim to predict the responses to various drugs, none have been consistently adopted in clinical practice.[93] In the personalized anti-TNF therapy in CD study, carriage of the HLA-DQA1*05 risk variant was associated with a higher risk of loss of response or treatment discontinuation due to failure among patients treated with adalimumab (hazard ratio [HR] 1.95, 95% CI 1.17–3.25).[94] However, this association was not observed in patients who received IFX (HR 1.55, 95%CI 0.97–2.48).[94] Beyond genetic markers, considerable attention has been directed toward baseline gut microbiota as a predictor of response to advanced therapies. Interestingly, in a prospective cohort of 79 IBD patients treated with UST or vedolizumab, no significant differences were observed in the baseline gut microbiome between responders and non-responders, indicating that combining microbial or metabolic characteristics did not enhance the predictive power for treatment response,[95] implying that predictive models using only gut microbiota data are limited to having predictive power only within the original cohort used for model fitting and fail to generalize to other cohorts.

The integration of multi-omics data, including clinical, genetic, transcriptomic, proteomic, microbiome, and imaging data, might improve the predictive power of treatment responses in IBD patients. By analyzing the calprotectin levels, moisture, and microbial load in stool samples of a large prospective cohort of 296 patients with active IBD initiating biological therapy, a model based on anthropometrics, clinical data, stool features, and dysbiosis detection predicted the treatment outcomes with 73.9% accuracy.[96] Currently, the application of AI to effectively integrate multi-omics data is increasingly regarded as a promising method for enhancing precision medicine in IBD. For instance, among 21 patients treated with vedolizumab, a machine learning model that combined clinical, metagenomic, metabolomic, and proteomic markers achieved an AUC of 96.3% (95% CI: 0.88–1) for predicting treatment response.[97] In comparison, the models that combined clinical data with metagenomic, metabolomic, or proteomic features individually achieved AUCs of 0.85, 0.77, and 0.81, respectively.[97] Moreover, a machine learning model using 31 selected features derived from DNA methylation and gene expression data integration demonstrated exceptional predictive performance for the response to IFX in CD patients (AUC = 1).[98] These findings highlight the potential of integrating multi-omics data through AI approaches to significantly enhance the predictive power of treatment response models, paving the way for more effective precision medicine for IBD.

Other treatments

Autologous hematopoietic stem cell transplantation (AHSCT) is effective in refractory CD patients but carries a high risk of serious adverse events, primarily attributed to using high-dose immunosuppressive agents, particularly cyclophosphamide, during the mobilization and conditioning regimens.[99] In an RCT, AHSCT with low-dose cyclophosphamide mobilization (1 g/m² with granulocyte colony-stimulating factor [(G-CSF] 5 μg/kg) decreased endoscopic disease activity.[99] However, this trial was halted because of suspected unexpected serious adverse reactions, including renal failure due to proven thrombotic microangiopathy in three participants and one death due to pulmonary veno-occlusive disease.[99] In a prospective observational study involving 14 refractory CD patients undergoing cyclophosphamide-free mobilization AHSCT with G-CSF 12–16 $\mu g \cdot kg^{-1} \cdot day^{-1}$ for 5 days, the clinical and endoscopic remission rates were 71% and 41.7% at 26 weeks and 64% and 25% at 52 weeks, respectively.[100] Importantly, no serious mobilization-related adverse events or CD worsening occurred.[100] In addition, adipose-derived allogeneic mesenchymal stem cell therapy, specifically darvadstrocel, has been used to treat perianal fistulizing CD. A real-world multicenter study evaluating the efficacy and safety of darvadstrocel demonstrated perianal clinical remission rates of 78.2% and 62.3% at weeks 26 and 52, respectively.[101] Adverse events were observed in 13.5% of the patients, with

perianal abscesses and proctalgia being the most frequently reported complications.[101]

The gut and brain communicate through the gut–brain axis, a bidirectional communication system that plays a crucial role in both the psychological well-being and overall prognosis of individuals with IBD. Treatments targeting the gut–brain axis may influence disease activity in IBD patients. A recent meta-analysis showed that psychological therapies have beneficial short-term effects on anxiety (standardized mean difference [SMD], –0.23; 95% CI, –0.36 to –0.09), depression (SMD, –0.26; 95% CI, –0.38 to –0.15), stress (SMD, –0.22; 95% CI, –0.42 to –0.03), and quality-of-life (SMD, 0.31; 95% CI, 0.16 to 0.46) scores in IBD patients, but not on disease activity (SMD, –0.01; 95% CI, –0.13 to 0.12).[102] In addition, the vagus nerve plays a key role in "inflammatory reflex". an innate neuroimmune mechanism that detects and suppresses inflammation in the intestines and other organs. A 16-week multicenter, open-label trial in Europe evaluated implanted vagus nerve stimulation in 17 biologically drug-refractory CD patients and showed a significant decrease in CD activity index at week 16 (mean ± standard deviation, -86.2 ± 92.8; $P = 0.003$), FC levels (-2923 ± 4104; $P = 0.015$), and mean serum TNF and interferon-γ levels (46–52%).[103] Device implantation and electrical stimulation of the vagus nerve are generally safe and effective in biologically refractory CD patients, highlighting the potential of neuromodulation as a novel therapeutic approach for IBD.

Given the significant role of gut microbiota dysbiosis in IBD pathogenesis, strategies aimed at modulating the gut microbiota, such as probiotics, prebiotics, synbiotics, and fecal microbiota transplantation (FMT), have emerged as promising approaches to restore microbial homeostasis and potentially prevent or treat IBD. A recent meta-analysis including 38 RCTs demonstrated that only FMT (relative risk [RR], 1.73; 95% CI, 1.15–2.60) and probiotics (RR, 1.67; 95% CI, 1.23–2.26) were significantly more efficacious than placebo in achieving clinical response, whereas synbiotics (RR, 1.20; 95% CI, 0.55–2.61) and prebiotics (RR, 1.03; 95% CI, 0.53–1.99) showed nonsignificant efficacy than placebo.[104] Subgroup analysis revealed that FMT, particularly when delivered via a combination of colonoscopy and enema, demonstrated significant efficacy and superiority in improving the clinical response and remission rates in UC patients. Regarding endoscopic remission and clinical relapse, multi-strain probiotics containing specific genera of *Lactobacillus* and *Bifidobacterium* exhibited significant efficacy and ranked as the most effective interventions for UC.[104] In contrast, no gut microbiome-targeted therapies were found to be significantly better than the placebo in CD patients.[104]

Future Directions

To enhance the prediction, diagnosis, and management of IBD, as well as to modify the natural course of the disease, further in-depth research is required in several key areas. First, identifying changes and biomarkers in the preclinical phase of IBD could help better understand the disease causes and initiation events, aiding prevention and prediction of disease development. Second, AI models using large multi-omics data could identify patients with high-risk progressive diseases at diagnosis and provide more advanced treatment options, enabling precisely targeting those who truly need it. Prospective disease modification trials are also urgently needed to evaluate the effectiveness of early intensified treatment in patients with severe disease or those at a risk of disease progression. Meanwhile, patients at a low risk of complications can be treated with step-up strategies. Third, developing novel technologies for earlier and more precise diagnosis, early detection of biological changes preceding symptom onset, identifying inflammation, and tracking the progress of inflammation through non-invasive approaches are challenging yet necessary and meaningful endeavors. In addition, home-based tests can provide real-time assessment and monitoring. Finally, despite the rapid progress in IBD therapeutic agents, including different target biologics and small-molecule drugs, approximately one-third of patients are primary non-responders to the initial treatment, and half eventually lose response over time.[4] How can the therapeutic ceiling be broken? The solution might be a combination of the following: (1) new drug research and development, (2) head-to-head trials to inform optimal sequencing of treatments, (3) precision medicine focusing on identifying and validating biomarkers to help identify the optimal treatments for individual patients and to predict the loss of response to a treatment or the need to modify the treatment, (4) ACT, and (5) development of other treatments to complement existing anti-inflammatory drugs, such as approaches targeting the gut–brain axis, including neuromodulation and psychological therapy, stem cell transplantation, and gut microbiome modulation therapy.

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Conflicts of interest

None.

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