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Inflammatory Bowel Disease (IBD)

Clinical Diagnosis and Treatment

Edited by
Moisés Tolentino B. Da Silva and Isabel Silva

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Guest Editors

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Editorial

Inflammatory Bowel Disease (IBD): Clinical Diagnosis and Treatment

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Inflammatory bowel disease (IBD) is a pathological condition that occurs in two different forms: Crohn's disease (CD) and ulcerative colitis (UC). The etiology is multifactorial and involves any part of the gastrointestinal tract in Crohn's disease (CD) and significant inflammation limited to the colon in ulcerative colitis (UC). The major symptoms of this incurable disease include severe bowel manifestations such as abdominal pain, diarrhea, constipation, and gastrointestinal discomfort that negatively affect patients' quality of life [1,2].

In recent years, the search for different types of treatment and diagnostic methods has led to the discovery of new possible biomarkers and other methods of providing a faster and more accurate diagnosis of inflammatory bowel disease [3]. Regarding the biomarkers of IBD, C-reactive protein (CRP) is an effective marker for assessing inflammatory bowel disease because it is appropriate for evaluating treatment efficacy through repeated measurement [4,5].

Another biomarker that has been studied extensively is leucine-rich α2 glycoprotein (LRG), a protein produced in cells such as hepatocytes, neutrophils, and macrophages that is induced by multiple inflammatory cytokines, such as tumor necrosis factor (TNF)-α, IL-22, IL-1β, and IL-6; it is more likely to reflect intestinal inflammation than CRP [6,7]. Fecal calprotectin (FCP) is a protein most abundant in the cytoplasm, granulocytes, and monocytes of intestinal epithelial cells. Assessing this calprotectin protein is essential to observe inflammatory cells infiltrating the intestinal mucosa, injuring the intestinal epithelial cells, and mixing with feces during inflammation [8].

On the other hand, the association between intestinal ultrasound (IUS), a noninvasive, accurate, and well-tolerated tool that provides real-time assessment of inflammatory bowel disease (IBD) activity [9,10], and FCP is a proper screening strategy to identify patients who truly require endoscopy for suspected IBD [11]. This Special Issue of the *Journal of Clinical Medicine* explores inflammatory bowel disease (IBD) and possible clinical diagnosis and treatment, providing a new comprehensive overview of IBD.

Akhmedzyanova et al. investigated the efficacy of telemonitoring in comparison with face-to-face appointments in Russian IBD patients. This study observed that telemonitoring effectively improved clinical, social, and organizational aspects of the Russian healthcare system for IBD patients [12]. Gisbert et al. observed that there are significant variations in the mistakes made when managing patients with IBD in clinical practice. These authors

suggest a clear need for the considerable dissemination of clinical practice guidelines among gastroenterologists and the implementation of ongoing training activities supported by scientific societies [13].

In ref. [14], Purnak et al. provide an overview of IBD treatments, modern biologic therapies, and different molecular agents for this disease. These studies focus on improving the symptoms and sustained clinical remission, morphological and functional healing, and providing a better quality of life for these patients. In this sense, different therapeutic approaches have been developed in recent years. Colwill et al., in their review, observed that mirikizumab, a monoclonal antibody directed against the p19 subunit of interleukin (IL)-23, has shown good efficiency and safety for use in ulcerative colitis and Crohn's disease patients, suggesting that it may be a suitable treatment for elderly patients and those with multiple comorbidities [15].

Regarding physical exercise and gastrointestinal disorders, different studies have investigated the role of exercise in IBD. In this sense, Severo et al. observed in their review that in recent years, new techniques of cellular and molecular biology, and specific gastrointestinal receptors and different hormones, could help us to understand the mechanisms of gastrointestinal changes associated with physical exercise at various intensities, both in experimental and clinical studies [16]. On the other hand, Cagir et al., in their study, described inflammation and oral manifestations during Crohn's disease (CD). These manifestations include nonspecific and specific lesions that can be overlooked in CD and are sometimes challenging to treat. In this study, 14.2% of CD patients had oral lesions (specific, nonspecific) and 1.2% of CD patients had specific oral lesions affecting their quality of life, inducing pain and weight loss [17].

Bermont et al. investigated the terminal ileitis often identified on computed tomography scans in emergency settings to differentiate CD from other causes of acute terminal ileitis and develop a model for CD diagnosis. These authors identify new predictors of CD amongst patients presenting with acute terminal ileitis through a comprehensive assessment of clinical, laboratory, and imaging characteristics [18]. Ayoub et al. observed a relationship between inflammatory bowel disease (IBD) and pregnancy. The risks of adverse pregnancy outcomes associated with IBD are crucial for effective pregnancy management and support. These authors assess the complications that occur during pregnancy in patients with IBD. Thus, the authors describe that patients with chronic inflammatory bowel diseases can safely become pregnant, provided that they are in remission before and during pregnancy [19].

Pueschel et al. investigate the relationship between inflammatory bowel disease, gastrointestinal function, and the modification of fecal and flatulence odor due to changes in inflammation associated with intestinal microbiota and metabolism. The authors observed the significance of dietary factors and nutrition in managing IBD symptoms, focusing on flatulence and fecal odor [20].

Górecka et al., in their study, investigate the association between inflammatory bowel disease and the complex interplay of immune and proteolytic mechanisms. In this sense, different biomarkers such as neutrophil elastase (NE), which may be released during inflammation, can be assessed. Thus, the authors evaluate the diagnostic and prognostic utility of urinary NE, elafin, an endogenous NE inhibitor, and their ratio in IBD patients. The authors conclude that all analyzed biomarkers—neutrophil elastase, elafin, and the NE/elafin ratio—demonstrated significant potential for diagnosing IBD [21]. Bilican et al. present another method of diagnosing IBD in their study, the intestinal ultrasound (IUS). This diagnostic method is a noninvasive tool used to manage inflammatory bowel disease (IBD), offering real-time, radiation-free assessment of bowel wall thickness, vascularity, and complications. The authors observed that IUS provides a patient-centered, cost-

effective imaging option for IBD management, reducing reliance on invasive procedures and radiation exposure while providing real-time insights into disease activity [22].

In conclusion, this Special Issue presents a variety of high-quality studies that contribute to advancing knowledge in the field of IBD associated with diagnostics and treatment.

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Conflicts of Interest: The authors declare no conflicts of interest.

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Article

Intestinal Ultrasound: Advancing Towards Broader Adoption—Insights from a National Survey in Turkey

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Abstract: Objective: Intestinal ultrasound (IUS) is increasingly valued as a noninvasive tool for inflammatory bowel disease (IBD) management, offering real-time, radiation-free assessment of bowel wall thickness, vascularity, and complications. While IUS is widely adopted in Europe, data on its use in Turkey is scarce. This study aims to address this gap. **Methods**: A nationwide, cross-sectional survey was conducted targeting 817 adult and 150 pediatric gastroenterologists in Turkey. The survey included 26 structured questions on demographics, familiarity with and use of IUS, and barriers to implementation. **Results**: A total of 191 gastroenterologists participated in this survey, with 56% being adult gastroenterologists (n = 107) and 44% pediatric gastroenterologists (n = 84). Regarding whether they participated in IUS training, 73% (n = 140) of the 191 respondents stated they had not received training. There were notable differences in how IUS was utilized among gastroenterologists: 29% (n = 31) of adult gastroenterologists performed IUS independently, compared to just 2% (n = 2) of pediatric gastroenterologists ($p < 0.001$). In total, 63% (n = 67) of adult gastroenterologists and 46% (n = 39) of pediatric gastroenterologists reported not using IUS. Altogether, 94% (n = 179) emphasized the necessity of educational opportunities, and 86% (n = 165) favored national guidelines. **Conclusions**: Our findings reveal that the current application of IUS in Turkey fails to correspond with its expected advantages in managing IBD. Limited educational opportunities are a major challenge, emphasizing the necessity for coordinated educational programs and national guidelines. The expanded adoption of the IUS might significantly improve Turkey's management of IBD. **What is known**: Intestinal ultrasound (IUS) is a non-invasive, cost-effective, and reliable imaging method increasingly recognized for its utility in diagnosing and monitoring inflammatory bowel disease (IBD). **What is new**: This is the first national survey assessing the awareness, usage patterns, and barriers to the adoption of IUS among gastroenterologists in Turkey. The study highlights significant gaps in training opportunities while also identifying strategies to promote IUS integration into routine clinical practice. The findings may encourage similar efforts in other regions where IUS remains underutilized, ultimately improving IBD management and patient outcomes globally.

Keywords: intestinal ultrasound; inflammatory bowel disease; survey

1. Introduction

Inflammatory bowel disease (IBD), which includes Crohn's disease (CD) and ulcerative colitis (UC), is a chronic relapsing disorder that significantly affects patients' quality of life and requires lifelong management. Traditionally, assessment of disease activity has relied heavily on clinical symptoms and invasive procedures such as endoscopy and cross-sectional imaging, including magnetic resonance enterography (MRE) and computed tomography enterography (CTE). While these methods provide comprehensive information about the extent and severity of inflammation, they have limitations, including procedural risks, the need for bowel preparation, and high costs [1].

Intestinal ultrasound (IUS) is increasingly recognized as a valuable, noninvasive imaging tool for IBD management. It allows for real-time, radiation-free assessment of bowel wall thickness, vascularity, and complications, such as strictures and abscesses, without the need for sedation or bowel preparation [2,3]. Multiple studies have demonstrated IUS reaches accuracy levels similar to traditional imaging modalities [4]. For instance, IUS has shown comparable sensitivity and specificity to MRE for assessing ileal disease and superior performance in evaluating colonic inflammation [5]. Additionally, IUS's portability and cost-effectiveness make it a practical option for frequent monitoring, particularly in the context of a treat-to-target strategy that aims for deep remission, including both clinical and endoscopic healing. Furthermore, IUS has the advantage of being well-tolerated by patients and lacks the risks associated with radiation, making it suitable for all patients, especially in settings where minimizing radiation exposure is crucial, such as in pediatric and pregnant populations [6]. ECCO guidelines recommend the application of IUS for monitoring disease activity and assessing response to treatment [7].

IUS is a diagnostic method that requires adherence to numerous standards and necessitates specialized training [8]. Despite the advantages and growing adoption of IUS in Europe and other regions, its use remains limited in Turkey. Until now, data regarding the application of IUS in Turkey has been scarce, which this study aims to address.

Our objective is to assess the current awareness, knowledge, and use of IUS among adult and pediatric gastroenterologists in Turkey. By identifying barriers and training needs, we seek to propose strategies that can facilitate the broader integration of IUS into routine clinical practice. This research could have important implications for improving IBD management, making disease monitoring more accessible and efficient, and ultimately, improving patient outcomes.

2. Methods

2.1. Study Design and Participants

We conducted a cross-sectional survey of adult and pediatric gastroenterologists in Turkey. The survey was disseminated via email with the assistance of the Turkish Society of Gastroenterology and remained open to responses from 1 November to 14 November, 2024. A total of 817 adults and 150 pediatric gastroenterologists were contacted via email, with a reminder email sent seven days later (Supplementary Materials Figure S1). A total of 191 gastroenterologists ultimately completed the survey. The survey was distributed through Google Forms (Google LLC, Mountain View, CA, USA), providing an accessible platform for respondents.

2.2. Survey Instrument

The survey consisted of 26 structured questions divided into three sections: (1) demographic information, (2) familiarity with and usage of IUS, and (3) experience with hepatobiliary ultrasound (HBUS) (Supplementary Materials Table S1). In this survey, the term IUS refers specifically to conventional transabdominal IUS. The questions covered

the frequency of IUS use, perceived barriers, prior training, and imaging preferences in the management of IBD. The survey was developed based on a literature review and refined through expert consultation to ensure clarity and relevance.

2.3. Statistical Method

Descriptive statistics were used to present the data, with categorical variables shown as numbers (n) and percentages (%). The comparison of categorical variables between groups was performed using the Pearson's chi-square test or Fisher's exact test, as appropriate. When expected cell counts in contingency tables were below five, a two-sided Fisher's exact test was applied instead of the Pearson's chi-square test.

A Type 1 error rate (alpha) of 0.05 was accepted. Data analysis was conducted using SPSS Statistics, version 29.0 (IBM Corp., Chicago, IL, USA).

3. Results

3.1. Demographics

A total of 191 gastroenterologists participated in this survey, with 56% being adult gastroenterologists (n = 107) and 44% pediatric gastroenterologists (n = 84). Demographic and professional characteristics of the respondents, including age, gender, years of practice, academic titles, areas of special interest, and institutional affiliations, are summarized in Table 1.

Table 1. Demographic characteristics of participants.

Characteristic	n (%)
Total Gastroenterologists	191
Adult Gastroenterologists	107 (56%)
Pediatric Gastroenterologists	84 (44%)
Age (years)	
Under 40	46 (24.1%)
40–50	87 (45.5%)
50–60	41 (21.5%)
Over 60	17 (8.9%)
Gender	
Male	104 (54.5%)
Female	87 (45.5%)
Professional Experience (years)	
Less than 3 years	59 (30.9%)
3–6 years	43 (22.5%)
6–10 years	15 (7.9%)
Over 10 years	74 (38.7%)
Academic Titles	
Fellow	127 (63.1%)
Specialist	30 (15.7%)
Associate Professor	34 (17.8%)
Professor	6 (3.4%)
Special Interest	
Inflammatory Bowel Disease	94 (49.2%)
Hepatology	78 (40.8%)
Institution Type	
University Hospital	87 (45.5%)
Training and Research Hospital	65 (34.0%)
Private Clinic	29 (15.2%)
Private Practice	11 (5.8%)
State Hospital	14 (7.3%)

3.2. Intestinal Ultrasound Usage

In addition to colonoscopy, various imaging methods were used for IBD diagnosis, with the combination of IUS with either MRE or CTE being the most commonly reported method (Figure 1).

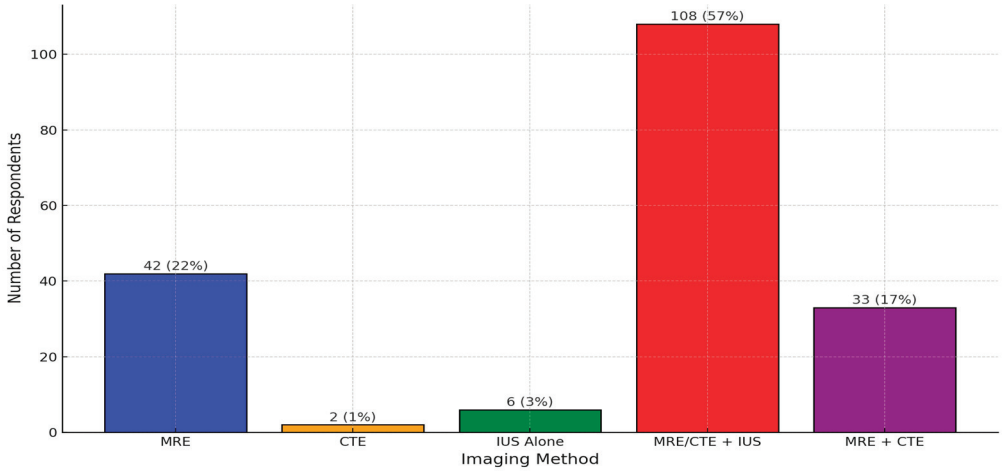

Figure 1. Imaging methods used for IBD diagnosis.

For IBD monitoring, 95% (n = 181) of respondents used colonoscopy, with 78% (n = 148) relying on fecal calprotectin as a biochemical marker. MRE was used by 61% (n = 116), while 30% (n = 58) employed IUS. Additionally, 89% (n = 169) used clinical scoring systems, such as the ulcerative colitis activity index and the Crohn's disease activity index, to assess disease activity.

When asked about the use of IUS, responses were categorized as follows: 27% (n = 52) of respondents requested it as a radiology consultation, 17% (n = 33) performed it themselves, and 56% (n = 106) reported not using IUS. Among those who used IUS, 9% (n = 18) used it rarely, 21% (n = 40) used it frequently, and 14% (n = 27) used it for every patient.

Figure 2 summarizes the proportion of respondents who received IUS training, along with the formats through which the training was received.

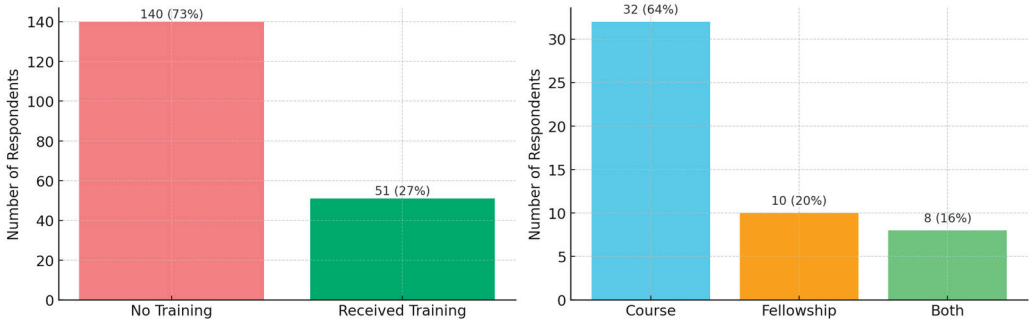

Figure 2. IUS training and training formats.

The primary purposes for using IUS were reported as follows: diagnosis in 28% (n = 54), assessment of treatment response in 36% (n = 68), and identification of complications in 35% (n = 66).

Self-assessed proficiency in using IUS showed notable variation among respondents, with the largest proportion reporting low proficiency levels. Further details are presented in Figure 3.

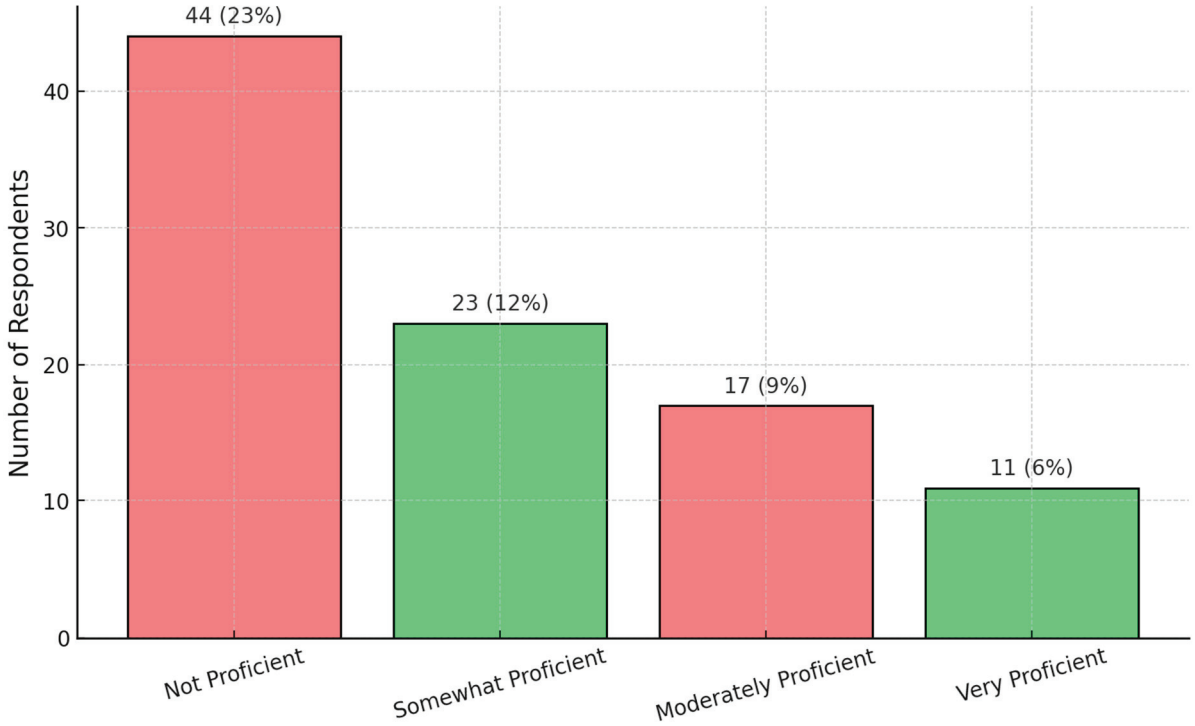

Figure 3. Self-assessed proficiency in using IUS.

Participants identified several perceived advantages of IUS, with non-invasiveness being the most cited at 95% (n = 182). Other advantages included bedside and outpatient applicability 86% (n = 165), lack of radiation exposure 82% (n = 156), cost-effectiveness 82% (n = 156), and the ability to visualize bowel wall layers and vascularity 77% (n = 147).

Respondents identified several challenges in using IUS, with lack of training opportunities being the most frequently reported issue, followed by time constraints, difficulty interpreting images, and insufficient equipment. Details are shown in Figure 4.

The analysis evaluated the relationship between IUS usage frequency and self-assessed proficiency. Among respondents who reported using IUS rarely, 22% (n = 2) identified themselves as not proficient, while 78% (n = 7) considered themselves proficient. For those who used IUS frequently, 32% (n = 7) were not proficient, and 68% (n = 15) were proficient. Similarly, among those who used IUS for every patient, 24% (n = 4) were not proficient, while 76% (n = 13) were proficient.

This data demonstrates that a higher percentage of those who use IUS more frequently (frequently or for every patient) self-assess as proficient compared to those who use it rarely. However, the association between IUS usage frequency and self-assessed proficiency was not statistically significant ($p = 0.837$).

Participants emphasized several strategies to promote the widespread use of IUS in Turkey, with increasing educational opportunities and attending IUS courses being the most frequently suggested. Other key recommendations included developing publications and national guidelines, providing financial support for equipment, organizing more courses at national congresses, and establishing specialized IUS units in hospitals. Notably, the majority of respondents expressed a strong interest in attending an IUS course if organized in Turkey (Figure 4).

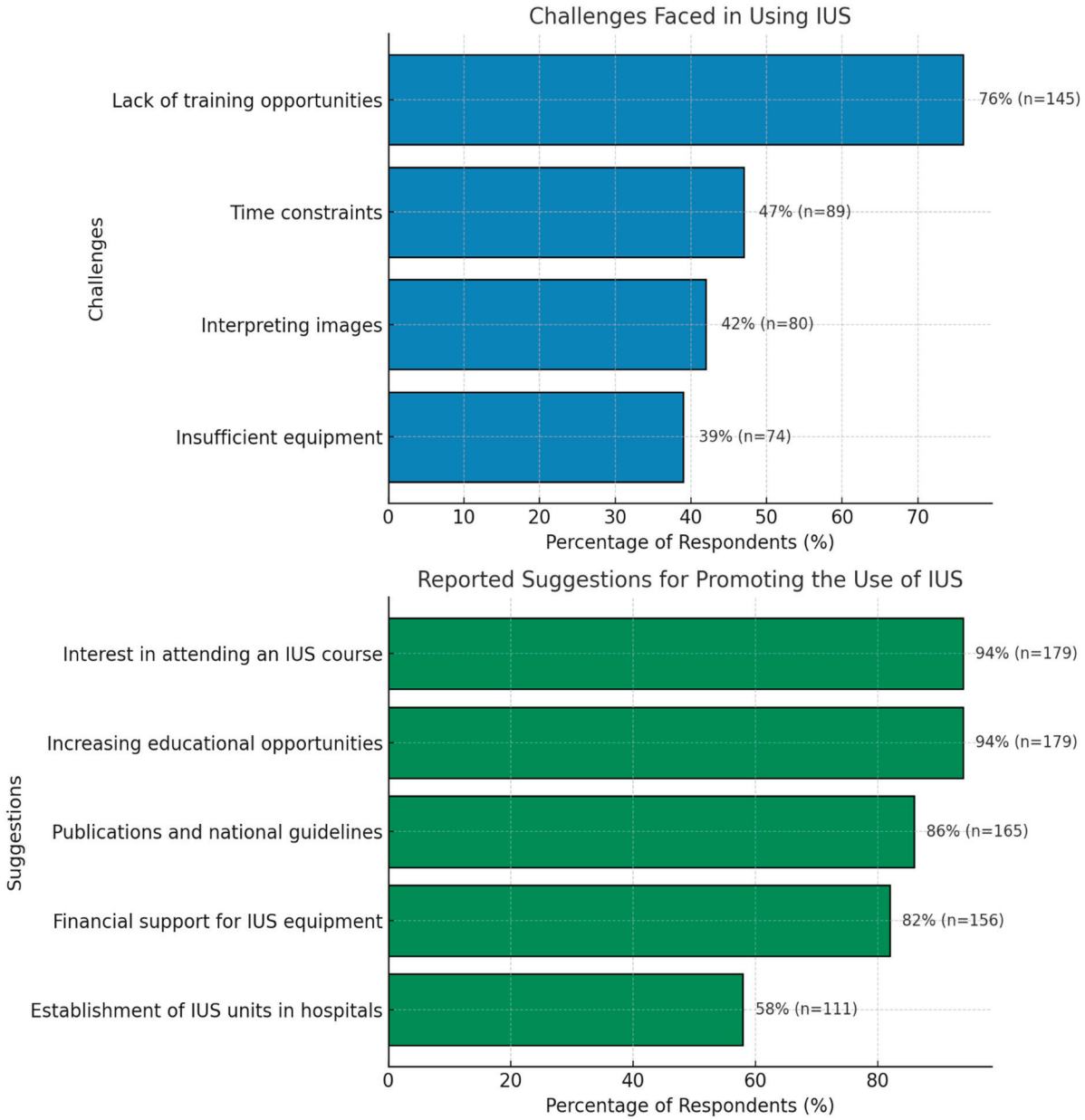

Figure 4. Challenges faced and suggestions for promoting the use of IUS.

3.3. Hepatobiliary Ultrasound Usage

Regarding the use of hepatobiliary ultrasound (HBUS), responses were as follows: 36% (n = 68) reported performing it themselves, 44% (n = 84) requested radiology consultation, and 20% (n = 39) did not use HBUS. Among those who used it, 11% (n = 20) used it rarely, 50% (n = 95) used it frequently, and 18% (n = 35) used it for every patient.

A significant overlap was observed between respondents who independently perform HBUS and those performing IUS, with nearly all independent IUS users also engaging in HBUS (Figure 5).

Training in HBUS was reported by 39% (n = 75), with 20% (n = 38) receiving it during their fellowship, 10% (n = 19) through specialized courses, and 9% (n = 18) through both avenues. Of the 75 respondents who reported having received training in HBUS and the 51 who reported training in IUS, 41 individuals indicated receiving training in both modalities. This overlap suggests a significant portion of those trained in one ultrasound technique are also trained in the other.

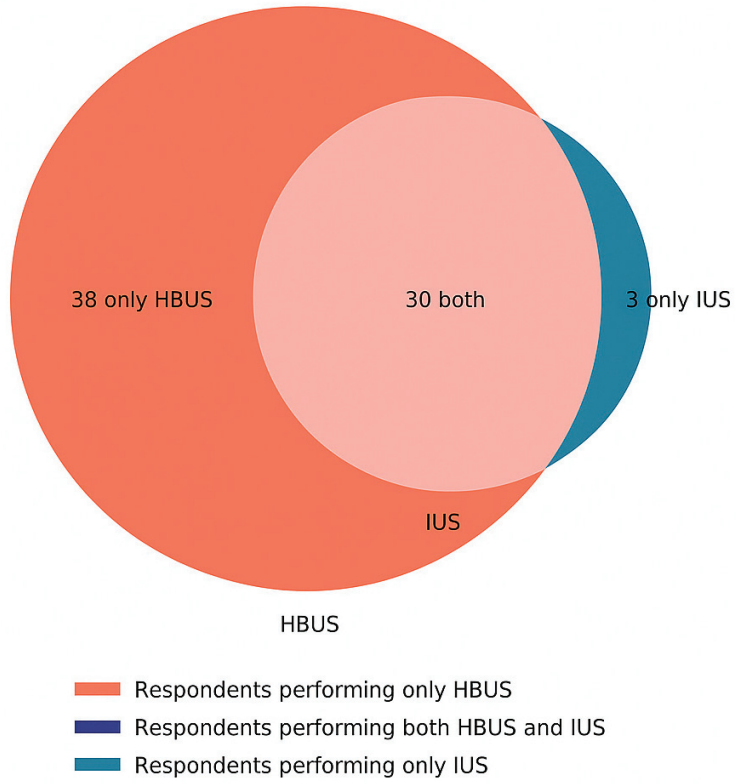

Figure 5. Overlap of respondents performing HBUS and IUS.

The primary purposes for using HBUS included monitoring choledocholithiasis, cholangitis or cholecystitis (93%, n = 178), cirrhosis (85%, n = 162), and steatosis (86%, n = 165), reflecting its role in managing hepatic complications in gastroenterology practice.

3.4. Comparison of IUS and HBUS Usage Between Pediatric and Adult Gastroenterologists

Significant differences were found in IUS usage patterns between pediatric and adult gastroenterologists ($p < 0.001$). Pediatric gastroenterologists were more likely to use IUS with radiology consultation, while adult gastroenterologists more commonly performed IUS independently. A substantial proportion of respondents in both groups reported not using IUS, as shown in Figure 6.

The use of HBUS also varied significantly between the two groups. Pediatric gastroenterologists were more likely to request radiology consultation for HBUS (70%, n = 59) compared to adult gastroenterologists (23%, n = 25), with a statistically significant difference ($p < 0.001$). On the other hand, adult gastroenterologists performed HBUS themselves more frequently (61%, n = 65) compared to pediatric gastroenterologists (4%, n = 3). When compared with IUS, fewer pediatric gastroenterologists (26%, n = 22) and adult gastroenterologists (16%, n = 17) reported not using HBUS.

Among pediatric gastroenterologists, 78% (n = 21) reported not feeling proficient in performing IUS, compared to 34% (n = 23) of adult gastroenterologists, reflecting a statistically significant difference ($p < 0.001$). Conversely, a greater proportion of adult gastroenterologists, 66% (n = 45), reported feeling proficient in performing IUS, compared to only 22% (n = 6) of their pediatric counterparts.

For HBUS, a similar trend was observed. Among pediatric gastroenterologists, 57% (n = 36) indicated that they did not feel proficient, whereas this figure was significantly lower among adult gastroenterologists, at 15% (n = 16). On the other hand, 85% (n = 88) of adult gastroenterologists reported feeling proficient in HBUS, compared to 43% (n = 27) of pediatric gastroenterologists ($p < 0.001$).

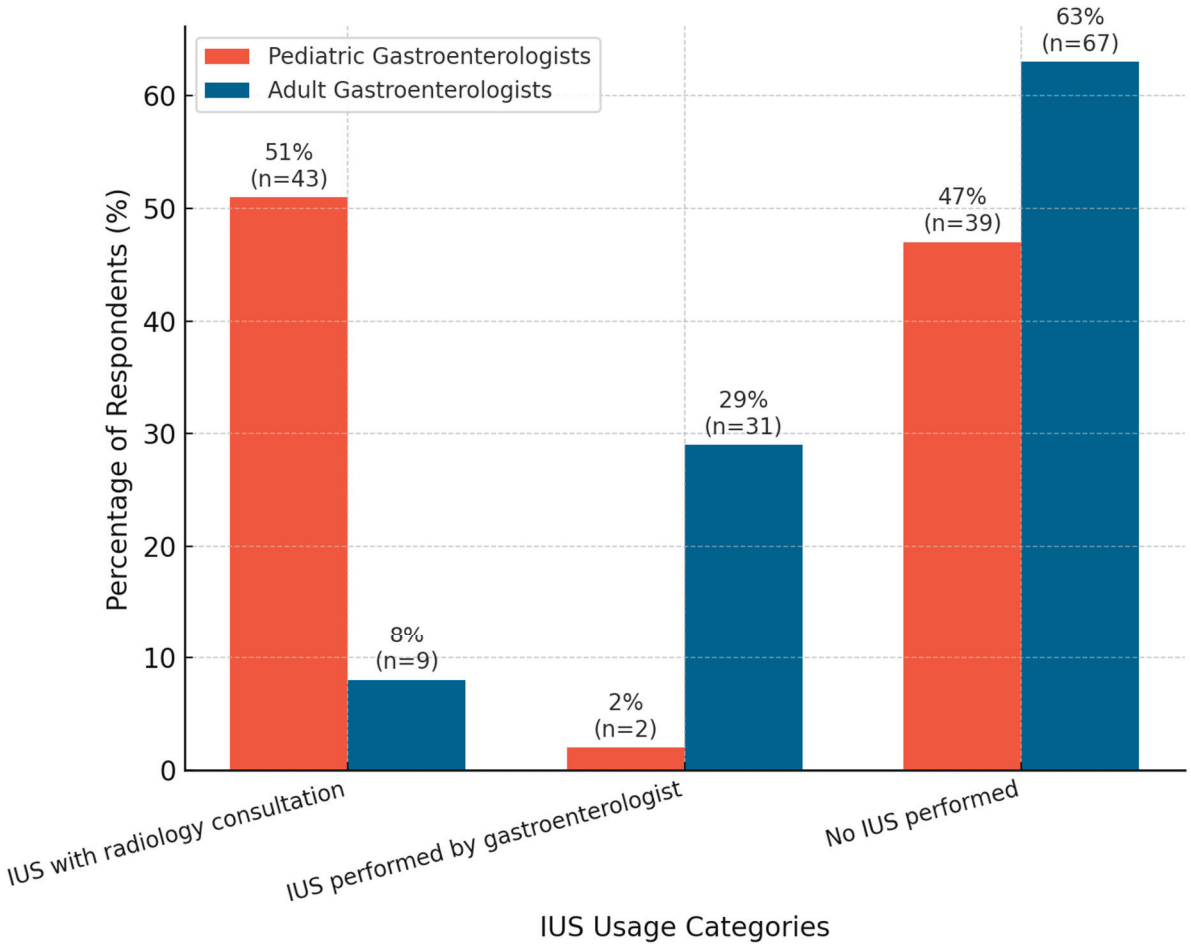

Figure 6. Comparison of IUS usage between pediatric and adult gastroenterologists.

The frequency of IUS usage was compared between pediatric and adult gastroenterologists. Among pediatric gastroenterologists, 13% (n = 6) reported using IUS rarely, 49% (n = 22) frequently, and 38% (n = 17) for every patient. In comparison, 30% (n = 12) of adult gastroenterologists used IUS rarely, 45% (n = 18) frequently, and 25% (n = 10) for every patient. Overall, the distribution of usage patterns showed differences between the two groups; however, the association was not statistically significant ($p = 0.140$).

The purposes of using IUS were analyzed and compared between pediatric and adult gastroenterologists, revealing statistically significant differences. Pediatric gastroenterologists reported using IUS for diagnostic purposes more frequently (80%, n = 36) compared to adult gastroenterologists (45%, n = 18), with the difference being statistically significant ($p < 0.001$). Similarly, a significant association was observed in the use of IUS to assess treatment response, with 71% (n = 32) of pediatric gastroenterologists using it for this purpose compared to 90% (n = 36) of adult gastroenterologists ($p = 0.030$). Additionally, IUS was used for identifying complications by 89% (n = 40) of pediatric gastroenterologists, which was significantly higher than the 65% (n = 26) reported by adult gastroenterologists ($p = 0.008$). These results indicate notable differences in the specific purposes for which IUS is utilized between the two groups.

When comparing the challenges faced by pediatric and adult gastroenterologists in using IUS, significant differences were observed in several areas. Lack of training opportunities was a more frequently reported challenge among pediatric gastroenterologists (87%, n = 73) compared to their adult counterparts (67%, n = 72) ($p = 0.002$). Similarly, insufficient equipment was reported by 49% (n = 41) of pediatric gastroenterologists, significantly

higher than the 31% (n = 33) reported by adult gastroenterologists ($p = 0.011$). Difficulty interpreting images was also noted more commonly among pediatric gastroenterologists (52%, n = 44) than adult gastroenterologists (34%, n = 36) ($p = 0.009$). In contrast, time constraints were reported by 42% (n = 35) of pediatric and 50% (n = 54) of adult gastroenterologists, with no statistically significant difference between the groups ($p = 0.226$).

4. Discussion

IUS has become an indispensable tool for managing IBD, offering unique advantages compared to other imaging modalities such as MRE and CTE. One of IUS's most notable benefits is its non-invasive nature, which allows for repeated assessments without the need for ionizing radiation. This aspect is especially crucial for IBD patients, many of whom require frequent monitoring due to the chronic and relapsing nature of conditions such as Crohn's disease and ulcerative colitis [9]. Furthermore, IUS has shown diagnostic accuracy comparable to that of MRE in detecting transmural inflammation, strictures, and abscesses, which are common in CD patients [10]. Beyond its accuracy, IUS provides real-time, point-of-care insights, making it invaluable in clinical settings where rapid decision-making is essential. Unlike MRE, which often requires scheduling and waiting times for both the scan and the results, IUS can be performed at the bedside, allowing clinicians to immediately assess treatment response and adjust management strategies as needed [11]. Additionally, IUS is more cost-effective than MRE or CTE, with studies indicating substantial cost savings when IUS is incorporated into standard IBD care pathways [12]. This financial accessibility further underscores IUS's suitability for broader implementation, particularly in regions with limited healthcare resources.

From a patient-centered perspective, IUS is highly tolerated and generally well-accepted, as it avoids the discomfort associated with bowel preparation and sedation, which are often required for colonoscopy and MRE. This is particularly advantageous for pediatric populations, where non-invasive, stress-free diagnostic tools are preferred [13]. IUS is increasingly recommended for pediatric patients with IBD due to its non-invasive nature and the ability to reduce radiation exposure, which is especially important for children. Current guidelines emphasize the role of IUS not only in the initial diagnosis but also in the ongoing management of pediatric IBD, as it offers a reliable assessment of disease activity and extent without the risks associated with repeated exposure to radiation from other imaging methods. By minimizing invasive procedures, IUS provides a child-friendly approach that aligns with the goals of safety and comfort in pediatric care [14]. The dynamic nature of IUS, which enables visualization of bowel wall thickness, vascularity, and motility in real-time, also contributes to its value in assessing disease activity and complications. This capability allows IUS to detect changes in bowel wall structure and vascular flow, markers of both acute inflammation and chronic damage, with accuracy comparable to that of cross-sectional imaging [15–17]. As IBD management continues to shift towards a treat-to-target approach, where achieving both clinical and endoscopic remission is essential, IUS emerges as a vital tool that aligns well with these goals, supporting frequent, low-risk monitoring.

While IUS has been validated as an effective and patient-centered tool for managing IBD, its adoption varies significantly across regions. In countries such as Germany and Italy, IUS has become an integral part of IBD management, supported by structured training programs that have set standards for its use and accuracy. For instance, in Germany, gastroenterologists are required to perform hundreds of supervised abdominal ultrasounds, including IUS, as part of their training, ensuring high competency levels among specialists. Italy has also incorporated IUS into routine IBD management within outpatient settings, where it is used alongside physical examinations and laboratory results to inform treatment

decisions. This integration minimizes the need for patients to visit radiology departments, reducing costs and enhancing convenience [18]. In contrast, countries such as the United Kingdom primarily rely on MRE and CTE, with IUS limited to select centers; ensuring high-quality IUS requires dedicated training in gastroenterology programs [19]. Of note, a North American survey highlighted that most pediatric gastroenterologists were interested in IUS but identified limited training and high inter-observer variability as key barriers [11]. Although the total number of participants represents only a fraction of all gastroenterologists in Turkey, our sample predominantly comprises clinicians working at tertiary-care centers, such as university hospitals and training and research institutions. These centers are the most likely environments for the adoption and promotion of IUS, particularly in managing complex IBD cases. A substantial proportion of respondents also reported a special interest in IBD or hepatology. Since multiple specialties could be selected, this reflects the common overlap in real-world gastroenterology practice.

In our survey on IUS utilization, we included questions on HBUS usage, reflecting our hypothesis that gastroenterologists are generally more familiar with this modality due to greater exposure during their formal training. European gastroenterology curricula emphasize abdominal ultrasound proficiency and ultrasound-guided liver biopsies as foundational skills [20,21], which are particularly relevant in Turkey, where liver biopsies are frequently performed using ultrasound [22,23]. This training and routine application likely contribute to the broader practice and higher proficiency in HBUS compared to IUS. The survey also revealed a disparity in ultrasound proficiency, with adult gastroenterologists reporting higher confidence than their pediatric counterparts, likely due to greater hands-on experience during fellowship. While most respondents had fewer than six years of professional experience, this represents a strategic opportunity. In Turkey, gastroenterology fellowship comprises a structured three-year training program and currently represents the only formal period during which ultrasonography training can be integrated into clinical education. There is no subspecialty training available for advanced IBD beyond fellowship. Consequently, early-career clinicians appear to us to represent the cohort whose awareness, motivation, and access to training should be supported to ensure the long-term, nationwide adoption of IUS. Additionally, the high representation of pediatric gastroenterologists strengthens the study, as pediatric and adult IBD care are increasingly interconnected. Many patients transition from pediatric to adult care around the age of 18, and shared follow-up during this transition is common. We believe that pediatric and adult IBD care are interconnected rather than operating separately.

Based on the survey results, well-established methods such as colonoscopy, fecal calprotectin, MRE, and clinical scoring systems are predominantly used for monitoring IBD activity. Although a subset of respondents reported using IUS for every patient, this should not be interpreted as evidence of widespread adoption. Our cohort largely consisted of clinicians based in tertiary centers where IUS is more likely to be available, and even within this group, the majority reported infrequent or no use. Furthermore, the observation that many frequent users did not feel proficient underscores the gap between clinical demand and formal training, reinforcing the urgent need for structured educational programs.

The ECCO e-Quality project provides a comprehensive framework to ensure consistent and high-quality care for IBD patients across Europe. One of its key recommendations highlights the need for at least two imaging techniques [MR or CT enterography or bowel ultrasound] to assess disease activity and complications [24]. Our study evaluates the current utilization of IUS in Turkey, revealing that, despite its inclusion in international guidelines as a recommended imaging modality, IUS remains underutilized due to factors such as limited training opportunities, lack of national guidelines, and varying levels of proficiency among gastroenterologists. These barriers underscore the importance of

structured educational initiatives and standardized protocols to better integrate IUS into clinical practice and align Turkey's practices with ECCO recommendations.

The International Bowel Ultrasound Group (IBUS) has established a comprehensive and internationally recognized curriculum in gastrointestinal ultrasound (GIUS) training, structured across three modules. Module 1 introduces GIUS through an intensive didactic course and hands-on workshop, while Module 2 provides four weeks of clinical training at IBUS-certified centers, allowing trainees to document over 200 GIUS cases. Module 3 concludes with an advanced workshop and final assessment at major conferences such as ECCO and Digestive Disease Week (DDW) [25]. Establishing a similar training structure in Turkey could significantly enhance local GIUS proficiency, particularly in IBD management.

Encouraging Turkish gastroenterologists to participate in IBUS programs, supported by financial aid and educational agreements with international centers, could further strengthen IUS training. Selected fellows could benefit from 3- to 6-month opportunities abroad, facilitated by the Turkish Society of Gastroenterology. To measure the impact of these initiatives, a follow-up survey in 3 to 5 years could benchmark progress in IUS utilization and proficiency, using the current survey as a baseline.

5. Conclusions

IUS offers a patient-centered, cost-effective imaging option for IBD management, reducing reliance on invasive procedures and radiation exposure while providing real-time insights into disease activity. Despite its widespread use in some European countries, limited training and the lack of standardized guidelines hinder broader adoption. Our survey, the first in Turkey, highlighted these barriers and underscored the need for structured educational programs and national guidelines. While the study's limited reach may have constrained its findings, it provides valuable insights to guide future training initiatives and facilitate the integration of IUS into routine clinical practice, both in Turkey and globally.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/jcm14144817/s1, Figure S1: Survey Process Flow for Gastroenterologists in Turkey (Nov 1–Nov 14, 2024); Table S1: Survey Questions.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this study are available on request from the corresponding author. The data are not publicly available due to privacy and ethical restrictions.

Conflicts of Interest: CH served as a speaker and/or advisory board member for AstraZeneca, AbbVie, Dr. Falk Pharma and the Falk Foundation, Galapagos, Janssen, Pfizer, Ferring, Takeda, Tillotts Pharma, and received grant support from Tillotts and Takeda. SLH received speaker honoraria

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Neutrophil Elastase and Elafin in Inflammatory Bowel Diseases: Urinary Biomarkers Reflecting Intestinal Barrier Dysfunction and Proteolytic Activity

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Abstract: Background: Inflammatory bowel disease (IBD), including ulcerative colitis (UC) and Crohn's disease (CD), is a chronic inflammatory disorder driven by a complex interplay of immune and proteolytic mechanisms. Neutrophil elastase (NE), released at sites of inflammation, plays a central role by promoting inflammation, degrading the extracellular matrix (ECM), and disturbing intestinal barrier integrity via NF-κB activation and E-cadherin degradation. Elafin, an endogenous NE inhibitor, mitigates proteolytic damage, reinforces the intestinal barrier, and exerts anti-inflammatory effects by suppressing NF-κB and reducing pro-inflammatory cytokines. Since the NE/elafin balance is critical in IBD, assessing their ratio may provide a more precise measure of proteolytic dysregulation. This study aimed to evaluate the diagnostic and prognostic utility of urinary NE, elafin, and their ratio in IBD patients. **Methods:** Urinary concentrations of NE and elafin were measured by immunoassay in 88 subjects including ulcerative colitis and Crohn's disease patients and healthy individuals. The diagnostic accuracy of these biomarkers was assessed using receiver operating characteristic (ROC) curve analysis. **Results:** Urinary NE levels were significantly elevated in both UC and CD patients compared to controls, with a 17-fold increase in the UC patients and a 28-fold increase in the CD patients ($p < 0.0001$). Elafin levels were also increased in IBD patients. The NE/elafin ratio was significantly increased in both disease groups, with a 4.5-fold increase in the UC and 5.6-fold increase in the CD patients compared to healthy controls. The ROC curve analysis demonstrated that the NE/elafin ratio is the most effective biomarker for distinguishing CD patients from healthy individuals (AUC = 0.896), with a high sensitivity (92.9%) and specificity (69.7%), making it a strong diagnostic tool. NE also showed an excellent diagnostic performance both in CD (AUC = 0.842) and UC (AUC = 0.880). The elafin urinary profile had a high diagnostic value, with a better accuracy in the UC patients (AUC = 0.772) than the CD patients (AUC = 0.674), though it was inferior to NE and NE/elafin. **Conclusions:** Our findings indicate that urinary NE, elafin, the and NE/elafin ratio have significant diagnostic value in differentiating IBD patients from healthy controls. The NE/elafin ratio and NE proved to be the most reliable urinary biomarkers in both CD and UC diagnosis, with a high predictive value and strong discriminatory power.

Keywords: inflammatory bowel disease; ulcerative colitis; Crohn's disease; neutrophil elastase; elafin; extracellular matrix; proteolytic balance; biomarker

1. Introduction

Inflammatory bowel disease (IBD) is a chronic immune-mediated inflammatory disorder, characterized by alternating episodes of flares and remissions. The pathogenesis of IBD is complex, involving genetic predisposition, gut dysbiosis, loss of intestinal barrier integrity, and an abnormal immune response to microbial or environmental antigens. The two main types of IBD are ulcerative colitis (UC) and Crohn's disease (CD), which differ significantly in terms of location and extent of lesions, as well as extraintestinal manifestations, possible complications, and the effectiveness of therapeutic approaches. The prevalence of IBD is increasing worldwide as the disease is more commonly diagnosed in patients between the ages of 18 and 35, as well as in the pediatric population. Therefore, considering the rising prevalence and the younger age at diagnosis, early detection is crucial to prevent the development of severe disease and potential complications [1–4]. At the same time, IBD diagnosis is often delayed due to the heterogeneity of clinical manifestations—especially in Crohn's disease—and the presence of non-specific symptoms, which may lead to misdiagnosis and further progression of the disease. Reliable and sensitive biomarkers may not only support early IBD diagnosis, but also help to predict its development several years before the onset of clinical symptoms. The diagnosis of IBD is currently based on invasive methods, such as endoscopic examination, while non-invasive ones are mainly limited to measurements of C-reactive protein (CRP) and fecal calprotectin. Elevated fecal calprotectin is observed not only in IBD but also in gastrointestinal infections and colorectal cancer, as well as dietary allergies and celiac disease [1,4]. Therefore, none of the currently studied biomarkers enable IBD diagnosis on their own, let alone effective differentiation between UC and CD. The management of UC and CD requires a more personalized approach and the use of biomarkers that could complement endoscopic examinations in the diagnostic process, as well as facilitate close monitoring of disease progression in order to minimize intestinal damage [5–7]. Consequently, there is a pressing need to identify new non-invasive biomarkers that could aid in the diagnosis of IBD and facilitate the differentiation between UC and CD.

The pathogenesis of IBD is related to the increased activation of immune cells, with neutrophils being among the first cells infiltrating the intestinal tissue during disease progression. At the site of inflammation, neutrophils neutralize pathogens through the generation of reactive oxygen species and the release of neutrophil extracellular traps (NETs) containing proteases such as neutrophil elastase (NE).

NE is not only the most abundant serine protease released from neutrophils, but also the most active one, as it accounts for approximately 80% of the proteolytic activity in the human body. The key role of NE is the neutralization of pathogens; however, it has also been suggested to play a role in modulating the inflammatory response by upregulating pro-inflammatory cytokines and thereby enhancing the inflammatory process. NE is also engaged, both directly and indirectly, via the activation of matrix metalloproteinases (MMPs), in the remodeling of the extracellular matrix (ECM) through the cleavage of collagen, laminin, fibronectin, and elastin, thereby contributing to the intestinal damage observed in IBD. Moreover, NE is implicated in another key aspect of IBD pathogenesis, namely the impairment of intestinal barrier integrity, as it can cleave tight junction proteins, such as E-cadherin [8–11]. Therefore, NE is actively engaged in the development of IBD by amplifying inflammatory processes, damaging intestinal tissue, and impairing intestinal barrier integrity. Considering the multifactorial involvement of NE in IBD pathogenesis, its measurement may be useful not only for the diagnosis of IBD but also as a marker of disease activity. Consequently, in this study the urinary profile of NE will be measured in patients with IBD (both CD and UC) as well as in healthy individuals.

Urine was chosen as the biological material for our study due to its non-invasive collection, allowing for easy and repeated sampling. Additionally, urine can accumulate proteolytic enzymes and their inhibitors, providing insight into the long-term activity of inflammatory processes occurring in IBD. Both NE (≈30 kDa) and elafin (≈6–12 kDa) have relatively small molecular weights, allowing them to freely pass through the glomerular filtration barrier. Unlike serum, where NE is tightly regulated by endogenous inhibitors, especially α1-antytrypsin, urine may better reflect its actual proteolytic activity and imbalances between NE and elafin.

Another biomarker analyzed in our study is elafin, one of the inhibitors of NE. Elafin is a serine protease inhibitor expressed in epithelial cells throughout the entire gastrointestinal tract, as well as in macrophages and neutrophils. Its anti-protease activity is relatively narrow, as it inhibits only neutrophil elastase and neutrophil proteinase 3; however, it can bind to both proteases with equally high affinity. Apart from its elastase inhibitor domain, elafin also possesses transglutaminase substrate domain, which enables its binding to ECM components, thereby protecting ECM from excessive proteolysis. Moreover, this protein demonstrates anti-inflammatory properties as it may inhibit the pro-inflammatory NF-κB pathway, thereby suppressing the inflammatory process [12,13]. During IBD, elafin may not only suppress the proteolytic activity of NE, but also attenuate the inflammatory response. Consequently, a disruption in the NE/elafin balance may lead to intestinal tissue damage, compromised intestinal barrier integrity, and an excessive inflammatory response—features characteristic for IBD. Therefore, in our study, we will evaluate not only the urinary profiles of NE and elafin but also the NE/elafin ratio to elucidate the proteolytic–anti-proteolytic balance in IBD patients. The aim of our study is to assess the utility of NE, elafin, and the NE/elafin urinary profile in the diagnosis of IBD, as well as in differential diagnoses between UC and CD. Additionally, the utility of these biomarkers in evaluating disease activity will also be evaluated.

2. Materials and Methods

2.1. Study Population

The study included 46 patients with inflammatory bowel disease and 42 healthy individuals. Among the patients with IBD, 30 were diagnosed with ulcerative colitis and 16 with Crohn's disease. The diagnoses of UC and CD were made at the Department of Gastroenterology of St. Barbara's Regional Specialist Hospital in Sosnowiec based on clinical symptoms, endoscopic examination, and laboratory tests. Disease activity was evaluated according to the Mayo endoscopic scale in patients with ulcerative colitis and Crohn's Disease Activity Index (CDAI) in patients with Crohn's disease. The inclusion criteria for the study group included newly diagnosed active disease and age over 18 years. Patients with unstable coronary disease, bacterial, fungal or viral infections, chronic liver or kidney disease, or toxic or fulminant colitis were excluded from participation in this study. Moreover, pregnant or breastfeeding women were excluded from the study. The inclusion criteria for the control group included age over 18 years and normal results in routine laboratory tests. Exclusion criteria included ongoing pharmacological treatment or/and surgical treatment within 12 months prior to the start of the study. Urine was selected as the biological material investigated in this study. Samples were collected from newly diagnosed patients with UC or CD before treatment, as well as from healthy individuals.

2.2. Methods

The concentration of elafin and NE were assessed in urine samples collected from patients with UC and CD, as well as from healthy individuals. Urinary excretion of elafin was evaluated using an ELISA test for elafin from Cloud-Clone Corporation (Houston,

TX, USA). The analytical sensitivity of this assay was 0.121 ng/mL, with an intra-assay precision of <10%. Levels of urinary NE were assessed with NE ELISA test from Immunodiagnostik AG Company (Berlin, Germany). The analytical sensitivity of the test used was 0.104 ng/mL, while the intra-assay precision was 6%. To minimize the effect of urine concentration variability, urinary NE and elafin levels were normalized to creatinine levels.

2.3. Statistical Analysis

Statistical analysis was performed using STATISTICA software, version 13.3 from StatSoft company (Cracov, Poland). The Shapiro–Wilk test was applied to evaluate the normality of the data distribution, while the significance of differences in urinary levels of elafin and NE between the analyzed groups was evaluated using Student's *t* test. To further assess the diagnostic utility of the analyzed biomarkers for UC and CD, an analysis of the receiver operating characteristic (ROC) curves was conducted. The correlation between urinary biomarker excretion and both disease activity and C-reactive protein was assessed using the Pearson or Spearman test, depending on the normality of the data distribution. The level of statistical significance was estimated as being lower than 0.05 in the tests performed.

3. Results

3.1. Characteristic of Patients

Subjects enrolled in this study included 46 patients with IBD (30 UC and 16 CD) and 42 healthy individuals. The clinical characteristics of the IBD patients are presented in Table 1. The UC patient group included 12 females and 18 males, with average age of 33 years old. All of the UC patients had active disease, with a median Mayo endoscopic score of three points. The intensity of the inflammatory response was evaluated using measurements of serum C-reactive protein (CRP) and calprotectin levels. The median CRP level in the UC group was 3.34 mg/L (1.2–15.2), indicating either no or low systemic inflammation. Given that the cut-off value for serum calprotectin in IBD remains under debate, we compared our results with those obtained by Meuwis et al. [14]. In their study, the serum calprotectin level in healthy individuals was 1318 ng/mL, while in the UC group in our study, it was 2782.9 ng/mL. The observed increase in serum calprotectin levels may therefore indicate ongoing gastrointestinal inflammation in patients with UC. Creatinine and sodium levels were within the normal range in all of the patients with UC, although one patient had a decreased potassium concentration and eight individuals had abnormal fasting glucose levels. The group of patients with CD included eight females and eight males, with an average age of 34 years. All of the patients with CD presented with moderately active disease with average CDAI score of 297.73 points. At the same time, the median CRP level was 13.6 mg/L, indicating more intense systemic inflammation in CD patients compared with those with UC. Moreover, serum calprotectin levels were higher in the CD than in the UC patients (3139.5 vs. 2782.9 ng/mL). All of the patients with CD had normal creatinine and potassium levels, whereas two patients were diagnosed with hyponatremia and one had an abnormal fasting glucose level.

Table 1. Clinical characteristics of patients.

Parameter	UC	CD
Number of patients	30	16
Sex [female/male]	12/18	8/8
Age [years]	33 ± 13	34 ± 9
Body Mass Index [kg/m^2]	24.3 ± 3.6	20.6 ± 3.4
Disease activity	Mayo endoscopic scale: 3 (2–3)	CDAI: 297.73 ± 38.88
C-reactive protein [mg/L]	3.34 (1.26–15.2)	13.6 (3.2–24.4)
Serum calprotectin [ng/mL]	2782.9 (1674.2–4754.5)	3139.5 ± 1361.6
Creatinine [mg/dL]	0.88 ± 0.15	0.91 ± 0.17
Sodium [mmol/L]	140 ± 1.89	138.06 ± 2.86
Potassium [mmol/L]	4.16 ± 0.41	4.27 ± 0.27
Glucose [mg/dL]	89.59 ± 12.80	86.70 ± 8.30

Data are presented as mean ± standard deviation in case of normally distributed data and median and interquartile range in non-normally distributed data.

3.2. Urinary Excretion of Elafin and Neutrophil Elastase in Patients with Ulcerative Colitis and Crohn's Disease and Healthy Individuals

In our study, the urinary excretion levels of elafin and NE were measured in patients with UC and CD and healthy individuals, and the results are presented in Table 2 and Figure 1. The mean concentration of elafin was 6.57 μg/g Cr in the UC group, 5.71 μg/g Cr in the CD group, and 3.10 μg/g Cr in the healthy individuals. In the UC group, we observed a statistically significant twofold increase in the elafin level compared to the control group ($p < 0.0001$). A similar nearly twofold increase was also noted in the CD group relative to the control group ($p < 0.0005$). At the same time no significant difference in the elafin profile was observed between patients with UC and CD. Another biomarker analyzed in this study was NE, which presented a significant seventeen-fold increase in the UC group compared to healthy individuals (3.83 vs. 0.22 μg/g Cr, $p < 0.0001$). Moreover, urinary levels of NE were almost 28 times higher in patients with CD compared to healthy individuals (6.17 vs. 0.22 μg/g Cr; $p < 0.0001$). Given that elafin is an inhibitor of NE, we also evaluated the NE/elafin ratio in both the study and control groups. Patients with both UC and CD presented significantly increased NE/elafin ratio compared to healthy individuals. Among UC patients, the observed increase reached 4.5-fold, while CD patients presented a 5.6-fold increase in the NE/elafin ratio compared to healthy individuals. At the same time, no significant difference was noted between the UC and CD groups.

Table 2. Urinary excretion of elafin and NE in patients with ulcerative colitis and Crohn's disease and healthy individuals.

Parameter	UC	CD	C	*p* UC vs. C	*p* CD vs. C	*p* UC vs. CD
elafin [μg/g Cr]	6.57 (3.69–20.88)	5.71 (3.12–6.80)	3.10 (1.46–4.59)	<0.0001	<0.0005	>0.05
NE [μg/g Cr]	3.83 (1.18–8.50)	6.17 (0.97–11.84)	0.22 (0.13–0.45)	<0.0001	<0.0001	>0.05
NE/Elafin ratio	0.59 (0.24–1.05)	0.73 (0.31–1.51)	0.13 (0.04–0.27)	<0.0001	<0.0001	>0.05

Results have been presented as median with interquartile range. C, healthy control; CD, patients with Crohn's disease; NE, neutrophil elastase; UC, patients with ulcerative colitis; μg/g Cr, μg/g creatinine.

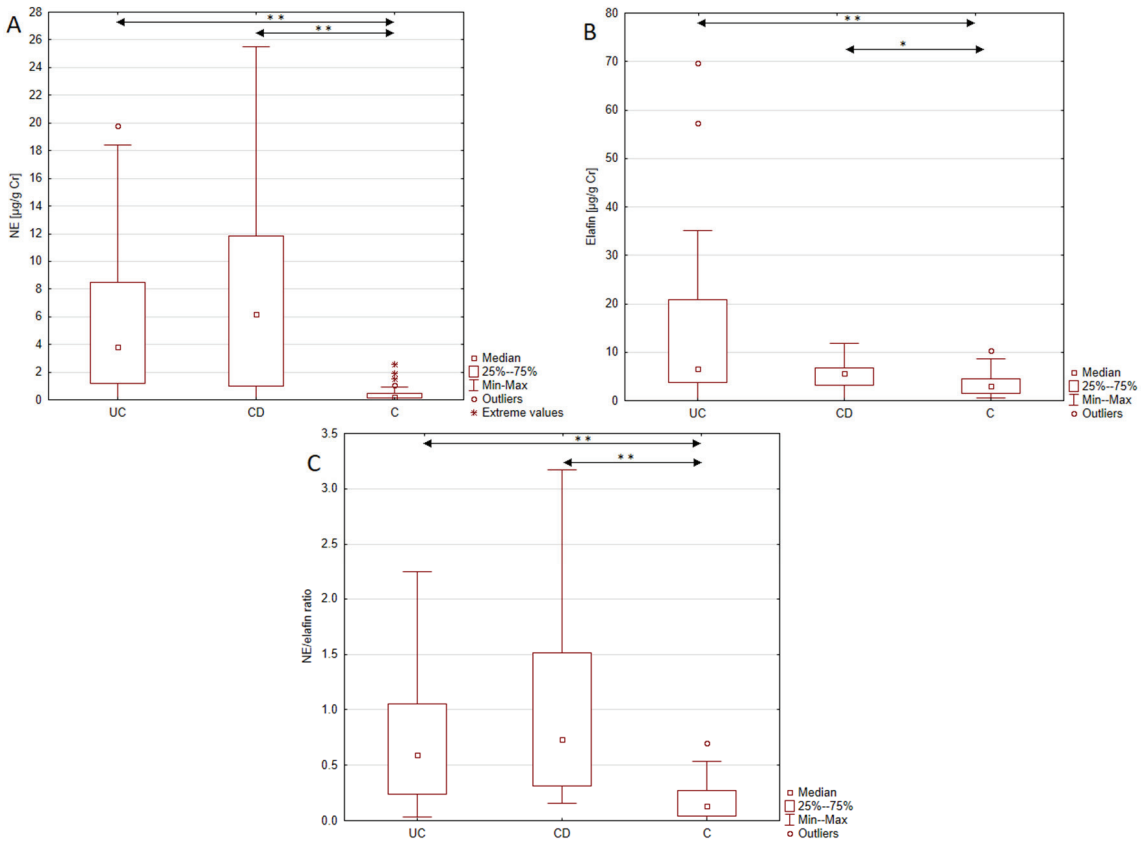

Figure 1. Urinary excretion of elafin and NE and the NE/elafin ratio in patients with ulcerative colitis, and Crohn's disease and healthy individuals; (**A**), urinary profile of neutrophil elastase in analyzed groups; (**B**), urinary profile of elafin in analyzed groups; (**C**), Neutrophil elastase/elafin ratio in analyzed groups. Data with statistical significance has been marked as * $p < 0.0005$; ** $p < 0.0001$.

3.3. Urinary Elafin and Neutrophil Elastase as Biomarkers of Ulcerative Colitis and Crohn's Disease

The aim of our study is to evaluate the role of urinary elafin and neutrophil elastase, along with the NE/elafin ratio, in the diagnosis and monitoring of ulcerative colitis and Crohn's disease. Therefore, to assess the diagnostic utility of these biomarkers we performed ROC curve analysis of the urinary profile of NE and elafin, as well as the NE/elafin ratio, with the results presented in Table 3 and Figure 2. In this study, higher diagnostic performance values were noted for the urinary NE/elafin ratio profile in CD patients. This biomarker demonstrated excellent accuracy in distinguishing CD patients from healthy individuals with an AUC of 0.896 (0.805–0.988). Moreover, the test exhibited 92.9% sensitivity, 69.7% specificity, a 56.5% PPV, and a 95.8% NPV, resulting in great recognition of CD patients, but with a simultaneous risk of CD overdiagnosis. The diagnostic performance of NE/elafin ratio was also promising in the group of patients with UC. ROC curve analysis revealed a strong ability of this biomarker to differentiate UC patients from healthy individuals, with an AUC of 0.815 (0.708–0.923). This test also showed high values of specificity (90.9%), PPV (85%) and NPV (73.2%), however lower value of sensitivity (60.7%), which may indicate its greater potential in excluding UC.

Table 3. ROC curve analysis of the urinary profile of the analyzed biomarkers.

Parameter	Analyzed Groups	AUC	Youden Index	Cut-Off	Sensitivity	Specificity	PPV	NPV
elafin	UC vs. C	0.772 (0.653–0.891)	0.48	5.89 µg/g Cr	65.5%	82.9%	73.1%	77.3%
	CD vs. C	0.674 (0.480–0.867)	0.45	4.92 µg/g Cr	69.2%	75.6%	47.3%	88.6%
NE	UC vs. C	0.880 (0.778–0.981)	0.68	0.76 µg/g Cr	85.7%	81.8%	80%	87.1%
	CD vs. C	0.842 (0.672–1)	0.72	0.82 µg/g Cr	86.7%	84.8%	72.2%	93.3%
NE/Elafin ratio	UC vs. C	0.815 (0.708–0.923)	0.52	0.40	60.7%	90.9%	85.0%	73.2%
	CD vs. C	0.896 (0.805–0.988)	0.63	0.25	92.9%	69.7%	56.5%	95.8%

AUC, area under the ROC curve; CD, Crohn's disease; NE, neutrophil elastase; NPV, negative predictive values; PPV, positive predictive value; UC, ulcerative colitis; µg/g Cr, µg/g creatinine.

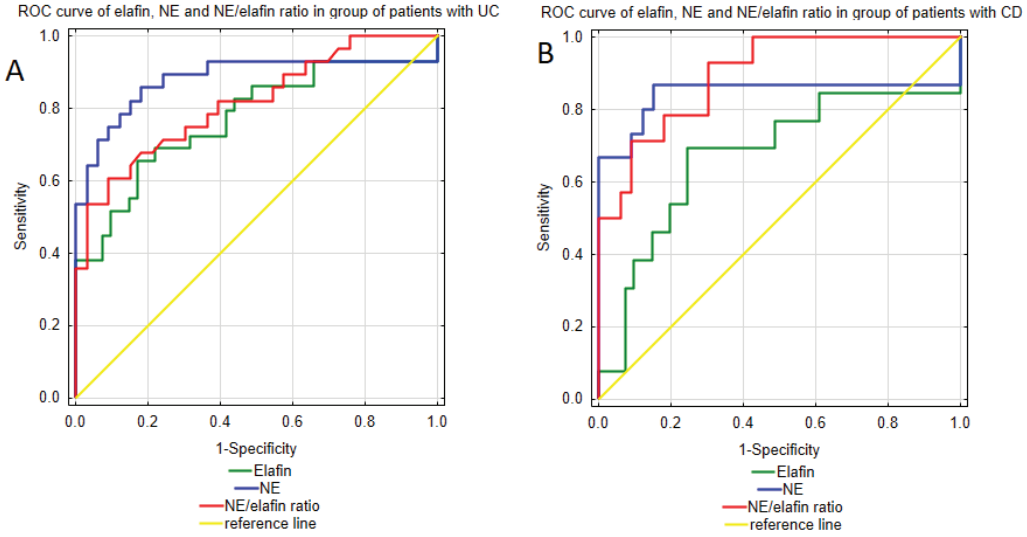

Figure 2. ROC curve of NE, elafin, and NE/elafin ratio as diagnostic biomarkers of UC and CD; (**A**), ROC curve of analyzed parameters as diagnostic biomarkers of UC group; (**B**), ROC curve of analyzed parameters as diagnostic biomarkers of UC group.

The urinary NE profile demonstrated strong performance in distinguishing CD patients from healthy individuals, with an AUC of 0.842 (0.672–1), as well as high sensitivity (86.7%) and specificity (84.8%). When analyzing the PPV and NPV (72.2% vs. 93.3%), however, this test exhibited greater reliability of negative test result. In group of patients with UC, the urinary NE profile also demonstrated excellent diagnostic performance effectively differentiating patients with UC from healthy individuals, with an AUC of 0.880 (0.778–0.981). Given the high values of sensitivity (85.7%) and specificity (81.8%), urinary NE measurements may be useful for accurate UC diagnosis. At the same time, the PPV and NPV were high, indicating the strong predictive value of both positive and negative test results.

Moreover, in this study, we assessed the diagnostic utility of elafin profile in both UC and CD. The elafin measurements presented strong discriminative ability in distinguishing patients with ulcerative colitis from healthy individuals, with an AUC of 0.772 (0.653–0.891), high specificity (82.9%) and satisfactory sensitivity (65.5%). Additionally, the PPV equaled 73.1% and the NPV was 77.3%, indicating strong predictive value of both positive and

negative test results. In group of patients with CD, diagnostic indicators were slightly lower. ROC curve analysis presented moderate ability of elafin assessments in differentiating patients with CD from healthy individuals with an AUC of 0.674 (0.480–0.867). Furthermore, the test had a sensitivity of 69.2% and specificity of 75.6%, indicating a similar ability to correctly identify both CD and healthy individuals within the population. However, the positive test results presented a lower PPV, indicating possible overdiagnosis of CD.

3.4. Utility of Urinary Biomarkers in Disease Activity Monitoring

In this study, apart from the diagnostic utility of the analyzed biomarkers, we also evaluated their usefulness in monitoring the disease activity. Statistical analyses revealed no significant correlation between the urinary profiles of elafin, NE, and the NE/elafin ratio with disease activity in either the UC and CD group. Similarly, no significant relationship was observed between the analyzed biomarkers and the CRP level in both study groups.

4. Discussion

The identification of reliable biomarkers for IBD is crucial for early and accurate diagnosis, which not only guides treatment strategies but also helps to predict the disease course. The accurate and early identification of UC or CD using reliable biomarkers may not only limit the extent of intestinal tissue injury, but also allows for prompt initiation of therapy, thereby increasing the likelihood of achieving clinical remission within the first few months of treatment [6]. Although fecal calprotectin has been identified as a diagnostic biomarker of IBD, its clinical utility remains restricted due to its lack of specificity in distinguishing IBD from other inflammatory gastrointestinal disorders. Therefore, in our research we aimed to identify new biomarkers that could support the diagnostic process for IBD and aid in differentiating UC from CD. The biomarkers assessed in this study (NE, elafin, NE/elafin ratio) were selected based on their active role in key processes related to the pathogenesis of IBD, including intestinal barrier disruption, excessive immune response, and intestinal tissue damage. Urine was chosen as the biological material for analysis due to its accessibility, non-invasive collection, and ability to reflect biochemical changes that occur during disease progression. In serum, NE activity is strictly regulated by endogenous inhibitors such as α1-antitrypsin (α1AT). However, in urine, the NE-α1-antitrypsin complex is typically absent or present only in trace amounts due to the high molecular weight of α1AT. Therefore, urine may provide a more accurate representation of NE's actual proteolytic activity while also reflecting the balance between NE and elafin, as both have low molecular weights.

To our knowledge, this is the first study demonstrating increased urinary excretion of NE in patients with IBD (both UC and CD) compared to healthy individuals. The observed increase in NE excretion reached 17-fold in UC and 28-fold in CD patients compared to the control group. The demonstrated upregulation of NE is in line with the results of Kuno et al. [15], who noted elevated expression of NE in mucosal biopsies from UC patients compared to controls. Researchers have also noted differences in NE levels between inflamed and non-inflamed tissues from UC patients, while no such difference was observed between non-inflamed UC tissue and control samples. Moreover, the level of NE correlated positively with the number of neutrophils and mononuclear cells, indicating a local inflammation-driven increase in NE during UC. Additionally, in a study conducted by Curciarello et al. [16], the NE activity in the mucosal tissue of IBD patients was elevated and increased over time, whereas it remained stable in the control group, suggesting both enhanced and prolonged NE activity in UC patients. NE also plays a role in ECM proteolysis, releasing pro-inflammatory cytokines deposited within the matrix and modulating the inflammatory response via Toll-like receptor 4 and the NF-κB pathway, thereby contribut-

ing to the development of inflammatory processes. Ginzberg et al. [17] demonstrated in a cellular model of the intestinal epithelium that NE migration across the epithelial barrier was associated with E-cadherin degradation, detachment of the epithelial monolayer, and the disruption of adherens junction integrity. These actions of NE may lead to increased intestinal and ulcer formation—key features of IBD. Additionally, some researchers indicate that NE may limit epithelial proliferation and induce epithelial-to-mesenchymal transition, resulting in impaired mucosal repair. Taken together, these findings highlight NE as a protease with a substantial contribution to intestinal tissue damage progression. This causal role of NE in the development of UC may explain its increased urinary excretion in UC patients [9,15,18]. In contrast, reports regarding NE expression in CD patients remain inconsistent. In our study, NE excretion in CD patients was significantly higher than in healthy individuals. However, in Kuno et al.'s [15] study, NE expression did not differ between CD patients and controls. The observed inconsistency may be related to differences in treatment and disease duration, as our study included only newly diagnosed, treatment-naïve patients, whereas the study by Kuno et al. involved CD patients diagnosed 15 months to 18 years prior to the study, many of whom received treatment with 5-amino salicylic acid or prednisolone. Conversely, Langhorst et al. [19] reported an increased expression of fecal NE in both CD and UC patients compared to patients with irritable bowel syndrome (IBS), identifying NE as a superior marker for IBD compared to CRP. Moreover, measurements of fecal NE allow active IBD to be differentiated from inactive IBD, indicating its potential role in monitoring the disease activity. Among the analyzed parameters, neutrophil elastase emerged as a promising biomarker for IBD diagnosis. Conducted ROC curve analysis demonstrated excellent discriminative ability of urinary NE in distinguishing Crohn's disease patients and healthy individuals. Moreover, the analysis revealed high sensitivity and specificity of NE urinary profile, supporting its potential as a diagnostic biomarker for CD. Considering the higher NPV compared to the PPV (93.32% vs. 72.2%), this test may overdiagnose CD. The ROC curve analysis of urinary NE in UC patients also yielded encouraging results, demonstrating a strong ability to differentiate patients with UC from healthy individuals with high specificity and sensitivity. These findings, together with the strong values of both the positive and negative test results, highlight the potential clinical application of urinary NE measurements in the diagnosis of UC.

Furthermore, this study demonstrated increased urinary excretion of elafin in both UC and CD patients compared to the control group. The results obtained are in line with results of Wang et al.'s [20] study, who noted increased serum elafin levels in IBD patients. Similar results were presented in Krawiec et al.'s [21] study, which was conducted in a pediatric IBD population. The up-regulation of elafin in IBD was also presented in a study by Schmid et al. [22], which reported increased elafin expression in inflamed intestinal tissue compared to non-inflamed tissue from IBD patients. The increase in elafin levels observed in IBD may be related to the inflammatory process, as this protein is constitutively expressed in intestinal epithelial cells, but its expression increases in response to inflammatory stimuli. Key triggers of elafin up-regulation include the IL-1β and TNF-α-two cytokines, which are known to play a pivotal role in IBD pathogenesis [23,24]. Beyond its role as an NE inhibitor, elafin is involved in maintaining intestinal barrier integrity and exerts anti-inflammatory effects. This protective function of elafin was demonstrated in the study conducted by Motta et al. [24] using both cellular and animal models of IBD. In that study, elafin not only inhibited TNFα-induced intestinal barrier permeability, but also improved the organization of tight junction proteins. Moreover, elafin administration suppressed the inflammatory response by reducing the levels of IBD-related pro-inflammatory cytokines including IL-6, IL-8, IL-17, TNF-α, as well as down-regulating the NF-κB pathway [24–26]. These findings suggest that despite its protective role against colitis and its up-regulated expression in

IBD, the effect of elafin may not be sufficient to suppress the pro-inflammatory processes underlying IBD. Nevertheless, given its involvement in the key pathological mechanisms of IBD—namely intestinal barrier integrity and inflammatory process—we assessed the diagnostic utility of elafin measurements in IBD. The urinary elafin profile proved useful in diagnosing both UC and CD, with a better diagnostic performance in UC patients. Urinary elafin measurements effectively distinguished UC patients from healthy individuals with high specificity and satisfactory sensitivity. Moreover, the urinary elafin measurements demonstrated a strong PPV and NPV, indicating a low incidence of false positive and false negative diagnoses. In CD patients, the elafin urinary profile also showed a strong ability to differentiate CD patients from healthy individuals with a slightly better sensitivity but a lower specificity, suggesting a higher susceptibility to false positive diagnoses. Additionally, in CD patients, urinary elafin levels exhibited a lower variability, suggesting greater stability of this biomarker in CD patients.

In this study, the increase in NE levels was accompanied by an elevation of elafin expression; however, this up-regulation of elafin may not counteract NE activity in IBD. Consequently, the protease–anti-protease balance may remain disrupted, contributing to intestinal tissue damage. These findings are supported by the study of Curciarello et al. [16], which assessed the protease–anti-protease balance in the mucosal tissue of IBD patients and healthy individuals. Despite increased elafin expression, patients with IBD exhibited enhanced NE activity, which was further reflected by a decreased elastin level, an extracellular matrix component degraded by NE. To exclude a reduced suppressive effect of elafin on NE, the researchers evaluated NE's sensitivity to elafin-mediated inhibition. Upon exposure to elafin, elastin proteolysis was diminished, confirming that NE remained responsive to elafin's inhibitory effects. These findings emphasize that measurements of NE and elafin concentrations alone may be insufficient to assess the proteolytic–anti-proteolytic balance during IBD. Assessments of the NE/elafin ratio may provide a more comprehensive reflection of the protease—anti-protease imbalance, which could directly contribute to the degradation of the extracellular matrix and subsequent damage of intestinal tissue observed in both UC and CD. Moreover, in a previously mentioned study by Curciarello et al. [16], an imbalance between NE and elafin was related to a loss of response to biological treatment in UC patients, likely due to NE's ability to neutralize anti-TNF-α agents. At the same time, this effect was mitigated by the administration of exogenous elafin. These findings suggest that the disruption of the NE/elafin balance may not only contribute to disease pathogenesis, but also to a loss of response to anti-inflammatory biological treatment in IBD patients. Therefore, in this study we additionally assessed the NE/elafin ratio to better illustrate the proteolytic–anti-proteolytic balance in UC and CD patients compared to healthy individuals. The results revealed a 4.5-fold increase in the NE/elafin ratio in patients with UC and a 5.6-fold increase in CD patients compared to healthy individuals, indicating an imbalance in proteolytic and anti-proteolytic activity in IBD. These findings correspond with the results obtained in the studies conducted by Motta et al. [25], Barry et al. [9], and Schmid et al. [21], which also demonstrated a disrupted proteolytic–anti-proteolytic balance during IBD and highlighted its causative role in intestinal tissue damage. Moreover, enhanced NE activity in IBD may not only drive inflammation but also contribute to abdominal pain. NE has been shown to cleave protease-activated receptor 2 (PAR2), leading to the sensitization of nociceptive neurons and subsequent development of neurogenic inflammation and pain [27,28]. Despite the recognized role of the protease–anti-protease balance in IBD pathogenesis, the NE/elafin ratio has not yet been considered as a potential diagnostic biomarker. Therefore, in this study, we assessed the NE/elafin excretion ratio to explore its potential utility in diagnosing UC and CD. Among the analyzed biomarkers, the NE/elafin ratio demonstrated the best

potential in distinguishing patients with Crohn's disease from healthy individuals, with a 92.9% of sensitivity, indicating a low risk of CD misdiagnosis. Similarly, in UC patients, the NE/elafin ratio effectively distinguished UC patients from healthy individuals, with 90.9% specificity and 60.7% sensitivity. These results suggest that the assessment of the NE/elafin ratio in UC patients is more prone to omit UC patients in population. Comparable results were observed considering NE urine profile, which biomarker effectively distinguished both UC and CD patients with high sensitivity and specificity. Regarding the AUC values of the analyzed biomarkers, the NE/elafin ratio and NE provided better diagnostic values compared to elafin measurements in urine. Given the potential role of NE/elafin as an indicator of treatment response—as suggested by Curciarello et al. [16]—measurements of this ratio might prove useful in monitoring therapeutic efficacy during biological treatment. Since the study cohort consisted exclusively of newly diagnosed patients who had not yet received biological treatment, the potential of this ratio as a treatment monitoring tool should be further analyzed in future studies.

The biomarkers—elafin, NE, and the NE/elafin ratio—evaluated in this study demonstrated potential for the early detection of both UC and CD, which could ultimately contribute to improved clinical outcomes through earlier intervention. A key strength of our study lies in the inclusion of only newly diagnosed UC and CD patients, allowing us to assess the diagnostic value of selected biomarkers. Additionally, the use of urine samples offers the advantage of a non-invasive, easily repeatable method of biomarker assessment. Moreover, due to the high molecular weight of α1-antitrypsin, its filtration into urine is significantly limited, which restricts the formation of NE-α1–antitrypsin complexes in urinary samples. As a result, urinary measurements of free NE may more accurately reflect its true proteolytic potential and the imbalance between NE and its physiological inhibitor, elafin. In this study, NE and elafin concentrations were normalized to the urinary creatinine level in each subject to minimize the effect of urine concentration variability. This standardization allows us to assess each biomarker in a single urine sample, reducing the need for 24 h urine collection. At the same time, referencing the urinary creatinine level helps to decrease the error related to intra- and inter-individual variability in the NE and elafin profiles among tested subjects. Nonetheless, this study has some limitations, among which the relatively small size of study groups may limit the ability to generalize the obtained results to a larger population of IBD patients. Consequently, the findings reported here should be interpreted with caution and validated in a larger independent cohort of patients with different disease manifestations, especially in the case of patients with Crohn's disease, to ensure greater variability in and the external validity of the analyzed biomarkers. Additionally, external validation would allow for the assessment of both intra-individual and inter-individual variability, which may influence the accuracy and reproducibility of urinary elafin and NE measurements in IBD patients.

5. Conclusions

In summary, all analyzed biomarkers—neutrophil elastase, elafin and the NE/elafin ratio-demonstrated significant potential for the diagnosis of both ulcerative colitis and Crohn's disease. Among them, the NE/elafin ratio emerged as the most promising biomarker, exhibiting a high sensitivity and specificity in distinguishing both UC and CD patients from healthy individuals, with a particularly greater accuracy in the CD group. Moreover, NE presented a comparable capability to differentiate both UC and CD patients from healthy subjects with high values of diagnostic indicators. Elafin presented a very good ability to diagnose IBD patients with a superior diagnostic performance in UC patients compared to CD patients, indicating a potentially greater diagnostic value in UC patients. Taken together, the biomarkers evaluated in this study may serve as supportive

non-invasive tools in the diagnostic workup of UC and CD; however, further studies on larger cohorts are warranted to validate these findings.

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Exploring Dietary- and Disease-Related Influences on Flatulence and Fecal Odor Perception in Inflammatory Bowel Disease

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Abstract: Background/Objectives: Inflammatory bowel disease (IBD) affects gastrointestinal function and may alter fecal and flatulence odor (intestinal odor) due to changes in inflammation, the gut microbiome, and metabolism. Investigating the relationship between dietary habits and intestinal odor in IBD is critical given the relationship between diet, gut health, and microbiome diversity. **Methods**: We performed a cohort analysis of a monocentric, cross-sectional study at a tertiary referral center and compared the perception of fecal and flatulence odor in 233 IBD patients (n = 117 women) with that of 96 healthy controls (HCs) (n = 67 women). In addition to a short screening questionnaire on highly processed foods (sQ-HPF), dietary behavior (Food Frequency Questionnaire (FFQ)), clinical (HBI, PMS) and biochemical (CRP, fecal calprotectin) parameters of disease activity, and adherence to a Mediterranean diet were assessed. **Results**: A notable predisposition towards elevated levels of intestinal malodor was identified in the IBD cohort when compared to the HC group. The analysis of dietary behavior in conjunction with intestinal malodor revealed more pronounced associations in the HC collective than in the IBD collective. The data further indicated that, in comparison to those in remission, IBD individuals with an active disease status exhibited a higher prevalence of intestinal malodor. In an adjusted logistic regression analysis of the influence of disease- and diet-specific factors on flatulence and fecal malodor in IBD, male sex was identified as a significant risk factor. **Conclusions**: This study highlights the significance of dietary factors in the management of IBD symptoms, with a particular focus on flatulence and fecal odor. Individuals with IBD demonstrated a higher propensity for intestinal malodor compared to HC, with active disease status further amplifying this prevalence. Dietary behavior showed stronger associations with malodor in the HC group than in IBD individuals, suggesting distinct interaction patterns between diet and gut health in these populations.

Keywords: inflammatory bowel disease; malodor perception; flatulence; highly processed foods; healthy control

1. Introduction

In the gastrointestinal tract, numerous gases are produced through chemical reactions or the metabolic processes of resident microbiota. These include hydrogen (H_2), methane (CH_4), and carbon dioxide (CO_2), along with smaller quantities of trace gases such as hydrogen sulfide (H_2S), nitric oxide (NO), and sulfur-based compounds [1]. The primary source of these gases is bacterial fermentation of dietary components. Despite ongoing research into the impact of dietary substrates on the human body, our knowledge of the dynamic processes involved in how food is metabolized in the gut remains limited and rudimentary. In the general population, the type and strength of flatulence and fecal odor are known to be influenced by nutritional choices—a diet with a high fiber or protein content can increase or change the odor that is perceived [1,2]. In addition, food intolerances and fermentable oligosaccharides, as contained in wheat or onions, can cause increased intestinal odor [3]. However, a change in odor can also be health-related: changes in fecal volatile organic compound (VOC) have been suggested as an indicator of inflammatory bowel diseases (IBDs) [4,5] as well as changes in disease progression for IBD [6]. It is well documented that IBD, including Crohn's disease (CD) and ulcerative colitis (UC), has a significant impact on the function of the digestive tract, resulting in a range of symptoms, including alterations in the odor of feces and flatulence [7]. The underlying pathophysiological changes associated with IBD, such as inflammation, malabsorption, and alterations in the gut microbiota, are thought to be primarily responsible for these distinct changes [7]. The presence of specific compounds, including hydrogen sulphide, which is produced during the fermentation of undigested food in the colon, is often linked to IBD [8]. Inflammation, which interferes with normal digestion, further exacerbates this process in individuals with IBD. An increased risk of developing inflammation and of experiencing an exacerbation of inflammation, meanwhile, has been associated with ultra-processed foods in general [9,10], but there may also be an increased risk of IBD from ultra-processed foods and dietary emulsifiers such as carboxymethylcellulose [11]. Achieving a sustained remission remains one of the most important treatment goals in IBD to prevent disease progression and subsequent complications. Ileocolonoscopy is currently regarded as the gold standard for assessing mucosal inflammation in IBD substantiated by histological assessment. However, frequent colonoscopies pose a significant burden for patients and are costly and resource-intensive for healthcare systems. As a result, there is a clear need for non-invasive markers that can reliably predict changes in disease status at an early stage. Accurately predicting changes in disease state at an early stage enables timely adjustments to treatment, which in turn enhances disease outcomes and helps to minimize drug-related side effects. Especially patient-reported outcome measures (PROMS) can be a fast point of care tool to assess patient characteristics on time. In this context, especially fecal and flatulence odor perception might have advantages, as it is non-invasive, frequent, and easy to apply. As only limited data exist on intestinal odor perception and the association with dietary habits and IBD activity, the objective of this study was to gain further insight into these specific relationships in individuals with IBD.

2. Materials and Methods

The study design is in accordance with the ethical standards set forth in the Declaration of Helsinki (2013). This monocentric study was conducted at a tertiary referral center and has been approved by the Ethics Committee of the Hannover Medical School (10847_BO_S_2023) and is registered in the German Clinical Trials Register (DRKS) under DRKS00032771 (https://drks.de/search/en/trial/DRKS00032771 (accessed on 26 November 2024)).

2.1. Participants and Setting

Between October 2023 and October 2024, a total of 275 IBD patients were screened for study participation at Hannover Medical School. Written informed consent was required before inclusion in the study. Eligibility criteria were a confirmed diagnosis of either UC or CD and a disease duration of at least three months. Individuals with conditions that precluded an assessment of the nature, extent, and potential consequences of the study were excluded. Patients younger than 18 were not eligible for study participation.

2.2. Healthy Controls

A total of 101 individuals were selected to participate in this monocentric, cross-sectional study between October 2023 and October 2024. Written informed consent was required before inclusion in the study. Diagnosis of inflammatory bowel disease was an exclusion criterion for enrollment in the healthy control cohort. Individuals with conditions that precluded an assessment of the nature, extent, and potential consequences of the study were excluded. Individuals younger than 18 were not eligible for study participation.

2.3. Variables and Definitions

2.3.1. Data Sources/Measurements

Data were collected via an online survey that was only accessible for study participants who provided written consent. Types of questions included information on sex and gender identity, body type (weight, height), age, marital status, employment status, and more. All individuals were asked to complete a food frequency questionnaire (FFQ) [12] and the German version of the Screening Questionnaire of Highly Processed Food Consumption (sQ-HPF) [13]. IBD-specific history, therapies, surgical history, and comorbidities were also included in the online questionnaire. Disease activity was assessed in investigator-administered interviews using either the German version of the Harvey–Bradshaw Index (HBI) [14] for CD patients or the German version of the Mayo Score, PMS [15], for UC patients. Disease extent was determined using the Montreal classification for CD patients and the anatomical pattern for UC patients [16].

2.3.2. Advanced Therapies

Current treatment with advanced therapies (ADT), including TNF-, interleukin (IL) 12/23 and interleukin (IL) 23, integrin antagonists, JAK inhibitors, and Sphingosine-1-phosphate receptor modulators, was documented for each patient and coded as a binary variable (current ADT treatment: yes/no) for logistic regression analysis.

2.3.3. Food Frequency Questionnaire Variables and Macronutrients

For Food Frequency Questionnaire (FFQ) scoring, average daily amounts of individual foods and beverages were calculated [12], while nutrient intakes were calculated using Federal Food Code (BLS) reference data [17]. Estimated energy intake (EEI) is reported in kilojoule (kJ), as is the sex-specific resting energy expenditure (REE).

2.3.4. Mediterranean Diet Score

Mediterranean diet adherence was adjusted from Trichopoulou et al. [18] based on sex means for selected food groups. One point was awarded for each positively associated food (vegetables, pulses and legumes, fruit and nuts, cereals, fish) if the consumption was equal to or higher than the mean value. For each of the negatively associated foods (meat, poultry, dairy products), one point was awarded if the consumption was less than the mean value. Fat intake was calculated based on the FFQ dietary analysis using the ratio of monounsaturated fat (g) to saturated fat (g). For ethanol intake, Trichopoulou et al.'s [18]

sex-specific values were used. The total MDS score is between 0 and 9, with 9 representing maximum compliance with the Mediterranean diet.

2.3.5. Malnutrition Universal Screening Tool

The German version of the Malnutrition Universal Screening Tool (MUST) has been used to identify adults who are potentially at risk of malnutrition [19,20]. The scoring is based on body mass index (BMI), unplanned loss of weight within the last 3 to 6 months, and acute illness with an involuntary fasting period of at least 5 days. The total score ranges from 0 to 6, with 0 indicating low risk and anything above 2 indicating high individual risk of malnutrition.

2.3.6. Disease Activity

Entity-specific Disease Activity Index cut-offs were used to determine disease activity and remission. For the binary assessment of disease activity, remission was defined as a Harvey–Bradshaw Index (HBI) of <5 [14] in CD patients or a partial Mayo score (PMS) of 0–1 [15] in UC patients.

2.3.7. Screening Questionnaire of Highly Processed Food Consumption

The percentage of habitual, highly processed food consumption out of total intake in grams per day was estimated using the German version of the Screening Questionnaire of Highly Processed Food Consumption (sQ-HPF) [13]. [Manuscript for the translated and validated German version of the sQ-HPF currently under review].

2.3.8. Highly Processed and Ultra-Processed Foods

All FFQ items corresponding to the translated version of the sQ-HPF were selected to calculate intake of highly processed foods and beverages. In comparison, with the sole exception of canned/preserved fruits, the intake of ultra-processed foods and drinks (UPFD) was calculated by critically identifying the class 4 NOVA food classification [21] items of the FFQ. For both the HPF and the UPFD, the daily energy content (kJ/d) and the total daily weight (g/d) were calculated.

2.3.9. Gastrointestinal Surgery

Surgery status was recorded and used as a binary variable (yes/no) in the analysis as a potential confounding and adjustment factor. Additionally, a binary variable for pouch/stoma (yes/no) was created.

2.3.10. Flatulence and Fecal Odor Perception

All study participants were asked whether they perceive individual flatulence and fecal odor as exceptionally strong (malodorous), with the answers being coded as binary variables (yes/no). Flatulence and fecal malodor were used as outcome variables for logistic regression analysis.

2.3.11. Laboratory Values

As part of the screening visit, biomaterials (blood and stool samples) were collected during routine outpatient clinic visits. Laboratory values included C-reactive protein (CRP) (mg/L) and calprotectin (mg/kg).

2.4. Statistical Analysis

The statistical analysis was conducted using the SPSS Statistics software, version 29.0.1.0 (SPSS, IBM, Armonk, NY, USA), and GraphPad PRISM, version 10.4.0 (GraphPad Software, Boston, MA, USA). The Shapiro–Wilk test was used to assess normal distribution.

Categorical outcomes are reported as totals and proportions. For group comparisons of categorical variables, the Bonferroni correction was applied to Fisher's exact test. Unless otherwise stated, all statistical tests were performed two-sided. Significance levels are indicated in figures as one asterisk for $p = 0.05$, two for $p = 0.01$, and three for $p < 0.001$. Student's *t*-test was used for odor-related comparisons of dietary variables within the healthy and IBD groups. Student's *t*-test was also used for odor-related comparisons of dietary variables between the groups (healthy vs. IBD). For IBD only, data were further analyzed using binary logistic regression to assess the probability of an association between disease and diet-related events with (a) flatulence malodor and (b) fecal malodor. The odds ratio (OR), 95% confidence interval (CI), and level of significance (p) are reported. To ensure the reliability of the adjusted model, we tested for multicollinearity of the variables associated with each other in the binary logistic regression model. Consequently, the variables GI surgery and Pouch/Stoma were not used simultaneously in the adjusted model. Results of logistic regression analysis (univariate and adjusted (multivariate)) are available as supplementary data (Tables S1 and S2: Adjusted logistic regression analysis of the influence of disease-specific and dietary-specific factors [. . .]). Meanwhile, the results of the fully adjusted multivariate logistic regression are reported on in the results section. Goodness of fit for the fully adjusted logistic regression model with the outcome flatulence malodor was assessed via Omnibus Tests of Model Coefficients ($p < 0.001$), R2 (Nagelkerkes: 0.485; Cox & Snell: 0.363), and the Hosmer–Lemeshow test ($p = 0.459$). The model performance was assessed via the classification table, which showed an overall percentage of 81.4%. Goodness of fit for the fully adjusted logistic regression model with the outcome fecal malodor was assessed via Omnibus Tests of Model Coefficients ($p < 0.001$), R2 (Nagelkerkes: 0.475; Cox & Snell: 0.350), and the Hosmer–Lemeshow test ($p = 0.776$). The model performance was assessed via the classification table, which showed an overall percentage of 80.5%.

2.4.1. Confounders and Bias

Each regression model was adjusted for confounders, including disease entity, sex, remission status, pouch/stoma, vegetarian status, and age, to control for potential confounding variables. A detailed description of the adjustment factors can be found in the Supplementary Materials. [Table S1A,B: Adjustment factors for Outcome [. . .]] Prior to data analysis, cases were screened for individuals currently nursing, revealing n = 2 IBD individuals and n = 2 HC individuals who were actively nursing during study participation. Dietary intake was immensely higher for nursing individuals, to avoid distortion of further analysis, data from all nursing individuals were consequently excluded. The estimated effect size (g) is reported in addition to the statistical significance (p), as (g) is independent of sample size, to account for the small subgroup study population of healthy controls. Recall surveys are susceptible to bias, and misreporting of dietary intake in patient-reported outcomes is not uncommon [22]. Over-reporting of actual intake is more common in men and under-reporting in women [23]. Black's adjustment [24] of Goldberg et al. [25] [was used to investigate possible misreporting of energy intake. Estimated energy intake (EEI) was calculated from the FFQ responses, while sex-specific resting energy expenditure (REE) was calculated using the Mifflin–St. Jeor equations [26], derived from the Harris–Benedict equations [27]. Study participants were also asked if they had started a diet or changed their diet in the previous 5 weeks to assess possible discrepancies between BMI and EEI.

2.4.2. Missing Data

Individuals who did not complete the dietary assessment and/or questions pertaining to odor perception were excluded from the analysis. For individual missing data, which could be assumed missing at random, cases were omitted on an analysis-by-analysis basis.

3. Results

3.1. Study Population

From 275 IBD individuals screened, n = 4 were defined as screening failures, resulting in n = 271 IBD patients enrolled in the study. Of those, n = 36 were excluded from this analysis due to missing data, while n = 2 were excluded due to nursing [Figure 1].

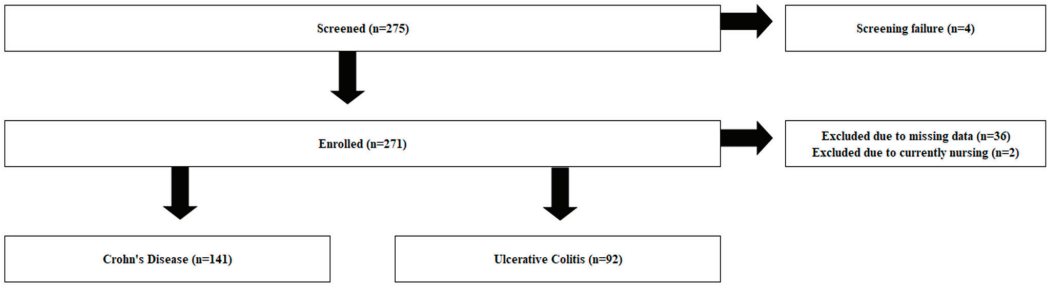

Figure 1. Flow chart of patient enrollment.

Sex distribution was well balanced (women n = 117 (50.2%)) with a skewed distribution of disease entities (Crohn's disease n = 141 (60.5%)). Of the 233 cases analyzed, n = 117 (52.9%) were in remission, and the median age was 39 [IQR: 30–50]. A total of 53 individuals (22.7%) had been diagnosed with one or more food allergies or intolerances. Additionally, 103 individuals (44.2%) had previously undergone nutritional counselling due to their IBD (Table 1).

Table 1. Baseline characteristics.

		Baseline
Demographics [Md[IQR] or n(%)]		**(n = 233)**
Disease entity	Crohn's disease	141 (60.5%)
	Ulcerative colitis	92 (39.5%)
Women		117 (50.2%)
Remission		117 (52.9%)
Location of Crohn's	L1:	35 (24.8%)
	L2:	25 (17.7%)
	L3:	67 (47.5%)
	L4:	14 (9.9%)
Crohn's behavior	B1:	51 (36.2%)
	B2:	66 (46.8%)
	B3:	24 (17%)
UC Montreal classification	Proctitis	6 (6.5%)
	Left–sided colitis	32 (34.8%)
	Pancolitis	54 (58.7%)
MUST	Low Risk	128 (54.9%)
	Medium Risk	49 (21%)
	High Risk	56 (24%)
One or more diagnosed food allergies/intolerances		53 (22.7%)
Disease duration in years		12.42 [6.84–19.5]
Nutritional counselling in the past due to IBD		103 (44.2%)
Gastrointestinal surgery		85 (36.5%)
BMI (kg/m^2)		24.16 [21.45–27.77]
Age (years)		39 [30–50]
Smoking status (current or former)		81 (34.9%)
Calprotectin (mg/kg)		92 [27.85–498.5]
C–reactive protein (mg/l)		1.7 [0.75–4.8]

Baseline characteristics of study participant demographic data are reported as totals and proportions [n(%)], or median and interquartile range [Md(IQR)]. UC = ulcerative colitis; MUST = malnutrition universal screening tool; BMI = body mass index; L1 = ileal; L2 = colonic; L3 = ileocolonic; L4 = isolated upper disease; B1 = non-stricturing, non-penetrating; B2 = stricturing; B3 = penetrating.

3.2. Healthy Controls

A total of 101 healthy individuals were screened. Of those n = 3 were excluded from further analysis due to missing data, and n = 2 were excluded due to nursing. Sex-distribution was skewed (women n = 67 (69.8%)), while median age was 30 [IQR: 23–39] (Table S3: Baseline characteristics of healthy controls).

3.3. Main Results

3.3.1. IBD Cohort vs. Healthy Controls

As a preliminary investigation, the olfactory perception of fecal matter and flatulence has been compared between individuals diagnosed with IBD and a control group of healthy individuals. Notable differences in the distribution of malodorous flatulence and feces have been identified between the groups, with a clear tendency towards higher levels of malodorous flatulence and feces in the IBD collective (Figure 2a,b).

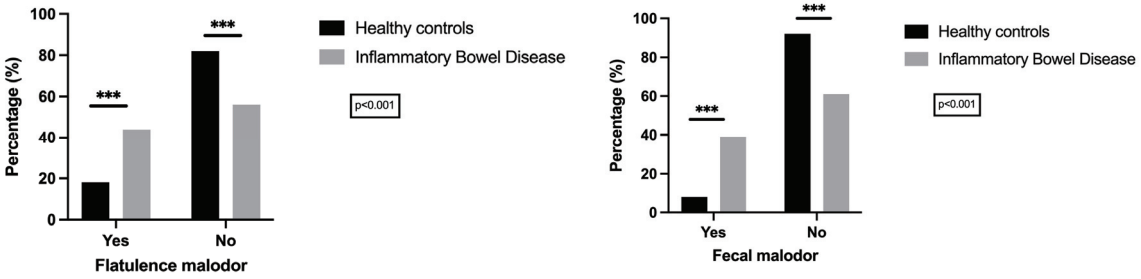

Figure 2. Percentual distribution of (**a**) flatulence malodor and (**b**) fecal malodor between IBD patients and healthy controls. Result of chi-square test shows significant differences in intestinal malodor perception between IBD patients and healthy controls (HCs) cohort for (**a**) flatulence malodor ($p < 0.001$) and (**b**) fecal malodor ($p < 0.001$). *** marks significance level $p < 0.001$.

To gain further insight into the potential association between dietary behavior and malodor perception, *t*-tests were conducted on a selection of dietary variables. The results indicated statistically significant differences both within and between the distinct groups. Starting with the analysis of dietary behavior and flatulence malodor perception, the difference in total daily food and beverage intake (g/d) in IBD was statistically significant ($p = 0.009$; g = −0.4). The malodorous group demonstrated a higher consumption of food and beverages per day (2718 (g/d) vs. 2165 (g/d)). Furthermore, the EEI (kJ/d) was observed to be elevated in this group (8773 (kJ/d) vs. 7588 (kJ/d); $p = 0.030$; g = −0.3). In the HC group, however, only the daily intake of fruits and nuts (g/d) was significant ($p = 0.023$; g = 0.5) between the odor perception groups. Here, the malodorous flatulence group consumed less on average per day (159 (g/d) vs. 242 (g/d)). The outcome-specific *t*-test between the groups showed significant differences, especially between HC and IBD without malodorous flatulence. Most pronounced differences between the groups have been found for sQ-HPF ($p = 0.001$; g = −0.5), MDS ($p = 0.002$; g = 0.4), Vegetables ($p \leq 0.001$; g = 1.0), Legumes ($p \leq 0.001$; g = 0.7), Meat ($p \leq 0.001$; g = −0.5) and Poultry ($p = 0.002$; g = −0.4) consumption. For the flatulence malodor outcome, daily legume intake was significant ($p = 0.018$; g = 0.9), as were daily HPF energy expenditure ($p = 0.008$; g = −0.4), daily UPFD energy expenditure ($p = 0.036$; g = −0.3), and daily EEI ($p = 0.036$; g = −0.3) (Table 2).

Table 2. Associations between dietary behavior and flatulence malodor perception in individuals with IBD and healthy controls.

		FLATULENCE IBD−Cohort						Healthy Controls							
Dietary Variables	**Malodor**	**n**	**Mean**	**SD**	**SEM**	**p_{t-test}**	***g***	**n**	**Mean**	**SD**	**SEM**	**p_{t-test}**	***g***	**$p_{t-test: Cohort}$**	***g***
sQ−HPF	No	130	6	3	0	0.212	−0.2	76	5	3	0	0.056	−0.5	**0.001**	−0.5
	Yes	102	7	3	0			17	6	3	1			0.635	−0.1
MDS	No	129	4	2	0	0.991	0.0	73	5	2	0	0.223	0.3	**0.002**	0.4
	Yes	100	4	2	0			17	4	2	0			0.731	0.1
Food and Beverages (g/d)	No	130	2165	1410	124	**0.009**	−0.4	74	2333	1070	124	0.204	−0.5	0.374	0.1
	Yes	102	2718	1692	168			17	2966	1917	465			0.583	0.1
Vegetables (g/d)	No	130	111	125	11	0.986	0.0	74	273	215	25	0.286	0.3	**<0.001**	1.0
	Yes	102	111	114	11			17	212	193	47			0.050	0.8
Legumes (g/d)	No	130	16	29	3	0.617	0.1	74	41	42	5	0.954	0.0	**<0.001**	0.7
	Yes	102	14	27	3			17	40	39	10			**0.018**	0.9
Fruits and nuts (g/d)	No	130	158	157	14	0.182	−0.2	74	242	189	22	**0.023**	0.5	**0.002**	0.5
	Yes	102	197	265	26			17	159	112	27			0.311	−0.2
Cereals (g/d)	No	130	223	146	13	0.403	−0.1	74	240	169	20	0.242	0.3	0.461	0.1
	Yes	102	240	151	15			17	190	91	22			0.191	−0.3
Fish (g/d)	No	130	13	16	1	0.202	−0.2	74	11	20	2	0.365	−0.2	0.432	−0.1
	Yes	102	16	20	2			17	16	10	3			0.908	0.0
Meat (g/d)	No	130	66	68	6	0.201	−0.2	74	35	32	4	0.150	−0.7	**<0.001**	−0.5
	Yes	102	77	64	6			17	65	81	20			0.485	−0.2
Poultry (g/d)	No	130	31	33	3	0.486	−0.1	74	18	25	3	0.078	−0.5	**0.002**	−0.4
	Yes	102	37	84	8			17	31	38	9			0.773	−0.1
Dairy products (g/d)	No	130	240	246	22	0.115	−0.2	74	313	265	31	0.272	−0.3	**0.048**	0.3
	Yes	102	299	326	32			17	406	469	114			0.246	0.3
Ethanol (g/d)	No	130	46	134	12	0.865	0.0	74	88	217	25	0.627	0.1	0.136	0.2
	Yes	102	49	82	8			17	62	105	25			0.568	0.1
HPF (g/d)	No	130	821	954	84	0.112	−0.2	74	588	645	75	0.140	−0.4	0.063	−0.3
	Yes	102	1075	1358	134			17	867	888	215			0.544	−0.2
HPF (kJ/d)	No	117	4826	2951	273	0.248	−0.2	69	3668	2312	278	0.684	−0.1	**0.006**	−0.4
	Yes	96	5348	3623	370			16	3915	1461	365			**0.008**	−0.4
UPFD (g/d)	No	130	561	878	77	0.143	−0.2	74	395	585	68	0.099	−0.4	0.149	−0.2
	Yes	102	762	1143	113			17	689	910	221			0.804	−0.1
UPFD (kJ/d)	No	130	3049	2230	196	0.129	−0.2	74	2293	1666	194	0.346	−0.3	**0.007**	−0.4
	Yes	102	3591	3186	315			17	2697	1156	280			**0.036**	−0.3
EEI (kJ/d)	No	130	7588	3790	332	**0.030**	−0.3	74	7420	3077	358	0.907	0.0	0.746	0.0
	Yes	102	8773	4473	443			17	7328	2071	502			**0.036**	−0.3
REE (kJ/d)	No	130	6507	1081	95	0.598	−0.1	74	6308	1109	129	0.647	−0.1	0.212	−0.2
	Yes	102	6589	1265	125			17	6444	1076	261			0.623	−0.1

Results of Student's *t*-test between malodor yes/no groups and the IBD and HC cohort are reported as arithmetic mean, standard deviation (SD), standard error of the mean (SEM), the level of significance (p), and the estimated effect size (g). P_{t-test} is printed bold when significant. Units of daily intake are reported as kilojoules (kJ) or grams (g) per day (d). IBD = inflammatory bowel disease; SD = standard deviation; SEM = standard error of the mean; sQ-HPF = screening questionnaire of highly processed food consumption; MDS = Mediterranean diet score. P_{t-test} is printed bold when significant.

For fecal malodor perception, the differences in the sQ-HPF score were significant in both the IBD and HC cohorts (IBD $p = 0.020$; g = −0.3; HC $p = 0.009$; g = −0.7). The group with the outcome of malodorous feces exhibited a higher score and, consequently, a higher proportion of highly processed foods in their daily diet (IBD = 7; HC = 7). No other significant difference was reported in the IBD cohort, whereas in the HC cohort the difference in daily energy intake from HPFs was significant ($p = 0.018$; g = −0.9) between the groups. The group exhibiting fecal malodor perception demonstrated a daily HPF energy intake of 5407 (kJ/d), while the group without fecal malodor exhibited a daily HPF energy intake of 3530 (kJ/d). The outcome-specific *t*-test between the groups revealed significant differences, particularly between the HC and IBD without fecal malodor groups. Most pronounced differences between the groups have been found for sQ-HPF ($p = 0.005$; g = −0.4), HPF ($p =< 0.001$; g = −0.5), MDS ($p = 0.008$; g = 0.4), Vegetables ($p =< 0.001$; g = 0.8), Legumes ($p =< 0.001$; g = 0.7), Meat ($p =< 0.001$; g = −0.4), and Poultry ($p = 0.004$; g = −0.4) consumption. With regard to the outcome of fecal malodor, only the daily legume intake exhibited a statistically significant difference between IBDs and HCs ($p = 0.049$; g = 1.2) [Table 3].

Table 3. Associations between dietary behavior and fecal malodor perception in individuals with IBD and healthy controls.

		FECAL													
		IBD-Cohort						Healthy Controls							
Dietary Variables	**Malodor**	**n**	**Mean**	**SD**	**SEM**	p_{t-test}	*g*	**n**	**Mean**	**SD**	**SEM**	p_{t-test}	*g*	$p_{t-test: Cohort}$	*g*
sQ−HPF	No	142	6	3	0	**0.020**	−0.3	87	5	3	0	**0.009**	−0.7	**0.005**	−0.4
	Yes	91	7	2	0			8	7	1	1			0.920	0.0
MDS	No	140	4	2	0	0.858	0.0	84	5	2	0	0.942	0.0	**0.008**	0.4
	Yes	90	4	2	0			8	5	2	1			0.290	0.4
Food and Beverages (g/d)	No	142	2264	1494	125	0.081	−0.2	85	2437	1261	137	0.856	−0.1	0.371	0.1
	Yes	91	2628	1638	172			8	2524	1558	551			0.862	−0.1
Vegetables (g/d)	No	142	120	141	12	0.270	0.1	85	263	210	23	0.440	0.3	**<0.001**	0.8
	Yes	91	102	95	10			8	203	221	78			0.238	0.9
Legumes (g/d)	No	142	16	32	3	0.737	0.0	85	40	42	5	0.937	0.0	**<0.001**	0.7
	Yes	91	15	19	2			8	39	29	10			**0.049**	1.2
Fruits and nuts (g/d)	No	142	176	193	16	0.937	0.0	85	231	184	20	0.267	0.4	**0.035**	0.3
	Yes	91	178	242	25			8	157	113	40			0.808	−0.1
Cereals (g/d)	No	142	229	149	12	0.904	0.0	85	223	145	16	0.082	−0.6	0.769	0.0
	Yes	91	231	149	16			8	323	239	84			0.114	0.6
Fish (g/d)	No	142	13	15	1	0.215	−0.2	85	10	12	1	0.273	−1.2	0.123	−0.2
	Yes	91	17	22	2			8	31	49	17			0.438	0.6
Meat (g/d)	No	142	66	68	6	0.173	−0.2	85	39	46	5	0.159	−0.5	**<0.001**	−0.4
	Yes	91	78	63	7			8	63	51	18			0.516	−0.2
Poultry (g/d)	No	142	30	29	2	0.297	−0.2	85	19	25	3	0.057	−0.7	**0.004**	−0.4
	Yes	91	40	90	9			8	38	47	17			0.954	0.0
Dairy products (g/d)	No	142	254	276	23	0.431	−0.1	85	331	321	35	0.657	0.2	0.056	0.3
	Yes	91	284	297	31			8	280	145	51			0.969	0.0
Ethanol (g/d)	No	142	51	134	11	0.579	0.1	85	66	171	19	0.186	−1.0	0.466	0.1
	Yes	91	42	73	8			8	254	361	128			0.141	1.8
HPF (g/d)	No	142	822	1076	90	0.075	−0.2	85	574	546	59	0.217	−1.1	**0.022**	−0.3
	Yes	91	1097	1248	131			8	1289	1485	525			0.682	0.2
HPF (kJ/d)	No	130	4838	3064	269	0.251	−0.2	79	3530	2007	226	**0.018**	−0.9	**<0.001**	−0.5
	Yes	84	5365	3573	390			8	5407	2855	1009			0.975	0.0
UPFD (g/d)	No	142	548	893	75	0.075	−0.3	85	395	523	57	0.298	−0.9	0.150	−0.2
	Yes	91	802	1145	120			8	964	1428	505			0.706	0.1
UPFD (kJ/d)	No	142	3090	2256	189	0.184	−0.2	85	2290	1565	170	0.204	−0.5	**0.002**	−0.4
	Yes	91	3572	3262	342			8	3031	1620	573			0.645	−0.2
EEI (kJ/d)	No	142	7709	3836	322	0.074	−0.2	85	7221	2804	304	0.075	−0.7	0.272	−0.1
	Yes	91	8702	4512	473			8	9126	3447	1219			0.796	0.1
REE (kJ/d)	No	142	6485	1188	100	0.371	−0.1	85	6303	1099	119	0.260	−0.4	0.250	−0.2
	Yes	91	6625	1122	118			8	6770	1261	446			0.731	0.1

Results of Student's *t*-test between malodor yes/no groups and the IBD and HC cohort are reported as arithmetic mean, standard deviation (SD), standard error of the mean (SEM), the level of significance (p), and the estimated effect size (g). P_{t-test} is printed bold when significant. Units of daily intake are reported as kilojoules (kJ) or grams (g) per day (d). IBD = inflammatory bowel disease; SD = standard deviation; SEM = standard error of the mean; sQ-HPF = screening questionnaire of highly processed food consumption; MDS = Mediterranean diet score. P_{t-test} is printed bold when significant.

3.3.2. Inflammation and Odor: Feces and Flatulence in IBD Patients

To further evaluate the relationship between intestinal inflammation and fecal and flatulence malodor, additional analyses have been conducted. Calprotectin, an objective measure of intestinal inflammation, showed a significant difference between IBD patients with and without malodorous feces ($p = 0.015$; g = −0.4), but not between IBD patients with and without malodorous flatulence ($p = 0.320$; g = −0.1). (Figure S1a,b: Comparison of mean fecal calprotectin (mg/kg) between (a) flatulence malodor group and (b) fecal malodor group). Furthermore, the Bonferroni correction to fisher's exact test showed statistical differences in the distribution of fecal and flatulence malodor between IBD patients in remission and those with an active disease status (fecal malodor: $p = 0.014$; flatulence malodor: $p = 0.050$) [Figure 3]. However, a subsequent analysis of the distribution of entity and remission status, stratified by malodor, revealed no statistically significant differences after the application of the Bonferroni correction. (Figure S2a–d: Distribution of entity and remission status, stratified by malodor) Therefore, logistic regression analysis was conducted to assess possible disease associations as well as dietary associations.

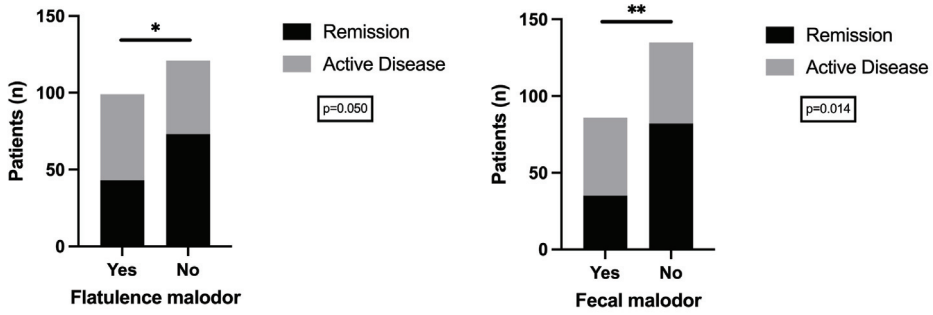

Figure 3. Distribution of IBD disease activity in comparison with (**a**) flatulence malodor and (**b**) fecal malodor. Result of Bonferroni correction to fisher's exact test shows significant differences in intestinal malodor perception between IBD patients in remission vs. active disease for (**a**) flatulence malodor ($p = 0.050$) and (**b**) fecal malodor ($p = 0.014$). Total number of IBD patients is given as n. * marks significance level $p < 0.05$ and ** marks significance level $p < 0.01$.

3.3.3. Determining the Influence of Disease-Specific and Dietary-Specific Factors on Flatulence Odor Perception in Patients with IBD

An adjusted logistic regression analysis of the influence of disease-specific and dietary-specific factors on flatulence odor perception in patients with IBD showed no statistically significant risk factors apart from fecal odor perception (OR: 0.1; 95% CI: 0.03–0.11; $p < 0.001$; adjusted OR: 0.1; 95% CI: 0.03–0.11; $p < 0.001$) and the total daily amount of food and beverages (OR: 1.0; 95% CI: 1.00–1.00; $p < 0.009$; adjusted OR: 1.0; 95% CI: 1.00–1.00; $p < 0.018$) [Table 4].

Table 4. Fully adjusted logistic regression analysis of the influence of disease-specific and dietary-specific factors on flatulence malodor in IBD patients.

		n	Outcome: Flatulence Malodor Fully Adjusted OR [95%CI]	*p*
Entity	CD (1)	134	0.5 [0.23–0.99]	0.046
	UC	86		
Strong faecal odor perception	No	134	0.1 [0.03–0.11]	<0.001
	Yes (1)	86		
Total daily amount of food and beverages (g/d)		220	1.0 [1.00–1.00]	0.019
Vegetarian	No	194	0.3 [0.09–0.75]	0.012
	Yes (1)	26		

Results of logistic regression analysis (univariate and adjusted (multivariate)) are reported as the odds ratio (OR), 95% confidence interval (CI), and level of significance (p). CD = Crohn's disease; UC = ulcerative colitis. Adjustment factors for the fully adjusted model: Sex, BMI, Fiber, Protein, Sugar, Total daily amount of food and beverages (g/d), Legumes, Cereals, Fish, Meat, Dairy Products, Eggs, sQ-HPF score, Remission status, Entity, vegetarian diet, age, fecal malodor, pouch/stoma. Reference groups are indicated as (1).

3.3.4. Determining the Influence of Disease-Specific and Dietary-Specific Factors on Fecal Odor Perception in Patients with IBD

An adjusted logistic regression analysis of the influence of disease-specific and dietary-specific factors on fecal odor perception in patients with IBD showed male sex as a statistically significant risk factors, the likelihood of fecal malodor was significantly increased in men (OR: 1.5; 95% CI: 0.89–2.56; $p = 0.127$; adjusted OR: 2.3; 95% CI: 1.13–4.61; $p = 0.021$). There were no further significant risk factors, apart from flatulence malodor (OR: 0.1; 95% CI: 0.03–0.11; $p < 0.001$; adjusted OR: 0.1; 95% CI: 0.02–0.11; $p < 0.001$) (Table 5).

Table 5. Fully adjusted logistic regression analysis of the influence of disease-specific and dietary-specific factors on fecal malodor in IBD patients.

		n	Outcome: Fecal Malodor Fully Adjusted OR [95%CI]	*p*
Sex	Men Women (1)	111 109	2.1 [1.01–4.31]	0.047
Strong flatulence odor perception	No Yes (1)	121 99	0.0 [0.02–0.10]	<0.001
sQ-HPF score		220	1.1 [1.00–1.31]	0.049

Results of logistic regression analysis (univariate and adjusted (multivariate)) are reported as the odds ratio (OR), 95% confidence interval (CI), and level of significance (p). Adjustment factors for the fully adjusted model: Sex, BMI, Fiber, Protein, Sugar, Total daily amount of food and beverages (g/d), Legumes, Cereals, Fish, Meat, Dairy Products, Eggs, sQ-HPF score, Remission status, Entity, vegetarian diet, age, flatulence malodor, pouch/stoma. Reference groups are indicated as (1).

4. Discussion

This comprehensive study aimed to investigate the relationship between dietary habits and perceived flatulence and fecal malodor in individuals with IBD and healthy controls. Furthermore, it sought to evaluate disease-specific parameters and potential associations with intestinal malodor in individuals with IBD. Percentual distribution of flatulence and fecal malodor perception between IBD patients and healthy controls showed vast differences, with further analysis revealing different dietary habits between the cohorts. It is well known that dietary behavior of IBD individuals differs from the general population [28,29], with IBD patients often modifying their diet habits after diagnosis, frequently avoiding certain foods [30] or adapting a low FODMAP diet [31]. This dietary adaptation may be indicated by the lower mean daily intake of legumes in the IBD cohort (16 g/d for no flatulence odor perception; 14 g/d for flatulence odor perception; $p = 0.617$; g = 0.1) compared with the healthy control group (41 g/d for no flatulence odor perception; 40 g/d for flatulence odor perception; $p = 0.954$; g = 0.0). While difficult-to-digest foods, such as legumes and cruciferous vegetables, are thought to contribute to increasing intestinal gas production [31], this difference in mean daily intake between IBD and HC cohorts for the flatulence malodor group was not only statistically but also clinically significant, as indicated by the effect size ($p = 0.018$; g = 0.9). In the analysis of fecal malodor between IBD and HC, this was also the case ($p = 0.049$; g = 1.2). As microbiome changes in IBD may contribute to this effect, different factors, most likely disease-specific, may influence malodors in IBD [32]. In individuals with IBD, the gut microbiome tends to exhibit reduced diversity and shows greater susceptibility to compositional shifts over time [33–35]. Moreover, changes in microbiota composition have been documented during both flare-ups and periods of clinical remission in inflammatory bowel disease [36,37]. These variations in microbial profiles may precede alterations in the biochemical disease trajectory and could potentially reflect underlying differences in fecal and flatulence malodor between IBD patients with different disease activity statuses, as well as between IBD patients and healthy controls. The observed variations in malodor between CD and UC individuals could potentially be accounted for by the distinction in the composition of the microbiome between these two entities, particularly during periods of remission [32,38]. Subsequent logistic regression analyses of fecal malodor in the IBD collective revealed a significant association with male sex. The perception of odor is subjective and therefore prone to bias. In addition, there are known sex differences in olfactory perception: women generally outperform men [39]. Individuals with IBD are accustomed to addressing inquiries pertaining to bowel movements, flatulence, and other physiological processes that are frequently regarded as taboo in public discourse. It seems implausible that women with IBD would not provide truthful responses. However, given that women in general tend to exhibit

heightened levels of social desirability bias, it is plausible that reporting bias may be more prevalent among women in the healthy control group [23]. It is therefore not possible to distinguish with certainty between social and/or biological factors when investigating the association between male sex and the perception of fecal malodor in individuals with IBD.

The present study—to the best of our knowledge—represents the first comprehensive investigation into the relationship between dietary behavior, disease activity, and perceived intestinal malodor in subjects with IBD compared to healthy controls.

Our analysis is strengthened by several factors, including the comparison with a healthy control cohort, the comprehensive dietary analyses, the consideration of potential sources of bias, and the adjustment of the analysis for potential confounding factors. However, the analysis is also constrained by the skewed distribution of IBD entities, as well as the absence of objective measures of flatulence and fecal odor. To overcome these limitations, future studies on intestinal odor perception could make use of quantitative measures on flatulence and fecal characteristics as odor measuring devices, gas chromatography, or in vitro fermentation and gas capsule systems to measure and assess selected gas species. In addition, investigation of additional biological associations as potential links between dietary behavior and odor (e.g., microbial analysis) would be beneficial to gain a deeper understanding of the precise systemic relationships involved. As retrospective measures of dietary behavior, such as the FFQ, may introduce recall bias, we adjusted for over- and under-reporting. Future studies should further highlight these limitations and implement strategies to objectively measure and validate dietary habits (e.g., 24 h dietary recall, objective dietary measurement tools such as urine and blood biomarkers). Moreover, as this is a monocentric setting, certain recruitment biases inherent to a tertiary referral center cannot be discounted. Future studies should aim for multicentric settings to broaden the generalizability of these findings.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/jcm14010137/s1, Table S1: Adjusted logistic regression analysis of the influence of disease-specific and dietary-specific factors on flatulence malodor in IBD patients; Table S2: Adjustment factors for Outcome: flatulence malodor; Table S3: Adjusted logistic regression analysis of the influence of disease-specific and dietary-specific factors on fecal malodor in IBD patients; Table S4: Adjustment factors for Outcome: fecal malodor; Table S5: Baseline characteristics of healthy controls. Figure S1a,b: Comparison of mean fecal calprotectin (mg/kg) levels between flatulence/fecal malodor group; Figure S2a–d: Distribution of entity and remission status, stratified by malodor.

Author Contributions: Conceptualization, M.W., L.P. and H.L.; methodology, M.W., L.P. and H.L.; formal analysis, L.P. and M.W.; data curation, L.P., S.N., L.K. and M.W.; writing—original draft preparation, L.P. and M.W.; writing—review and editing, L.P., M.W., H.W. and H.L.; visualization, L.P.; supervision, M.W.; project administration, M.W. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: The study design conforms to the Declaration of Helsinki (2013). This monocentric study was conducted at a tertiary referral center and has been approved on 24 May 2023 by the Ethics Committee of the Hannover Medical School (10847_BO_S_2023) and registered in the German Clinical Trials Register (DRKS) under DRKS00032771.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding author.

Conflicts of Interest: The authors declare no conflicts of interest.

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Pregnancy in Inflammatory Bowel Disease: Data from a Real-World Cohort in Germany

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Abstract: Background: Inflammatory bowel disease (IBD) frequently manifests at a young age, during the peak fertility years. Understanding the risks of negative pregnancy outcomes associated with IBD is crucial for effective pregnancy management and support. Additionally, it is essential to provide patients with the necessary knowledge to make informed choices and foster their confidence in navigating pregnancy while maintaining effective disease management. Although IBD frequently appears during the peak fertility years, knowledge about managing pregnancy in the context of IBD remains limited and often inaccurate among both physicians and patients. Our study aims to assess the complications occurring during pregnancy in patients with IBD, considering the level of disease activity, and to evaluate the standard of care provided to patients with chronic inflammatory conditions through a cohort analysis. **Methods**: Patients with IBD who had children were included in this single-center mixed-method (retrospective and prospective) study. Clinical data, disease progression, course of pregnancy, and complications were examined in women. Outcomes for children of men with IBD were also analyzed. To supplement the data, a survey addressing various pregnancy-related topics, including all patients from the university outpatient clinic for IBD, was conducted over a period of six months. **Results**: A total of 410 patients were screened retrospectively between 2010 and 2021. In total, 134 patients who had children were included in the study: 51.4% (n = 69) had Crohn's disease, 44% (n = 59) had ulcerative colitis, and 4.6% (n = 6) had unclassified inflammatory bowel disease. Of the women, 85% (n = 34) were in remission for at least three months before pregnancy, 14.6% (n = 6) experienced an acute flare-up during pregnancy, and 10.3% (n = 4) and 7.7% (n = 3) had active disease at the time of delivery and during breastfeeding, respectively. Patients with IBD who were in remission before pregnancy did not experience a higher risk of pregnancy complications (no cases of pre-eclampsia or placental abruption were reported in this group). However, the rates of gestational diabetes and fever during pregnancy were 10% for those in remission, compared to 25% for those with active disease. **Conclusions**: Patients with IBD in remission did not present an increased risk of pregnancy complications. However, our survey indicates that those with active disease at conception were more likely to experience complications such as gestational diabetes and fever. These findings underscore the importance of adequate patient education regarding the safety of various IBD medications during pregnancy in order to avoid pregnancy-related complications.

Keywords: inflammatory bowel disease; pregnancy; ulcerative colitis; Crohn's disease

1. Introduction

Inflammatory bowel diseases (IBDs)—including Crohn's disease (CD) and ulcerative colitis (UC)—are complex disorders of the digestive tract characterized by chronic inflammation. These diseases are a growing global health concern, with increasing incidence worldwide [1]. They significantly affect the quality of life of patients and place a considerable burden on healthcare systems. Despite extensive research efforts, the precise causes of IBDs remain only partially understood. It is believed that a combination of genetic, immunological, and environmental factors contributes to the development of these diseases [2].

A total of 50% of IBD patients are diagnosed before the age of 35 [3]. Women in this age group are often in their peak fertility years and may be planning pregnancies. For this patient group, the potential impact of pregnancy on IBD activity is of particular interest, especially in the context of family planning [4]. Patients with IBD worry about the activity of their disease during pregnancy and the potential complications for their children. Additionally, female patients have concerns about the use of IBD medications during pregnancy, fearing that these drugs might adversely affect their children. These issues have significantly influenced the family planning decisions of numerous women diagnosed with IBD over the past five decades [5].

A survey focusing on women diagnosed with IBD indicated that 46% of the respondents experienced a shift in their perspective on childbearing due to IBD. Moreover, 16% of these women opted not to have children—a number significantly higher than the 6.2% observed in the general population [3,4,6]. Disease activity at the time of conception is an important predictor of the disease course during pregnancy and pregnancy outcomes. If the IBD is inactive at the time of conception, the likelihood of a disease flare is comparable to that in non-pregnant patients [7,8]. Conversely, if the disease is active at conception, there is a 60% chance that the disease will remain active or worsen during pregnancy [9,10].

Several IBD medications show no discernible negative effects on pregnancy or fertility. Moskovitz et al. studied 207 medications in 113 pregnant IBD patients, and they found that many IBD medications had no significant side effects on pregnancy outcomes [11]. Nevertheless, most patients—mostly due to a lack of effective medical advice before and during pregnancy—fear the side effects of IBD medications and their impacts on the child.

Several studies have reported that mothers with IBD have a higher risk of preterm birth or stillbirth; however, it has not been conclusively proven that IBD with controlled disease activity can increase the risk of preterm birth or stillbirth [12–14]. Men with IBD also worry that their disease could negatively affect their children, as well as their fertility.

Given the advancements in the management of IBD in recent decades, concerns regarding the impacts of pregnancy on disease activity may be overstated [15]. To provide further insight into the correlation between IBD activity and adverse events during pregnancy, we assessed the pregnancy outcomes in IBD patients in relation to disease activity in a cohort analysis for this single-center study. In addition, we assessed patient perspectives using a structured questionnaire focused on pregnancy-related issues in IBD patients. This tool included demographic details, disease and treatment history, pregnancy outcomes, and patient experiences with pre-pregnancy counseling, allowing for systematic data collection to assess the impacts of IBD on pregnancy, allowing us to gain more comprehensive insights into their experiences and concerns (in Supplementary Materials).

2. Materials and Methods

2.1. Study Design

Our study involves both a retrospective data analysis and a prospective cohort questionnaire analysis, conducted at the Department of Gastroenterology, University Hospital of Augsburg, in southern Germany.

2.2. Patient Selection

All IBD patients in our department between 2010 and 2021 were screened. We included female and male patients who had become pregnant or fathered a child. The IBD patients in our clinic were exclusively cared for by physicians with advanced expertise in IBD. The inclusion criteria for participants required them to be over 18 years of age, have a confirmed diagnosis of IBD (CU, UC, or IBD-U), and provide written informed consent for participation in the study. Patients were excluded if they demonstrated a limited capacity to consent.

2.3. Data Collection

2.3.1. Retrospective Analysis

We obtained data from available electronic medical records. The following parameters were recorded: demographic data (age, gender), comorbidities, age of diagnosis, disease duration, and pattern of involvement—for UC, involvement was categorized as pancolitis, left-sided colitis, or proctitis; for CD, involvement included the small bowel, colon (or both), or upper gastrointestinal tract. Additional data included hospital admissions, prior medical treatments (with details on duration, response, side effects, and discontinuation), steroid treatment (including duration), and any surgical treatments. Remission status, vaccination status during pregnancy, anemia, and biomarkers, including calprotectin and C-reactive protein (CRP), were also documented. We aimed to investigate whether pregnancy affects fecal calprotectin levels in order to test its reliability as a tool for assessing IBD activity during pregnancy [16], and to assess the impact of pregnancy on CRP levels in these patients [17]. We assessed disease activity and treatment during pregnancy, birth, and breastfeeding.

Other recorded factors included treatment modifications during pregnancy (and their reasons), pregnancy complications, flare-ups, duration of pregnancy, birth outcomes, and breastfeeding practices. For male participants, complications during their partner's pregnancy and the health of their children were also considered.

2.3.2. Prospective Survey

We also issued a prospective cohort survey addressing family planning choices among all patients in our outpatient IBD clinic. In addition to the previously listed parameters, participants provided information on their family planning choices, fertility treatments, family history, and additional maternal and newborn outcomes. These included ultrasound examination, routine 4-week pediatric examination, complications associated with breastfeeding, lifestyle changes during pregnancy, and advice received from physicians during pregnancy.

2.4. Disease Activity and Pregnancy Complications

Additionally, we investigated the correlations between disease activity and pregnancy complications. Pregnancy complications primarily included pre-eclampsia, gestational duration, gestational diabetes, fever during pregnancy, premature detachment of the placenta, mode of delivery, and birth weight. We selected these specific pregnancy complications based on their frequency in the general population, in order to assess whether they occurred more frequently in patients with IBD [18].

While all flares in each patient were considered as a single variable, we analyzed pregnancy complications individually to examine their individual impact on IBD patients. We performed a disease activity score analysis on IBD patients who completed the prospective questionnaires. Relevant data for calculating the disease activity scores were collected in 21 of 80 surveyed female patients who provided the necessary information.

We used the Crohn's Disease Activity Index (CDAI) for patients with CD [19], where a score above 150 indicates active disease. For the CDAI, interpreting and quantifying symptoms such as "liquid stools" was challenging because they are difficult to define precisely. As a result, we estimated stool frequency using data from the questionnaires,

recognizing the inherent difficulties in accurately capturing daily symptom variability. Moreover, extraintestinal manifestations were recorded, including arthritis/arthralgias, iritis/uveitis, and skin manifestations. This score was calculated for 12 patients with Crohn's disease. These limitations are clearly stated to provide transparency and context to the findings presented (Table S1).

The Mayo score was intended for patients with UC. For the Mayo score, it was not possible to obtain endoscopic findings close to the time of conception in all patients. Therefore, we calculated the partial Mayo score, which excludes the endoscopic component, for 9 patients with UC. This approach allowed us to continue to evaluate disease activity for patients with UC, where scores of 0–1 indicate remission and scores of 2–9 represent varying degrees of mild to severe activity [20] (Table S2).

This study was performed in accordance with Good Clinical Practice and the Declaration of Helsinki. It was approved by the Ethics Committee at the University of Regensburg, Regensburg, Germany (#23-3208-101).

2.5. Statistics

Patient demographics and baseline characteristics were summarized using descriptive statistics. Continuous variables related to the study population, medication, newborn outcomes, breastfeeding, and pregnancy complications are presented as medians with ranges, indicating the minimum and maximum sample values. For comparisons of birth outcomes in relation to remission status before pregnancy, continuous variables such as birth weight and gestational duration are expressed as means with standard deviations. Categorical variables are reported as absolute frequencies and percentages.

To assess the associations between categorical variables, Fisher's exact test was applied when sample sizes were small; specifically, when any cell in the contingency table contained fewer than five observations. In all other cases, the Chi-squared test was used.

Interval-scaled variables were compared using the Mann–Whitney U-test for independent samples, with a significance level set at 0.05. Data management, along with descriptive and inferential statistical analyses, was performed using IBM SPSS (version 27), while graphics were generated in Excel (version 2303).

3. Results

3.1. Patient Demographics

3.1.1. Retrospective Data (2010–2021)

We retrospectively analyzed a total of 410 patients diagnosed with inflammatory bowel disease (IBD) in the outpatient clinic of the University Hospital Augsburg.

Among these patients, 134 had children and were thus included in the study. This group consisted of 80 females (59.7%) and 54 males (40.3%), with a median age of 46.5 years (range: 27–85 years) at the time of the study. The initial diagnosis was made at a median age of 32 years (range: 9–77 years). Breakdown by disease type revealed 69 patients (51.4%) with Crohn's disease (CD), 59 (44.0%) with ulcerative colitis (UC), and 6 (4.6%) with unclassified IBD (IBD-U). Additional retrospective data on patient characteristics, including clinical remission rates and smoking habits, are detailed in Table 1.

At the time of data collection, 91.25% (n = 73) of the included female patients and 66.7% (n = 36) of the male patients were in remission. We also investigated additional factors that could negatively affect pregnancy outcomes, such as alcohol and smoking.

Only 2.5% (n = 2) of the female patients and 5.6% (n = 3) of the male patients regularly consumed alcohol. Furthermore, 5.0% (n = 4) of the women and 1.9% (n = 1) of the men were regular smokers.

Table 1. Study population and clinical presentation of all the study participants who had children (prospective and retrospective) including age, diagnosis, remission status, and family history.

	Females	Males
number of patients	80 (59.7%)	54 (40.3%)
age (median)	65.5 (range 46–85)	54.5 (range 27–67)
diagnosis (CD:UC:IBD-U)	42 (52.5%):33 (41.2%):5 (6.3%)	27 (50.0%):26 (48.1%):1 (1.9%)
age at initial diagnosis, median	33.5 (range 17–77)	33 (range 9–75)
illness duration until pregnancy	7 (range 3–21) years	4 (range 2–10) years
surgical intervention	25/80 (31.3%)	20/54 (37.0%)
clinical remission *	73/80 (91.25%)	36/54 (66.7%)
family history of IBD	9/80 (11.25%)	5/54 (9.3%)
allergies	33/80 (41.3%)	3/54 (5.6%)
weight (median), in kg	68 (range 43–92)	81 (range 67–111)
smoking	4/80 (5%)	1/54 (1.9%)

Abbreviations: CD, Crohn's disease; UC, ulcerative colitis; IBD-U, inflammatory bowel disease unclassified; IBD, inflammatory bowel disease. * Under therapy at the time of data collection.

3.1.2. Prospective Data (From 2023)

For a subset of these patients, prospective data were collected from May 2023 onward. This follow-up allowed us to capture any recent changes or emerging trends within the demographic profile, especially as they relate to ongoing disease activity and lifestyle adjustments. The prospective data supplemented the retrospective findings by highlighting current remission rates and any updated demographic information.

All study population data are listed in Table 1.

3.2. Disease Characteristics

The median duration from disease onset to the first pregnancy was 6 years. At the time of data collection (cut-off 12/2023), 109 out of 134 (83.9%) patients were in remission under their current therapy. Furthermore, 24.5% had a positive family history of IBD, and 45 out of 134 (33.5%) patients underwent surgery due to their inflammatory bowel disease. The most common surgery performed was ileocecal resection, followed by surgical incision of anal abscesses. Hemicolectomy and partial small intestine resection were also reported (see Table 2).

Table 2. Surgical interventions of all patients who had children, detailing types of procedures performed and their respective frequencies within the study cohort.

Surgery Type	Number of Patients with Surgery	%
surgical abscess drainage	13/134	9.7%
ileocecal resection	24/134	17.9%
small bowel resection	6/134	4.5%
hemicolectomy	8/134	6.0%
total colectomy	4/134	3.0%
revision or adhesiolysis	3/134	2.2%
sigmoid resection	1/134	0.7%
stoma	7/134	5.2%
ileoanal pouch	16/134	12.0%

A total of 7 out of 134 (5.2%) patients had a stoma at the time of the study. On average, patients had been hospitalized twice due to their chronic inflammatory bowel disease since the initial diagnosis. The pattern of disease involvement was also analyzed, with Figure 1 showing that CD patients were primarily affected in the small intestine (including the ileocecal valve), followed by involvement of both the small and large intestine. In patients

with ulcerative colitis, the initial pattern of involvement was mostly pancolitis, followed by left-sided colitis and, finally, proctitis (see Figure 2).

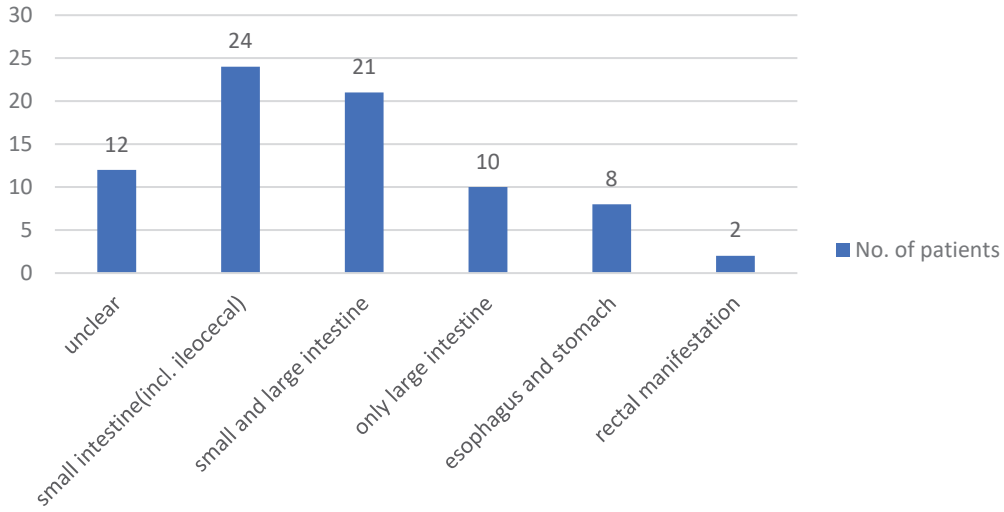

Figure 1. Distribution of disease patterns in CD patients in the study cohort.

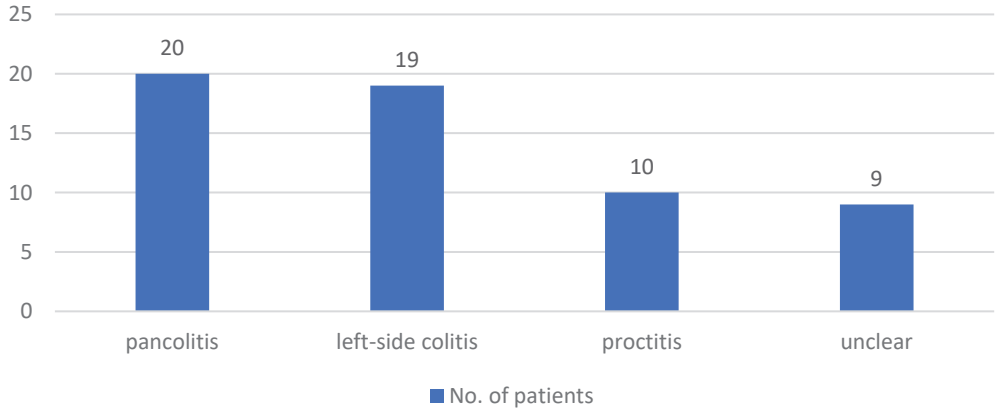

Figure 2. Distribution of disease patterns in UC patients in the study cohort.

Furthermore, we analyzed comorbidities in patients who had children, with gastrointestinal comorbidities being the most common, including conditions such as gastritis, reflux esophagitis, and liver or biliary tract diseases. Cardiovascular disease was the second most common comorbidity in our patient cohort. These and other comorbidities are detailed in Figure 3.

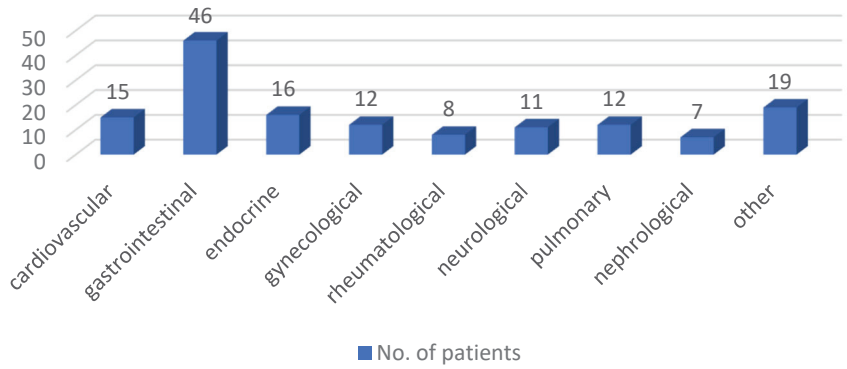

Figure 3. Presence of comorbidities in all IBD patients who had children, highlighting common gastrointestinal and cardiovascular conditions in the cohort.

3.3. Medication

Within the study, we analyzed the IBD medications for all 134 patients. It is worth noting that patients with an uncomplicated disease course and no need for specific treatment were less likely to be seen at our university hospital outpatient clinic. The most frequently used medications were 5-Aminosalicylic Acid (5-ASA), followed by TNF-alpha blockers. Systemic glucocorticoids were mostly used for short-term flare-up therapy. Some patients had undergone long-term steroid treatment before being referred to our outpatient clinic, with the goal of establishing a steroid-free treatment plan.

Table 3 details the most commonly used medications by the IBD patients, along with treatment response and duration (in months), excluding medications used during pregnancy or breastfeeding.

Table 3. IBD medication statistics at the time of data collection for all IBD patients who had children, including response rates and average duration of therapy.

Medication	No. of Patients	Treatment Response	Duration of Therapy (in Months) in Months (Average)
5-ASA (oral and rectal)	82	53 (64.6%)	33.5 (range 2–288)
topical glucocorticoids	63	35 (55.5%)	22.7 (2–288)
systemic steroids	70	49 (70.0%)	19.9 (2–96)
thiopurine	58	34 (58.6%)	38.1 (2–120)
calcineurin antagonist	2	2 (100%)	22.0 (2–42)
methotrexate	8	2 (25.0%)	31.0 (3–180)
TNF-alpha blockers	75	60 (80%)	34.5 (2–120)
integrin antagonists	41	33 (80.4%)	20.2 (3–60)
interleukin-12/23 antibodies	37	28 (75.6%)	20.7 (3–68)
janus kinase inhibitors	5	3 (60.0%)	10.0 (3–18)

3.4. Pregnancy

In this cohort analysis, patients were retrospectively screened and analyzed between January 2021 and December 2021, while the prospective questionnaire was administered over a six-month period beginning in May 2023.

At the time of conducting the patient survey, 3 out of 80 (3.8%) female patients were pregnant. Of the 80 included female patients who had children, data on pregnancy outcomes could be analyzed for 40 women; furthermore, 23 out of 40 (57.5%) surveyed patients consulted a doctor for pre-pregnancy advice.

As it is crucial to achieve disease remission prior to planning pregnancy, the focus was on maintaining remission for at least three months before conception.

Of the surveyed patients, 34 out of 40 (85.0%) were in remission for at least three months before conception. One of the surveyed patients had received fertility treatments.

An overview of the pharmaceutical treatments during pregnancy, at the time of birth, and during breastfeeding is detailed in Figure 4.

TNF-alpha blockers were most commonly used during pregnancy. Due to acute IBD flares, systemic glucocorticoids were temporarily prescribed for 3 out of 39 patients, with initial doses ranging between 20 and 30 mg. The dosages were subsequently tapered and discontinued over the course of treatment. 5-ASA was also used as maintenance therapy in part of the patient cohort. None of the surveyed patients discontinued their ongoing medication on their own.

At the time of conception, 6 out of 40 patients (15.0%) experienced an active IBD flare. By the time of delivery, 4 out of 40 patients (10.0%) were not in remission. During breastfeeding, 3 out of 39 patients (7.7%) were not in remission (see Figure 5).

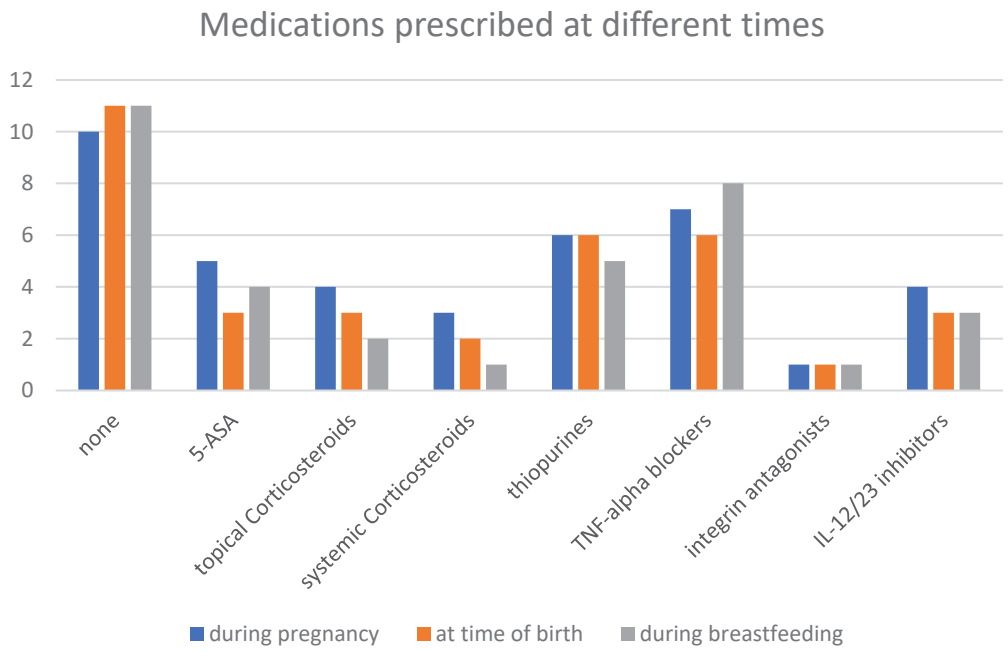

Figure 4. Overview of prescribed medications for surveyed IBD patients used during pregnancy, at the time of birth, and during breastfeeding.

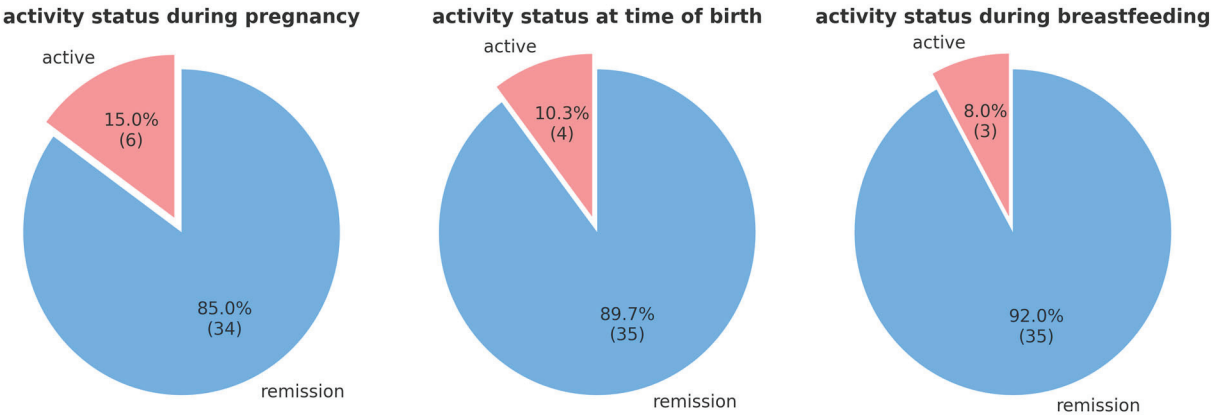

Figure 5. IBD activity at different timepoints (during pregnancy, birth, and breastfeeding) for surveyed female patients with IBD.

Regarding other parameters during pregnancy, 20% of patients exhibited anemia, which was managed with iron, vitamin B12, or folate supplementation as required. The median CRP value at the time of pregnancy was 0.78 mg/dL (range 0.08–5.54). The median fecal calprotectin value was 77.5 µg/g (range 33.6–228). Pregnancy showed no significant effect on the change in fecal calprotectin levels.

Only 12.5% of the patients experienced gestational diabetes. Due to side effects (pancreatitis), IBD treatment (azathioprine) was adjusted for one patient during pregnancy. Ultrasound examinations and amniotic fluid levels were unremarkable in 21 out of 23 (91.3%) surveyed patients during pregnancy. There were no cases of pre-eclampsia or premature placental detachment within the included patient cohort.

We analyzed the disease activity status during pregnancy, at the time of birth, and during breastfeeding. We found that 14.6% (n = 6) of the patients experienced at least one acute flare during pregnancy. At the time of birth, the proportion was 10.3% (n = 4) and, during breastfeeding, it was 7.2% (n = 3).

3.5. Pregnancy Outcomes

3.5.1. Delivery Method

The proportion of women who underwent cesarean section was 30% (12/40), comparable to the cesarean rate in Germany among non-IBD patients (32.1%) [17]. Anesthesia administered included 60% general anesthesia and 40% epidural (see Table 4). Within the patient cohort, 92.5% (n = 37) of the surveyed women experienced no complications during birth. One patient (1/40, 2.5%) suffered stalled labor, and another experienced placental insufficiency. In both cases, the women were in remission. However, the woman who experienced stalled labor had a pouch. One patient had an abortion for personal reasons. The specific reasons for cesarean sections in the majority of cases were not sufficiently documented or explored in this study.

Table 4. Delivery methods and anesthesia types in female IBD patients, along with complication rates during childbirth.

delivery method	spontaneous: 20/40 (62.5%) C-section: 12/40 (37.5%)
anesthesia	general: 9/15 (60.0%), epidural 6/15 (40.0%)
complications	none: 37/40 (93.8%), stalled labor: 1/40 (2.5%) placental insufficiency: 1/40 (2.5%)

3.5.2. Outcomes (Newborns)

The median gestation period was 38.9 weeks (range 37–43). The median birth weight was 3005 g (range 1830–4000). The median height of newborns was 50.1 cm (range 1830–4000). Two newborns suffered from pneumonia at birth. Otherwise, the remaining children (38/40, 95%) were born healthy. Routine 4-week pediatric examination (U3) showed no abnormalities in any of the children (see Table 5).

Table 5. Outcomes for newborns of IBD patients, including birth weight, gestational age, and any complications.

gestational age at birth (median)	39 weeks (range 37–43)
birth weight (median)	3005 g (range 1830–4000)
birth height (median)	50.1 cm (range 41–55)
child abnormalities	none: 38/40 (95.0%), pneumonia: 2/40 (5.0%)
pediatric check-up	normal: 40/40 (100.0%)

3.5.3. Breastfeeding

Breastfeeding data were available for a total of 21 included female patients, with 81% (17/21) able to breastfeed within the first hour. None of the mothers were advised against breastfeeding. The median duration of breastfeeding was 5 months. The survey and retrospective data analysis revealed that 3 out of 56 children of IBD patients showed gastrointestinal symptoms, such as diarrhea (see Table 6).

Table 6. Details on breastfeeding and IBD symptoms in children of patients with IBD, including counseling provided and breastfeeding duration.

breastfeeding within the first hour possible	17/21 (81.0%)
breastfeeding counseling (1: Yes, 2: No)	17/21 (81.0%)
breastfeeding duration (median)	5 months (range 1–13)
discouraged from breastfeeding	0/21 (0.0%)
gastrointestinal symptoms in children	2/38 (5.3%)

3.6. Outcomes in Men

The evaluation of outcomes for the children was possible for 32 men. None of the surveyed male patients reported that the birth of their children was associated with complications or that the children exhibited gastrointestinal symptoms (see Table 7).

Table 7. Pregnancy outcomes for partners of male IBD patients, including preterm birth and miscarriage rates.

Outcome	Preterm Frequency
preterm birth	0/32 (0.0%)
miscarriage	0/32 (0.0%)

3.7. Experience About Pregnancy Counseling

The survey included an open question regarding how well women with IBD felt supported by their physicians in navigating pregnancy. Only nine patients provided responses to this question. Seven of them felt well advised and had no further concerns or worries about pregnancy complications related to their disease activity. In two cases, patients were erroneously advised against pregnancy by their former physicians.

3.8. Correlation Between Remission Before Pregnancy and Pregnancy Complications

After analyzing all retrospective and prospective data from women with IBD who had children during their disease, we investigated the correlation between remission prior to pregnancy (at least three months before conception) and pregnancy complications. None of the women in either group (in remission or not) experienced pre-eclampsia. The duration of pregnancy was also not significantly different between the groups.

It is important to note that the group of patients with active disease was small. In Table 8, we outline various parameters regarding pregnancy outcomes in the IBD patients.

Table 8. Pregnancy outcomes in IBD patients: detailed examination of clinical and laboratory parameters including gestational diabetes, CRP levels, and ultrasound findings.

Characteristic	Frequency
current pregnancy	3/80 (3.8%)
fertility treatment	1/80 (1.3%)
consulted a doctor for advice	23/40 (57.5%)
in remission at least 3 months before pregnancy	34/40 (85.0%)
fever during pregnancy	2/24 (8.3%)
complaints during pregnancy (diarrhea, abdominal pain)	8/40 (20.0%)
flare during pregnancy	6/40 (15.0%)
self-discontinued therapy during pregnancy	0/40 (0.0%)
therapy discontinued due to side effects	1/40 (2.5%)
anemia	3/15 (20.0%)
CRP (median), mg/dL	0.78 mg/dL (range 0.08–5.54)
fecal calprotectin (median), µg/g	80 µg/g (range 33.6–600)
gestational diabetes	3/24 (12.5%)
duration of pregnancy (median), in weeks	39 (37–40)
sonography during pregnancy	normal in 21/23 (91.3%)
amniotic fluid volume	normal in 21/23 (91.3%)
pre-eclampsia	0/23 (0.0%)
premature detachment of placenta	0/23 (0.0%)
previous pregnancies	15/22 (68.2%)
steroid therapy during pregnancy	3/37 (8.1%)
vaccinations (COVID-19, influenza, whooping cough)	6/26 (23.1%)
changed lifestyle during pregnancy	34/40 (85.0%)
abortion (for personal reasons)	1/40 (2.5%)

The total number of respondents varies across different metrics in this table. This variation occurs because not all surveyed patients answered every question. Such differences in response rates are common in surveys and reflect the voluntary participation of respondents.

We analyzed the correlations between remission prior to pregnancy and pregnancy complications (see Table 9). Gestational diabetes occurred more frequently in patients with active disease than in those in remission (25.0% vs. 10%). Additionally, patients with active disease experienced fever during pregnancy more often than patients in remission (25% vs. 5.0%).

Table 9. Analysis of correlation of pre-conception remission status with pregnancy complications in IBD patients, detailing the incidence of gestational diabetes, fever, and other pregnancy outcomes.

	In Remission Before Pregnancy				
	Yes (n = 34)		No (n = 6)		p-Value
pre-eclampsia	0/20	0.0%	0/4	0.0%	1.000
duration of pregnancy (median), in weeks	38.90 (SD = 1.51)		37.75 (SD = 0.83)		0.172
gestational diabetes	2/20	10.0%	1/4	25.0%	0.437
fever during pregnancy	1/20	5.0%	1/4	25.0%	0.437
ablatio placentae	0/20	0.0%	0	0.0%	1.000
birth weight	2983.57 (SD = 729.422)		3155.00 (572.756)		1.000
spontaneous delivery	16/30	53.3%	3/5	60.0%	1.000
cesarean section	11/30	36.7	1/5	20%	1.000

4. Discussion

In our study, we analyzed pregnancies and pregnancy-related complications in patients with IBD in relation to disease activity, within a cohort attending a high-level care facility. Our cohort analysis showed that effective therapy before and during pregnancy is essential for a complication-free pregnancy and healthy child outcomes. Additionally, our analysis revealed consistent pregnancy outcomes within our cohort, supported by recent studies indicating that effective management is essential for positive pregnancy outcomes [19].

4.1. Medical Safety During Pregnancy

Furthermore, proper medical consultation before conception is crucial to alleviate patient concerns about complications and the exacerbation of inflammatory bowel disease (IBD) symptoms. Not only is adequate IBD medication important, but lifestyle changes also play a significant role. Several studies have demonstrated that smoking is a significant risk factor for pregnancy complications in patients with IBD [21,22].

It is also important that IBD therapy continues during pregnancy; furthermore, breastfeeding should not be discontinued without consulting the treating physician. During routine consultations in our clinic, we advised against discontinuing medications during pregnancy without prior consultation [23,24].

Several studies have shown that administering mesalamine during pregnancy does not increase the risk of pregnancy complications, when compared to untreated IBD patients or non-IBD patients [24,25].

Clinical data on TNF-alpha inhibitors, such as infliximab or adalimumab, suggest their safety during pregnancy, with no associated adverse pregnancy outcomes having been observed [11]. These findings offer reassurance to both patients and healthcare providers concerning the safety profile of TNF-alpha inhibitors when used during pregnancy in women with IBD [26].

Several studies have argued that conventional steroid therapy does not adversely affect pregnancy. However, attention should be paid to the placental passage of specific steroids, such as prednisolone. On the other hand, budesonide, which is commonly used in treating IBD, is minimally absorbed from the intestine into the bloodstream, making it safer during pregnancy [27–29].

Vedolizumab and Ustekinumab are safe during pregnancy, with minimal adverse effects and lower drug levels in newborns. Final doses are recommended 8–12 weeks before delivery, and breastfeeding is likely safe due to low milk concentrations. For Ustekinumab, live vaccines should be delayed for a year post-birth, unless the drug is cleared from the infant [30]. In addition, Ustekinumab has shown high efficacy, particularly in patients with CD who have therapy-resistant disease activity [31]. Pregnancy outcomes with Ustekinumab are comparable to those without IBD [32].

The CESAME study indicated that IBD patients who received thiopurines during pregnancy did not have a significantly increased risk of preterm birth, low birth weight, or congenital abnormalities, compared to those receiving other therapies or no therapy at all [33].

JAK inhibitors, including tofacitinib and filgotinib, are contraindicated during pregnancy according to the 2022 ECCO guidelines, and should be discontinued before conception [34].

Pregnancy should be avoided in patients receiving S1P modulators, such as ozanimod, and for at least 3 months after discontinuation. Effective contraception is strongly recommended during ozanimod treatment [35].

In general, except for methotrexate, JAK inhibitors, sphingosine 1-phosphate (S1P) modulators, and thalidomide, most IBD medications are regarded as safe and well tolerated during pregnancy, without an increased risk of complications [36,37]. Notably, our study provides evidence supporting this overall safety profile with concrete data on the favorable tolerability of the previously mentioned medications. Within our study group, medications including 5-ASA, topical corticosteroids, thiopurines, TNF-alpha blockers, integrin antagonists, and IL-12/23 inhibitors were primarily administered during pregnancy and breastfeeding. These treatments exhibited no adverse events or pregnancy-associated complications, emphasizing their safety for use in this specific patient population [38]. As noted, well-controlled disease activity (clinical remission) is the most critical prognostic factor for an uncomplicated pregnancy.

4.2. Pregnancy Complications

Our study revealed no significant correlations between pregnancy complications and inflammatory bowel disease when the disease activity is well managed (i.e., in remission). The outcomes for the children of mothers with IBD in remission before and during pregnancy were not significantly worse, when compared to data for mothers without IBD, although it was noted that these children had comparatively lower birth weights. Breastfeeding was also uncomplicated, and only 5.3% of the respondents (2 out of 38) reported IBD-typical symptoms in children.

4.3. Surgical History

IBD patients with a history of surgical interventions might experience a more complicated course regarding family planning. For example, several studies have shown that IBD patients with an ileoanal pouch have an increased risk of infertility—necessitating fertility treatments for those desiring children—and may also be more prone to pregnancy complications [39]. In general, the literature shows that cesarean sections are more common in IBD patients, when compared to the general population [40]. Additionally, a cesarean section is strongly recommended for cases of active perianal Crohn's disease, while ileal pouch surgery may be a potential consideration for a cesarean section [36,37]. In our study, one woman who had an ileoanal pouch experienced stalled labor, illustrating the potential complications that can arise during pregnancy in patients with a surgical history.

Miscarriage was reported in only one case, which was due to personal reasons. Several studies have been unable to determine whether chronic inflammatory bowel diseases pose a risk factor for miscarriage. According to Mahadevan et al., there were no significant differences in the rates of therapeutic abortions and congenital anomalies between groups,

nor in the frequency of congenital anomalies among children whose mothers suffered from UC or CD [41].

In our study, we observed a decrease in the number of pregnant IBD patients with active disease as pregnancy progressed (six patients during pregnancy and three during lactation). A similar finding has been reported by van der Giessen et al., who found a significant decrease in proinflammatory cytokines with advancing pregnancy. This supports the hypothesis that pregnancy is safe and potentially beneficial for IBD patients, in terms of disease activity [42].

4.4. Patient Education and Support

The ECCO guidelines also confirm our hypothesis that uncomplicated pregnancy is possible for IBD patients. The diagnosis of IBD during pregnancy introduces additional concerns and anxiety, which are addressed through collaborative efforts in monitoring and treating the disease during this life stage. Achieving and maintaining disease remission is crucial for a successful and uneventful pregnancy [43].

Furthermore, the data concerning male participants should not be overlooked. Men with IBD also experience concerns about the potential impact of their disease on their partner's pregnancy and the health of their offspring. This underscores the importance of involving both partners in counseling sessions to ensure that men receive adequate information and support regarding family planning and, thus, can confidently pursue parenthood despite their condition. Given that family planning choices are often regarded as private, they are not always openly discussed in physician–patient interactions. It is essential to actively address this topic in physician–patient interactions to improve patient decision making and experiences regarding pregnancy. It is critical that IBD patients be informed of the potential risks associated with discontinuing their medications without medical advice in order to ensure that remission is maintained [44].

With regard to post-onset IBD, the literature indicates that pregnancy outcomes in patients with post-onset IBD are comparable to those of patients with a pre-pregnancy diagnosis of IBD [45].

The survey results highlight that, despite the risk of disease exacerbation during pregnancy, informed counseling and support from healthcare professionals can significantly alleviate patient concerns and support their decision to pursue pregnancy.

4.5. Limitations and Future Research

It should be noted that not all study participants fully completed the questionnaire during the collection of prospective data, and some patients did not provide any information regarding the course of their pregnancy or the condition of their children. As a result, it can be noted that the total numbers for some variables in the included tables vary from other variables.

Additionally, retrospective data could not be completely collected due to patients discontinuing treatment at our center (e.g., for reasons such as relocation). Nevertheless, the available data were carefully analyzed to conduct as meaningful an analysis as possible.

Further prospective studies in larger cohorts are needed to analyze and define the correlations between pregnancy and chronic inflammatory bowel diseases in order to identify which patients should be considered at higher risk regarding pregnancy more precisely.

5. Conclusions

Patients with chronic inflammatory bowel diseases can safely become pregnant, provided that they are in remission before and during pregnancy, as seen in our cohort. The survey results highlight the importance of achieving remission prior to conception, as patients in this state tended to experience fewer complications. In contrast, those with active disease faced a higher likelihood of issues such as gestational diabetes and fever during pregnancy. A professional doctor–patient relationship and consultation are essential

to alleviate patient concerns. If disease activity persists during pregnancy planning, it is advisable to postpone pregnancy until stable remission is achieved.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/jcm13247710/s1. Supplementary material: English-translated prospective questionnaire; Table S1: parameters and scoring criteria of the Crohn's Disease Activity Index (CDAI) for surveyed female patients with Crohn's disease during pregnancy; Table S2: parameters and scoring criteria of the partial Mayo score for surveyed female patients with ulcerative colitis during pregnancy.

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Institutional Review Board Statement: This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee at the University of Regensburg, Regensburg, Germany (nr. 23-3208-101) (26 January 2023), for studies involving humans.

Informed Consent Statement: Due to the retrospective, non-interventional nature of the study based solely on data generated and documented during clinical routine processes, informed and written consent was not required but is covered by the Bavarian hospital law (BayKrG).

Data Availability Statement: All data generated or analyzed during this study are included in this article and its Supplementary Materials. Further inquiries can be directed to the corresponding author.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

IBD	inflammatory bowel disease
CD	Crohn's disease
UC	ulcerative colitis
IBD-U	inflammatory bowel disease unclassified
GI	gastrointestinal
TNF	tumor necrosis factor
JAK	janus kinase
5-ASA	5-aminosalicylic acid
CRP	C-reactive protein

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Evaluation of Acute Terminal Ileitis in Hospitalized Patients: Development of a Predictive Model to Distinguish Crohn's Disease from Other Etiologies

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Abstract: Background/Objectives: Terminal ileitis (TI) is often identified on CT scans in emergency settings. Diagnosing Crohn's disease (CD) as a cause of TI is crucial due to its significant long-term implications. This study aimed to differentiate CD from other causes of acute TI and develop a predictive model for CD diagnosis. **Methods**: A retrospective case-control study was conducted at Shamir Medical Center including adults diagnosed with acute TI from January 2012 to December 2020. Patients with a history of inflammatory bowel disease or prior intestinal surgery were excluded. Patients were categorized into CD and non-CD groups based on their subsequent clinical course. A logistic regression model was developed and subsequently validated with additional patients hospitalized between 2021 and 2023. **Results**: Among 135 patients, 37 (27.4%) were diagnosed with CD. CD patients were younger (median age 27 vs. 39 years, $p = 0.003$), predominantly male (83.8% vs. 51%, $p = 0.001$), and had higher rates of chronic abdominal pain, diarrhea, anemia, and weight loss prior to hospitalization. Significant laboratory differences included higher platelet counts ($p = 0.006$) and lower mean corpuscular volume (MCV) ($p = 0.001$) in CD patients. Radiologic signs of complicated disease were more common in CD (35.1% vs. 4.1%, $p < 0.001$). The predictive model incorporating gender, abdominal pain history, and MCV showed an area under the curve (AUC) of 0.87, with a sensitivity of 100% and specificity of 63.6% in the validation group of 18 patients. **Conclusions**: This study identified key predictors of CD in patients presenting with acute TI and developed a predictive model with a substantial diagnostic capability. Use of this model for early identification and treatment of CD may potentially improve patient outcomes. Further prospective validation of this model is warranted.

Keywords: Crohn's disease; terminal ileitis; abdominal pain

1. Introduction

Terminal ileitis (TI), inflammation within the terminal ileum, is often identified on CT scans in the emergency-room setting. The differential diagnosis of TI is vast and encompasses a spectrum of etiologies ranging from reactive changes secondary to appendicitis, infections, drug reactions, neoplastic processes, vasculitis, and Crohn's disease (CD) [1,2]. In regions such as Israel, where the incidence of CD is notably high at 14.9 per 100,000 individuals, it is important to identify cases of CD who present with TI [3].

Symptoms such as abdominal pain, weight loss, and chronic diarrhea often raise the suspicion of CD, particularly in younger patients [4]. However, these symptoms do not consistently correlate with the diagnosis [5,6]. Establishing the diagnosis of CD requires a

combination of endoscopy and histological examination [7] Historically, long-term follow-up was deemed necessary to definitively distinguish those with CD, a chronic disease, from other patients presenting with an acute resolving form of TI from infectious etiologies [8]. More recent efforts have aimed to integrate commonly available laboratory results and imaging studies with initial clinical symptoms to develop risk-stratification tools and models. These tools are designed to predict the likelihood of small bowel CD at the first patient presentation, although accurately diagnosing new-onset CD remains a challenge [9].

Emerging evidence suggests that the course of autoimmune conditions, such as rheumatoid arthritis (RA), may be altered favorably by the early initiation of anti-inflammatory therapy [10,11]. Similarly, early intervention in CD may alter the disease's trajectory, potentially preventing progression to irreversible bowel damage and the need for surgery [12]. Indeed, the transition to irreversible bowel damage in CD can occur within the first year of disease onset [13]. In one population-based cohort study, 18.6% of patients with Crohn's disease experienced penetrating or stricturing complications within 90 days after diagnosis [14]. The consequences of a delayed diagnosis can be profound, often necessitating urgent and early surgical intervention for CD-related complications [15]. Conversely, initiating early treatment with agents such as thiopurines or TNF inhibitors within the first year of diagnosis is associated with reduced rates of surgical intervention and improved efficacy during maintenance therapy in adults [16–18].

This study aimed to investigate the causes and outcomes of patients presenting with acute TI, as diagnosed on a CT scan, particularly focusing on its role as a marker of the initial presentation of CD. By comparing those subsequently diagnosed with CD and those with other etiologies, we sought to construct and validate a statistical model to accurately predict which patients with TI would present with new-onset CD.

2. Materials and Methods

2.1. Patients

The study included adults aged 18 and older diagnosed with TI based on a CT scan showing inflammation of the terminal ileum. TI cases associated with abscesses, fistulae, or colitis were included. All abdominal CT scans were performed according to the standard protocol for emergency room studies and interpreted by a senior radiologist. Patients whose TI resulted from conditions such as appendicitis or diverticulitis, those with a known history of inflammatory bowel disease (IBD), or those who had previous intestinal surgery were excluded.

2.2. Ethical Considerations

The study was approved by the medical center's Ethics Committee (IRB No: 064-23-ASF; approval date 16 April 2023). The need for informed consent was waived given the anonymous and retrospective nature of the study.

2.3. Study Outcomes

The primary objective of the study was to identify predictors for acute TI secondary to CD as opposed to other causes of TI. The secondary objective was to determine the outcomes of patients hospitalized with acute TI secondary to new-onset CD.

2.4. Study Designs

A single-center, retrospective case-control study was performed to evaluate patients diagnosed with acute TI and hospitalized at Shamir Medical Center between January 2012 and December 2020. Data were systematically collected from the patients' medical records, focusing on demographic information (age, gender), past medical history, clinical presentation (details of symptoms at presentation and chronic symptoms during the one year prior to hospitalization), laboratory test results (complete blood count [CBC]; biochemical profiles; C-reactive protein [CRP] levels; ALT; AST; neutrophil-to-lymphocyte ratio

[NLR]; platelet-to-lymphocyte ratio [PLR]), imaging studies (associated findings on CT scans relevant to the TI diagnosis), and endoscopic examinations.

2.5. Follow-Up

Patients were followed longitudinally to collect data on their health outcomes following hospitalization, with particular attention to subsequent diagnoses and required surgical and medical interventions.

Patients were divided into two comparison groups: one consisting of patients subsequently diagnosed with Crohn's disease following their initial TI presentation (CD group) and another comprising patients with TI not attributed to Crohn's disease based on diagnostic investigations and follow-up (non-CD group). The CD was diagnosed according to ECCO recommendation based on colonoscopy results, with biopsy results from TI in association with the clinical course and CT findings over follow-up [19]. By comparing the CD group and non-CD group, a statistical model was developed for predicting CD at the time of first presentation with TI (see below). To validate the model, an additional 18 patients with TI hospitalized between May 2022 and July 2023 were analyzed to test whether the model could accurately predict cases of CD. The patients included in the validation cohort met the same inclusion and exclusion criteria as the initial TI cohort.

2.6. Statistical Analyses

Categorical variables were summarized as frequency and percentage. Continuous variables were evaluated for normal distribution using a histogram. Since all continuous variables were skewed, they were reported as median and interquartile range. The Chi-square test and Fisher Exact Test were applied to compare categorical variables between those with and without CD, while the Mann–Whitney Test was used to compare continuous variables.

Multivariable logistic regression using a forward likelihood ratio selection method was used to identify predictors for CD and to build the prediction model ($p < 0.05$ was set for variable inclusion). The area under the receiver operating characteristic curve, the discrimination slope, and the box plot were used to evaluate how the model could allow discrimination between patients with and without CD. The discrimination slope was calculated as the absolute difference in the average predictions for patients with and without CD. The Maximal Youden index was used to identify the cut-off value. Sensitivity and specificity in the learning and validation groups were reported.

All statistical tests were 2-sided and $p < 0.05$ was considered statistically significant. SPSS was used for all statistical analyses (IBM SPSS Statistics for Windows, version 28, IBM Corporation, Armonk, New York, NY, USA, 2021).

3. Results

3.1. Demographic Data and Clinical Presentation

In total, 1027 patients were hospitalized with enteritis or colitis during the study period. Of these, a total of 135 patients met the inclusion criteria and became the TI cohort (Figure 1). Of these, 98 (72.6%) were in the non-CD group and 37 (27.4%), in the CD group. Details of their demographics and medical history can be seen in Table 1. The median age for the entire cohort was 35 years, with the non-CD group being older (median age 39 years) compared to the CD group (median age 27 years) ($p = 0.003$).

Of the total cohort, 81 (60%) were males and 54 (40%) were females. Males constituted a higher percentage in the CD group compared to the non-CD group (83.8% vs. 51%, $p = 0.001$).

A positive family history of CD was more prevalent in the CD group (12.1%) compared to the non-CD group (2.3%), which was statistically significant ($p = 0.049$).

Patients in the CD group experienced a significantly higher incidence of complaints of abdominal pain within the year prior to hospitalization (45.9% vs. 13.3%, $p < 0.001$) compared to the non-CD group, as well as a significantly higher rate of diarrhea (21.6% vs.

8.2%, $p = 0.04$). Additionally, patients with CD had a higher incidence of anemia (21.6% vs. 8.2%, $p = 0.041$) and weight loss (27.3% vs. 4.7%, $p = 0.001$) prior to hospitalization.

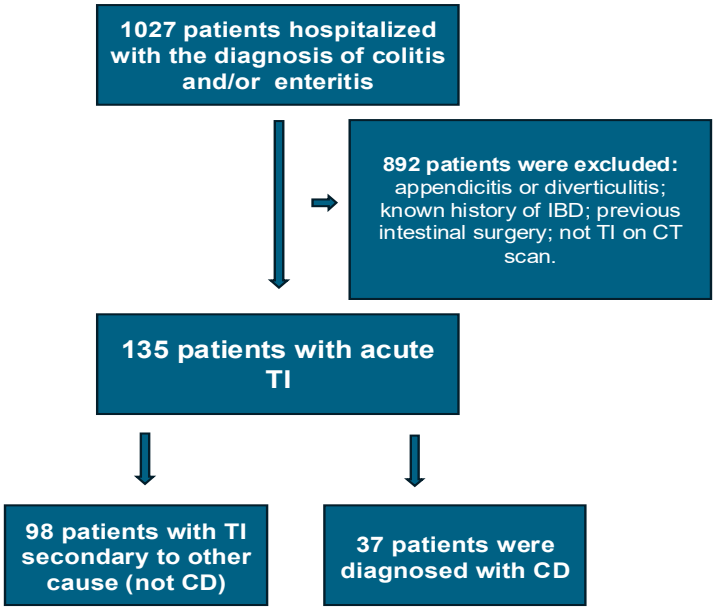

Figure 1. Flowchart of the study population.

Table 1. Demographics and symptoms before hospitalization.

	All $n = 135$ (%)	Non-CD $n = 98$ (%)	CD $n = 37$ (%)	p Value
Age (median [IQR])	35 (24;52)	39 (27;54)	27 (22;38)	0.003
Gender				
Male	81 (60)	50 (51)	31 (83.8)	0.001
Female	54 (40)	48 (49)	6 (16.2)	
Smoking	58 (43)	39 (39.8)	19 (51.4)	0.226
Family history of CD (n = 119)	6 (5)	2 (2.3)	4 (12.1)	0.049
Abdominal pain within the past year	30 (22.2)	13(13.3)	17 (45.9)	<0.001
Diarrhea within the past year	16 (11.9)	8 (8.2)	8 (21.6)	0.04
Anemia within the past year (n = 134)	16 (11.9)	8 (8.2)	8 (21.6)	0.041
Weight loss (n = 119)	13 (9.6)	4 (4.7)	9 (27.3)	0.001

Overall, 58 (43%) patients reported smoking, with no significant difference between the groups (39.8% in non-CD vs. 51.4% in CD, $p = 0.226$).

Nearly all patients presented acute abdominal pain (98.5%), with no significant difference between groups. Other symptoms, such as peritoneal signs, diarrhea, and fever, were similar between the groups (Table 2).

Table 2. Clinical presentation in hospitalization.

Clinical Presentation	All $n = 135$ (%)	Non-CD $n = 98$ (%)	CD $n = 37$ (%)	p Value
Abdominal pain	133 (98.5)	96 (98)	37 (100)	>0.999
Peritoneal signs	17 (12.6)	13 (13.3)	4 (10.8)	>0.999
Diarrhea	63 (46.7)	49 (50)	14 (37.8)	0.206
Fever	53 (39.3)	39 (39.8)	14 (37.8)	0.835

3.2. Laboratory Test Results

In a comparative study of laboratory results at the time of hospitalization between the CD group and the non-CD group, several significant differences were observed (Table 3). Platelet counts were significantly higher in the CD group (mean 273 $\times$ 10^9/L vs. 224 $\times$ 10^9/L in non-CD, p = 0.006). The mean corpuscular volume (MCV) was lower in the CD group (mean 82 fL vs. 87 fL in non-CD, p = 0.001). Additionally, the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) were higher in the non-CD group (NLR 6.1 and PLR 181 vs. NLR 4.5 and PLR 141 in CD, p values 0.011 and 0.001, respectively).

Table 3. Laboratory test results from the first day of hospitalization.

	All ***n*** **= 135 (IQR)**	**Non-CD** ***n*** **= 98 (IQR)**	**CD** ***n*** **= 37 (IQR)**	***p*** **Value**
WBCs ($\times 10^3/\mu L$)	10.9 (8.2;13.9)	10.4 (7.5;13.5)	11.7 (10.2;14.1)	0.116
HB (g/dL)	13.7 (12.8;14.9)	13.7 (12.8;15.0)	13.7 (12.7;14.3)	0.374
PLTs ($\times 10^3/\mu L$)	232 (187;280)	224 (187;261)	273 (190;346)	0.006
MCV (fL)	86 (82;89)	87 (84;90)	82 (77;85)	0.001
LYMs ($\times 10^3/\mu L$)	1.5 (1.2;2.0)	1.6 (1.2;2)	1.5 (1.1;1.8)	0.063
NEUs ($\times 10^3/\mu L$)	8.3 (5.6;11.2)	7.7 (5.0;11.1)	9.3 (7.1;11.4)	0.073
CRP (mg/L)	62 (27;127.7)	58 (18;122)	86 (40;134)	0.098
ALT (U/L)	14 (10;19)	15 (11;21)	12 (7.5;17.0)	0.008
AST (U/L)	16 (13;21)	17 (14;22)	15 (10.5;18.0)	0.004
NLR		4.5 (2.9;8.6)	6.1 (4.7;9.3)	0.011
PLR		141 (104;184)	181 (137;301)	0.001

Values are presented as median (interquartile range). WBCs: White blood cells; NEUs: neutrophils; LYMs: lymphocytes; PLTs: platelets; ALT: alanine aminotransferase; AST: aspartate aminotransferase; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio.

3.3. CT Scan Results in CD vs. Non-CD PATIENTS

On CT, a significantly higher percentage of patients with CD (35.1% vs. 4.1% in non-CD, $p < 0.001$) presented radiologic signs of complicated disease (including collections, fistulas, or obstruction). Colitis was notably less common in CD patients, with only one case (2.7%) (Table 4).

Table 4. CT findings in patients with TI.

CT Findings	**CD** ***n*** **= 37 (%)**	**Non-CD** ***n*** **= 98 (%)**	***p*** **Value**
TI with collection, fistula, or obstruction	13 (35.1)	4 (4.1)	<0.001
TI with colitis	1 (2.7)	14 (14.3)	0.068
TI alone	23 (62.2)	80 (81.6)	0.018

3.4. Evaluation and Treatment during Hospitalization

Fecal cultures were obtained from only 25 patients (18.5%). Of these, the cultures were positive for *Campylobacter jejuni* in only two cases. Most patients (96.3%) were treated with a regimen of empiric antibiotics (either Ceftriaxone with Metronidazole or Ciprofloxacin with Metronidazole). Only two patients received steroids. All patients improved with empiric treatment and were discharged home.

3.5. Follow-Up and Outcomes

Follow-up data were available for a mean of 5.7 $\pm$ 2.5 years. Fourteen patients (37.8%) in the CD group were readmitted to the hospital within half a year since their first hospitalization. There were no readmissions in the non-CD group. Ten patients (27%), all from the CD group, underwent surgery (ileocecectomy) over the next few years due to CD, with seven of them undergoing surgery within a year of their TI presentation. No other specific causes from TI in the non-CD group were found during follow-up.

3.6. Multivariable Analysis and Model Construction

A logistic regression analysis was performed using the forward selection method, which considered all the significant variables in the univariate analyses to identify factors that increase the risk of CD in patients presenting with TI (Table 5). This revealed that being male (odds ratio [OR] = 6.25, 95% CI: 2.12–18.46), having a history of chronic abdominal pain prior to TI presentation (OR = 4.21, 95% CI: 1.44–12.34), and having a lower MCV (OR = 0.87, 95% CI: 0.80–0.95) all significantly increased the risk of having CD.

Table 5. Multivariate analysis of risk factors for CD in patients presenting with TI.

Variable	OR	95% CI	*p* Value
Gender (Male)	6.25	2.12–18.46	0.001
Pain before	4.21	1.44–12.34	0.009
MCV (fL)	0.87	0.80–0.95	0.002

Hence, the probability of having CD could be calculated by using the following equation:

$$P(CD) = 1/(1 + \exp(-Z)).$$

$$Z = 8.926 + 1.833 \text{ if male} + 1.439 \text{ if pain before} - 0.135 \times \text{MCV}$$

where P(CD)—probability of having CD; MCV—mean corpuscular volume.

The logistic model showed good discrimination and calibration abilities. The area under the curve was 0.815 (95% CI: 0.734, 0.897) (Figure 2), and the discrimination slope was 0.30. The Maximal Youden index indicated a cutoff value of 0.3, which provided a sensitivity of 70.3%, specificity of 81.6%, positive predictive value (PPV) of 59.1%, and negative predictive value (NPV) of 87.9%. (Figure 3).

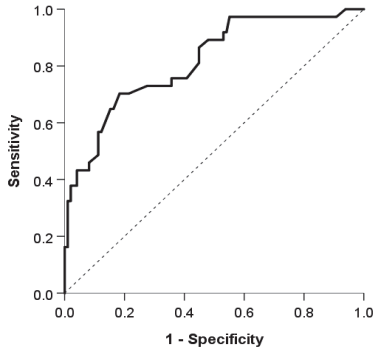

Figure 2. The area under the the receiver operating characteristic curve used to evaluate the discrimination ability of our model.

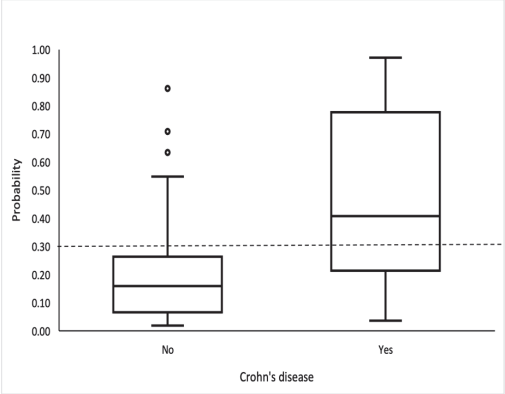

Figure 3. Box-and-whisker plot shows probability for CD. Bottom and top of boxes indicate 25th and 75th percentiles, respectively. Horizontal lines inside boxes indicate median values.

3.7. Validation of the CD Prediction Model

Eighteen patients with acute TI were included in a validation group. With a mean follow-up of 18.3 ± 5.7 months, seven (38.9%) were subsequently diagnosed with CD. Overall, 55.6% were men and the median age was 28 years (21–54), with the non-CD age being 29 (21–62) and the CD age, 27 (21–51).

The model showed a good discrimination ability between patients with and without CD with an AUC of 0.87 (95% CI 0.704–1.00, $p < 0.01$), using the cut-off value of 0.3. The sensitivity was 100%, specificity was 63.6%, NPV was 100%, and PPV was 63.6%.

4. Discussion

Our study provided descriptions and outcomes of patients presenting with acute TI which allowed us to create and validate a model aimed at identifying those presenting with new-onset CD. CD is notoriously challenging to manage, largely due to its complex and often unpredictable clinical course. Among the 37 patients with CD included in our study, a significant proportion (37.8%) required hospital readmission within six months of their initial diagnosis. Furthermore, 27% of these patients underwent surgical interventions, most of which occurred within a year since their initial hospitalization. The results are consistent with earlier research showing a high rate of surgery within the first 3 years after being diagnosed with CD, especially within the first 6 months [20]. However, the surgical rate was significantly higher than previously reported data, which indicated a 16.3% risk of surgery one year after CD diagnosis [18].

Nearly all patients with acute TI (96.3%) received empirical antibiotic treatment, with all showing positive clinical and laboratory responses, and were discharged for outpatient follow-up. Only 18.5% completed investigations including fecal cultures, with *Campylobacter jejuni* identified in just two instances. Although a specific cause of inflammation was not identified in most cases, the rapid and favorable response to antibiotics suggests that infectious causes were likely the primary etiology. However, this approach may not be applicable in regions where tuberculosis (TB) is endemic, as TB-associated ileitis can mimic the clinical and radiologic presentation of CD [21,22].

Patients with CD as the cause of TI had a more complicated course with higher rates of readmission and surgery compared to the milder outcomes of the non-CD patients. This finding aligns with the broader literature on CD which characterizes the disease as a chronic, relapsing condition with a high risk of complications and poor long-term outcomes if not diagnosed and managed promptly [13,14].

Demographic analysis revealed that patients with TI due to CD were younger and predominantly male. These findings align with previous research indicating a higher incidence of CD in younger individuals [3,23]. However, while male predominance was more significant in patients hospitalized with TI due to CD, this differs from epidemiologic studies where no significant difference between males and females with CD was observed [3,24]. Additionally, a positive family history of similar conditions was significantly more common in the CD group, which is consistent with findings from previous studies [24,25].

Patients with TI due to CD experienced more frequent gastrointestinal symptoms prior to their acute TI episode, including abdominal pain, diarrhea, anemia, and weight loss, compared to their non-CD counterparts. In the multivariable analysis, the most significant of these was a history of abdominal pain, which may reflect the chronic inflammatory nature of small bowel CD [26,27].

Laboratory results were comparable between patients with CD and those without. Key inflammatory markers, including WBC count, neutrophil count, and CRP levels, were elevated to similar extents in both groups, indicating that these markers are not effective in identifying the underlying cause of TI in acute situations. Notably, patients with CD had somewhat higher platelet counts, possibly pointing to a distinct element of their inflammatory response. This contrasts with prior research where both WBCs and platelet levels were markedly higher in CD patients and used as part of a predictive model for TI in primary care settings [9]. The non-CD group exhibited an elevated neutrophil-to-

lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), suggesting a different inflammatory profile. Although hemoglobin levels were similar across groups, the MCV was significantly lower in the CD group, which may indicate chronic iron deficiency due to the illness.

Radiologic findings revealed that CD patients were more likely to present with complications such as collections, fistulas, or obstructions, reflecting the intramural inflammation in CD. In contrast, the presence of colitis was markedly higher in non-CD patients, likely due to infectious enterocolitis, and this too may assist clinicians in differentiating CD from other causes of ileitis.

Due to the diagnostic complexities of CD, several studies have focused on developing predictive models to aid physicians in identifying patients likely to have CD [28–30]. A notable advancement in this field came from Sachdeva et al., who integrated clinical, laboratory, radiological, and colonoscopic data into a robust algorithm. This algorithm adeptly classifies patients with chronic isolated TI into specific and nonspecific etiologies, demonstrating excellent diagnostic accuracy [31]. In addition, Shen and colleagues have created a predictive model targeting small bowel CD, specifically for evaluating lower abdominal symptoms in a primary care setting [9]. This model incorporates both clinical assessments and laboratory data, including inflammatory markers. However, the efficacy of these models was reduced in cases of acute TI, where inflammatory markers are elevated across various conditions and endoscopy findings are less discriminating.

Therefore, to address this gap, our study introduces a tailored model for identifying CD in patients with acute TI. Utilizing forward stepwise logistic regression, we identified gender, complaints of abdominal pain prior to the acute TI episode, and MCV as significant predictors of CD. With an AUC of 0.87, sensitivity of 70.3%, specificity of 81.6%, PPV of 59.1% and NPV of 87.9%, our model demonstrates a substantial capability to differentiate between CD and non-CD cases. This model, when used in conjunction with clinical judgment and radiologic findings, could significantly enhance the early diagnosis of CD, leading to timely and more targeted therapeutic interventions.

While this study provides valuable insights, there are some limitations due to its retrospective nature and single-center design. There was the potential for selection bias in identifying cases of TI, and potential issues with the accuracy of medical records and lack of prospectively collected data on symptoms. Future research should focus on multi-center, prospective studies with larger study populations to validate these findings and refine the predictive model in a larger group of validation patients. Incorporating more specific data, such as genetic markers, medication use, physical activity, and detailed dietary histories could also enhance the model's accuracy. Moreover, examining the impact of early diagnostic interventions on long-term outcomes of CD could substantiate the benefits of early diagnosis and treatment initiation.

5. Conclusions

This study identified predictors of new-onset CD amongst patients presenting with acute TI through a comprehensive assessment of clinical, laboratory, and imaging characteristics. The predictive model developed provides a valuable framework for the early identification of CD, which is crucial for improving patient outcomes through timely and targeted therapeutic strategies. Future prospective studies further validating this predictive model may aid healthcare providers in assessing patients with TI, ultimately improving the quality of life and disease prognosis for CD patients.

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Specific Oral Manifestations in Adults with Crohn's Disease

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Abstract: Background: Oral manifestations of Crohn's disease (CD) include non-specific lesions and specific lesions directly related to intestinal inflammation. Oral lesions that can be overlooked in CD are sometimes challenging to treat. **Methods**: In this retrospective single-center study, patients with CD aged over 18 years who complied with follow-up and treatment were included. Clinical definitions of specific oral lesions included pyostomatitis vegetans, glossitis with fissuring, lip swelling with fissuring, cobblestoning, and orofacial granulomatosis. Experienced dentists confirmed the specific lesions in each case. Three groups of patients were identified: those without oral lesions, those with non-specific oral lesions, and those with specific oral lesions. The groups were compared based on demographics, disease extent and behavior (based on the Montreal classification), extraintestinal involvement, biologic and steroid treatment, and the requirement of resective surgery. **Results:** A total of 96 patients (14.2%) with oral lesions were found among the 676 patients with CD (59.7% male, median age 38 years) who were followed for 6.83 years (IQR 0.5–29.87 years). Eight patients (1.2%, 9 lesions) had specific oral lesions, while eighty-eight patients (13%) had non-specific lesions. Orofacial granulomatosis (n = 3), cobblestoning (n = 2), glossitis with fissuring (n = 2), and lip swelling with fissuring (n = 2) were among the specific lesions. The majority of patients (75%) with specific lesions were male, and their median age was 46.5 years (range: 23–68 years). Disease localization was commonly ileocolonic (50%), and perianal disease was present in 25% of patients. Three patients were active smokers. Extraintestinal manifestations were peripheral arthritis/arthralgia (n = 7) and sacroiliitis (n = 1). All specific lesions were associated with moderate-to-severe disease. Five patients improved with biologic therapy, and two patients with immunomodulatory therapy. **Conclusions**: Specific oral lesions in CD were associated with active disease and improved with immunomodulators or biologic therapy. Close cooperation between gastroenterologists and dentists is essential for early diagnosis and optimal management of CD.

Keywords: Crohn's disease; extraintestinal manifestations; oral manifestations; granulomatous cheilitis; cobblestoning

Main Points:

- Oral lesions that may be neglected by gastroenterologists may affect quality of life due to pain and weight loss.
- Specific oral lesions were detected in almost 1% of patients with CD.
- Peripheral arthralgia and peripheral arthritis were significantly more likely to occur among patients with oral lesions.
- A multidisciplinary approach can prevent delays in diagnosis.
- Biologic treatments are effective in specific oral lesions in CD.

1. Introduction

Transmural inflammation, which can affect any part of the gastrointestinal tract, from the oral cavity to the anus, is a characteristic of Crohn's disease (CD) [1]. In addition to intestinal involvement, CD can manifest in various other organs, referred to as extraintestinal manifestations (EIMs) [2]. Well-defined EIMs in CD include arthritis (peripheral or axial), erythema nodosum, pyoderma gangrenosum, uveitis, episcleritis, primary sclerosing cholangitis, and aphthous stomatitis. However, several rare EIMs, such as polyarteritis nodosa, cutaneous vasculitis, pseudotumor cerebri, myasthenia gravis, and specific oral lesions (cobblestoning, lip swelling, orofacial granulomatosis, pyostomatitis vegetans), can be easily overlooked [3,4].

EIMs in CD might not be clinically obvious or easy to detect, posing a challenge for treating clinicians. Multidisciplinary management in CD practices can improve clinical outcomes and quality of life [5]. EIMs may present concurrently with flare-ups in the underlying CD and respond to the treatment of intestinal inflammation, or they can manifest independently of the disease course. Genetic risk factors associated with EIMs are common to both ulcerative colitis and CD [6]. Compared to nonsmokers, smokers have a higher likelihood of presenting with EIMs in CD [7].

Oral involvement in CD includes not only aphthous stomatitis but also periodontitis. Periodontitis, a chronic inflammatory disease, is characterized by gingival pain, redness, and oozing, which eventually leads to tooth loss due to damage to the alveolar bone and connective tissue. Aphthous stomatitis presents with typical aphthous lesions, similar to those found in the ileum or colon, manifesting as round or oval painful ulcers with a yellow pseudomembranous base and erythematous borders, frequently located on the buccal or labial mucosa. Rare oral manifestations of CD include orofacial granulomatosis (also known as cheilitis granulomatosis), cobblestoning, lip swelling, and glossitis with fissuring [8].

Estimates of the prevalence of oral lesions in CD vary widely, ranging from 5% to 50%. Aphthous stomatitis was shown to be the most prevalent manifestation in previous studies that reported a high frequency of oral involvement; though, the significant variance in this frequency is not well understood. However, sufficient data on specific oral lesions are still lacking, and the correlation between oral involvement and clinical outcomes has not been established [9–11]. This study aimed to determine the frequency and characteristics of oral lesions (specific and nonspecific), and the effects on the disease course in patients with CD.

2. Materials and Methods

2.1. Study Population and Data Collection

Patients with CD who were over 18 years of age and complied with their follow-up and treatment between June 2013 and February 2023 were included in this retrospective single-tertiary-center study. Patients were excluded from the study if they had malignant lesions, oral candidiasis, Behcet disease, or any other illness that manifested as oral lesions. The study excluded patients with indeterminate colitis, who were non-adherent to therapy, or had irregular follow-ups. While typical oral lesions were evaluated by gastroenterologists, atypical lesions were also assessed by a dentist. In each case, expert dentists confirmed the presence of specific lesions. The patients were divided into three groups: patients with no oral lesions, those with nonspecific oral lesions, and those with specific oral lesions. Demographic data, location and behavior of the disease, extraintestinal involvement, need for steroid and biologic treatment, and need for resective surgery were compared across all groups. The location and behavior of the disease was based on the Montreal classification [12]. All methodologies were conducted following the ethical guidelines outlined by the institutional research committee, the 1964 Helsinki Declaration, its subsequent amendments, or similar ethical standards. The institutional review board approved this study. (Approval date: 15 February 2023, number: E2-23-3385).

2.2. Management

All patients underwent a detailed medical history and physical examination, including an oral examination at the time of diagnosis and subsequent visits. Oral lesions, other extraintestinal manifestations, perianal fistula, joint examination, and skin findings were evaluated. Data such as smoking habits, family history of IBD, and surgical history were noted. Comprehensive evaluation was integrated into the civilian medical record system. Relevant data were obtained from the civil medical registry system, hospital medical registry system, and national medical system.

When only aphthous stomatitis was detected, the treatment of the intestinal disease remained unchanged, and antiseptic mouthwash and local steroid therapy were applied for symptomatic relief. In the presence of specific oral lesions, antiseptic mouthwash and local steroid treatments were also used. For patients who did not achieve clinical improvement, the clinician escalated the current treatment, regardless of the presence of active intestinal disease. While monotherapy or combination therapy with immunomodulators (IMs) was prescribed to biologically naïve patients, dose escalation or switching was managed in biologically experienced patients. Patients with nonspecific oral lesions and those without oral lesions had follow-up every three months, whereas patients with specific oral lesions were followed up in the first and third months following the initiation of treatment and then at 3-month intervals.

2.3. Definitions

Clinical definitions of specific oral lesions were pyostomatitis vegetans, lip/cheek swelling with fissuring, cobblestoning, and orofacial granulomatosis. Aphthous stomatitis manifests as painful, oval, or round-shaped ulcers with an erythematous edge and a yellow pseudomembranous base, resembling typical aphthous lesions observed in the colon or ileum. Orofacial granulomatosis, also known as cheilitis granulomatosis, commonly presents with chronic diffuse swelling of the lips or lower part of the face, oral ulceration, hyperplastic gingivitis, and mucosal tags resulting from granulomatous inflammation of unknown etiology [13]. Cobblestoning results from a combination of deep, transverse, and longitudinal ulcerations that divide sections of intact mucosa. These lesions typically consist of mucosal-colored papules that form firm plaques on the buccal mucosa and palate. Oral cobblestoning is considered pathognomonic for Crohn's disease [14]. Deep linear ulcerations and lip swelling with vertical fissures commonly occur in the buccal sulci with hyperplastic folds and may also be observed in the midline lip [15]. Pyostomatitis vegetans, rarely associated with Crohn's disease, is thought to be primarily linked to the diagnosis of ulcerative colitis. It is characterized by the development of numerous converging erythematous, white, or yellow pustules [16,17].

2.4. Statistical Analysis

Data analysis was performed using IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, NY, USA). The normality of the distribution of continuous variables was assessed using the Kolmogorov–Smirnov test. As all continuous variables were non-normally distributed, they were presented as median (minimum-maximum) and compared using the Kruskal–Wallis test followed by Tamhane's T2 post hoc test. Categorical variables were expressed as frequencies (percentages) and compared using the Chi-square test. A p value < 0.05 was considered statistically significant.

3. Results

A total of 676 patients with CD, 404 (59.7%) males and 272 (40.3%) females, were included. The median age at diagnosis was 38 years with a median follow-up of 6.83 years (IQR 0.5–29.87 years). Among the study population, 255 (37.7%) were current smokers, 168 (24.9%) were ex-smokers, and 94 (13.9%) had a family history of IBD. Disease behavior was classified as inflammatory (B1) in 529 (78.3%) patients, stricturing (B2) in 45 (6.7%), and penetrating (B3) in 102 (15.1%). Perianal involvement was observed in 193 (28.6%) patients.

EIMs were detected in 388 (57.3%) patients at the time of diagnosis or subsequent visits. The median Crohn's Disease Activity Index (CDAI) score at diagnosis was 305.5 (214.5–395). In total, 366 patients (54.2%) received immunomodulators (IMs) (304 azathioprine and 62 methotrexate), while 308 patients (45.5%) underwent biologic therapy. Resective surgery was performed in 229 (33.9%) patients during the follow-up period (Table 1).

Table 1. Demographic characteristics of patients with CD.

	Total *n* = 676
Age at onset of Crohn (years)	38 (11–65)
Total disease duration (years)	6.83 (0.5–29.87)
Female/Male	272 /404
Smokers (Current/Ex/None), *n* (%)	255 (37.7)/168 (24.9)/253 (37.4)
Family history of IBD, *n* (%)	94 (13.9)
CD (Disease location), *n* (%)	
Ileal (L1)	297 (43.9)
Colonic (L2)	76 (11.2)
Ileo-colonic (L3)	299 (44.2)
Upper GI disease (L4)	4 (0.6)
CD (Disease behavior), *n* (%)	
Inflammatory disease (B1)	529 (78.3)
Stenosing (B2)	45 (6.7)
Penetrating (B3)	102 (15.1)
CD P (Perianal disease)	193 (28.6)
Specific oral manifestation, *n* (%)	8 (1.18)
Cobblestoning	2
Orofacial granulomatosis	3
Glossitis (with fissuring)	2
Lip swelling (with fissuring)	2
Extra-intestinal manifestations, *n* (%)	
Aphthous ulcer	88 (13.01)
Peripheral arthralgia	166 (24.6)
Peripheral arthritis	49 (7.2)
Ankylosing spondylitis	25 (3.7)
Erythema nodosum	17 (2.5)
Sacroiliitis	11 (1.6)
Uveitis	10 (1.5)
Prımary Sclerosing Cholangitis	8 (1.2)
Episcleritis	3 (0.4)
Pyoderma gangrenous	3 (0.4)
Medication (Conventional), *n* (%)	
Mesalazine	490 (72.5)
Sulfasalazine	61 (9)
Budesonide	80 (11.8)
Steroids	291 (43)
Thiopurine	304 (45)
Methotrexate	62 (9.2)
Biological therapy, *n* (%)	
Adalimumab	132 (19.5)
Infliximab	121 (17.9)
Vedolizumab	32 (4.7)
Ustekinumab	14 (2.1)
Sertolizumab	9 (1.3)
Resective surgery, *n* (%)	229 (33.9)
Baseline CRP (mg/L), median (IQR)	6.6 (0.29–167)
Baseline HB (mg/dL), median (IQR)	13 (7.2–18)
Baseline Albumin (g/dL), median (IQR)	4.2 (2–5.2)
Baseline CDAI (CD), median (IQR)	305.5 (214.5–395)

CD = Crohn's disease, IBD = inflammatory bowel disease, CRP = C-reactive protein, HB = hemoglobin, CDAI = Crohn's disease activity index. Variables are summarized by median (minimum–maximum) and frequency (%).

Patients were categorized into three groups: those with no oral lesions (n = 580), nonspecific oral lesions (n = 88), and specific oral lesions (n = 8). No significant differences were observed among the groups regarding age at Crohn's onset, total disease duration, disease location, behavior, and perianal involvement. When comparing EIMs, peripheral arthralgia and peripheral arthritis were significantly more common in patients with specific and nonspecific oral lesions compared to those with no oral lesions ($p < 0.001$). Sacroiliitis was more prevalent in patients with specific oral lesions than in those with no oral lesions ($p < 0.001$). The need for steroid and biologic therapy and resective surgery did not differ significantly among the groups (Table 2).

Table 2. Discussion of the characteristic features of patients with CD with no oral lesions, with nonspecific oral lesions, and with specific oral lesions.

	Patients with no Oral Lesions (n = 580) (1)	**Patients with Nonspecific Oral Lesions (n = 88) (2)**	**Patients with Specific Oral Lesions (n = 8) (3)**	**P**	**P 1–2**	**P 1–3**	**P 2–3**
Age at onset of Crohn (years), *n* (%)	38 (11–65)	39 (14–58)	33 (18–55)	0.552	-	-	-
Total disease duration (years), *n* (%)	6.49 (0.5–29.87)	7.72 (0.61–22.76)	10.32 (5.72–16.64)	0.100	-	-	-
Smokers (current or ex), *n* (%)	364 (62.8)	56 (63.6)	3 (37.5)	0.333	-	-	-
CD (Disease location), *n* (%)							
Ileal (L1)	255 (44)	40 (45.5)	2 (25)	0.536	-	-	-
Colonic (L2)	66 (11.4)	8 (9.1)	2 (25)	0.380	-	-	-
Ileo-colonic (L3)	255 (44)	40 (45.5)	4 (50)	0.915	-	-	-
Upper GI disease (L4)	4 (0.7)	-	-	0.717	-	-	-
CD (Disease behavior), *n* (%)							
Inflammatory disease (B1)	449 (77.4)	73 (80)	7 (87.5)	0.410	-	-	-
Stenosing (B2)	40 (6.9)	5 (5.7)	-	0.684	-	-	-
Penetrating (B3)	91 (15.7)	10 (11.4)	1 (12.5)	0.560	-	-	-
CD P (Perianal disease), *n* (%)	171 (29.5)	20 (22.7)	2 (25)	0.415	-	-	-
Extra-intestinal manifestations, *n* (%)							
Peripheral arthralgia	108 (18.6)	51 (58)	7 (87.5)	**<0.001**	**<0.001**	**<0.001**	0.141
Peripheral arthritis	30 (5.2)	16 (18.2)	3 (37.5)	**<0.001**	**<0.001**	**0.008**	0.191
Ankylosing spondylitis	21 (3.6)	4 (4.5)	-	0.781	-	-	-
Sacroiliitis	7 (1.2)	3 (3.4)	1 (12.5)	0.016	0.133	**0.006**	0.298
Erythema nodosum	12 (2.1)	5 (5.7)	-	0.118	-	-	-
Pyoderma gangrenous	2 (0.3)	1 (1.1)	-	0.571	-	-	-
Uveitis	8 (1.4)	2 (2.3)	-	0.763	-	-	-
Episcleritis	3 (0.5)	-	-	0.779	-	-	-
Primary sclerosing cholangitis	8 (1.4)	-	-	0.512	-	-	-
Baseline CRP (mg/L), median (IQR)	6.7 (0.4–167)	4.75 (0.29–150)	6.9 (2–52.9)	0.418	-	-	-
Baseline HB (mg/dL), median (IQR)	13 (8.3–17.6)	12.95 (7.2–18)	15.2 (10.6–15.4)	0.782	-	-	-
Baseline Albumin (g/dL), median (IQR)	4.2 (2–5.2)	4.1 (2.7–5.1)	4 (3.9–4.7)	0.862	-	-	-
Need for steroid, *n* (%)	250 (43.1)	35 (39.8)	6 (75)	0.156	-	-	-
Biological therapy, *n* (%)	178 (30.7)	23 (26.1)	5 (62.5)	0.097	-	-	-
Resective surgery, *n* (%)	193 (33.3)	33 (37.5)	3 (37.5)	0.720	-	-	-

Significant p values are in bold. CD = Crohn's Disease, GI = Gastrointestinal, CRP = C-reactive protein, HB = Hemoglobin. (-) = No. Variables are summarized by median (minimum–maximum) and frequency (%).

Oral lesions were present in 96 (14.2%) patients. Specific oral lesions were found in eight patients (1.2%), with nine lesions in total, as one patient had both orofacial granulomatosis and lip swelling with fissuring. Nonspecific lesions were observed in 88 (13%) patients. The specific lesions included orofacial granulomatosis (n = 3), cobblestoning (n = 2), glossitis with fissuring (n = 2), and lip swelling with fissuring (n = 2). Patients with specific lesions were predominantly male (75%) with a median age of 46.5 years (range 23–68 years). All specific lesions were detected after CD diagnosis. In patients with specific oral lesions, disease location was ileal (25%), colonic (25%), and ileocolonic (50%), with perianal disease being present in 25% of patients. Disease behavior was inflammatory in seven patients and penetrating in one patient. Concurrent EIMs included peripheral arthritis/arthralgia (n = 7) and sacroiliitis (n = 1) (Table 3). All specific lesions were associated with moderate-to-severe disease activity (median C-reactive protein level 35.5 mg/L, and median CDAI 313).

Table 3. Characteristic features of patients with CD with specific oral lesions.

	1. Case	**2. Case**	**3. Case**	**4. Case**	**5. Case**	**6. Case**	**7. Case**	**8. Case**	**Total, *n* (%), Median (IQR)**
Age at oral lesion detected (years)	46	51	68	30	47	31	23	48	46.5 (23–68)
Female/Male	M	M	M	F	M	M	M	F	2/6 (25–75%)
Smokers (Current/Ex/None)	N	N	C	C	N	C	N	N	3/5 (37.5/62.5%)
CD (Disease location)									
Ileal (L1)						+	+		2 (25%)
Colonic (L2)		+						+	2 (25%)
Ileo-colonic (L3)	+		+	+	+				4 (50%)
Upper GI disease (L4)									
CD (Disease behavior)									
Inflammatory disease (B1)	+	+	+		+	+	+	+	7 (87.5%)
Stenosing (B2)									
Penetrating (B3)				+					1 (12.5%)
CD P (Perianal disease)		+	+						2 (25%)
Resective surgery		+		+				+	3 (37.5%)
Extra-intestinal manifestations									
Peripheral arthralgia	+	+	+	+	+	+		+	7 (87.5%)
Peripheral arthritis	+	+			+				3 (37.5%)
Sacroiliitis				+					1 (12.5%)
Medication									
Current treatment before oral lesion	IM	IFX	ADA	IM	IM	IM	IM	IM	
Oral lesion treatment	IM	UST	UST	IFX	IM + steroid	IM + ADA	IM + ADA	IM + steroid	
CRP (mg/L)	21	52.9	20	151	58.7	8.9	6	50	35.50 (6–151)
CDAI	280	346	278	480	374	252	357	227	313 (227–480)

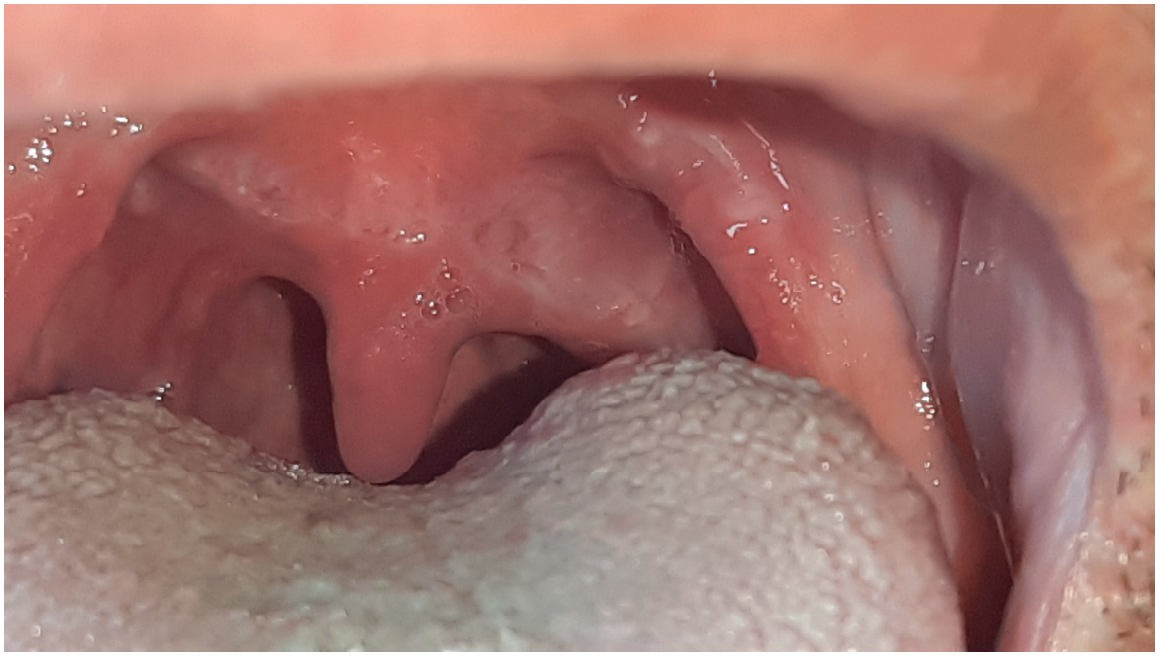
CD = Crohn's disease, CRP = C-reactive protein (when oral lesion detected), CDAI = Crohn's disease activity index (when oral lesion detected). Variables are summarized by median (minimum–maximum) and frequency (%) (+ = Yes) (F = female; M = male; C = current; N = none; IM = immunmodulator).

Seven patients improved with IMs combined with systemic steroids or biologic therapy. The lesions regressed in all five patients who received biologic treatment. Three of them were biologic-naïve, with two patients improving with adalimumab (ADA) and one with infliximab (IFX). Two patients were already receiving biologic treatment; one was managed by switching from ADA to IFX. In this patient who underwent cobblestoning on the palatal mucosa, the oral lesion did not regress with IFX, so treatment was escalated to ustekinumab (UST), leading to lesion healing (Figure 1a; before treatment, Figure 1b; after treatment). The other patient with orofacial granulomatosis was managed by switching from ADA to

UST (Figure 2). Three patients were treated with IMs with or without systemic steroids. One patient with glossitis with fissuring recovered with IM monotherapy (Figure 3a; before treatment, Figure 3b; after treatment), while another patient with lip swelling with fissuring responded to IM combined with systemic steroids (Figure 4a; before treatment, Figure 4b; after treatment). Biologic treatment was planned for the last patient when the lesion did not improve with IM and systemic steroid combination. However, the patient with cobblestoning on the buccal mucosa declined biologic therapy, and the lesion persisted (Figure 5).

(**a**)

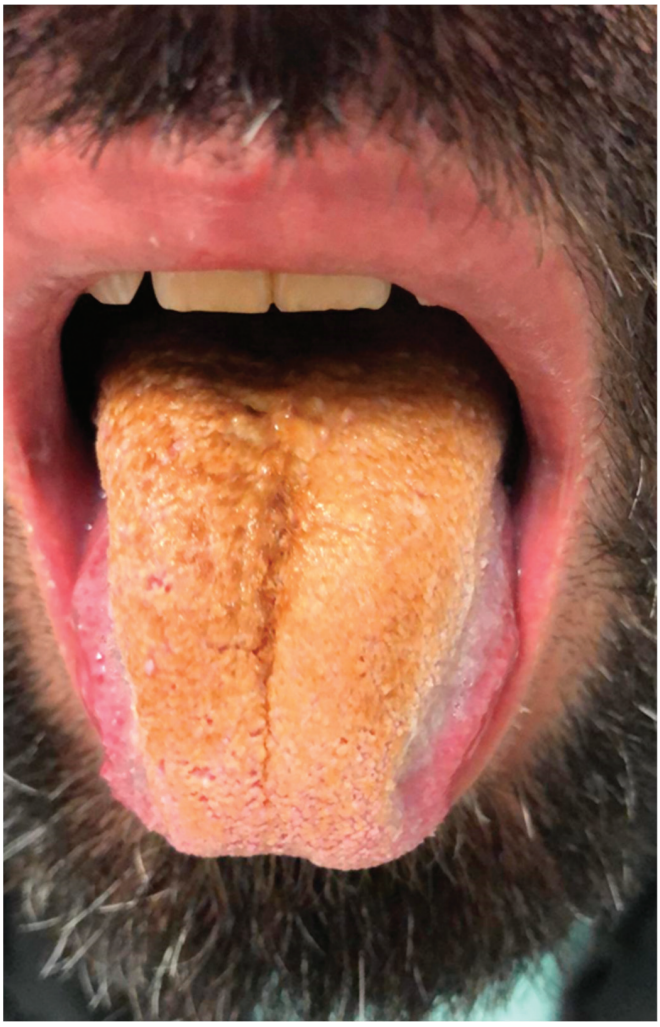
Figure 1. *Cont.*



(**b**)

Figure 1. (**a**). Cobblestoning on the palatal mucosa in a patient with Crohn's disease before treatment. (**b**). Resolution of cobblestoning on the palatal mucosa following treatment with ustekinumab.

Figure 2. Orofacial granulomatosis.



(**a**)

(**b**)

Figure 3. (**a**). Glossitis with fissuring in a patient with Crohn's disease before treatment. (**b**). Improvement in glossitis with fissuring after treatment with immunomodulatory monotherapy.

(a)

(b)

Figure 4. (**a**). Lip swelling with fissuring in a patient with Crohn's disease before treatment. (**b**). Resolution of lip swelling with fissuring following treatment with a combination of immunomodulators and systemic steroids.

Figure 5. Persistent cobblestoning on the buccal mucosa in a patient with Crohn's disease who declined biologic therapy.

4. Discussion

This study evaluated the treatment of specific oral lesions occurring at diagnosis or follow-up in patients with CD and its impact on clinical outcomes. Oral lesions are common in CD, with a prevalence ranging from 5% to 50% in various studies [10,18,19]. Most oral lesions are associated with active intestinal disease. Specific oral lesions, including cobblestoning, orofacial granulomatosis, lip/cheek swelling with fissuring, and pyostomatitis vegetans, are rare. The diagnosis and management of specific oral lesions can be challenging for clinicians. Multidisciplinary integrated management plans in IBD practices can improve patient outcomes and facilitate the diagnosis of specific oral lesions [11,20]. Several studies have investigated specific oral lesions in CD, with dentists participating in multidisciplinary teams [21–23]. Harty et al. [24] evaluated the ability of gastroenterologists to detect and accurately identify specific oral lesions at the time of diagnosis in children with CD. Consultant gastroenterologists found abnormalities in the mouth in only nine (45%) patients with oral CD. In the current study, specific lesions were also evaluated by an experienced dentist. Galbraith and colleagues [25] detected specific oral lesions in nine patients without typical clinical findings of CD. They argued that specific oral lesions may be the only finding in CD and that the diagnosis of CD should be considered in the presence of these unexplained lesions. Similarly, Vavricka et al. [2], in their cohort study of an adult population, detected oral lesions in 27.8% of patients before CD diagnosis (median time: 5 months before CD diagnosis).

The pathological explanation of oral lesions is considered to be either the spread of intestinal inflammation or an independent inflammatory event with a genetic or environmental trigger comparable to CD [2,26]. In the current study, all patients with specific oral lesions had moderate-to-severe active disease. In contrast, some adult studies have shown

that oral lesions can be seen independently of disease activity [14,24,25]. This discrepancy may be better explained by previous pediatric studies: considering that oral lesions are more common in the pediatric population than in adults and that there are difficulties in diagnosing CD in children, it is plausible that oral lesions can present unrelated to disease activity in this age group. The association of nonspecific oral lesions with disease activity is widely accepted [9,10,14,15].

In addition to the treatment of intestinal inflammation and perianal disease, topical treatments with antiseptic mouthwashes and local steroids are recommended for oral lesions. Anti-TNF agents have been reported to improve the condition. While control of intestinal disease and local treatments may be sufficient for managing nonspecific oral lesions, current treatment may need to be escalated for specific oral lesions [27–29]. Therapeutic options include topical and systemic steroids, immunosuppressive agents, and biologic treatments [21,30]. Philips et al. [13] reported that in a multicenter study of twenty-eight patients, orofacial granulomatosis improved in twenty-three patients, with the use of anti-TNFs in nine patients, vedolizumab in one, ustekinumab in one, and thalidomide in two. However, five cases were resistant to therapies, including anti-TNFs. In the current study, specific oral lesions improved in five patients with biologic treatment and two patients with IMs with or without systemic steroids. Among patients managed with biologic treatment, three were biologic-naïve, and lesions regressed in two patients with the use of adalimumab (ADA) and one patient with infliximab (IFX). In the two patients who were already receiving anti-TNF treatment, their lesions improved after escalating to ustekinumab (UST). Biologic agents appear to be effective in managing specific oral lesions.

In the study, peripheral arthralgia/arthritis was detected significantly more frequently in patients with oral lesions (specific or nonspecific) compared to patients without oral involvement. Joint involvement that occurs in the course of Crohn's disease may be correlated with the activation of the disease or may present independently of disease activity. Moreover, the involvement of more than one EIM is common in Crohn's patients in whom EIMs were detected in previous studies [3,31]. There was no statistical difference when the relationship between oral involvement and poor clinical outcomes was compared among the three groups. The findings showed that oral lesions, rather than being a poor prognostic indicator, may occur in the clinical course of existing moderate-to-severe disease.

The study had some limitations. Firstly, its retrospective design and the relatively low number of patients with specific oral lesions. Secondly, although specific oral lesions were evaluated by an experienced gastroenterologist and a dentist, the diagnosis was made clinically. Lastly, whether oral lesions should be considered EIMs is a matter of debate. It has become our mainstay in evaluating specific oral lesions as EIMs because they can cause periodontitis. The strengths of the study were its long-term follow-up period, clinical visits, and regular recordings.

5. Conclusions

This study showed that 14.2% of CD patients had oral lesions (specific, nonspecific), and 1.2% of CD patients had specific oral lesions. Oral lesions seen in Crohn's disease, which gastroenterologists must consider, can significantly affect patients' quality of life and cause pain and weight loss. A multidisciplinary approach can prevent delays in diagnosis and improve patient outcomes. Close cooperation between gastroenterologists and dentists is essential for early diagnosis and optimal management. Specific oral lesions in CD were associated with active disease and immunomodulators or biologic therapy has proven to be effective in managing specific oral lesions associated with CD.

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Review

Physical Exercise as a Therapeutic Approach in Gastrointestinal Diseases

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Abstract: Background/Objectives: Physical exercise can have significant consequences for the gastrointestinal tract, which is why there have been studies into its influence on the treatment of conditions such as colorectal cancer, inflammatory bowel diseases (IBD), and irritable bowel syndrome (IBS), being that there is epidemiological evidence that exercise has a protective effect against colon cancer. This review aims to demonstrate the mechanisms of action of physical exercise in the gastrointestinal tract, as well as the benefits of exercise in diseases associated with the digestive system, in addition to gathering training recommendations in treating different gastrointestinal diseases. **Results:** Physical exercise modulates gastrointestinal motility, permeability, immune responses, and microbiota composition, with both beneficial and adverse effects depending on intensity and duration. Regular moderate exercise is associated with improved quality of life in IBD and IBS, reduced colorectal cancer risk, and potential symptom relief in constipation. However, high-intensity exercise may exacerbate gastroesophageal reflux symptoms and increase the risk of gastrointestinal bleeding. While aerobic exercise has been extensively studied, the effects of resistance training on gastrointestinal health remain underexplored. **Conclusions**: New methodologies and techniques, such as molecular biology and the study of gastric receptors, have led to advances in understanding the gastrointestinal changes associated with physical exercise. These advances cover different exercise intensities and are being investigated in both experimental models and clinical studies.

Keywords: exercise; gastrointestinal diseases; therapeutics

1. Introduction

Research involving exercise physiology has long focused on the responses and adaptations of the respiratory, cardiovascular, neuroendocrine, and neuromuscular systems,

considering that many health and quality-of-life benefits of regular exercise arise from these systems' responses and adjustments [1,2]. Another area of study that deserves significant attention concerns the systemic repercussions of physical exercise, particularly its effects on the gastrointestinal tract [3–5].

After the first experiments performed by Beaumont on gastrointestinal function during exercise during the 1800s, which were never published, Anton Julius Carlson, an American Physiologist, became a pioneer in publishing on the subject [6]. After Carlson, research on exercise and the gastrointestinal tract was sparse. However, in the late 1960s, driven by the consumption of energy drinks and the practice of running, there was a greater interest in the study of gastrointestinal function and physical exercise. From the 1980s onwards, several researchers began to investigate the effects of exercise on the gastrointestinal tract through clinical and epidemiological studies, particularly in terms of harmful effects [7].

Among these repercussions, gastrointestinal symptoms in physical exercise practitioners and athletes are typical, such as nausea, diarrhea, vomiting and intestinal bleeding, particularly in high-intensity training. On the other hand, physical exercise also prevents several diseases related to the gastrointestinal tract, such as colon carcinoma, diverticulitis, cholelithiasis, and constipation. Thus, several studies have demonstrated an interest in the relationship between exercise and the gastrointestinal tract, with an emphasis on the prevention and treatment of diseases, as well as the optimization of athletic performance, given that the stomach and intestines are essential for the digestion and absorption of macronutrients and micronutrients required by active muscles [8,9].

Regarding the mechanisms related to the effects of exercise on the gastrointestinal tract, its impact on the composition of the intestinal microbiota, its antioxidant and anti-inflammatory action, which may have protective action, reducing permeability in the gastrointestinal tract [10–12]. In this sense, this review aimed to (1) demonstrate the mechanisms by which physical exercise acts on the gastrointestinal system; (2) show recent evidence of the effects of training in the treatment of diseases of the gastrointestinal tract, such as gastroesophageal reflux disease (GERD), irritable bowel syndrome (IBS), inflammatory bowel diseases (IBD), and colorectal cancer; and (3) about training recommendations in the treatment of different gastrointestinal diseases.

2. Results

2.1. Basic Concepts About Physical Exercise

According to the World Health Organization [13], physical inactivity is the fourth leading risk factor for global mortality, accounting for 5.5% of deaths per year, among various risk factors such as dyslipidemia, obesity, and hypertension. Research highlighting the importance of an active lifestyle is growing exponentially and supports the notion that improved quality of life is associated with reduced periods of physical inactivity [14].

Physical activity recommendations vary based on intensity and duration. According to various health institutions, it is recommended to engage in 150 min of moderate physical activity per week, 75 min of vigorous activity, or a combination of these intensities [15]. These levels are sufficient to provide health benefits. However, when weekly exercise time is increased to 300 min, there is an additional advantage in reducing overall mortality, suggesting that a higher volume of physical activity may have even more significant benefits [16]. Another way to monitor physical activity levels is through daily step counting. Studies show that walking more than 7000 steps per day significantly reduces the risk of various conditions related to physical inactivity, such as cardiovascular diseases, diabetes, and obesity [17,18].

The literature consistently shows that regular physical exercise is associated with a reduced risk of premature mortality and contributes to the prevention of more than

25 pathologies, including chronic medical conditions such as hypertension, breast and colon cancer, type II diabetes, gestational diabetes, and gallstones. A dose-dependent correlation between physical exercise and primary and secondary prevention of chronic disorders has been demonstrated, in addition to a positive association with adolescent health [19,20].

In this way, the WHO introduced physical activity and physical exercise in the World Public Health Agenda, launching the "General Strategy for Food, Physical Exercise and Health" and describing actions necessary to increase physical activity globally [21]. In addition to the "Global Physical Activity Recommendations for Health", published in 2010, highlighting the primary prevention of Chronic Noncommunicable Diseases (CNDs) through physical activity [22].

In this sense, the WHO defines physical activity as any body movement produced by skeletal muscle that results in energy expenditure above the rest, including physical activity practice during work, playing, and domestic activities. Physical exercise is any planned activity, structured and systematized, involving body movements of skeletal muscle of contraction and relaxation. It aims to improve physical fitness components, using energy substrates above resting values [23].

Physical exercise can be characterized in two ways: (i) intermittent and (ii) continuous. Regarding intermittent exercise, its primary energy source is the phosphagen system, which is the fundamental fuel for short-duration, high-intensity activities such as 100 m sprints in athletics, 50 m and 100 m swimming, weightlifting, and cycling sprints, among others [24]. The ATP-Creatine Phosphate (CP) energy system provides a rapid but short-lived energy source, depleting its stores in approximately 10 s. During high-intensity activity, ATP is broken down into ADP and inorganic phosphate (Pi) by ATPase, releasing energy. Creatine phosphate (CP) serves as an energy reservoir, donating its phosphate group to ADP via creatine kinase (CK) to rapidly regenerate ATP, ensuring continued energy supply for short-duration, high-power activities [25].

In the phosphagen system, intense exercise can lead to the development of acidosis, increasing the reduction of pyruvate to lactate and reducing the proton transport capacity via NADH+ (nicotinamide adenine dinucleotide), thus increasing lactate production and the release of free hydrogen ions (H+). Suppose the buffering capacity of this proton is overwhelmed. In that case, it results in a decrease in pH, which can cause fatigue through several mechanisms, such as plate acidosis, the inhibition of phosphofructokinase, the inhibition of the SERCa (Sarcoplasmic Endoplasmic Reticulum Ca^{2+}-ATPase) pump, lower calcium conductance, reduced troponin/tropomyosin interaction, and the stimulation of type C fibers in the central nervous system, inducing a "burning" discomfort [26,27].

The aerobic system uses the oxidative phosphorylation system as an energy source for ATP production with subsequent energy generation. This energy system is utilized in long-duration, low-intensity exercises requiring greater aerobic capacity, such as 5000 m and 10,000 m races, marathons, open-water swims, and long-duration cycling events [28].

Exercise results in numerous changes in the gastrointestinal tract (metabolic improvements, reduction in chronic systemic inflammation, lower serum insulin levels, improvements in the gut microbiota associated with preservation of the intestinal barrier and improved bile acid homeostasis). Most of these effects depend on the volume and intensity applied, although low-intensity exercises do not describe significant damage [29]. Extreme exercises and dehydration states are reported as causes of gastrointestinal symptoms by 70% of athletes, and intestinal ischemia is considered the leading cause of nausea, vomiting, abdominal pain, and diarrhea [30].

2.2. Gastrointestinal Motility and Exercise

Gastrointestinal motility results from the activity of the musculature of the digestive tract. This intrinsic muscle activity is called motility. This varies according to the segment and circumstances, notably the dietary condition. Segmentation contractions predominate in motor behavior shortly after food ingestion, where neighboring gastrointestinal segments contract simultaneously and continuously [31]. Already under fasting, the migratory motor complex occurs, a pattern of cyclic and consecutive motility, passing from the stomach until reaching, about 90 min later, the ileocecal valve. Given the similarity in morphology, such variation in activity stems from neurohumoral regulatory mechanisms [32,33].

The motility of the gastrointestinal tract is primarily coordinated by the neurons of the myenteric plexus, which are present along the gastrointestinal tract. The myenteric plexus regulates peristalsis by modulating muscle wall contraction, both the frequency and intensity of contraction. The essential stimulus for the myenteric plexus comes from the mechanical distension of the gastric wall through food, as well as from the irritation of the epithelium and the activity of the extrinsic nervous system [34]. Although the human stomach is anatomically a single viscera, its motor behavior is quite distinct in the proximal and distal portions. In the proximal portion, the accommodation of the ingested food occurs without significant changes in intraluminal pressure, thanks to receptive relaxation. After the gastric secretions are mixed, the food passes to the distal stomach, from where it is emptied and gushes into the small intestine [35].

With its slow, sustained contractions, the proximal stomach plays a key role in regulating intragastric pressure and gastric emptying of liquids. In contrast, the distal stomach, with its peristaltic contractions, plays a crucial role in mixing gastric secretions with food and in the grinding process, especially in the gastric emptying of solids [36].

Through vigorous contractions that even occlude the stomach lumen, the chyme advances towards the pylorus, which, when contracted, prevents the passage of solids, which undergo retropulsion and are progressively crushed until liquefaction. Once in liquid form, the material is quickly evacuated in the interval between waves of contractions, thanks to gastric tone. Therefore, the sensory perception of gastric fullness is correct, depending on the nature of the food, as liquids are emptied more quickly and solids more slowly. On the other hand, the indigestible material is only emptied from the stomach when the migrating motor complex takes control during fasting [37,38].

Physical exercise per se promotes physiological adjustments, whether in the neuromuscular, cardiovascular, respiratory, endocrine systems or even in the gastrointestinal tract. However, such adjustments do not occur uniquely and linearly in the various systems, as they depend on the exercise's time, intensity, volume, nature, and energy sources governing such activities [39].

Another critical point of exercise on the gastrointestinal tract is related to the possible risks and benefits caused by this practice. In this sense, the impact of exercise and physical activity on the gastrointestinal tract has taken the scientific community's interest in an emerging way. For more than two decades, research has focused primarily on the risks of strenuous exercise, especially gastrointestinal symptoms. However, over the past few years, interest has also turned to the potential benefits of physical exercise on the gastrointestinal tract. Several studies indicate an inverse relationship between physical exercise and the risk of gastrointestinal diseases, such as colon cancer, diverticulitis, colitis, and constipation [40–43]. Table 1 shows some risks and benefits of exercise in gastrointestinal tract.

Acute physical exercise influences gastric motility in a dose-response relationship with intensity, with low-intensity exercises seeming to accelerate the gastric emptying rate. In contrast, there is a delay in gastric emptying at high intensity. Different modalities, such as

the volume of food intake, the osmolality of energy drinks, and the duration of exercise, also seem to affect gastric motility [44].

Table 1. Summary of the main benefits and risks of exercise on the gastrointestinal tract. Adapted from Silva et al. [9].

	Benefits	Risks
Esophagus	None	Acid reflux induction
Stomach	Light Exercise Accelerates Gastric Emptying	High-Intensity Exercise Delays Gastric Emptying and Inhibits Acid Production
Small bowel	None	High-Intensity Exercise Interferes with Absorption and Induces Bleeding
Colon	Exercise Reduces the Risk of Colon Cancer and Diverticulitis	High-Intensity Exercise Induces Bleeding
Liver	None	None

Studies indicate the direct benefits of aerobic exercise on the gastrointestinal tract [45–47]. Resende et al. [45] highlight that moderate-intensity exercise can improve VO_2 peak and positively influence gut microbiota composition in non-obese men. Specifically, the study observed an increase in the relative abundance of Streptococcus and a decrease in an unclassified genus from the *Clostridiales* order. Additionally, VO_2 peak was positively associated with *Roseburia*, *Sutterella*, and *Odoribacter*, while BMI negatively correlated with *Desulfovibrio* and *Faecalibacterium*. These microbial changes suggest potential benefits for gut function, including enhanced short-chain fatty acid (SCFA) production, improved gut barrier integrity, and reduced inflammation, all of which may contribute to better digestion and metabolic regulation. Performing moderate-intensity aerobic exercise on a treadmill (at 75% of maximum heart rate) for 25 min increased gastric compliance in healthy men and women, which refers to the stomach's ability to expand in response to food or liquid intake while maintaining intragastric pressure. Still, it did not alter these individuals' satiety perception [48]. Changes in gastric compliance can be attributed to neuroendocrine adaptations promoted by exercise [48,49]. It is noteworthy that physical exercise can induce repercussions on the autonomic nervous system, thus influencing the gastrointestinal tract. The vagus nerve mediates an increase in function via the parasympathetic nervous system, which reduces sympathetic excitability and maintains sympathovagal balance [50,51].

In another study, Carvalho et al. [52] found that acute anaerobic exercise was able to increase gastric accommodation, which refers to the stomach's ability to relax and expand in response to food intake and reduce satiety in healthy men, these effects being mediated by the secretion of lactate, CK and some plasma cytokines, such as interleukins (IL)-6, -13 and tumour necrosis factor α (TNF-α). In addition, one of the possible explanations for this phenomenon concerns the activation of cholinergic pathways that increase gastric tone and the release of nitric oxide, promoting increased gastric accommodation mediated by physical exercise [52,53]. Table 2 shows common perceptions of the gastrointestinal effects of exercise and their scientific evidence.

Table 2. Physical exercise perceptions on gastrointestinal disorders.

Category	Effects Observed	Evidence	Conclusions
Gastroesophageal reflux	Symptoms of gastroesophageal reflux are commonly observed during exercise.	Suggestive	Some activities like running can cause transient lower esophageal sphincter relaxation, increased abdominal pressure, and decreased esophageal clearance during exercise, leading to reflux episodes without pathological evidence [54].
	Exercise can exhibit protection against GERD.	Convincing	In two systematic reviews, higher levels of recreational physical activity reduce the risk of GERD. One also found a reduced risk of esophageal adenocarcinoma [55,56].
Gastrointestinal motility	Exercise alters gastric emptying and digestion.	Unclear	1. The effects seem to be different according to exercise intensity. Light exercise seems related to gastric emptying acceleration, while high-intensity exercise delays. 2. Acute and chronic exercise also have been implicated in different effects on gastric emptying. 3. Ingested food/drink or supplements can influence gastric emptying responses to exercise. 4. Evidence also focuses on the capacity of exercise to regulate gastric emptying in some clinical conditions, such as chemotherapy, IBD, diabetes mellitus, and hypertension [48,53,57–61].
	Exercise changes intestinal motility.	Unclear	Some evidence shows that exercise can alter gastrointestinal motility by changing the myoelectric activity of gastrointestinal cells, reducing motility, while other evidence found no alterations [44,62,63]. These effects can also be mediated by diet before the training and mechanical effects of exercise.
Constipation	Exercise can relieve chronic constipation.	Limited evidence	In a systematic review and meta-analysis, the authors found that exercise significantly improved the symptoms of patients with constipation, and aerobic exercise positively impacted constipation. However, the methodological issues and standardization of exercise protocols can limit scientific evidence [64].
Cancer risk	Exercise may reduce digestive cancer risk.	Convincing	Systematic reviews and metanalysis found that exercise protects against digestive cancers [65,66].
Gastrointestinal bleeding	Strenuous exercise can cause bleeding in the gastrointestinal tract	Suggestive	Athletes can face some GI bleeding from the upper or lower GI tract, with severity linked to effort intensity and duration. Key factors include splanchnic hypoperfusion, GI wall trauma, and NSAID use. Proper nutrition, hydration, exercise regulation, and supplements can alleviate symptoms such as nausea, vomiting, cramping, diarrhea, and potential hemorrhage [67].

Legend: GERD: gastroesophageal reflux disease; GI: gastrointestinal tract; IBD: inflammatory bowel disease; NSAIDs: non-steroidal anti-inflammatory drugs.

2.3. Intestinal Permeability and Exercise

Practitioners of physical exercise, especially those of long duration, such as marathons, triathlons, and adventure races, present significant biochemical and physiological changes, which have become the target of research for a better understanding of these phenomena aiming at better performance. The manifestation of gastrointestinal symptoms in athletes is one of the most common causes of loss of sports performance in training and competitions. Some studies have pointed to a range of 30 to 83% of gastrointestinal symptoms among runners, mainly considering complaints related to the lower gastrointestinal tract (diarrhea, rectal incontinence, rectal bleeding, and abdominal pain). In addition, women are more susceptible to these problems when compared to men, and some modalities report more complaints, such as cyclists and triathletes [11,68].

The type of exercise and training variables related to intensity and volume of food intake during exercise play a fundamental role in the etiology of gastrointestinal injuries [69]. Although exercise dramatically influences the entire gastrointestinal tract, the intestinal segments deserve greater attention, considering that through them, nutrients are absorbed, and most of the gastrointestinal symptoms associated with exercise alter the intestinal permeability [70]. Changes in intestinal permeability refer to the diffusion-mediated passage of molecules larger than 150 Da through the intestinal barrier, particularly via tight junctions and other intercellular pathways, as desmosomes [71].

Tight junction proteins are key regulators of paracellular transport in the intestinal barrier, including claudins, occludins, and zonulins. The dysregulation of these proteins can lead to increased intestinal permeability, compromising barrier integrity. One of the primary factors contributing to this dysfunction is alterations in the gut microbiota, which influences tight junction expression, intestinal immune responses, and exercise-induced thermal stress [3,68,70].

There are many causes of changes in intestinal permeability caused by exercise, such as mechanical factors, where it is well described that runners suffer from intestinal disorders caused by mechanical forms of acceleration/deceleration, as well as neuromuscular alterations resulting from psoas muscle hypertrophy, which presses the gastrointestinal tract, generating gastrointestinal symptoms [69].

The mesenteric circulation and gastrointestinal symptoms in long-distance runners may be influenced by mesenteric lymphatic vessel contractility, and probiotics present significant diagnostic and therapeutic challenges [72]. Smarkusz-Zarzecka et al. [72] conducted a randomized controlled trial evaluating the effects of a multi-strain probiotic supplement on gastrointestinal symptoms and serum biochemical parameters in long-distance runners. After a 3-month intervention, participants in the probiotic group reported a reduction in constipation, with women experiencing greater overall health improvements than men. However, no significant changes were observed for diarrhea, reflux, or IBS-like symptoms compared to the placebo. These findings suggest that probiotics may play a role in modulating gut function and systemic metabolism, particularly in endurance athletes prone to gastrointestinal disturbances.

Many athletes use aspirin or other non-steroidal anti-inflammatory drugs (NSAIDs) for analgesia. While effectively controlling pain, NSAIDs disrupt oxidative phosphorylation and inhibit cyclooxygenase (COX) enzymes in the gastrointestinal mucosa. In addition to these effects, NSAIDs likely contribute to cytoskeletal disruption and impaired calcium homeostasis, generating free radicals that cause oxidative damage. This process may weaken tight junctions and desmosomes, further compromising intestinal barrier integrity. Prolonged or intense exercise, when combined with NSAID use, exacerbates intestinal permeability, as demonstrated by Van Wijck et al. [73].

Prolonged exercise especially for endurance runners, can increase gastrointestinal symptoms' incidence and severity [44]. The occlusion of blood flow can be improved with a higher intensity and/or duration of exercise and/or environmental heat stress [74]. The transient ischemic state during physical exercise causes damage to the GI tissues, triggering an inflammatory response. Studies show that when blood flow is restored—reperfusion—cells continue to undergo necrosis, and a cascade of inflammatory mediators (pro-inflammatory cytokines, neutrophils, adhesion molecules) are signaled to repair the damaged tissue [75].

Another important factor related to permeability is intestinal ischemia. This can occur as early as 10 min after performing high-intensity exercise, measured by gastric tonometry. Splanchnic hypoperfusion for 20 to 60 min in a cyclist at 70% VO_2max intensity, followed by 10 min of reperfusion, causes rapid ATP breakdown to AMP, activating hypoxanthine. During the reperfusion cycle, hypoxanthine is reduced to xanthine by the calcium-activated enzyme xanthine oxidase. The increase in calcium may result from calcium pump dysfunction during ischemia. Xanthine oxidase releases hydrogen peroxide, a potent free radical that causes tissue disruption and the breakdown of tight junction proteins. Thermal stress during exercise can also lead to the impairment of tight junction proteins, which are responsible for maintaining the morphological structure of intestinal cells and the gastrointestinal barrier function [76,77]. These effects of physical exercise on the gastrointestinal tract can be seen in Figure 1.

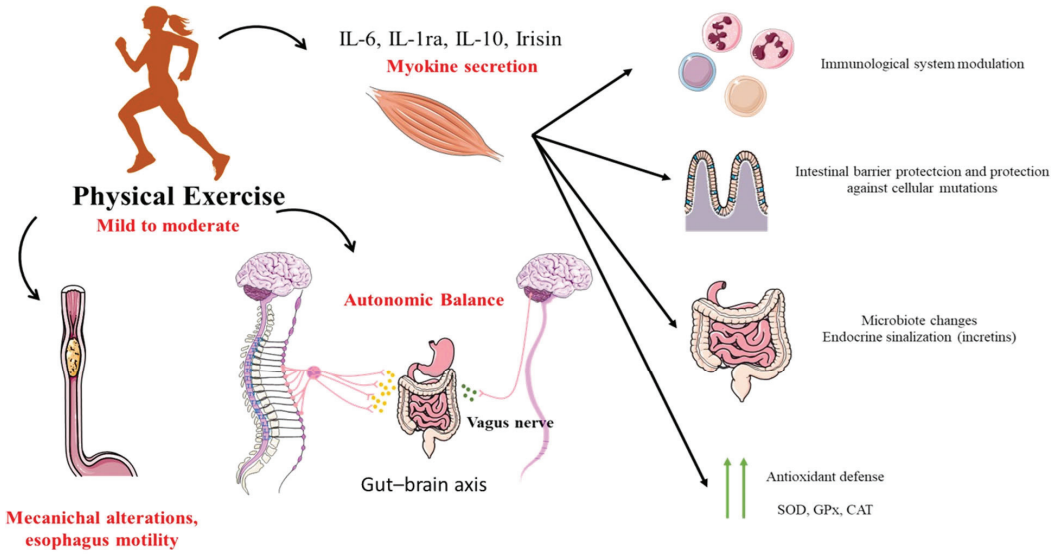

Figure 1. Regular physical exercise modulates the beneficial effects in different systems, preventing and auxiliary such as therapy form in gastrointestinal disorders. Physical exercise promotes the release of myokines, which can act in the modulation of the immune system, in the maintenance of the intestinal epithelial barrier and protection against mutations, and by promoting changes in the microbiota and endocrine signaling and increasing the antioxidant defense. Another physical exercise action modulates the autonomic balance, regulating the sympathetic and parasympathetic functions that innervate the gastrointestinal tract. In addition, the mechanical changes promoted by physical exercise can alter gastroesophageal motility in a dose–response relationship with intensity, and low-intensity exercises seem to induce an acceleration of the gastric emptying rate. In contrast, there is a delay in gastric emptying at high intensity.

2.4. Gastrointestinal Disease and Exercise

On the other hand, exercise can be beneficial in treating several gastrointestinal disorders. Table 3 summarizes studies exploring physical activity's effects on various gastrointestinal conditions.

Table 3. Results of clinical trials that evaluated the therapeutic effect of physical exercise on gastrointestinal diseases.

Author/Year	Localization	Exercise Group	Control	Type of Disease	Exercise Protocol	Duration	Main Results
Brown et al. (2018) [78]	USA	Low dose (n = 14) High dose (n = 13)	13	Patients with colon cancer in stages I-III	Treadmill aerobic exercise (50–70% HRmax)	Low-dose group (150 min/week) High-dose group (300 min/week) 6 months of intervention	A questionnaire measured the best score on the quality-of-life test. There was no effect on gastrointestinal symptoms.
Collings et al. (2003) [79]	USA	Athletes Race (n = 10) Cycling (n = 10) Weightlifting (n = 10)	-	GERD	Aerobic exercise 65% (60 min) and 85% (20 min) of HRmax	Fasting exercises and postprandial (45 min after meals) 60 min Rest 20 min	Weightlifters—more heartburn and reflux. Runners—mild symptoms and moderate reflux. Cyclists—mild symptoms and reflux. Strenuous exercise induces significant reflux and related symptoms in conditioned people.
Cronin et al. (2019) [80]	Ireland	13	7	Crohn's Disease and Ulcerative Colitis	A combined program of aerobic and resistance training of moderate and progressive intensity	8 weeks of intervention	Improved aerobic capacity. Improved body composition. There was no difference in disease activity. There were no changes in the α and β-diversities of the intestinal microbiota.
Daley et al. (2008) [81]	England	28	28	Patients with IBS	Customized training	12 weeks	There was no difference in the quality-of-life score between the groups. The trained group showed significant improvement in the symptoms of constipation.
Klare et al. (2015) [82]	Germany	15	15	Crohn's Disease and Ulcerative Colitis	Moderate intensity running	10 weeks	Improved quality of life. There was no exacerbation of gastrointestinal symptoms.
Mendes-Filho et al. (2014) [83]	Netherlands	10 healthy volunteers	-	Investigation of possible effects on GERD	After a standard meal and rest Aerobic exercise (treadmill) 60% (30 min) and 85% (20 min) of HRmax	30 min Rest 20 min	Longer time with esophageal pH <4, frequency, and duration of reflux episodes. Decreased contractility and duration of peristaltic contractions. A hiatal hernia was detected during the exercise but not during rest.

Legend: GERD: gastroesophageal reflux disease; IBS: irritable bowel syndrome.

2.4.1. Gastroesophageal Reflux Disease

Gastroesophageal reflux disease (GERD) is a gastrointestinal motility dysfunction characterized by the irregular reflux of stomach contents leading up to the esophagus, causing mucosal damage and several other symptoms [84]. Heartburn (pyrosis), a burning sensation or discomfort due to increased acidic juice in the stomach with pain and bitter taste in the mouth, and regurgitation, characterized by the involuntary return of gastric contents to the esophagus, are common in GERD, accompanied by extraesophageal symptoms such as teeth erosion, epigastric pain, laryngitis, and cough [85,86]. GERD affects the quality of life of individuals and can progress to erosive esophagitis, esophageal stricture, Barrett's esophagus, and esophageal adenocarcinoma [87]. Patient improvement is associated with the use of proton pump inhibitor drugs, the first line of drugs used for treatment, and the modification of the patient's lifestyle [88].

Light to moderate physical exercise generates benefits for GERD, while high-intensity exercise, depending on the type and duration, can be considered a risk to the patient's health [56,89]. A fibre-rich and low-fat-rich diet is also recommended to prevent reflux symptoms [90]. The inspiratory of diaphragmatic muscle training helps improve the pressure on the gastroesophageal junction, reducing the progression and symptoms of the disease [91]. It is considered that the lower esophageal sphincter region is responsible for the prevention of gastroesophageal reflux, and because of this, respiratory training exercises on the diaphragm indicate improvement in patients evaluated by esophageal pH monitoring, quality-of-life scores and use of proton pump inhibitors [92–94].

High-intensity physical activity increases the possibility of reflux episodes in patients affected by the erosive form with a positive correlation of VO2 $\geq$ 70% in a stress exercise test; however, light and short-term exercises do not affect the occurrence of reflux, even in patients with overweight or obesity [83]. Exercise causes worsening symptoms of gastroesophageal reflux related to a decrease in blood flow by about 80% by activating adrenergic receptors in athletes and untrained individuals. It may intensify symptoms during dehydration [9,95]. Usually, some athletes have oesophagal reflux in high-intensity exercises, which require a lot of physical effort and prolonged duration, associated with a worsening in postprandial exercises, which increases with the increase in resistance. GERD presents complexity in its symptomatology to other upper gastrointestinal diseases, making it difficult to differentiate from angina, and may also increase asthma symptoms [96].

Collings et al. [79] analyzed the effect of running, cycling, and weightlifting on 10 subjects from each sport with a three-month clinical history of heartburn during exercise. Exercises were standardized at 65% (60 min) and 85% (20 min) of maximum heart rate, and effects were observed in fasting or after a 15-min interval diet. Worsening of gastroesophageal reflux was observed in postprandial cases compared to fasting. Within the three modalities, weightlifting showed more significant reflux and heartburn. Running showed symptoms and moderate reflux, while cycling showed little worsening of the condition. It is reiterated that intense physical exercise causes considerable reflux and worsens other symptoms in athletes.

In this context, running, rowing, weightlifting, and cycling athletes have common upper gastrointestinal characteristics such as heartburn, epigastric pain, regurgitation, nausea, and vomiting. GERD is the primary disease that causes these symptoms in the upper gastrointestinal tract in athletes. The symptomatology of the disease is usually caused by exercise; GERD by exertion affects more individuals who have GERD at rest. However, it can affect only athletes when associated with physical exercise [97,98].

Corroborating the study, ten healthy volunteers who practiced some physical activities were submitted to a treadmill for 30 min (60% of maximum heart rate) with rest and then running for 20 min (85% of maximum heart rate) before exercise. A standardized meal.

The pH of the esophageal region was much more acidic (<4), and there was a decrease in esophageal sphincter pressure, a reduction in peristaltic contractions causing more significant episodes of reflux [54].

In this context, athletes in sports such as running, rowing, weightlifting, and cycling commonly exhibit gastrointestinal characteristics such as heartburn, epigastric pain, regurgitation, nausea, and vomiting. GERD is identified as the primary condition causing these symptoms in the upper gastrointestinal tract in athletes. The symptoms of the disease are usually triggered by exercise, and exercise-induced GERD affects individuals who already have GERD at rest; however, it can affect athletes only when associated with physical exercise [99,100].

2.4.2. Inflammatory Bowel Disease (IBD)

Inflammatory bowel diseases (IBD) comprise two primary forms of clinical manifestation: Crohn's disease, which is characterized by transmural inflammation of the intestinal mucosa, consisting of any part of the gastrointestinal tract from the mouth to the anus, and ulcerative colitis, which involves only inflammation in the colonic mucosa, with more significant activity in the rectal region [101,102].

The chronic inflammation characteristic of IBD involves the mucosal and submucosal layers of the gastrointestinal tract, leading to symptoms such as bleeding, abdominal pain, diarrhea, malnutrition, and increased intestinal permeability [101]. Among the factors involved in the pathogenesis of these diseases, genetics, dysregulation in the intestinal microbiota, and environmental factors such as diet and physical inactivity stand out [103,104].

Physical exercise improves the inflammatory condition of Crohn's disease and ulcerative colitis. The regular practice of moderate-intensity walking or running three times a week for 10 weeks in patients with Crohn's disease with mild to moderate disease activity appears to improve these individuals' quality of life and well-being [105]. Walking three times a week at 60% of maximum heart rate enhanced patients' quality of life with Crohn's disease without exacerbating disease activity [40]. Additionally, physical exercise provides further benefits, including improving gut microbiota composition and exerting antioxidant and anti-inflammatory effects, which may have a protective role in reducing gastrointestinal permeability [8,10,41].

Data on the relationship between physical exercise and IBD are more consistent for Crohn's disease compared to the scarce research developed with patients with ulcerative colitis. In a study developed in the United Kingdom, Chan et al. [106] observed that patients with Crohn's disease and ulcerative colitis have limitations in physical exercise. However, patients who regularly practice some sports report improvements in the disease symptoms.

The performance of physical exercise leads to increased physical fitness, bone mineral density, quality of life, and reduced stress and anxiety associated with IBD without adverse effects related to exercise interventions [107]. It is essential to mention that training recommendations for patients with IBD should be lower than those for healthy individuals due to the inflammatory responses induced by exercise, particularly high-intensity exercise [10]. Performing acute low-intensity exercise or high-intensity interval exercise in pediatric patients with Crohn's disease also does not appear to exacerbate the inflammatory condition of the disease [108].

According to the European Crohn's and Colitis Organization, Pérez [109] recommends exercise for Crohn's disease. As for aerobic activity, 20–30 min of low-intensity walking is recommended, at 60% of maximum heart rate, 3 days a week and evolving according to the patient's progress. Regarding resistance training, using elastic bands or free weights is recommended, as it is an individualized program according to age, conditioning level,

goals, and exercise preferences. Elsenbruch et al. [110] found improvement in quality of life in patients with ulcerative colitis in remission, with no changes in clinical and physiological parameters after a structured program of moderate-intensity physical exercise, Mediterranean diet, and cognitive behavioral therapy once a week for 10 weeks.

Physical exercise improves the quality of life. It can be considered an alternative therapy in IBD due to the role of skeletal muscle in the secretion of myokines such as irisin, IL-6, IL-15, and IL-1ra released during and after the exercise session. Regarding irisin, it is vital in regulating metabolic functions in adipose tissue, which are altered in the presence of Crohn's disease and ulcerative colitis [10]. Myokines play a crucial role in modulating gut microbiota composition and gastrointestinal function. Irisin, a myokine released during exercise, has been shown to influence gut microbiota, exerting anti-inflammatory effects within the gastrointestinal tract. Additionally, muscle activity enhances the synthesis of brain-derived neurotrophic factor (BDNF), which may help protect intestinal cells against mutations, promoting gut health and overall homeostasis. Furthermore, certain interleukins (ILs) function as anti-inflammatory mediators and play a role in appetite regulation within the gastrointestinal tract. This endocrine signaling network, which links skeletal muscle and gut function, is called the muscle–gut axis [10,52].

Another substance secreted by skeletal muscle that deserves to be highlighted is IL-6 since, despite being considered a pro-inflammatory factor, it induces anti-inflammatory responses such as an increase in IL-10 and IL-1ra and stimulates the secretion of peptides like glucagon 1 (GLP-1), which may act in the repair of the intestinal mucosa after damage related to the pathogenesis of IBD [10].

In addition, exercise seems to play an essential role in improving the diversity of the intestinal microbiota, which is usually dysregulated in Crohn's disease and ulcerative colitis, being one of the factors that can aggravate or predispose to the emergence of these diseases [3,10,111]. In a systematic review, Koutouratsas et al. [112] show pre-clinical and clinical studies that regular exercise increases the presence of beneficial bacteria, such as Bacteroidetes, Clostridium septum, *Prevotella*, *Bifidobacterium*, and *Roseburia*, while reducing the abundance of *Proteobacteria*, a group often linked to intestinal inflammation. These changes promote the production of SCFAs, strengthen the intestinal barrier, modulate the immune response, and inhibit pathogenic bacterial adhesion, suggesting a plausible mechanism through which exercise benefits IBD patients.

2.4.3. Irritable Bowel Syndrome (IBS)

Irritable Bowel Syndrome (IBS) is one of the most diagnosed gastrointestinal disorders, being related to the manifestation of abdominal pain and discomfort and changes in bowel habits, and can be mixed, diarrheal, or constipation-related [113]. Patients with IBS also suffer from extra-intestinal symptoms such as migraine, depression, fatigue, and fibromyalgia [114].

Some lifestyle interventions, such as physical exercise, have been suggested to improve gastrointestinal and extra-intestinal symptoms [115]. The mechanisms by which training improves the symptoms of patients with IBS would be related to changes in intestinal blood flow, neuroendocrine and immunological changes, changes in intestinal motility, reduced stress, and improved well-being promoted by exercise [116].

Patients with IBS, when advised weekly to increase cardiorespiratory fitness by practising 20–60 min of moderate to vigorous physical activity 3 to 5 times a week, showed a significant improvement in these patients' symptom scores after 12 weeks of counselling [117]. In another study, Johannesson et al. [118] also found improvement in gastrointestinal and psychological symptoms, such as fatigue, depression, and anxiety.

The attenuation of gastrointestinal symptoms in patients with IBS after aerobic training for 24 weeks may be due to the attenuation of the inflammatory process, with a reduction in plasma concentrations of cytokines (IL1β, IL-6, IL-8, IL-10 and TNF-α), reduction in oxidative stress markers, such as xanthine oxidase (XO), plasma malondialdehyde (MDA), and nitric oxide (NO), and increased antioxidant activity, such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) [119,120].

Various training modalities (yoga, walking exercises, swimming, cycling, and other sports activities) have shown an effect. They can be considered an affordable and effective therapy for treating and managing IBS [119]. Notably, the literature on the subject has focused more on evaluating the effects of aerobic training on anaerobic training, with data on the latter still scarce. In its guidelines, the American College of Gastroenterology [121] hypothesizes that physical exercise can be an adjunctive therapy for IBS. However, evidence from clinical trials is still scarce, and it isn't easy to establish a recommendation.

2.4.4. Colorectal Cancer

Colorectal cancer is one of the most diagnosed cancers in both men and women in Brazil and worldwide, encompassing tumours that originate in the colon, rectum, and anus [122,123]. Its incidence rate is increasing considerably, with an estimated 2.5 million survivors expected by 2035 [124]. Among the risk factors associated with the manifestation of colorectal cancer are age over 50, poor lifestyle and dietary habits, economic development, obesity, physical inactivity, smoking, excessive alcohol consumption, diets high in red or processed meats, fats, sugary foods, and refined grains, and diets low in calcium, fruits, fibre, and vegetables [125].

Regular physical activity and exercise are also associated with a lower risk of colorectal cancer and other types of cancer through various mechanisms, such as the regulation of the cell cycle, improved immune function, protective action in the gastrointestinal tract via mediators secreted by skeletal muscle, mainly via myokines and exosomes, and increased antioxidant and anti-inflammatory responses [126]. Mechanistically, the main effects of colorectal cancer prevention linked to physical exercise include the redirection of insulin-like growth factor (IGF), reduced inflammation, cell death via apoptosis, epigenetic changes, and regulation of leptin and ghrelin levels [127].

Research has shown the benefits of physical exercise in treating patients with colorectal cancer, improving physical conditioning, functional and mental capacity, stress, and quality of life, enhancing immune function, oxidative stress, and prognosis [78,127,128]. A supervised 18-week exercise program for colorectal cancer patients undergoing chemotherapy reduced fatigue and proved to be safe and feasible [129].

Neoadjuvant exercise, as a prehabilitation strategy, is associated with lower morbidity in patients with colorectal cancer, considering that the primary treatment for this type of cancer is surgical. Improvement in physical fitness components is linked to better recovery and a lower recurrence rate in colorectal cancer [130,131]. It is important to note that some adverse effects of oncological treatments include peripheral neuropathy, fatigue, cardiovascular risk, pulmonary complications, immune and endocrine dysfunction, gastrointestinal motility alterations, anxiety, depression, and muscle weakness [132]. Thus, physical training can alleviate these symptoms and improve the quality of life in patients undergoing chemotherapy [127,133].

Among the mechanisms involved in the positive effects of physical exercise on colorectal cancer prognosis are modulation of the gut microbiota, with increased production of short-chain fatty acids that have anti-inflammatory effects, an increase in the population of Bifidobacterium, and a reduction in species such as *Fusobacterium nucleatum* and

lipopolysaccharide-producing bacteria, which are pro-inflammatory, promoting increased intestinal permeability and metastasis [134].

Regarding the types of physical exercise and studies on other conditions that affect the gastrointestinal tract, most research has focused on the benefits and protocols of aerobic exercise. There is still a significant gap in clinical trials investigating the effects and establishing recommendations for resistance training in patients with colorectal cancer [127].

2.4.5. Summary Recommendations of Physical Exercise in GI Dysfunctions

Based on the literature discussion, physical exercise can benefit various gastrointestinal diseases with appropriate intensity and modality.

- In patients with IBD, including Crohn's disease and ulcerative colitis, walking or light-to-moderate running (60% of maximum heart rate) three times per week for 10 weeks improves the quality of life without exacerbating inflammation, while moderate-intensity aerobic and resistance training can help reduce inflammatory markers.
- For individuals with IBS, moderate aerobic activities such as walking, light running, and swimming aid in reducing abdominal pain and improving intestinal motility, whereas high-intensity exercise may worsen symptoms.
- In GERD, low-to-moderate-intensity exercises such as walking, light weight training, and yoga support weight management and diaphragm strengthening, while high-impact exercises and those performed right after meals should be avoided.
- In colorectal cancer, both prevention and post-treatment, regular aerobic exercise and moderate resistance training reduce inflammatory markers and the risk of recurrence.

Adjusting exercise intensity and frequency to maximize benefits without worsening gastrointestinal symptoms is essential in all these conditions.

3. Conclusions

In summary, the study of physical exercise on digestive physiology is quite old. However, this theme has been explored better in recent years, given the new methodologies for investigating the various intestinal segments. In addition, with techniques such as molecular biology and the study of specific gastric receptors and hormones, it was possible to understand better the mechanisms involved in gastrointestinal changes associated with physical exercise at various intensities, both in experimental models and clinical studies in humans.

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Review

Role of Mirikizumab in the Treatment of Inflammatory Bowel Disease—From Bench to Bedside

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Abstract: Mirikizumab is a monoclonal antibody directed against the p19 subunit of interleukin (IL)-23 to inhibit its interaction with the IL-23 receptor. IL-23 is a key cytokine involved in initiating and perpetuating the inflammatory cascade in inflammatory bowel disease (IBD). Mirikizumab is the first agent from the novel anti-IL-23p19 drug class to be licensed for ulcerative colitis and the first to present long-term endoscopic, histologic, symptomatic, and quality-of-life outcomes. More recently, the VIVID trial programme has led to the approval of mirikizumab in moderate to severe Crohn's disease. This review explores the history of its development, discusses key immunopharmacological properties unique to the drug, and details the available clinical trials and real-world evidence supporting its use in IBD.

Keywords: mirikizumab; inflammatory bowel disease; IL-23p19 inhibitor

1. Introduction

The last decade has seen a significant increase in the number of advanced therapy (AT) options available to clinicians for the treatment of inflammatory bowel disease (IBD). Historically, pharmacological treatment options were limited to 5-aminosalicylic acids, thiopurines, and corticosteroids, but that changed in the 1990s with the emergence of the first clinical trials demonstrating the efficacy of infliximab, a monoclonal antibody targeting tumour necrosis factor-alpha (anti-TNFα) in both Crohn's disease (CD) [1] and later ulcerative colitis (UC) [2]. Since these landmark trials, the therapeutic armamentarium has grown considerably to include other anti-cytokine drugs, such as Janus kinase inhibitors and interleukin (IL)-12 and/or IL-23 inhibitors, and anti-leucocyte trafficking agents that include the anti-integrins and sphingosine-1-phosphate receptor modulators. However, there remains a significant proportion of patients who fail to respond to, lose response to, or are intolerant of these ATs, creating an unmet need for novel therapies.

IL-23 has been identified as a dominant regulatory cytokine involved in both innate and adaptive immune systems and as playing a critical role in multiple immune-mediated inflammatory diseases (IMIDs) [3,4]. It has been implicated in the pathogenesis of psoriatic skin and joint inflammation, rheumatoid arthritis, and IBD [5]. Since its discovery, targeting IL-23 has been an area of significant research interest when developing new treatments for

IMIDs, and ustekinumab, a monoclonal antibody that inhibits both IL-12 and IL-23, has been shown to be effective in several IMIDs, including IBD [6–9].

IL-23 is a heterodimer of the p40 and p19 subunits. Whilst p40 is also found in IL-12, p19 is unique to IL-23, and this specificity makes it an attractive target for novel therapies. This has led to the development of several agents that act as p19 inhibitors (p19i) and the accumulating safety and efficacy clinical trial data are promising. Mirikizumab (Omvoh, Lilly) was the first p19i to be licenced for the treatment of UC following the LUCENT trial programme [10] and is being appraised by regulators for use in CD in Europe and the United Kingdom after receiving approval from the FDA. This review examines the pharmacology of mirikizumab and the history of its drug development, the clinical trial and real-world data underpinning its use in IBD, and a discussion on where it will likely be positioned in treatment algorithms for IBD.

2. Understanding the Pharmacological Basis of Mirikizumab

IL-23 is a member of the IL-6 cytokine family [11], and it was discovered in the late 1990s, with subsequent studies identifying IL-23 as a major effector cytokine involved in innate and adaptive immune responses. It is a driver of aberrant inflammation in autoimmune disorders of the skin [12], joints, lungs, and gut. The p40 subunit is shared with IL-12, with the p19 subunit unique to IL-23 [13]. IL-23 is produced by immune cells, including activated dendritic cells, in response to toll-like receptor (TLR) signaling [11]. Myeloid cells that express Fc-gamma receptor 1 (FcγRI), or CD64, have been identified as a primary source of IL-23 in inflamed gut tissue. Genetic variants in the region of IL-23 and IL-23R have been associated with altered susceptibility to the development of IBD, and high serum IL-23 levels have been identified in patients, particularly in subjects with co-existent arthritis [14,15]. Together, this suggests a role for the IL-23 pathway as an attractive therapeutic target in IBD.

IL-23 plays a key role in the differentiation and maintenance of CD4+ T helper 17 (Th17) cells, a T cell subset identified as critical to the pathogenesis of both UC and CD [13,16,17]. IL-23 induces strong proliferation of Th17 cells, resulting in the production of proinflammatory cytokines, including IL-17A, IL-17F, IL-21, and IL-22 [13]. Furthermore, IL-23 can act on neutrophils to induce the production of pro-inflammatory IL-17 and IL-22 [18]. Despite success in treating immune-mediated skin conditions [19], blockade of IL-17 has been shown either to be ineffective or to worsen CD in clinical trials [20,21], suggesting an additional protective role for IL-17 in supporting gut barrier function [22]. Serum IL-23 levels correlate with disease activity in UC and a reduced ratio of tolerogenic regulatory $CD4^+$ T cells to proinflammatory Th17 cells in peripheral blood [16]. Blockade of IL-23 holds the potential, therefore, to modulate the function of Th17 cells in autoimmune disease whilst permitting immune responses to invasive pathogens [23].

The IL-23 receptor is composed of the IL-23R and IL-12Rβ1 subunits. Whilst IL-23R is responsible for initiating downstream intracellular signalling pathways, IL-12Rβ1 stabilises binding through interactions with the p40 subunit of IL-23 [24]. Binding of IL-23 leads to recruitment and activation of intracellular Janus (JAK2) and tyrosine kinases (TYK2), followed by phosphorylation and nuclear translocation of signal transducer and activation of transcription (STAT) 3 and 4 transcription factors [11].

2.1. The Development of Clone 9F2.25.38: Mirikizumab

Given the importance of IL-23 in the inflammatory cascade, multiple attempts at discovering new therapeutic agents targeting this pathway have been undertaken. The development of what became mirikizumab started with in vitro models using BALB/c mice that were immunised with human IL-23. Spleen cells from these mice were then harvested and sorted using fluorescence activation to identify those with IL-23 binding activity. These were then cultured for 2 weeks with EL4-B cells following which they were assayed for positive binding to IL-23 and a lack of binding to IL-12. Reverse-transcription polymerase chain reactions were subsequently used to isolate heavy and light chain variable region genes from the desired cells, which were subsequently cloned into murine antibody expression vectors. The resulting antibodies were then assessed and characterised for antigen binding affinity and their ability to block IL-23R binding using either human or murine spleen cell assays. This process identified clone 9F2 which completely inhibited IL-23 binding to its receptor without binding to IL-12. This clone was then successfully humanised and optimised for affinity and biophysical properties, such as chemical stability, resulting in four high-affinity variants. Further in vitro studies assessing protein characteristics such as affinity, aggregation, and expression levels resulted in clone 9F2.25.38 being designated as mirikizumab [23].

Further evaluation using in vitro animal studies demonstrated that mirikizumab binds to IL-23 with high specificity, with no measurable binding to IL-12, preventing interaction between IL-23 and IL-23R but not the interaction with IL-12Rβ1 [23,25]. Human T cell assays confirmed that mirikizumab was able to block IL-23-induced IL-17 production whilst preserving the function of IL-12. These results were replicated in studies on mice and cynomolgus monkeys, demonstrating good efficacy and safety and allowing the progression to human clinical trials.

2.2. Pharmacokinetics of Mirikizumab

Mirikizumab (Omvoh, Lilly, Indianapolis, United States, LY3074828) is a neutralising humanised IgG4 monoclonal Ab directed against the p19 subunit of IL-23 (Figure 1) and was the first p19i approved in the United Kingdom for moderate-to-severe UC in 2023. Mirikizumab induction is administered as three four-weekly 300 mg intravenous infusions, followed by four-weekly maintenance dosing of 200 mg delivered subcutaneously from week 12. Mirikizumab, unlike the other p19i, also offers an extended 24-week induction or re-induction if patients lose response. The drug has a half-life of 9.3 days, shorter than that of risankizumab (21–29 days) and guselkumab (17 days [25]), with time to peak mirikizumab concentration being five days for subcutaneous dosing. Although a quarter of patients in phase III trials developed anti-mirikizumab antibodies (ADAs) during treatment, immunogenicity did not seem to affect drug availability, with only 2.6% of patients having reduced serum mirikizumab concentrations in the presence of ADAs [26]. Previous studies have demonstrated that low serum albumin levels in the context of active IBD can affect monoclonal antibody trafficking and clearance [27,28]. Whilst lower serum albumin concentrations have been associated with higher mirikizumab clearance, the effect size was small and is unlikely to have a clinically meaningful effect on mirikizumab levels [29]. Studies have also suggested dose adjustment for weight is not required [26].

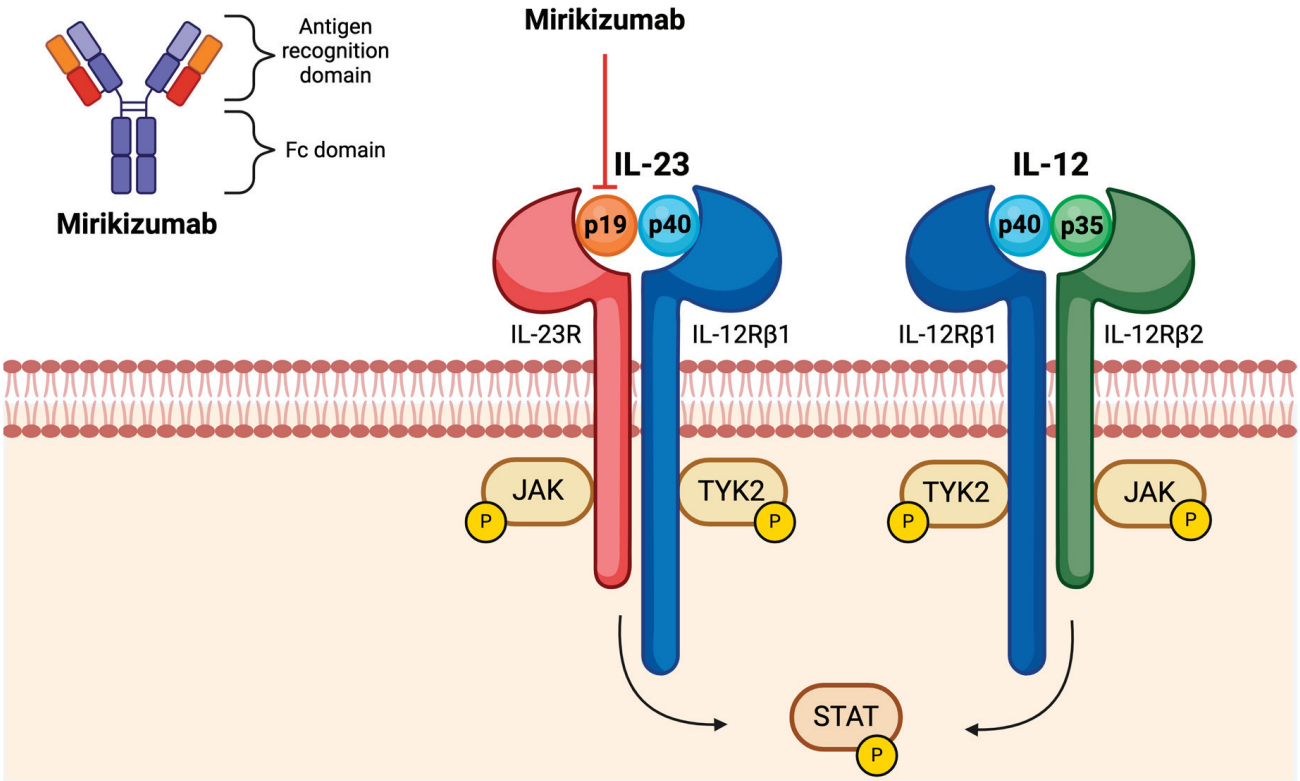

Figure 1. Mirikizumab is a humanised IgG monoclonal antibody specific to the p19 subunit of IL-23. Interleukin (IL)-23 is a heterodimeric cytokine comprised of p19 and p40 subunits. The p40 subunit is also shared by the heterodimeric cytokine IL-12, which is additionally comprised of a p35 subunit. The receptor for IL-23 is composed of an IL-12Rβ1 and IL-23R chain. The receptor for IL-12 is composed of two different subunits, IL-12Rβ1 and IL-12Rβ2. Binding of IL-23 or IL-12 to their respective receptor results in conformational changes in the receptor, which induce autophosphorylation of Janus kinase (JAK) 2 and tyrosine kinase (TYK) 2, leading to activation of signal transducers and activators of transcription (STATs).

3. Pivotal Clinical Trials

3.1. Ulcerative Colitis

LUCENT-1 was a phase-3 induction randomised control trial (RCT), which investigated 1281 patients with moderate-to-severely active UC and randomised them in a 3:1 ratio to receive intravenous mirikizumab (300 mg) or placebo (no active treatment) every 4 weeks for 12 weeks (Figure 2) [10]. Individuals had failed glucocorticoids, immunomodulators, or AT and were excluded if prior therapy included an IL-23 inhibitor (ustekinumab, tildrakizumab, guselkumab, or risankizumab). At week 12, mirikizumab was superior at achieving the primary endpoint of clinical remission (24.2% vs. 13.3%; 11.1% difference; 99.875% CI 3.2 to 19.1; $p < 0.001$) and all major secondary endpoints, including urgency numerical rating score (NRS) ($p < 0.001$). A single induction trial was needed to demonstrate efficacy across all primary and secondary endpoints with 99.875% confidence intervals by using a familywise error of 0.00125 (instead of the standard hypothesis testing threshold of $p < 0.05$).

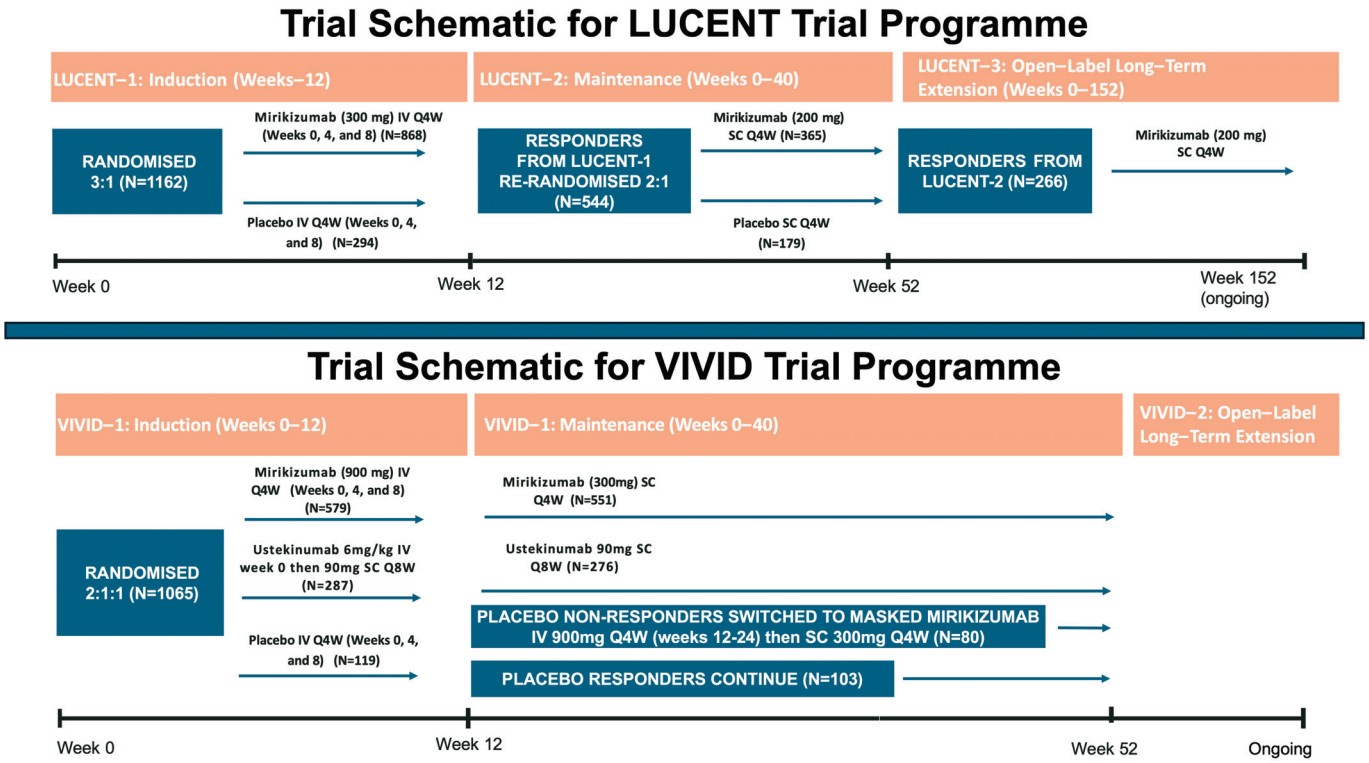

Figure 2. Schematic of the trial designs for LUCENT and VIVID trial programmes.

In the LUCENT-2 maintenance trial [10], 544 responders from LUCENT-1 were re-randomised 2:1 to receive subcutaneous mirikizumab (200 mg) or placebo (no active treatment) in a 2:1 ratio from weeks 12 to 52. Mirikizumab non-responders ($n = 272$) received three doses of intravenous open-label mirikizumab (300 mg) every 4 weeks and were reassessed for clinical response 12 weeks later. Those who had responded received open-label subcutaneous mirikizumab (200 mg) every 4 weeks through week 40. Responders to the placebo in the induction period continued to receive a blinded placebo in the maintenance period. Any patient with a loss of response after week 12 of the maintenance period discontinued maintenance mirikizumab or placebo and received three doses of open-label mirikizumab (300 mg), 4 weeks apart, as rescue therapy. At week 40, mirikizumab was superior at maintaining clinical remission compared to placebo (49.9% vs. 25.1%, 23.2% difference; 95% CI, 15.2 to 31.2; $p < 0.001$) with 97.8% of mirikizumab-treated patients in remission being glucocorticoid-free. Among the 272 patients reinduced with mirikizumab after inadequate primary response, 53.7% had a clinical response, and 11.4% had clinical remission by week 12 (week 24 overall). Clinical remission was maintained in 72.2% of these patients, and 36.1% had clinical remission at week 40. Secondary clinical, endoscopic, and histological endpoints also favoured mirikizumab over placebo, with a significantly greater number of individuals meeting the secondary endpoints. Improvement from baseline in urgency NRS remained stable throughout the maintenance trial in the mirikizumab group, whereas patients re-randomised to placebo lost some of the improvement gained during the induction trial.

LUCENT 3 is an ongoing single-arm, open-label, long-term extension study assessing the safety and efficacy of mirikizumab [30]. Individuals from LUCENT 1 or 2 who would benefit from further treatment received subcutaneous mirikizumab (200 mg) every 4 weeks, with interim analysis results published after a continuous treatment period of 104 and 152 weeks [30]. Those treated with a placebo were not included in the analyses. Approximately 25% of patients in the intention-to-treat population had missing data at week 152,

either sporadically missing or due to early discontinuation; therefore, endpoint analysis is provided for non-responder imputation (NRI—patients who discontinued treatment or were missing endpoint assessments were treated as non-responders), observed cases (patients with missing data were not included and missing data were not imputed) and modified non-responder imputation (m-NRI—discontinuation treated as non-response but sporadic missing data imputed). Using NRI, OC, and m-NRI, week 52 responders were in response at week 152 in 71.6%, 94.9%, and 81.6% of cases and in remission in 49.5%, 56.1%, and 65.5% of cases, respectively. Data were similar for biologic-failed and biologic-naive subgroups.

The mirikizumab-responder group had a ≥3 change in urgency score and ≥1 change for both stool frequency and rectal bleeding that was maintained through week 152. Over 80% of individuals had ≥30% improvement in abdominal pain from baseline to week 152.

During the first 52 weeks, 23.6% of mirikizumab-treated patients had anti-drug antibodies; however, less than 2% of mirikizumab-treated patients had antibody titre ≥1:160 associated with lower trough mirikizumab concentrations (<0.511 μg/mL, 5th percentile) and reduced clinical response. During the LUCENT-3 extension, only a further 0.6% developed antibodies.

Safety signals and adverse event (AE) rates were low throughout the LUCENT trial programme and are discussed in greater detail below.

These studies notably included participants up to the age of 80, who are an often-excluded demographic in clinical trials. Given the rising prevalence in the older population, this is particularly meaningful as the observed safety profile can be generalised to the older population.

3.2. Crohn's Disease

The phase 3 randomised, double-blind, placebo and active-controlled VIVID-1 trial compared mirikizumab to placebo (no active treatment) and ustekinumab in 1065 individuals with moderately to severely active Crohn's disease. Participants were randomised 6:3:2 to mirikizumab (900 mg IV at weeks 0–12, then 300 mg SC every 4 weeks at 12–52 weeks), ustekinumab (~6 mg/kg IV dose, then 90 mg SC every 8 weeks to week 52) or placebo (Figure 2) [31]. Note that the dose of mirikizumab for induction was three times higher for CD than for UC, based on the dose-ranging phase II trials.

Both co-primary endpoints of the study were met: patient-reported outcome (PRO) clinical response at week 12 plus week 52 endoscopic response (mirikizumab 38.0% vs. placebo 9.0%, $p < 0.000001$) and week 12 PRO clinical response plus week 52 Crohn's Disease Activity Index (CDAI) clinical remission (mirikizumab 45.4% vs. placebo 19.6%, $p < 0.000001$). Mirikizumab demonstrated superiority over placebo across all secondary endpoints, and significant reductions in abdominal pain, stool frequency, C-reactive protein (CRP), and faecal calprotectin were observed as early as weeks 4–6.

The trial also showed non-inferiority to ustekinumab in CDAI clinical remission at week 52 after accounting for multiplicity ($p = 0.113$), although superiority in endoscopic response was not achieved ($p = 0.51$) despite higher numerical response rates in the mirikizumab arm. Statistically significant reductions in CRP and faecal calprotectin were observed with mirikizumab compared to ustekinumab. Additionally, mirikizumab demonstrated numerically higher, but not statistically significant, rates of clinical remission by PRO and corticosteroid-free CDAI remission at week 52 compared to ustekinumab. Numerical, but not statistical, superiority was also demonstrated for mirikizumab over ustekinumab for CDAI and endoscopic response rates in those with previous biologic failure (Table 1).

Table 1. Breakdown of primary endpoints in the pivotal trials comparing results for biologic naïve patients and those with previous biologic failure. In the VIVID data, biologic failure was either an anti-TNF antibody or an anti-integrin antibody. For the LUCENT data, biologic failure also included those with previous treatment failure to tofacitinib.

	Biologic Failed			Biologic Naive		
	Placebo	**Mirikizumab**	**Ustekinumab**	**Placebo**	**Mirikizumab**	**Ustekinumab**
	***n* (%)**	***n* (%)**	***n* (%)**	***n* (%)**	***n* (%)**	***n* (%)**
VIVID-1: N	97	281	139	102	298	148
Clinical Response by PRO week 12 and Clinical Remission by CDAI Week 52	12 (12.4)	122 (43.4)	-	27 (26.5)	141 (47.3)	-
Clinical Response by PRO week 12 and Endoscopic Response by SES-CD Week 52	6 (6.2)	103 (36.7)	-	12 (11.8)	117 (39.3)	-
Clinical Remission by CDAI Week 52	12 (12.4)	144 (51.2)	58 (41.7)	27 (26.5)	169 (56.7)	81 (54.7)
Endoscopic Response by SES-CD Week 52	6 (6.2)	126 (44.8)	55 (39.6)	12 (11.8)	154 (51.7)	78 (52.7)
LUCENT 1: N	118	361	-	171	492	-
Clinical Remission Week 12	10 (8.5)	55 (15.2)	-	27 (15.8)	152 (30.9)	-
LUCENT 2: N	64	128	-	114	229	-
Clinical Remission Week 40	10 (15.6)	59 (46.1)	-	35 (30.7)	118 (51.5)	-

PRO: Patient-reported outcome. CDAI: Crohn's Disease Activity Index. SES-CD: Simple Endoscopic Score for Crohn's Disease.

The safety profile of mirikizumab was favourable, with lower rates of adverse events (AEs) compared to placebo. Anti-drug antibodies were detected in 12.6% of patients treated with mirikizumab, predominantly low-titre and transient, with a neutralizing activity that did not significantly affect drug efficacy.

4. Real-World Experience with Mirikizumab

Given the recent licensing of mirikizumab in UC, little real-world clinical data are available for its use outside of a clinical trial setting. A small study in 17 UC patients reported a modest reduction in clinical activity and faecal calprotectin, with a reduction in median Simple Clinical Colitis Activity Index (SCCAI) from 7 to 5 at weeks 8–12 of treatment [32]. Notably, 16 patients had received at least one previous biologic therapy, 12 had received $\geq$2, and four patients received $\geq$4, suggesting that mirikizumab may be effective in a biologic-experienced real-world cohort. No adverse events were reported in the short follow-up period.

5. Safety

A key strength of ustekinumab, the first IL-12 and IL-23 antagonist approved to treat IBD, is its robust long-term safety profile, which has been demonstrated in both clinical trials [6,7] and from real-world evidence [33]. Given their similar mechanism of action, there has been an expectation that p19i will have similar safety profiles, allowing widespread use without high levels of treatment cessation or complications. Thus far, the safety data from the randomised control trials that brought mirikizumab to the market have found low levels of serious adverse events (SAE) in both UC and CD, offering a positive outlook for its long-term use.

5.1. Ulcerative Colitis

For UC, the LUCENT trial programme found low rates of SAEs in both the induction and maintenance phases (2.1% and 3.3%, respectively, when excluding worsening UC), which were lower than those treated with placebo [10]. Common adverse events included nasopharyngitis, arthralgia, headache, and rash and were present at levels comparable to other advanced therapies (Table 2).

Table 2. Key safety data from the LUCENT trial programme [10] and VIVID trial [31].

	LUCENT Trials—UC				VIVID Trial—CD		
	Induction Trial		Maintenance Trial				
	Placebo (*n* = 321)	**Mirikizumab (*n* = 958)**	**Placebo (*n* = 192)**	**Mirikizumab (*n* = 389)**	**Placebo (*n* = 211)**	**Mirikizumab (*n* = 630)**	**Ustekinumab (*n* = 309)**
Any adverse event	148 (46.1)	426 (44.5)	132 (68.8)	251 (64.5)	154 (73.0)	495 (78.6)	239 (77.3)
Any adverse event, excluding ulcerative colitis	141 (43.9)	421 (43.9)	116 (60.4)	241 (62.0)		N/A	
Serious adverse event	17 (5.3)	27 (2.8)	15 (7.8)	13 (3.3)	36 (17.1)	65 (10.3)	33 (10.7)
Serious adverse event, excluding ulcerative colitis	7 (2.2)	20 (2.1)	10 (5.2)	13 (3.3)		N/A	
Discontinuation rate due to adverse event	23 (7.2)	15 (1.6)	16 (8.3)	6 (1.5)	20 (9.5)	32 (5.1)	8 (2.6)
Death †	0	0	1 (0.5)	0	1 (0.5)	0	1 (0.3)
Malignancy ‖	0	2 (0.2)	1 (0.5)	1 (0.3)	1 (0.5)	2 (0.6)	0
Non-melanoma skin cancer (not included in malignancy count)	0	0	1 (0.5)	0	1 (0.5)	1 (0.2)	0

† There were two deaths during the follow-up period for the LUCENT induction trial: one from sudden cardiac arrest and one from disseminated intravascular coagulation. The death in the placebo group during the maintenance trial was due to coronavirus disease 2019. ‖ In the mirikizumab group during the LUCENT induction trial, both cancers were colon adenocarcinoma. During the maintenance trial, nonmelanoma skin cancer (basal-cell carcinoma) occurred in one patient in the placebo group and gastric cancer in one patient in the mirikizumab group.

The LUCENT 1 and 2 trials found that serious infection, described as an adverse event (AE) of interest, was similar or lower in those treated with mirikizumab compared to placebo. With regards to opportunistic infections in the mirikizumab-treated cohorts, six patients developed herpes zoster infection, which was unrelated to corticosteroid use; four developed candidiasis; four developed cytomegalovirus, and one was diagnosed with intestinal tuberculosis. Only one patient treated with a placebo developed an opportunistic infection in the form of a herpes zoster infection. The rates of malignancy were low with four reported cancers in the 1217 mirikizumab-treated patients compared to none in the placebo-treated group; two were diagnosed with colorectal adenocarcinoma, one with gastric cancer and one with non-melanomatous skin cancer. One potential signal was with regards to elevations in liver enzymes which were more frequent in mirikizumab treated patients compared to placebo. In LUCENT 1 and 2, 27 patients developed deranged liver enzymes compared to nine in the placebo cohort, although none of these patients met the criteria for Hy's law. Depression was reported in four patients during the maintenance phase who received mirikizumab and in no patients who received a placebo.

Safety data from the open-label extension LUCENT 3 study included data from 285 patients at week 152 [30]. Common AE rates were similar to the LUCENT 1 and LUCENT 2 data and 8.8% of patients developed an SAE, with 5.3% of patients discontinuing treatment

due to an AE. The commonest was the development of COVID-19 infection (22.4%), reflective of the fact it was held during the pandemic and the worsening of UC (15.9%). Rates of infusion or injection-site reactions were higher with mirikizumab than placebo: 4 (0.4%) patients in the induction trial and 34 (8.7) in the maintenance trial. Regarding SAEs of interest, there was one reported malignancy, six opportunistic infections, five cerebrocardiovascular events, and one major adverse cardiac event. Eleven patients treated with mirikizumab developed elevations of alanine aminotransferase, but none met the criteria for Hy's law. Three patients reported depression, and one patient attempted suicide, although it should be noted they had a history of suicide attempts prior to enrolment in the trial. There was one death from thrombotic thrombocytopenic purpura on day 463 of the trial.

5.2. Crohn's Disease

The VIVID-1 study compared mirikizumab to both placebo and ustekinumab in treating moderate to severe CD and found that the rates of AEs, SAEs, and discontinuation were similar in mirikizumab and ustekinumab populations and both were lower than the placebo group [31]. The most common AE were COVID-19 infection, anaemia, arthralgia, headache, upper respiratory tract infection, nasopharyngitis, and diarrhoea, and all occurred with a higher adjusted incidence ratio in the placebo group. Infusion site reactions (0.2%) and injection site reactions (10.8%) were higher in mirikizumab than in the placebo (0 and 6.5%, respectively, for the placebo cohort). Seven patients treated with mirikizumab developed opportunistic infections: one oral candidiasis, one typhoid fever, and five herpes zoster infections compared to none in the placebo cohort. Mild elevations in liver enzymes were seen in 6.2% of mirikizumab-treated patients, but none met the criteria for Hy's law. Three participant deaths occurred: one pulmonary embolism in the placebo cohort, one sepsis in the ustekinumab arm, and one worsening of CD in a placebo non-responder who switched to mirikizumab at week 12. No deaths were considered to be drug-related.

5.3. Pregnancy and Lactation

There are very limited data available with regard to the safety of mirikizumab in pregnancy and lactation. Pre-clinical studies performed on 30 pregnant cynomolgus monkeys found no adverse development events to those born of mothers given mirikizumab at 79 times the maximum human dose during organogenesis whilst pregnant. There were no mirikizumab-related adverse events in mothers, foetuses, or infants followed up with 6 months after birth, and the overall incidence of embryonic/foetal loss was within the historical control data. Whilst mirikizumab was detected in all infants at 28 days after birth, the concentration in maternal milk was not assessed. There was also no evidence of an impact on fertility in monkeys administered 30 times the maximum human dose.

In the previously described clinical trials assessing mirikizumab in humans, 28 pregnancies were reported. There were three spontaneous abortions, and six elective terminations occurred. Eight infants were born without major congenital abnormalities, with one born preterm at 34 weeks [34]. The outcomes of four pregnancies were unknown, and seven were still in utero at the time of data analysis [34].

There are no data on maternal use of mirikizumab and transmission in breast milk or its impact on the infant. Given its large molecular size, it is unlikely to be excreted in large amounts in breast milk [35]; however, it is known that human immunoglobulins are excreted in breast milk early after birth, and therefore, it is possible that mirikizumab is passed into the breast milk post-partum [36]. The impact of this on the infant is unknown.

Whilst data are limited, its safety profile is expected to be similar to that of other monoclonal antibodies in IBD, and decisions should be made on a case-by-case basis after honest and clear discussions with the patient.

5.4. Safety from Real-World Evidence

The relatively short time that mirikizumab has been licenced means that there is only a small amount of real-world safety data currently available. A study presented by Lande et al. [32] at ECCO 2024 followed 17 patients with UC over a four-month period who were treated with mirikizumab and found no AE reported during this period.

In summary, with regards to safety, whilst larger real-world studies over longer time periods are still required in order to fully understand the long-term safety profile of mirikizumab, the evidence thus far available demonstrates low overall risks to patients of SAE and a comparable safety profile to ustekinumab.

6. Positioning

Targeting IL-23 and IL-12 holds an established position in the paradigm of IBD treatment through the widespread use of ustekinumab, which has been proven to be an efficacious and safe therapy. Given this, the question of when to use mirikizumab, particularly in preference to ustekinumab, remains unanswered.

The LUCENT trials previously discussed have demonstrated that mirikizumab is an effective therapy for UC, including in patients who have previously been treated with an anti-TNFα or JAK inhibitor. Sub-group analysis from these data demonstrated that in patients with one anti-TNFα failure, significantly more patients achieved clinical response at week 12 compared to placebo (64.4% vs. 34.1% $p = 0.001$), clinical remission at week 52 (44.3% vs. 17.2%, $p = 0.017$), and symptomatic remission at week 52 (63.9% vs. 34.5%, $p = 0.005$) [37]. When comparing this to a sub-group analysis of patients with previous biologic failure (32.6% of whom had failed both an anti-TNFα and vedolizumab) from the UNIFI trial, which assessed ustekinumab in UC, at week 8, 57.2% of those treated with ustekinumab achieved clinical response (vs. 27.% placebo, $p = 0.001$), and at week 44, 39.6% were in clinical remission (vs. 17% placebo, $p = 0.001$) [38]. Whilst not a direct head-to-head comparison, these data potentially suggest a slightly greater efficacy of mirikizumab in biologic-exposed patients.

Given the lack of direct comparative data, network meta-analyses (NMA) have attempted to inform on the relative superiority of AT, although to date, few have included mirikizumab. One study, performed under a Bayesian framework by Dignass et al. [39] in October 2024, compared the randomised clinical trial data from multiple currently licenced advanced therapies for UC. They compared clinical response, remission, and mucosal healing in both induction and maintenance phases and, importantly, given the known impact of a previous anti-TNFα on the efficacy of advanced therapies, sub-divided patients into biologic/JAKI naïve and biologic/JAKi exposed cohorts. In the naïve cohort, upadacitinib and infliximab were superior compared to all other therapies for clinical response and remission during induction but in the maintenance assessment, mirikizumab was found to be superior compared to anti-TNFα, vedolizumab, tofacitinib, ozanimod and upadacitinib 15 mg and comparable to ustekinumab and upadacitinib 30 mg. In those patients with previous biologic/JAKi treatment, in both induction and maintenance, upadacitinib (45 mg and 30 mg, respectively) was superior for clinical response and remission. Mirikizumab was broadly comparable to ustekinumab across both the naïve and exposed cohorts. There was no significant difference in this study when assessing SAE. An important negative point was that it did not include risankizumab in the analysis as it was not at the time licenced for UC. Ananthakrishnan et al. [40] have since produced an NMA, which included risankizumab, and found that, whilst mirikizumab and ustekinumab were similarly effective at inducing remission in UC in biologic-naïve patients, both were inferior to risankizumab regardless of previous biologic exposure. However, further NMAs or head-to-head trials are required to corroborate these findings.

With regards to CD, the VIVID-1 study suggested that when comparing clinical and endoscopic endpoints, there was a numerical trend towards a greater response with mirikizumab than ustekinumab. The study also demonstrated non-inferiority to ustekinumab when assessing clinical remission by CDAI. An NMA by Vuyyuru et al. [41], which included data from 20 clinical trials focusing on endoscopic outcomes, found that in CD, anti-TNFα agents appear to be superior, followed by JAKi and p19i, and in biologic-exposed patients, both JAKi and p19i appear to be the most effective therapies. There is a paucity of data with regard to mirikizumab in CD, and further data from RCTs, head-to-head studies, and NMAs are required before we can clearly define the positioning of mirikizumab in CD.

The lack of currently available real-world evidence also means that when deciding which treatment to use, we are reliant on NMAs, even with the known limitations, particularly with regard to the heterogeneity of study design, duration, and endpoints. Taken overall, the available data suggest that mirikizumab is an effective treatment in UC; however, it may be inferior to risankizumab, which was approved for use in UC by the Food and Drug Administration in June 2024 and the National Institute of Health and Care Excellence in the UK in August 2024, and head-to-head studies are needed.

As well as the comparative data, there are other factors that will be relevant when positioning mirikizumab such as cost and practicalities of administration. The newly licenced ustekinumab biosimilars offer significant cost savings to healthcare providers, and it may, therefore, be mandated by funding bodies that these agents are used ahead of mirikizumab. The requirement for intravenous loading adds further cost and will put additional strain on infusion suite capacity; therefore, agents that can be loaded subcutaneously, such as the guselkumab [42], may be preferred by some healthcare systems.

7. Conclusions

Mirikizumab has been shown to be efficacious for UC and CD, and it promises to be an important AT in the coming years. The reassuring safety data suggest it may be a suitable treatment for elderly patients and those with multiple comorbidities. Future areas of research include ascertaining treatment positioning in the landscape of IBD therapies and understanding its safety and efficacy in special populations, such as extreme age classes, different ethnicities, and those with multiple comorbidities. Other research areas include its potential use in advanced combination therapy regimens and identifying appropriate treatment response predictors.

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Abbreviations

Anti-TNFα	Anti-Tumour Necrosis Factor Alpha
AE	Adverse events
AT	Advanced Therapy
CD	Crohn's disease
FDA	Food and drug administration
IBD	Inflammatory bowel disease
JAKi	Janus Kinase inhibitors
MACE	Major adverse cardiovascular event
P19i	IL23 p19 Inhibitors
RCT	Randomised controlled trial
SAE	Serious adverse events
UC	Ulcerative colitis

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Review

Optimal Management of Patients with Moderate-to-Severe Inflammatory Bowel Disease

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Abstract: Inflammatory bowel disease (IBD), encompassing Crohn's disease (CD) and ulcerative colitis (UC), is a chronic and often debilitating condition requiring complex and individualized management. Over the past few decades, advancements in understanding IBD pathophysiology have led to a transformative shift in therapeutic approaches. This article provides a comprehensive overview of the evolution of IBD treatments, from early symptom-focused therapies to modern biologics, small molecule agents, and emerging treatment strategies. We discuss therapeutic goals centered on achieving clinical remission, endoscopic/mucosal healing, and enhancing patient quality of life. Additionally, we explore the rationale for the early and personalized use of biologic therapies in moderate-to-severe cases, review the current FDA-approved agents as of 2024, and highlight the advantages and limitations of these treatments. Special attention is given to the evolving role of novel oral therapies, including Janus kinase inhibitors and sphingosine-1-phosphate receptor modulators, and future new directions. This paper aims to guide clinicians in navigating the expanding therapeutic landscape of IBD, emphasizing patient-centered decision-making and addressing ongoing challenges in achieving optimal disease control.

Keywords: inflammatory bowel disease; biologic therapies; immunomodulators; dulators Janus kinase (JAK) inhibitors

1. Introduction

Inflammatory bowel disease (IBD), which includes Crohn's disease (CD) and ulcerative colitis (UC), represents a chronic and challenging condition that necessitates intricate and tailored treatment strategies. Advances in our understanding of IBD pathophysiology over recent decades have profoundly altered therapeutic paradigms. This paper examines the progression of IBD treatment approaches, tracing the shift from symptom-based therapies to modern options, such as biologics, small molecules, and other emerging strategies. We discuss key therapeutic objectives, such as achieving clinical remission, promoting endoscopic/mucosal healing, and improving quality of life for patients. The article also addresses the importance of the timely, individualized use of biologics in moderate-to-severe cases, reviews FDA-approved therapies available in 2024, and considers their respective benefits and drawbacks. Particular focus is placed on the growing role of innovative oral therapies, including Janus kinase inhibitors and sphingosine-1-phosphate receptor modulators, while future new possibilities are also considered. This article aims to support clinicians as they navigate the evolving landscape of IBD treatment, promoting patient-centered choices and addressing persistent obstacles in achieving optimal disease management.

1.1. Historical Evolution and Advancements in IBD Treatment

Inflammatory bowel disease (IBD), which encompasses both Crohn's disease (CD) and ulcerative colitis (UC), has a lengthy and complex history of treatment. Table 1 presents a chronological overview of the most significant developments in the history of IBD treatment,

including the introduction of pivotal drugs and therapeutic approaches over time. The initial therapeutic options were primarily directed towards symptom management rather than disease modification. Corticosteroids, such as prednisone, were primarily utilized due to their potent anti-inflammatory effects [1]. However, the long-term use of steroids was associated with adverse effects, including osteoporosis, steroid-induced diabetes, and an increased risk of infection. In addition to steroids, 5-aminosalicylic acids (5-ASAs), including sulfasalazine and mesalamine, constituted the primary means of managing mild-to-moderate UC. However, they proved ineffective in maintaining CD.

Table 1. Historical timeline of IBD treatments.

Year	Treatment
1979	Steroids, Sulfasalazine
1980	Antibiotics, Azathioprine, 6-MP
1993	5-ASA
1994	Budesonide
1995	Methotrexate
1998	Infliximab
2007	Second-generation anti-TNF agents
2014	New biologic agents
2015	Biosimilars
2019	Oral immunomodulators

In the 1980s, purine analogs, initially developed for the prevention of organ transplant rejection, were identified as a potential treatment for IBD. Drugs such as azathioprine and 6-mercaptopurine (6-MP) were subsequently employed extensively in maintenance therapy, particularly in the case of CD. They proved effective in preventing relapses and reducing the necessity for steroids. However, the most significant concern regarding these drugs is their adverse effects, particularly the development of lymphoma [2].

Another notable advancement was the introduction of methotrexate, an immunomodulatory agent that functions by inhibiting dihydrofolate reductase, thereby suppressing the immune system. Methotrexate was identified as a potential alternative for patients who did not respond to or could not tolerate azathioprine or 6-MP [3].

The late 1990s saw a significant advancement in the treatment of IBD with the advent of biologic therapies. In 1998, infliximab became the first biologic agent to be approved for the treatment of IBD. It targets tumor necrosis factor-alpha (TNF-α), a cytokine involved in systemic inflammation, and provides a more targeted approach, significantly improving outcomes for some patients with moderate-to-severe CD and UC who were refractory to conventional therapies. Subsequently, other anti-TNF agents, including adalimumab, certolizumab pegol, and golimumab, were incorporated into the therapeutic armamentarium [4].

As knowledge of the immune pathways involved in IBD expanded, new biologics targeting different molecules were developed. These included vedolizumab, an integrin inhibitor that selectively blocks lymphocyte trafficking to the gut, and ustekinumab, which inhibits interleukin -IL-12 and IL-23, cytokines involved in the inflammatory process. The advent of biosimilars—biologic products that are highly similar to existing biologics—has resulted in a reduction in treatment costs due to their lower price point. Biosimilars such as infliximab-dyyb and adalimumab-atto have been approved for use in IBD, offering cost-effective alternatives that do not compromise efficacy [5].

In recent years, small molecule therapies, such as Janus kinase (JAK) inhibitors and sphingosine-1-phosphate (S1P) receptor modulators, have emerged as important options for patients who are intolerant to or have failed biologic therapies. These agents offer the

convenience of oral administration and expand the therapeutic options for managing IBD. This evolution in treatment reflects a deeper understanding of IBD pathophysiology, which has led to the development of more targeted, effective, and less costly therapies. As a result, what was once a debilitating condition has become a manageable disease with a range of therapeutic options [6].

1.2. Therapeutic Goals in IBD

The management of IBD has undergone a notable evolution, shifting from a primary focus on symptom control to a more comprehensive strategy aimed at achieving deep and sustained clinical remission and even histologic healing. The primary therapeutic goals now encompass both clinical and endoscopic outcomes, with the objective of improving long-term disease control and patient quality of life [7–9].

The primary objective in the management of inflammatory bowel disease (IBD) is to achieve clinical remission, which is defined as the absence of symptoms such as abdominal pain, diarrhea, and rectal bleeding. Achieving remission frequently necessitates the administration of induction therapy with corticosteroids, biologics, or small molecules, depending on the severity of the disease. In cases of mild disease, 5-ASA agents may prove sufficient; however, in instances of moderate-to-severe disease, biologics or small molecule immunomodulators are often required.

Once remission is achieved, it is of the utmost importance to prioritize proper and long-term maintenance management. The objective of maintenance therapy is to prevent the occurrence of flare-ups and disease progression, thereby reducing the risk of complications such as strictures, fistulas, the necessity for surgical intervention, and dysplastic changes.

Based on an extensive review of the existing literature, our extensive experience, and despite extensive research with the development of various agents for the treatment of IBD, the overall clinical response and mucosal/histologic healing rates remain modest. Approximately 50–60% of patients achieve a clinical response, while clinical remission is attained in only about 30–35% of cases. These figures underscore the ongoing challenges in IBD management, emphasizing the necessity for continued research and the development of more efficacious therapies [10].

1.3. Management of Moderate-to-Severe IBD Patients

Moderate UC and CD present with more frequent symptoms and moderate inflammation but generally lack severe systemic impact. Patients with moderate UC may have up to six bloody stools per day with mild abdominal pain, while moderate CD often involves intermittent pain, diarrhea, and minimal weight loss, with only mild elevation in inflammatory markers. Severe UC and CD are characterized by frequent, intense symptoms and significant systemic involvement. In severe UC, patients experience more than six bloody stools daily, intense abdominal pain, and often deep ulcerations throughout the colon. Severe CD is marked by intense abdominal pain, significant weight loss, and complications such as strictures or fistulas, reflecting deep ulcerations, widespread inflammation often involving multiple GI segments. Severe cases in both conditions typically present with markedly elevated inflammatory markers and profound fatigue, anemia, and hypoalbuminemia. The specific scores or criteria used to stratify patients are beyond the scope of this review; however, patients are generally categorized based on these clinical, endoscopic, and biochemical characteristics [11,12].

The management of patients with moderate-to-severe IBD necessitates a more assertive and personalized approach, given the complexity and severity of the disease. A principal objective of treatment strategies is to control inflammation, prevent complications, and improve long-term positive outcomes through early and intensive therapy. For patients with moderate-to-severe IBD, the early introduction of biologics, such as anti-TNF agents, vedolizumab, ustekinumab or IL-23 inhibitors are often recommended [12–14]. A substantial body of evidence, derived from extensive experience and rigorous scientific studies, has demonstrated that the early introduction of biologics, particularly in patients

with poor prognostic factors, can result in superior outcomes, including higher rates of remission, mucosal healing, and a reduced need for surgical intervention.

The top-down approach entails initiating biologic therapy as the primary treatment option, rather than reserving it for patients who have not responded to conventional therapies. This strategy is particularly advantageous for patients with aggressive disease phenotypes, such as young patients with extensive CD or those with severe UC. Specific patient characteristics render the top-down approach an especially suitable course of action. Table 2 provides a summary of these criteria. The following table enumerates specific criteria that suggest a more aggressive approach to IBD treatment, thereby elucidating the rationale for early intervention in these patient groups [15].

Table 2. Criteria for the top-down approach in IBD.

Criteria	Rationale
Younger patients (<30 years) and early disease	Younger patients often have a more aggressive disease course and may benefit from early intensive therapy.
Significant hypoalbuminemia and persistent anemia	Hypoalbuminemia and anemia are markers of severe inflammation and poor prognosis, warranting more aggressive treatment.
Extensive anatomic involvement	Patients with extensive disease (e.g., pancolitis in UC or ileocolonic involvement in CD) are at higher risk for complications and may require early biologic therapy.
Significant extraintestinal manifestations (EIMs)	EIMs such as arthritis, uveitis, or pyoderma gangrenosum may indicate a more systemic inflammatory response, justifying early biologic use.
Severe anorectal disease	Patients with severe anorectal CD, including fistulas, abscesses, or strictures, often require aggressive treatment to prevent complications.
Deep and extensive ulcerations	Endoscopic findings of deep and extensive ulcerations are indicative of severe disease and warrant early biologic therapy.
Stricturing and/or penetrating CD	Patients with stricturing or penetrating disease are at high risk for complications, including obstruction and fistula formation, and may benefit from early intervention.
Prior surgical interventions	Patients who have already undergone surgery for IBD are at risk for recurrence and may benefit from early biologic therapy to prevent further complications.
Family history of severe CD	A family history of severe CD may suggest a more aggressive disease course, prompting earlier intervention.
Heavy smokers	Smoking is a well-known risk factor for more severe CD, and smokers may benefit from more aggressive treatment.

In cases where a patient does not respond to or loses response to a specific biologic, switching to a different biologic with a distinct mechanism of action (e.g., from an anti-TNF to an integrin inhibitor, IL-12/23 inhibitor, or IL-23 inhibitor) may prove an effective course of action. Small molecule immunomodulator therapies, such as JAK inhibitors or S1P modulators, provide additional options for younger patients with IBD who have not responded to biologics. These agents provide a distinct mechanism of action and

may prove efficacious in patients with refractory disease. In certain instances, surgical intervention may be imperative and should not be postponed for patients with intractable disease, particularly those with complications such as strictures, fistulas, or abscesses. It should be noted that surgical intervention is not a curative measure; however, it can be an integral component of a comprehensive management strategy for select patients with CD, particularly those with Crohn's ileitis.

1.4. FDA-Approved Agents in 2024

As of 2024, the landscape of treatments for IBD has expanded significantly, with a wide range of drugs approved by the Food and Drug Administration (FDA) offering targeted, individualized treatment options for patients with varying disease phenotypes and severities. Table 3 presents a list of medications that have been approved by the FDA for the treatment of IBD.

Table 3. FDA-approved IBD therapeutic options in 2024.

Category	Agents
Anti-TNF Agents	Infliximab for UC and CD, Adalimumab for UC and CD, Certolizumab for CD, Golimumab for UC
Biosimilars	Biosimilars for UC and CD
Integrin Inhibitors	Vedolizumab for UC and CD, Natalizumab for CD
Anti-IL 12/23 Agents	Ustekinumab for UC and CD
Anti-IL-23 Agents	Risankizumab for CD and UC, Mirikizumab for UC, Guselkumab for UC
Oral Immunomodulators	Tofacitinib for UC, Ozanimod for UC, Upadacitinib for UC and CD, Etrasimod for UC

2. Biologic Therapies

2.1. Anti-TNF Agents

Infliximab is a chimeric monoclonal antibody targeting TNF-α that has been approved for both CD and UC. This has been a transformative treatment for patients with moderate-to-severe disease [16].

Infliximab was the inaugural biologic therapy to be approved for the treatment of CD. It is a chimeric antibody, derived from mice, administered intravenously over a period of 2–3 h. The initial treatment regimen comprises three infusions over a six-week period, followed by maintenance doses every two months in the event of significant improvement [16,17].

Although infliximab is generally well tolerated, infusion reactions have been documented on rare occasions. Given the pivotal role of tumor necrosis factor (TNF) in the immune system, the use of infliximab and analogous biologics may elevate the risk of infections such as tuberculosis and hepatitis B. Consequently, patients must undergo screening for these infections prior to initiating treatment, and live vaccines should be avoided throughout the course of therapy [17].

Adalimumab is a fully human monoclonal antibody against TNF-α which has also been approved for both CD and UC. Adalimumab provides the advantage of subcutaneous administration, which is more convenient for patients than intravenous infliximab [18].

Following an initial loading dose, administered in two injections over a period of two weeks, the maintenance dose is administered every other week [19]. This medication is generally well tolerated, with the most frequent adverse effect being localized cutaneous reactions at the injection site, such as pruritus, erythema, or edema. Adalimumab may also be an effective alternative for individuals who have not responded to or are unable to tolerate infliximab [10].

The secondary loss of response with both infliximab and adalimumab is very important due to immunogenicity that varies between 35 to 70% depemdent on the length of maintenance therapy.

Certolizumab pegol is a subcutaneous and pegylated humanized anti-TNF antibody fragment that has been approved for the treatment of CD. Pegylation serves to diminish the immunogenicity of the drug and extend its half-life [20].

In 2008, the United States Food and Drug Administration (FDA) approved the use of this medication for the treatment of moderate-to-severe CD in patients who have not responded adequately to conventional therapies. Certolizumab is administered via subcutaneous injection, with two doses administered over a two-week period, followed by monthly injections for maintenance. It has been demonstrated to be an efficacious treatment for inducing and maintaining remission in CD, with a comparable safety profile to that of infliximab and adalimumab. In some patients who are unable to tolerate other TNF alpha agents, this medication can be effective [10].

Golimumab is approved for UC; golimumab is another subcutaneous anti-TNF agent that offers flexibility in treatment regimens [21].

The main side effects include nasopharyngitis, pharyngitis, laryngitis, rhinitis, and tuberculosis reactivation [22].

2.2. Biosimilars

The advent of biosimilars for infliximab (e.g., infliximab-dyyb and infliximab-abda) and adalimumab (e.g., adalimumab-atto) has facilitated broader access to biologic therapies, offering cost-effective alternatives that do not compromise efficacy or safety. The availability of these agents is contributing to a reduction in healthcare costs and an increase in treatment accessibility for a broader patient population.

These FDA-approved agents provide clinicians with a toolkit that allows them to customize treatment plans to the specific needs and circumstances of each patient. Biosimilars are supported by the majority of insurance companies in Europe and, recently, in the United States. The Biologic Price Competition and Innovation Act was enacted as part of the Affordable Care Act in 2010 [23–25].

2.3. Integrin Inhibitors

Natalizumab, an α4 integrin inhibitor, was initially approved by the FDA for the treatment of CD. Subsequently, this very effective drug was withdrawn from the market due to an increased risk of progressive multifocal leukoencephalopathy [26]. The half-life of natalizumab is prolonged, with the maximum concentration achieved one to two hours following intravenous administration. The terminal half-life is between 10 and 11 days, necessitating administration every four weeks [22].

Vedolizumab is an α4β7 integrin inhibitor that selectively targets the gut, reducing inflammation without the adverse effects associated with systemic immunosuppression. This relatively most safest biologic agent has been approved for both CD and UC and has been shown to be particularly beneficial for patients at high risk of infection. Although there is a theoretical risk of progressive multifocal leukoencephalopathy (PML) due to its potential effect on lymphocyte trafficking to the brain, there have been no reported cases of PML associated with its use at this time [27].

Although vedolizumab is slower to take effect than natalizumab, peak levels are reached within 1–2 h after infusion. The terminal half-life is considerably longer, at approximately 25 days, thereby enabling administration at 8-week intervals [13,28].

2.4. Interleukin Inhibitors

Ustekinumab targets interleukin-12 and interleukin-23, which are cytokines that are involved in the immune response. It has been approved for both CD and UC, offering a novel mechanism of action for patients who have not responded to anti-tumor necrosis factor (anti-TNF) therapy [29]. Ustekinumab is a fully human IgG1k monoclonal antibody that

binds to the p40 subunit of IL-12/23. It inhibits the binding of IL-12 and IL-23 to IL-12Rb1, thereby preventing the initiation of downstream signaling cascades and the production of cytokines. The U.S. Food and Drug Administration (FDA) has granted approval for ustekinumab for the treatment of psoriasis, Crohn's disease, and ulcerative colitis.

Ustekinumab is administered intravenously (IV) for induction therapy at a dose of 6 mg/kg, followed by maintenance with 90 mg subcutaneously (SC) every 8 weeks.

In patients with refractory CD, ustekinumab demonstrated a clinical response rate of 49% at week 22, which was significantly higher than the 27% observed in the placebo group [29,30].

Following the induction phase, maintenance therapy resulted in 60% of patients achieving clinical remission at one year and 51% maintaining remission after five years [28]. Furthermore, ustekinumab exhibited superior efficacy compared to vedolizumab in patients with refractory CD. However, the healing of perianal fistulas with this very expensive biologic agent was limited to 28% [31].

In patients with moderate-to-severe UC, ustekinumab demonstrated superior efficacy compared to placebo for both induction and maintenance therapy, with response rates of 62% and 31%, respectively [14].

Rare but serious side effects include reversible posterior leukoencephalopathy syndrome (RPLS), characterized by symptoms such as headache, confusion, and vision changes, along with an increased risk of infections [30,32]

Risankizumab and *Mirikizumab* are humanized monoclonal antibodies that selectively target the p19 subunit of IL-23, thereby inhibiting the production of IL-17, TNF-alpha, IL-21, and INF-gamma.

The phase 3 ADVANCE and MOTIVATE trials were conducted to assess the efficacy of risankizumab as an induction therapy for patients with moderately to severely active CD. Patients were administered either 600 mg or 1200 mg of intravenous risankizumab or placebo at weeks 0, 4, and 8. The results of the trials demonstrated that both doses of risankizumab resulted in a significantly greater improvement in clinical remission and endoscopic response compared to placebo at week 12. In the ADVANCE trial, the clinical remission rates were 45% with 600 mg of risankizumab and 42% with 1200 mg, in comparison to 25% with placebo. Endoscopic response rates were 40% and 32% with 600 mg and 1200 mg of risankizumab, respectively, in comparison to 12% with placebo. The results of the MOTIVATE trial were comparable, with risankizumab demonstrating consistent efficacy in patients who had previously failed to respond to other biologic therapies. Risankizumab was generally well tolerated across both trials [33].

In a head-to-head clinical trial comparing risankizumab and ustekinumab in patients with moderate-to-severe CD who had previously failed anti-TNF therapy, risankizumab demonstrated superior efficacy. By week 24, 58.6% of patients treated with risankizumab achieved clinical remission, compared to 39.5% of those treated with ustekinumab. At week 48, risankizumab was also more efficacious in achieving endoscopic remission, with 31.8% of patients exhibiting improvement versus 16.2% in the ustekinumab group. Both drugs exhibited comparable safety profiles, although risankizumab demonstrated a slightly lower incidence of serious adverse events. In conclusion, risankizumab proved to be a more efficacious agent for inducing and maintaining remission in CD [33–36].

The main side effects of risankizumab include upper respiratory tract infections, headaches, and injection site reactions. Serious adverse events, though rare, may include severe infections and hypersensitivity reactions, and there is an observed risk of malignanciessuch as cutaneous basal and squamous cell carcinoma [37].

Mirikizumab was administered with an intravenous loading dose of 300 mg at weeks 0, 4, and 8, followed by a subcutaneous dose of 200 mg every 4 weeks. In patients with moderately to severely active ulcerative colitis, the clinical remission rate was 24.2% at week 12, compared to 13.3% with placebo. At week 40, the remission rate was 49.9% with the drug and 25.1% with placebo for maintenance therapy. Additionally, the drug

demonstrated favorable outcomes in terms of endoscopic remission and bowel urgency, with a low incidence of adverse events, including headache and nasopharyngitis [38].

Both agents demonstrated efficacy in patients who had previously failed therapy targeting tumor necrosis factor (TNF) as well as in patients who had not yet received TNF-targeting therapy. The incidence of adverse events was low, with the most commonly reported being headache, arthralgia, upper respiratory tract infections, and hepatotoxicity [33–36].

Guselkumab is an interleukin-23p19 subunit antagonist that works by inhibiting the binding of IL-23to its receptor on the cell surface. IL-23 plays a critical role in the pathogenesis of inflammatory bowel diseases like UC by promoting cytokine production and immune system activation. By blocking this interaction, guselkumab helps reduce inflammation and the immune response in the gut, which is beneficial for patients with moderate-to-severe UC. Recently, the FDA approved guselkumab for the treatment of moderately to severely active ulcerative colitis.

The QUASAR phase 2b study evaluated the efficacy and safety of guselkumab, in patients with moderately to severely active UC. The double-blind, placebo-controlled trial randomized patients to receive either 200 or 400 mg of intravenous guselkumab or placebo. The primary endpoint, clinical response at 12 weeks, was significantly higher in the guselkumab groups compared to placebo, with improvements also observed in clinical remission, symptomatic remission, endoscopic improvement, and histo-endoscopic mucosal healing. Safety profiles were comparable across all groups, and guselkumab showed promise as a safe and effective treatment for UC [39].

The VEGA study was a randomized, double-blind, phase 2 trial aimed at assessing the efficacy of combination therapy with guselkumab and golimumab compared to monotherapy with either drug in patients with moderately to severely active ulcerative colitis. The trial involved 214 participants and measured clinical response at 12 weeks, with results showing that 83% of patients in the combination group achieved clinical response compared to 61% and 75% in the monotherapy groups. While the combination therapy demonstrated promising efficacy, it did not meet the predefined statistical significance criteria for clinical remission compared to guselkumab alone. The most common adverse events included ulcerative colitis exacerbation, upper respiratory infections, and headaches, with no deaths or cases of malignancy reported during the induction period. The findings suggest that guselkumab and golimumab combination therapy may provide enhanced clinical responses in UC treatment, warranting further investigation in larger studies [40].

The DUET-CD and DUET-UC trials are ongoing phase 2b studies that are randomized, double-blind, and placebo-controlled, involving patients with moderate-to-severe active CD and UC, respectively. Participants are assigned to one of six groups, which include guselkumab, golimumab, and JNJ-78934804 (a combination of guselkumab and golimumab) at high, mid, and low doses, as well as a placebo group. The primary objective is to evaluate clinical remission and endoscopic response across treatment groups at week 48 [41,42].

Recently, the FDA approved guselkumab for the treatment of moderately to severely active UC. Active and promising trials are pending in patients with moderate-to severe CD.

3. Oral Small Molecule Therapies

3.1. Janus Kinase (JAK) Inhibitors

Tofacitinib is an oral, rapidly acting Janus kinase (JAK) inhibitor that primarily targets JAK1 and JAK3, and which has been approved for the treatment of UC. It provides an alternative to biologics for patients who have failed to respond to other treatments, particularly for those who prefer oral administration. However, its use necessitates meticulous observation due to the potential for adverse effects, including thromboembolism and an elevated risk of herpes zoster infection [43,44].

Phase 3 studies (Octave) demonstrated the efficacy of the treatment in achieving higher rates of clinical remission in patients with UC, both in the induction (8 weeks) and maintenance (52 weeks) trials [45]. A meta-analysis substantiated the efficacy of the treatment in patients with refractory UC s while also demonstrating a favorable safety profile [46]. A comparative analysis of tofacitinib and vedolizumab in patients with UC who had failed to respond to anti-TNF therapy revealed that tofacitinib demonstrated superior efficacy with comparable safety profiles, thereby establishing it as a promising therapeutic alternative for UC [47].

A recent meta-analysis revealed that tofacitinib markedly enhanced health-related quality of life across a range of domains, including bowel symptoms (diarrhea, abdominal discomfort), systemic symptoms (fatigue), emotional function (decreased anxiety, depression), and social function (enhanced participation in daily activities). Tofacitinib demonstrated the greatest efficacy in improving health-related quality of life during the maintenance phase, underscoring its capacity to sustain long-term quality of life enhancements for patients with UC [48]. However, over 65 years patients who already have an increased cardiovascular diseases, especially smokers, tofacitinib is not a safe treatment option. *Upadacitinib* is a selective JAK1 inhibitor with a relatively favorable adverse event profile. The drug has demonstrated efficacy in both CD and UC [49]. Sandborn et al. demonstrated that upadacitinib was more efficacious than a placebo in patients with UC during the induction period. However, the study also revealed that upadacitinib induced elevations in serum lipid levels and creatine phosphokinase [44,50].

In a phase 3 study, the group receiving upadacitinib demonstrated significantly superior clinical improvement compared to the placebo group, both during the induction and maintenance phases in patients with moderate-to-severe UC [51].

The most commonly reported adverse effects were increased creatine phosphokinase levels -not clinically significant-, nasopharyngitis, and acne [44,51].

A recent multicenter retrospective study, which included 31 patients diagnosed with UC or CD, demonstrated that treatment with upadacitinib following prior tofacitinib therapy resulted in substantial clinical improvements. In patients with UC, upadacitinib not only provided substantial symptom relief but also resulted in a notable reduction in inflammatory markers. These findings underscore the efficacy of upadacitinib as a viable treatment option for UC, particularly in instances where tofacitinib proved to be either ineffective or poorly tolerated [52].

A recent meta-analysis has compared the efficacy of various biologics and small molecule therapies in the treatment of UC by focusing on patient-reported outcomes and health-related quality of life. The data from the 54 studies demonstrated that upadacitinib exhibited the highest efficacy in achieving clinical remission based on patient-reported outcomes, including stool frequency and rectal bleeding, during both the induction and maintenance phases [48].

The use of JAK inhibitors, such as upadacitinib and tofacitinib, may be beneficial for treating refractory ulcerative colitis (UC) and acute severe UC in patients unresponsive to standard treatments and biologics. A recent study demonstrated successful remission with upadacitinib following multiple treatment failures, highlighting JAK inhibitors as promising options for achieving remission in challenging cases [53].

3.2. Sphingosine-1-Phosphate (S1P) Receptor Modulators

Ozanimod is an oral agonist of the S1P1 and S1P5 receptors and has been approved for the treatment of UC. The drug reduces lymphocyte trafficking to the gut, thereby decreasing inflammation. The oral administration of the drug and its favorable safety profile make it a compelling option for especially younger patients with UC. Ongoing research trials are currently underway to assess the efficacy of this treatment in patients with moderate-to-severe CD [44,54–56].

Given the involvement of S1P signaling in cardiovascular functions, the use of S1PR1 modulators such as ozanimod may potentially result in the occurrence of cardiac side effects, including bradycardia and atrioventricular block [57].. Ozanimod has been demonstrated to be an efficacious treatment for moderate-to-severe UC, both during the induction phase (8–10 weeks) and the maintenance phase (24–52 weeks). This resulted in a higher rate of clinical remission compared to the placebo [54,58]. The most commonly observed adverse effects were mild elevations in liver enzymes, respiratory infections, and headaches. However, these were generally not severe enough to result in treatment discontinuation. In conclusion, ozanimod is regarded as an efficacious and well-tolerated therapeutic option for the management of UC [58,59].

A recent analysis demonstrated the efficacy of ozanimod in the treatment of patients with moderate-to-severe UC who had not yet received advanced therapies, including biologics and Janus kinase inhibitors. Improvements were observed as early as week 2, with significant differences evident by week 4. By week 10, 23% of patients receiving ozanimod had achieved clinical remission, compared to just 6.6% of those receiving the placebo. At week 52, 41.4% of patients remained in remission, and this continued into the open-label extension, where 91% maintained a clinical response through week 94. The safety profile was comparable to that observed in previous studies, with mild infections and elevations in liver enzymes being the most frequently reported adverse effects. In conclusion, ozanimod demonstrated a robust and sustained efficacy in these patients, establishing it as a promising early intervention before the introduction of more advanced therapeutic modalities [60].

Etrasimod is a S1P1 receptor modulator that offers comparable advantages to ozanimod and may provide an additional efficacious oral alternative for patients' management with UC. Clinical trials are currently underway to evaluate the efficacy and safety of this treatment in patients with moderate-to-severe CD [61].

In the phase 2 Oasis trial, treatment with 2 mg of etrasimod resulted in significantly greater improvements in modified Mayo Clinic scores compared to placebo after 12 weeks, with only mild adverse effects reported [46]. Furthermore, the open-label extension of the Oasis study, conducted over a period of 52 weeks, corroborated the favorable safety profile of 2 mg of etrasimod in patients with UC [61].

The ELEVATE trials built upon the findings of the earlier Oasis trial by providing long-term data on the efficacy and safety of etrasimod in the treatment of moderate-to-severe UC. While the Oasis trial demonstrated short-term benefits over a 12-week period, the ELEVATE trials evaluated both the induction and maintenance phases. The ELEVATE UC 52 trial, in particular, extended to 52 weeks and demonstrated sustained clinical remission. Furthermore, detailed endpoints, such as endoscopic and histological improvement, were assessed, thereby underscoring etrasimod's capacity to maintain remission and its favorable safety profile in a more expansive patient population [62].

4. Choice of First IBD Therapy

The selection of the initial therapeutic intervention in IBD represents a pivotal decision that has the potential to markedly influence the disease trajectory and overall quality of life of the patient. A reliable serologic biomarker for IBD patients is currently lacking. In light of the aforementioned considerations, it is not surprising that this is a frequently posed question by the community of gastroenterologists seeking guidance on the optimal initial treatment option. The decision-making process is influenced by a number of factors, including the severity of the disease, the location and extent of the inflammation, the patient's comorbidities, and the presence of extraintestinal manifestations. In practice, we utilize IBD disease modifiers and the corresponding recommended first-line treatment options, as predicted in Table 4. Furthermore, patient preferences, potential adverse effects, and cost are additional factors that contribute to the determination of the most appropriate initial management strategy [12,44,63,64].

Table 4. Common disease modifiers and recommended first-line therapy options.

Disease Modifier	First Treatment Choice	Reason
IBD and Pregnancy	Anti-TNFs, Vedolizumab	Fewer Adverse Effects: These drugs have a well-established safety profile during pregnancy.
IBD in Elderly Patients (>60 y/o)	Vedolizumab, Ustekinumab, Anti-IL-23s	Lower Infection Risk: These agents have a favoralesafety profile, particularly in reducing infection risks.
IBD and Malignancy History (e.g., Lymphoma)	Vedolizumab, Ustekinumab, Anti-IL-23s	Safer Profile: These agents are associated with a lower risk of malignancy compared to TNF inhibitors.
IBD and Psoriasis	Ustekinumab	Combined Effect: Effective for both IBD and psoriasis, making it a dual-purpose treatment.
IBD and Multiple Sclerosis (MS)	Ozanimod	Effective in treating both conditions.
IBD and Low Albumin Levels	Tofacitinib, Upadacitinib, Ozanimod, Etrasimod	on-alb-dependent: These therapies are effective without needing albumin for drug transport.
CD with Perianal Involvement	Anti-TNF (e.g., Infliximab, Adalimumab), Ustekinumab	Best Studied: Anti-TNFs have the most evidence supporting their efficacy in treating perianal CD.

4.1. New Oral Agents in Development

The landscape of IBD treatment has undergone a notable transformation with the advent of new oral agents, offering more efficacious and patient-centric alternatives. These innovative therapeutic agents are designed to target specific pathogenic pathways involved in the development of IBD. They offer distinct advantages over traditional treatments, particularly for patients who prefer oral administration or are intolerant to injectable therapies.

4.2. Janus Kinase (JAK) Inhibitors

Itacitinib is a selective JAK1 inhibitor that has demonstrated potential for future therapeutic applications in the treatment of immune-mediated diseases. The clinical trials investigating the efficacy of this agent in patients with IBD are still ongoing [44].

Ritlecitinib and *brepocitinib* are oral inhibitors targeting JAK3/TEC and TYK2/JAK1, respectively. Both have demonstrated efficacy in the treatment of immune-mediated inflammatory conditions and are currently being investigated for their potential use in the management of IBD.

A phase 2b randomized, double-blind, placebo-controlled study was conducted to evaluate the efficacy and safety of these two oral agents as induction therapies over an eight-week period. Both ritlecitinib and brepocitinib demonstrated a dose-dependent improvement in total Mayo scores, with higher doses resulting in a greater reduction compared to the placebo. The primary endpoints, including clinical remission, endoscopic improvement, and histologic remission, demonstrated statistically significant positive outcomes with both drugs. Furthermore, the study demonstrated that both agents were well tolerated, with the majority of adverse events being mild or moderate. Infections were the most commonly observed adverse event, though no cases of herpes zoster were reported to be serious. In conclusion, both drugs demonstrated promising efficacy and acceptable short-term safety profiles. However, further long-term studies are necessary to fully understand their benefit–risk profiles for the management of UC patients [65].

Deucravacitinib is a novel orally administered TYK2 inhibitor that selectively targets the TYK2 enzyme without significantly affecting JAK1-3.

The phase 2 LATTICE-UC study was conducted to evaluate the efficacy and safety of deucravacitinib in patients with moderately to severe UC who had an inadequate or

lost response to previous therapies. In this 12-week, double-blind study, 131 patients were randomly assigned to receive either deucravacitinib (6 mg twice daily) or placebo. The primary endpoint was clinical remission, yet the study did not achieve its primary or secondary endpoints. Notably, in patients who had previously undergone biologic therapy, clinical remission rates were higher with deucravacitinib (16.1%) than with the placebo (0%). Notwithstanding the numerical enhancements in symptomatic Mayo scores, the results remained statistically insignificant. The majority of adverse events were mild to moderate, and further trials are required to investigate the potential for higher doses [66].

4.3. Sphingosine-1-Phosphate (S1P) Receptor Modulators

Amiselimod is an oral selective modulator of the S1P1 receptor that has demonstrated promising results in the treatment of UC, with a rapid onset of action and only mild side effects. Amiselimod has demonstrated efficacy in reducing T-helper cell infiltration in chronic colitis models, thereby suggesting its potential as a treatment option for UC.

The objective of the phase II study was to assess the safety and efficacy of Amiselimod in patients with moderate-to-severe CD. Over a 14-week period, 78 participants were randomly assigned to receive either the investigational drug, Amiselimod (0.4 mg), or a placebo. The primary objective was to achieve a 100-point reduction in the Crohn's Disease Activity Index (CDAI) by week 12. Although Amiselimod was generally well tolerated, with the majority of adverse effects being mild to moderate, it did not demonstrate superior efficacy compared to the placebo in achieving clinical response or remission. No new safety concerns were identified during the course of the trial [67].

4.4. Oral Integrin Inhibitors

The migration of lymphocytes to the gut mucosa represents a pivotal element in the pathogenesis of IBD. Chemokines and selectins play a pivotal role in this process, facilitating the adhesion of T cells to endothelial cells. Recently, novel small molecule oral therapeutic agents for the management of IBD patients have been developed that specifically target adhesion molecules. Examples of such agents include AJM300, PN-943, and MORF-057.

AJM300 is a gut-restricted antagonist of the α4 integrin subunit that prevents the binding of α4β7 and α4β1 integrins on T cells to adhesion molecules, thereby inhibiting lymphocyte migration into the gut. Although AJM300 theoretically carries a risk of PML due to its potential impact on lymphocyte trafficking to the brain, there have been no documented cases of PML associated with its use to date. In light of the currently available evidence, AJM300 appears to be a promising new treatment option for inducing remission in patients with moderately active UC, pending further studies with long-term results [44].

PN-943 is a small molecule that functions as an integrin antagonist by blocking the α4β7 receptor, with its effects largely confined to the gut. PN-943 is an oral small molecule that functions as an integrin antagonist by blocking the α4β7 receptor, with its effects largely confined to the gut. In a recent phase 2 study, which was double-blind, placebo-controlled, and conducted across multiple centers over 12 weeks, PN-943 demonstrated superior clinical remission rates compared to placebo in patients with ulcerative colitis, while exhibiting minimal adverse effects. A phase 3 trial for this promising oral therapy has yet to be conducted. [44,68].

MORF-057 is another oral small molecule that inhibits the α4β7 receptor. The phase 2a open-label study evaluated the safety, tolerability, pharmacokinetics, and efficacy of MORF-057 in patients with moderately to severe UC. Thirty-five patients received 100 mg twice daily for 12 weeks, with 89% completing the induction period. The primary endpoint, a reduction in the Robarts Histology Index (RHI), was met with a significant decrease of −6.4 points ($p = 0.0019$). Additionally, 25.7% of patients achieved clinical remission, and 45.7% saw a clinical response. Pharmacokinetic analysis confirmed >99% receptor occupancy at week 12. The treatment was well tolerated, with low rates of treatment-

emergent adverse events, primarily UC exacerbation and anemia. Ongoing trials are underway to further assess efficacy and determine optimal dosing [69].

4.5. Oral IL-23 Receptor Blocker

JNJ-2113 is a first-in-class orally administered peptide that has been specifically designed to inhibit the IL-23 receptor, a key regulator in the activation of T cells in patients suffering from moderate-to-severe dermatological, rheumatological, and gastroenterological conditions driven by IL-23. Recent research has established the pharmacodynamic efficacy of JNJ-2110 through the use of both in vitro and ex vivo models involving rat colon tissue, as well as in vitro studies utilizing human colon explants and biopsies obtained from healthy volunteers. Similarly, JNJ-2113 has demonstrated in vitro activity in human colon explants. These findings are of great significance in advancing JNJ-2113 as a potential therapeutic agent for the treatment of IBD [70].

Following the demonstration of a notable impact with this agent in adults with moderate-to-severe plaque psoriasis, a phase 2 study was initiated to assess the safety and efficacy of JNJ-2113 in comparison with a placebo in patients with moderate-to-severe UC [71].

4.6. Oral TNF Agents

TL1A is a member of the tumor necrosis factor (TNF) family. TL1A interacts with its receptor, death receptor 3 (DR3), thereby influencing a number of cell lineages. ABX464, a prototype of TL1A, is an oral small molecule that modulates a specific microRNA, leading to the downregulation of proinflammatory cytokines and TH17+ cells [44]. In a phase 2b trial involving 254 patients with UC, ABX464 demonstrated significant efficacy in inducing clinical remission at daily doses of 25 mg, 50 mg, and 100 mg. These results were achieved without any major adverse events, and the drug demonstrated superior efficacy compared to a placebo [72,73].

A phase 2b trial was conducted to assess the efficacy and safety of *ABX464* = a small molecule that upregulates miR-124 in immune cells, in patients with moderate-to-severe UC. The study involved 254 patients, who were assigned to receive one of three doses of ABX464 (100 mg, 50 mg, or 25 mg) or a placebo. The results at week 8 demonstrated a notable improvement in the Modified Mayo Score in all ABX464 groups in comparison to the placebo, thereby indicating the efficacy of the drug in reducing disease severity. Furthermore, the rates of clinical response, clinical remission, and endoscopic improvement were higher in the ABX464 groups. The most commonly reported adverse effects were headaches, with dose-dependent adverse effects. The long-term 48-week open-label extension demonstrated sustained or improved efficacy, supporting the potential of ABX464 as a therapeutic option for patients with UC [44,73].

Verification of TL1A's antifibrotic effects in human trials could prove particularly beneficial for patients with CD and other conditions. GSK298772, a promising oral small molecule targeting TL1A, has shown very encouraging results in a recent study, particularly in terms of safety and dosing, with further research on this agent ongoing [74].

It is noteworthy that a number of crucial parenteral TL1A agents are currently in development. The preliminary investigations into the parenteral TL1A agents demonstrated their efficacy in IBD patients, with only minor adverse effects. Furthermore, these agents have been shown to possess genetic biomarkers and may also reduce the formation of strictures by decreasing fibroblast activity and the deposition of collagen [75].

RVT-3101 is a monoclonal antibody that targets TL1A, preventing its interaction with DR3 and thereby reducing inflammation. In a phase 2a trial, RVT-3101 demonstrated notable improvements in clinical remission and endoscopic healing in patients with UC, with a favorable safety profile [76]. The drug is currently being investigated further in phase 2b/3 trials for both UC and CD.

PRA-023 is a TL1A inhibitor that competitively inhibits the TL1A/DR3 interaction, thereby reducing inflammatory activity in the gut. PRA-025 is currently in the early

stages of clinical development, with preclinical studies indicating robust anti-inflammatory activity. Phase I clinical trials are currently being conducted to evaluate the safety and efficacy of the drug in patients with moderate-to-severe UC and CD [77].

It is our contention that oral small molecule agents will play a significant role in the management of patients with moderate-to-severe IBD. These FDA approved or investigational promising oral agents offer several advantages over traditional biologics, including the convenience of oral administration, their rapid onset of action, and the potential for more targeted control of inflammation with fewer adverse effects. Furthermore, these agents offer flexibility in combination with other therapies, rendering them suitable for the management of complex severe cases of IBD. Furthermore, these agents are more efficacious in patients with marked hypoalbuminemia and exhibit minimal immunogenicity, rendering them appealing alternatives for long-term management, as detailed in Table 5.

Table 5. Advantages of oral small molecule agents in the management of patients with IBD.

Ease oral intake
Comparatively much cheaper
Predictable pharmacokinetic studies
Durable effectiveness comparable with biologics
Fast-on action and fast-off outcome
No immunogenicity
Effective in IBD patients with significant hypoalbuminemia
Potential for combination treatment with biologic agents

5. Limitations

While this paper provides an overview of the current therapeutic landscape for moderate-to-severe IBD, several limitations should be acknowledged. First, the rapidly evolving field of IBD treatment means that new therapies and evidence emerge frequently; thus, some of the information presented here may soon be supplemented by newer findings. Additionally, although we discuss various therapeutic options, the response to IBD treatments remains highly individualized, with variability influenced by genetic, environmental, and microbiome-related factors that are beyond the scope of this review. Furthermore, while we highlight the promise of novel treatments such as emerging oral therapies, the long-term safety and efficacy of these options require further research and validation in large, diverse patient populations. Finally, the focus of this paper on clinical management limits our discussion of economic factors, healthcare accessibility, and patient-reported outcomes, which are important components in achieving optimal patient-centered care in IBD management.

6. Conclusions

The management of moderate-to-severe inflammatory bowel disease has transformed significantly over the past few decades, with advancements in targeted therapies and a more personalized approach to treatment. Current strategies focus not only on alleviating symptoms but also on achieving sustained clinical remission, endoscopic/mucosal healing, and enhanced patient quality of life. The availability of biologics, small molecule therapies, and the promise of novel treatments offer a diverse array of options for clinicians to tailor therapy to individual patient needs. Despite these advancements, achieving optimal disease control remains challenging, and further research is needed to refine treatment protocols, improve long-term outcomes, and reduce the burden of inflammatory bowel disease on patients' lives. The future of inflammatory bowel disease management lies in continued innovation, addressing unmet needs, and ensuring accessibility to effective therapies, ultimately working toward transforming inflammatory bowel disease from a debilitating condition to a manageable one.

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Review

Common Mistakes in Managing Patients with Inflammatory Bowel Disease

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Abstract: Introduction: Errors are very common in medical practice and in particular, in the healthcare of patients with inflammatory bowel disease (IBD); however, most of these can be prevented. **Aim:** To address common errors in the management of IBD. **Methods:** Our approach to this problem consists in identifying mistakes frequently observed in clinical practice (according to our experience) in the management of patients with IBD, then reviewing the scientific evidence available on the subject, and finally proposing the most appropriate recommendation for each case. **Results:** The most common mistakes in the management of IBD include those related to diagnosis and differential diagnosis, prevention, nutrition and diet, treatment with different drugs (mainly 5-aminosalicylates, corticosteroids, thiopurines, and anti-TNF agents), extraintestinal manifestations, anemia, elderly patients, pregnancy, and surgery. **Conclusions:** Despite the availability of guidelines for both disease management and preventive aspects of IBD care, a considerable variation in clinical practice still remains. In this review, we have identified common mistakes in the management of patients with IBD in clinical practice. There is a clear need for a greater dissemination of clinical practice guidelines among gastroenterologists and for the implementation of ongoing training activities supported by scientific societies. Finally, it is desirable to follow IBD patients in specialized units, which would undoubtedly be associated with higher-quality healthcare and a lower likelihood of errors in managing these patients.

Keywords: Crohn's disease; ulcerative colitis; inflammatory bowel disease; mistake; error; misconception

1. Introduction

In daily clinical practice, constant decision making is a necessity, and each decision is susceptible to potential errors [1–5]. Mistakes are very common in clinical practice, but importantly, most of them can be prevented. Over two decades ago, the Institute of Medicine released a groundbreaking report titled "To Err is Human: Building a Safer Health System", revealing that approximately 100,000 Americans die annually from preventable errors in hospitals [6]. This publication significantly altered the discourse on healthcare quality, reshaping perceptions of care quality, garnering interest from payers and employers in enhanced care and patient safety, and prompting substantial increases in research support [5].

It is not our intention to address the topic of safety or the analysis of types of errors, although every doctor should be familiar with the fundamental literature on this subject [1–5]. However, it is worth recognizing that a good review of knowledge can have an impact (prevention) on certain human errors. Some errors (rule-based mistakes) arise from automatically applying a learned rule, either because it is not appropriate in a specific situation or because it is fundamentally flawed. The other type of error can stem from simple ignorance. In fact, historically, medical errors have often been attributed to unawareness. However, the rapid expansion of knowledge poses a new challenge: information overload.

It is acknowledged that some degree of variation is inherent in medicine due to its dual nature as both art and science [7]. However, in many instances, current care processes surpass the anticipated levels of natural variation, potentially indicating suboptimal overall care [7]. When faced with the same set of facts, different healthcare providers often make different diagnoses and prescribe different therapies [7–9]. The wide variations in practice may stem from the need for more evidence, the possibility of multiple equally effective approaches, or the insufficient consolidation and dissemination of existing evidence through guidelines [10]. Despite the widespread availability of guidelines and protocols, marked variation persists across all medical fields, reflecting poor quality of care [7,11,12].

In gastroenterology, inflammatory bowel disease (IBD)—including both Crohn's disease (CD) and ulcerative colitis (UC)—is particularly prone to deviations from guidelines and notable variations in care processes [10,13–19]. There are at least two factors that establish IBD as a target for variation: (1) the presentation of IBD is heterogeneous, and the multiple presentations of the disease mandate different diagnostic and therapeutic approaches; and (2) the treatments for IBD are varied, and new treatments are always being developed and disseminated [7]. Significant variations in IBD care create a need for better information dissemination, and identifying factors predicting extremes in resource utilization may aid in targeting areas requiring improved knowledge or additional education [7].

While, in general, a consensus exists on diagnostic decision making in IBD, substantial variation persists in therapeutic decisions [7]. Specialist IBD clinics generally provide superior care, but even in these settings, a relevant minority of patients may not meet certain criteria [20]. Vignette surveys measuring decision-making variations highlight disparities between community gastroenterologists and IBD experts, emphasizing the need for further investigations into practice patterns [10]. Additionally, some studies reveal that patients with IBD who are referred for a second opinion often have not received previous or optimal medical therapy [21,22]. In a study recently conducted by our group, we aimed to identify the most common errors in the outpatient management of patients with IBD [22]. Consecutive patients diagnosed with IBD who were seen for a second opinion in our IBD Unit were included. Data on the strategies employed by physicians who had previously treated them were obtained and compared with currently recommended diagnostic and therapeutic procedures/guidelines. This study demonstrates that errors in the management of IBD patients are very frequent, both among general gastroenterologists but also among IBD specialists [22].

Previous studies have suggested that there is often a gap between guidelines and clinical practice [23], as well as between patients' and physicians' perspectives [24]. Adherence to guidelines—for example, European Crohn's and Colitis Organisation (ECCO) guidelines—appears to be suboptimal overall for both therapeutic care and preventive health aspects of chronic disease management [23].

The present review aims to address common errors (according to our experience) in IBD (Table 1). Our approach to the problem will consist in identifying mistakes frequently observed in clinical practice in the management of patients with IBD, then reviewing the scientific evidence available on the subject, and finally proposing the most appropriate recommendation for each case.

Table 1. Summary of the most common mistakes in managing patients with inflammatory bowel disease.

•	**DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS**
✓	"When admitting previously diagnosed UC patients with rectal bleeding, it is not necessary to rule out an enteric infection as it is evident that it is a flare-up of their IBD"
✓	"Clostridioides difficile infection should only be considered in IBD patients who have recently received antibiotics"
✓	"Assume that all cases of proctitis are ulcerative proctitis"
✓	"The endoscopic lesions of UC are always continuous"

Table 1. *Cont.*

✓	"In severe UC flare-ups, a complete colonoscopy is necessary to precisely define the extent of the disease and choose the most appropriate treatment"
✓	"An obstructive picture in patients with CD is always due to intestinal stenosis as a consequence of their underlying disease"
✓	"The clinical manifestations of toxic megacolon are very characteristic, so its diagnosis is usually straightforward"
✓	"CMV infection, whenever present, always plays a causative role in the flare-up of UC or in the episode of corticosteroid refractoriness"
•	**PREVENTION**
✓	"For patients with CD who smoke, repeatedly emphasizing the necessity of quitting smoking may not be so crucial"
✓	"Early screening for latent tuberculosis is not necessary, it is sufficient to screen only when the patient already requires immunosuppressive treatment"
✓	"Routinely assessing the need for vaccination at the time of diagnosis is not necessary in patients with IBD"
•	**NUTRITION AND DIET**
✓	"Self-imposed food restrictions help prevent the onset of IBD flare-ups and aid in controlling their activity"
✓	"Patients admitted for an IBD flare benefit from complete fasting, as it reduces disease activity. The administration route for nutritional supplements should be parenteral, as it is more effective and better tolerated than enteral feeding"
•	**5-AMINOSALICYLATES**
✓	"Aminosalicylates are equally effective for treating CD and UC"
✓	"The combination of oral and topical aminosalicylates is deemed unnecessary, as each treatment alone demonstrates similar efficacy"
✓	"The total dose of aminosalicylates should be split into at least two daily administrations, as a single daily dose is less effective"
•	**CORTICOSTEROIDS**
✓	"Corticosteroids are generally used appropriately (only when necessary)"
✓	"Corticosteroids are effective in patients who are already receiving treatment with immunomodulators or biological agents"
✓	"It is recommended to start with low or intermediate doses of corticosteroids, and only use full doses if no response is observed"
✓	"At least 10 days must be waited before considering a patient with severe UC treated with intravenous corticosteroids as corticosteroid-refractory"
✓	"Faced with a patient with severe UC resistant to corticosteroids in whom a CMV infection is detected and antiviral treatment is initiated, it is necessary to immediately and completely discontinue the steroids"
✓	"Since bone loss does not begin to occur until several months after the start of corticosteroid treatment, it is not necessary to initially administer prophylactic therapy for osteopenia"
•	**THIOPURINES**
✓	"It is advisable to split the dose of thiopurines into several intakes to facilitate gastric tolerance"
✓	"In patients who develop digestive intolerance to azathioprine, thiopurine drugs should be permanently discontinued"
✓	"Thiopurines should always be stopped and non-thiopurine therapy used instead if liver abnormalities are detected"
✓	"Thiopurines should always be discontinued if myelotoxicity is detected"
✓	"Withdrawal of thiopurines (when administered as monotherapy) should be strongly recommended in all patients after several years in remission"
•	**ANTI-TNF AGENTS**
✓	"Anti-TNFs are not useful to treat stricturing CD, which will always require endoscopic dilation or surgery"
✓	"De-escalation of anti-TNF treatment (either reducing the dose or increasing the administration interval) in IBD is generally recommendable"
•	**EXTRAINTESTINAL MANIFESTATIONS**
✓	"In hospitalized UC, thromboprophylaxis is not indicated, as they are usually young (and therefore at low risk) and have rectal bleeding (which could worsen with anticoagulation)"
✓	"Ocular manifestations of IBD are never an emergency, and therefore, patients experiencing them should be referred to the ophthalmologist for deferred, outpatient evaluation"

Table 1. *Cont.*

•	**ANEMIA**
✓	"Anemia (i.e., low hemoglobin levels), but not iron deficiency (i.e., low ferritin levels), is the only significant laboratory finding"
✓	"The impact of anemia on the quality of life of patients with IBD is quite limited"
✓	"Since mild anemia is common in patients with IBD, and its clinical impact is only evident when the anemia is severe, iron therapy is rarely necessary"
✓	"When administering oral iron treatment, higher-than-usual doses should be used because its absorption is often decreased in patients with IBD"
✓	"In patients with IBD, intravenous iron administration should be reserved for cases of severe anemia (e.g., hemoglobin < 8 g/dL)"
•	**ELDERLY PATIENTS**
✓	"In elderly patients with IBD, the use of biological drugs should be avoided at all costs"
•	**PREGNANCY**
✓	"During pregnancy, endoscopic examinations should not be performed even if they are clearly indicated, due to the risk of harming the fetus"
✓	"In pregnant women, due to the risk that the medications pose to the fetus, efforts should be made to administer the minimum possible treatment for IBD, even if it means that some intestinal activity persists"
✓	"Biological agents are not safe during pregnancy, and therefore, they should be discontinued before the third trimester"
✓	"Breastfeeding is contraindicated while the mother is undergoing treatment with biological agents"
✓	"In children exposed in utero to biologics, non-live inactivated vaccines are less effective and safe"
✓	"In children exposed in utero to biologics, all live-attenuated vaccines are safe"
✓	"Administration of a live-attenuated vaccine to a breastfed infant while the mother is receiving anti-TNF agents is not recommended unless infant anti-TNF serum levels are undetectable"
•	**SURGERY**
✓	"In CD, surgery always represents the failure of medicine and is only indicated when medical treatments fail"
✓	"In patients with acute severe UC, surgery should be delayed as much as possible"
✓	"Most drugs used in IBD treatment (corticosteroids, thiopurines, and biologics) equally increase the risk of postoperative complications"
✓	"Previous failure with an anti-TNF agent does necessarily warrant switching to a drug with a different mechanism of action (such as vedolizumab or ustekinumab) to prevent post-operative recurrence of CD"

ABBREVIATIONS: anti-tumor necrosis factor (anti-TNF), cytomegalovirus (CMV), Crohn's disease (CD), inflammatory bowel disease (IBD), ulcerative colitis (UC).

2. Diagnosis and Differential Diagnosis

2.1. When Admitting Previously Diagnosed UC Patients with Rectal Bleeding, It Is Not Necessary to Rule Out an Enteric Infection as It Is Evident that It Is a Flare-Up of Their IBD

Intestinal infections can mimic the clinical and even endoscopic manifestations of UC [25]. Additionally, various infectious agents can cause superinfection in patients with IBD, which can trigger a relapse or worsen a flare-up of this disease [26]. Therefore, in every patient admitted for a presumed flare of UC, infectious causes of diarrhea should be excluded [27]. Thus, even if the diagnosis of UC is already known, it is advisable to request stool cultures to rule out a possible infection by *Salmonella*, *Shigella*, *Campylobacter*, or *Escherichia coli* [27]; *Clostridioides difficile* (*C. difficile*) infection, in particular, is addressed in the following section.

However, the actual yield of routine pathogen determination in stool in clinical practice for patients with a supposed IBD relapse is not clearly established and appears to be relatively low. A recent trial in which systematic stool studies were conducted in patients presenting with an IBD flare showed that stool cultures were positive in only 4% of cases [28]. More recently, other researchers have confirmed these disappointing results by prospectively evaluating over 2 years the incidence of intestinal superinfection by enteropathogens (through systematic stool cultures) in 99 IBD flare-ups requiring hos-

pitalization; this diagnostic strategy detected only five bacterial infections (by *C. jejuni*), representing just 5% of cases, and no correlation between the infection and the course of the disease could be demonstrated [29].

However, it is important to highlight that while collectively the number of patients with supposed IBD relapse and concomitant bacterial infection seems low, the consequence of correctly identifying such infections is very significant at the individual level. Furthermore, the increasing use of drugs that significantly modify the response to infections in IBD (immunomodulators, biological agents, and small molecules) may lead to a higher frequency of infectious complications.

It has been suggested that symptoms and signs (such as a high fever and marked leukocytosis) may sometimes lead a clinician to suspect infection as a cause of an IBD flare-up. Nevertheless, although it can be difficult or even impossible to differentiate between an IBD flare and enteroinvasive diarrhea, steroid treatment should not be delayed while awaiting stool culture results (which may take several days) in patients with a previously established UC diagnosis or a well-founded suspicion of this disease [27].

2.2. C. difficile Infection Should Only Be Considered in IBD Patients Who Have Recently Received Antibiotics

C. difficile infection has been associated with IBD exacerbations [30]. It is generally considered that every patient admitted for a severe IBD flare should be systematically examined for *C. difficile* toxin in their stools, regardless of whether they have previously received antibiotic treatment [30]. IBD is an independent risk factor for *C. difficile* infection, even in the absence of traditional risk factors such as antibiotic exposure and hospitalization [31,32]; additionally, patients do not always accurately remember if they have taken antibiotics, particularly if this occurred several weeks before the onset of colitis. A meta-analysis including 12 studies reported a significant association between community-acquired *C. difficile* infection and IBD [33]. A population-based study revealed that patients with IBD were approximately five times more likely to develop *C. difficile* than patients without IBD [34]. Furthermore, *C. difficile* is significantly more frequent in IBD patients experiencing flares than in those with inactive IBD [35]. In fact, *C. difficile* negatively impacts short- and long-term IBD-related outcomes, including hospitalization, colectomy, and mortality rates [36–38]. Finally, regarding the effect of *C. difficile* infection treatment on IBD activity, some studies have shown a beneficial effect of antibiotic treatment on IBD [39].

Accordingly, the ECCO guidelines on the prevention, diagnosis, and management of infections in IBD concludes that "screening for *C. difficile* infection is recommended at every disease flare in patients with IBD and especially in patients receiving immunosuppressive therapy" [40]. In the same way, the guideline for diagnostic assessment in IBD jointly organized by the ECCO and the European Society of Gastrointestinal and Abdominal Radiology (ESGAR) concludes that "all patients with a suspected new flare of IBD should be investigated for infection, including exclusion of *C. difficile* infection" [41].

2.3. Assume That All Cases of Proctitis Are Ulcerative Proctitis

The increase in the incidence of IBD and the growing awareness among healthcare professionals about this problem have led to improved diagnosis for these patients. However, we must not forget that other diseases can present with manifestations that mimic IBD [42,43]. In this regard, sexually transmitted infections can manifest with symptoms, endoscopic findings, and histological features that overlap with those of IBD, posing a challenge in terms of differential diagnosis [44]. In fact, the endoscopic appearance (inflammation or ulcers) and histologic changes (acute inflammation) in the mucosa in infective and inflammatory colitis may be nearly indistinguishable [45,46]. Other conditions that typically mimic IBD include ischemic colitis and diverticular colitis.

In recent years, the incidence of proctocolitis due to sexually transmitted infections has increased, especially in individuals with high-risk sexual practices [47]. The most frequently implicated microorganisms are *Neisseria gonorrhoeae*, *Chlamydia trachomatis* (caus-

ing lymphogranuloma venereum), *Treponema pallidum*, and the monkeypox virus, which caused a pandemic outbreak in 2022.

Almost a third of patients presenting with mucoid bloody diarrhea and suspected IBD have an infective etiology, and in addition, patients with IBD are prone to bacterial superinfection [48]. The most common enteric pathogens involved are *Campylobacter*, *Salmonella*, *Shigella*, *Amoeba*, and *C. difficile*.

In a patient diagnosed with IBD who presents with any atypical clinical, endoscopic, or histological feature or a lack of response to treatment, it is recommended to rule out other diagnoses. A medical history that addresses their intestinal and extraintestinal symptoms, travels, and sexual behavior (unprotected passive anal intercourse) is required. To reach a definitive diagnosis, thorough endoscopic and histological evaluation of the lesions is necessary, and microbiological tests and serologies are usually also needed.

2.4. The Endoscopic Lesions of UC Are Always Continuous

No endoscopic feature is specific for CD or UC. The most useful endoscopic features of UC are considered to be continuous, and there is confluent colonic involvement with a clear demarcation of inflammation and rectal involvement [41]. However, although the endoscopic involvement of UC typically begins in the rectum and extends continuously, more or less proximally, several series have described cases of discontinuous or segmental lesions. For example, the involvement of the right colon (or the inflammation of the periappendicular area) has been observed in patients with left-sided colitis, or some patients may even have an intact rectum [49–60]. In fact, any segment is susceptible to containing segmental lesions, but the periappendicular area and the cecum appear to be the most likely sites for these discontinuous lesions [59]. While rectal sparing or patchy involvement typically raises suspicions of CD, it does not appear that these patients are subsequently diagnosed more frequently with CD [60,61]. Thus, the presence of segmental lesions alone does not exclude a UC diagnosis.

In any case, during the first exploration (without previous medical treatments), the initial assessment of the disease extent should be very detailed to facilitate diagnosis and classification. After the administration of topical treatment, there may be a disproportionate improvement, or even apparent normality, of the distal colonic segments (especially the rectum) compared to the more proximal area [50,51,62]. This may be misinterpreted as segmental colonic involvement. It has also been suggested that systemic treatment (oral or intravenous) may also be responsible for the non-uniform improvement of colonic mucosa, resulting in the more evident disappearance of lesions in some portions of the colon than others [50,63].

2.5. In Severe UC Flare-Ups, a Complete Colonoscopy Is Necessary to Precisely Define the Extent of the Disease and Choose the Most Appropriate Treatment

Firstly, it is important to emphasize that in a severe UC flare-up (in a patient with an already established diagnosis), detailed knowledge of the extent of the disease will not change the therapeutic approach, as intravenous steroid treatment (or in some cases, biological agents or small molecules) will be necessary regardless of the length of colonic involvement. Secondly, it should be noted that a colonoscopy could trigger a toxic megacolon in these severely ill patients [27], probably due to the distension caused by the procedure, which in turn affects the blood supply to the colon wall, increasing the mucosal uptake of bacterial products [64]. Therefore, complete colonoscopies should be avoided as much as possible in severe cases of UC (or CD). Consequently, if endoscopic examination of the colon is necessary, it should be as limited as possible—exploring only the rectum and, at most, the most distal part of the sigmoid colon—and carried out with utmost care, inflating the least amount of air possible and aspirating at the end of the procedure [41,63]. This brief and limited endoscopic examination will be sufficient to assess the severity of the lesions (keep in mind that in UC, the most apparent involvement is usually found in the most distal

segment) and to obtain biopsies from the rectum to assess the patient for cytomegalovirus (CMV) infection.

2.6. An Obstructive Picture in Patients with CD Is Always Due to Intestinal Stenosis as a Consequence of Their Underlying Disease

Intestinal stenosis due to CD produces a series of symptoms typical of any intestinal obstructive process: colicky pain, abdominal distension, vomiting, and the worsening of symptoms after food intake. Although the onset of symptoms of a partial obstruction can be abrupt, stenotic CD almost never presents in a "catastrophic" manner as a total obstruction, and in most cases, there is no associated vascular involvement [65]. Therefore, the identification of a complete obstruction should suggest another cause, such as adhesions secondary to a previous surgery, a hernia, or an intestinal volvulus. It is essential to distinguish strangulation due to these latter complications, which require immediate surgery, from an obstruction secondary to luminal narrowing caused by CD [65]. Initially, this differentiation is often impossible since there are no pathognomonic signs of strangulation, although its clinical presentation is usually more severe. Therefore, strict observation, with the monitoring of clinical, radiological, and laboratory evolution, is of paramount importance. Finally, it should be noted that an uncomplicated intestinal obstruction due to CD almost invariably resolves spontaneously (or with medical treatment) and rapidly (i.e., within two or three days), so the absence of evident improvement within this timeframe should raise suspicion of another diagnosis and prompt consideration of surgical treatment [13].

2.7. The Clinical Manifestations of Toxic Megacolon Are Very Characteristic, So Its Diagnosis Is Usually Straightforward

The characteristic clinical features of toxic megacolon typically include bloody diarrhea refractory to medical treatment for a week or more (although sometimes the onset of symptoms can be faster) [64]. In patients with UC, unlike in CD, continuous abdominal pain is rare (although colicky pain relieved by defecation is common), so its presence, in a patient with severe UC, suggests the possibility of a toxic megacolon [66]. Additionally, since severe abdominal pain is not typical in a UC flare, its appearance might suggest the possibility of colonic perforation [66].

However, diagnosing a toxic megacolon is not always straightforward. Although diarrhea is almost always initially present, later it may be decreased or even evolve into constipation, probably due to the loss of colonic motility (referred to as a "false improvement") [67]. Accordingly, physical examinations typically reveal decreased or absent bowel sounds and increased abdominal tympanism [67]. Finally, steroid treatment may mask the symptoms and signs of toxic megacolon, making early diagnosis even more challenging [67]. Therefore, to accurately diagnose this condition, it is necessary to initially perform a plain abdominal X-ray in every patient with a severe IBD flare, regardless of whether they present abdominal pain or diarrhea, and subsequently and frequently (e.g., every 24 or 48 h) during the follow-up of the flare, mainly in the case of no observed improvement.

2.8. CMV Infection, Whenever Present, Always Plays a Causative Role in the Flare-Up of UC or in the Episode of Corticosteroid Refractoriness

Numerous studies have been published evaluating the role of CMV infection in patients with IBD [68]. Additionally, several studies have suggested an etiological role of this infection, especially in corticosteroid-refractory UC [68]. Furthermore, adequate responses to antiviral therapy (e.g., ganciclovir) have been repeatedly described in corticosteroid-refractory UC [69]. However, in some cases, antiviral treatment has failed to induce clinical remission or prevent surgery [69]. Moreover, clinical improvements have been observed in some patients with UC with concomitant CMV infection who received only steroid treatments (without antiviral therapy), indicating that, at least in some instances, this microorganism may merely act as a commensal or "innocent bystander" [70]. The practical

recommendation arising from this conclusion is that, regardless of the decision to administer treatment against CMV, the underlying disease (UC) should not be left untreated.

3. Prevention

3.1. For Patients with CD Who Smoke, Repeatedly Emphasizing the Necessity of Quitting Smoking May Not Be So Crucial

Despite the known association between smoking and the increased need for steroids, immunosuppressants, and surgery for CD and the improvements in disease course that occur with smoking cessation [71,72], not all smokers with CD receive proper counseling [23]. Although counseling regarding smoking cessation appears to have improved compared with previous studies [73,74], there is still room for improvement. It is imperative that gastroenterologists familiarize themselves with the resources and strategies available for smoking cessation [75], as unassisted attempts to quit have been associated with a low chance of success, with only 3–5% of such attempts resulting in long-term abstinence [71].

3.2. Early Screening for Latent Tuberculosis Is Not Necessary; It Is Sufficient to Screen Only When the Patient Already Requires Immunosuppressive Treatment

We understand that "early" screening for latent tuberculosis is conducted when there is still no indication for biological (or small-molecule) therapy, and ideally, it should be performed at the diagnosis of IBD, before the patient receives immunosuppression, and preferably with a low inflammatory burden [76]. Often, at diagnosis, there is a high inflammatory burden that makes early screening impossible. Therefore, in these cases, screening should be performed at a later period when the patient is in a state of immune competence. Early latent tuberculosis infection screening is recommended for all IBD patients since all of them could potentially require future treatment with biological agents or small molecules [40,77]. The SEGURTB study has shown that the likelihood of a positive result in the early tuberculin skin test (performed before an indication for biological therapy but not necessarily at diagnosis, without associated immunosuppression and with a low inflammatory burden) is double that of the mandatory tuberculin skin test performed right before starting an anti-TNF [76].

In the case of a positive early screening test, it is advisable to delay tuberculosis chemoprophylaxis until the patient receives biological treatment or small molecules [76]; we must avoid over-treating (with isoniazid) patients who will not need treatment with biological agents or small molecules. Moreover, early chemoprophylaxis would not protect against new contacts with *M. tuberculosis* that may occur in the interval between the positive early test and the start of biological/small molecule therapy. It is essential to explain this recommendation to the patient, considering that although performing chemoprophylaxis for a positive early screening test is not considered strictly incorrect, it does not seem justified from an epidemiological perspective [77].

3.3. Routinely Assessing the Need for Vaccination at the Time of Diagnosis Is Not Necessary in Patients with IBD

Patients with IBD are at an increased risk of infection, in part owing to the disease itself, but mostly because of treatment with immunosuppressive drugs [78], and they are likely to need immunosuppressive therapy during the course of their disease.

The fatality rate of fulminant hepatitis A virus (HAV) infection has been estimated to be up to 2% in adults over 40 years, and a higher rate is suggested in immunosuppressed patients [40]. The reactivation of hepatitis B virus (HBV) is a well-known complication of immunosuppression [79,80]. The risk of CMV reactivation is increased in IBD patients exposed to corticosteroids or thiopurines but not in those treated with anti-TNF agents [81]. CMV-seropositive patients receiving immunosuppressors are at risk of virus reactivation, whereas seronegative patients acquire primary CMV infection infrequently [40]. Primary Epstein–Barr virus (EBV) infection in EBV-negative patients appears to be a risk factor for lymphoproliferative disease [82]. Thus, the ECCO guidelines on the prevention, diagnosis, and management of infections in IBD states that "serological screening for hepatitis A, B, C,

HIV, EBV, CMV, varicella zoster virus, and measles virus (in the absence of documented past infection or vaccination for the latter two) is recommended for all IBD patients at baseline" [40]. Furthermore, some vaccines, particularly live-agent vaccines, cannot be safely administered to immunocompromised IBD patients. Additionally, the response rate to certain vaccines, such as hepatitis B, is often low in IBD patients on immunosuppressors or anti-TNF therapy [83–85]. All of this underscores the recommendation that the optimal time for immunization is at diagnosis, before starting any immunosuppressive treatment.

Thus, the current method for preventing opportunistic infections in IBD patients involves a comprehensive clinical and laboratory work-up (the use of standardized checklists may be useful) before beginning treatment with immunosuppressors/biological therapies/small molecules, with catch-up vaccinations for incomplete series [86]. The vaccination schedule should also include combined vaccinations against tetanus, diphtheria, and inactivated poliomyelitis every 10 years, annual influenza vaccination, and pneumococcal vaccination every 5 years.

In spite of these guidelines, vaccines are underutilized in IBD patients, indicating a gap in immunization against vaccine-preventable illnesses despite significant risk factors [87–91]. In some studies, the primary reason for non-immunization was that the vaccine was not offered, highlighting the need for better patient education by healthcare providers and also the need for education among healthcare professionals [92]. In this respect, gastroenterologists' knowledge of appropriate immunizations for IBD patients is clearly deficient [88].

4. Nutrition and Diet

4.1. Self-Imposed Food Restrictions Help Prevent the Onset of IBD Flare-Ups and Aid in Controlling Their Activity

In IBD patients, reduced oral intake can significantly contribute to the onset of malnutrition. This reduction can result from various factors, including self-imposed food restrictions, decreased hunger, diminished pleasure from eating, mood changes, and even medical advice [93,94]. In a prospective, multicenter study including 1271 IBD patients from outpatient clinics, a questionnaire was applied to obtain data on the patients' dietary behavior and beliefs [95]. The vast majority of the IBD patients had self-imposed food restriction behaviors in order to prevent a disease flare and because of fear of worsening disease symptoms during a flare [95]. Other studies have also described a high prevalence of self-reported food avoidance and restrictive dietary behavior in patients with IBD [95–99]. Many beliefs of the patients could be perpetuated by professional dietary advice [93,100]. However, scientific evidence to support specific dietary advice in patients with IBD is currently lacking [101], while dietary restrictions predispose individuals with IBD to nutrition-related complications and have a negative psychosocial influence.

4.2. Patients Admitted for an IBD Flare Benefit from Complete Fasting, as It Reduces Disease Activity; The Administration Route for Nutritional Supplements Should Be Parenteral, as It Is More Effective and Better Tolerated Than Enteral Feeding

Malnutrition is frequently associated with IBD during active phases [102]. Furthermore, patients admitted for a severe flare of IBD are often malnourished, in a catabolic state, and will also be required to fast for the frequent tests they undergo. However, neither total parenteral nutrition nor absolute fasting have proven effective in treating IBD [103–105]. González-Huix et al. compared the role of total enteral and parenteral nutrition as adjunctive therapy to steroids in severe UC, and found that while they were equivalent, the former was more cost-effective and associated with fewer adverse effects [105]. This is not surprising as enteral nutrition is more physiological and lacks the complications associated with parenteral nutrition, such as catheter-related infections or various metabolic issues [106].

Maintaining a patient with UC (even if severe) on absolute fasting in an attempt to achieve "intestinal rest" is not only not beneficial but worsens their malnutrition status and can be harmful. Absolute fasting deprives colonocytes of contact with short-chain

fatty acids, vital for their metabolism and repair [107]. Only in cases of IBD complicated by intestinal obstruction, massive bleeding, a toxic megacolon, or suspected perforation should fasting and total parenteral nutrition be considered. Conversely, patients with IBD (mainly hospitalized ones) should be evaluated for the need for artificial nutrition, typically through oral supplements. In summary, if nutritional support is required, enteral nutrition should be the preferred alternative, a recommendation reflected in the aphorism stating "when the intestine works, use it" [108].

5. Aminosalicylates

5.1. Aminosalicylates Are Equally Effective for Treating CD and UC

Aminosalicylates (5-ASA) are unequivocally regarded as the primary choice for both treating and sustaining remission in UC [109–111]. However, the role of 5-ASA in the management of CD has been a subject of controversy [112–114]. An initial meta-analysis of three placebo-controlled trials of Pentasa® in patients with active CD showed a mean reduction of 63 points in the Crohn's Disease Activity Index (CDAI), compared to a 45–point reduction with a placebo (a small difference of only 18 points) [115]. More recently, the ECCO working group conducted a meta-analysis of seven randomized controlled trials comparing induction therapy with oral mesalazine or sulfasalazine versus a placebo in patients with active CD [116]. The results showed similar clinical remission rates between 5-ASA therapy and a placebo, consistent with findings of a meta-analysis conducted by the Cochrane collaboration [117]. Additionally, adverse-event-related treatment withdrawals were comparable between the treatment and placebo groups. Accordingly, the ECCO guidelines recommend against the use of 5-ASA for the induction of CD remission [116]. Finally, it should be mentioned that one published network meta-analysis noted a small statistically significant effect on clinical remission among the study arms which evaluated 5-ASA at daily doses of >2.4 g/day [118]; however, another network meta-analysis was unable to confirm this dose effect [119].

Regarding maintenance treatment, initially, a Cochrane systematic review found no evidence to suggest that oral 5-ASA preparations are superior to a placebo for the maintenance of medically induced remission in patients with CD [120]. In total, 11 placebo-controlled clinical trials evaluated doses ranging from one to four g per day [120]. Treatment durations varied from 4 to 36 months, with a 12-month evaluation being the most common. No statistically significant benefit was found for clinical outcomes with oral 5-ASA. No benefit was observed based on disease location, including in patients with colonic-only involvement. Accordingly, the ECCO guidelines recommend against the use of oral 5-ASA as maintenance therapy in CD [116]. Finally, while there have been some suggestions of benefits for maintaining remission in small-bowel CD after surgical resection, the effect sizes are, in any case, very small [121,122].

A survey featuring five vignettes to gather provider beliefs about the appropriateness of therapies for CD has assessed the level of agreement between community gastroenterologists and IBD experts, with the latter presumably adhering more closely to practice guidelines [7]. For managing a patient with newly diagnosed CD, 75% of community providers recommended the use of 5-ASA products, compared to less than half (44%) of the experts [7].

5.2. The Combination of Oral and Topical Aminosalicylates Is Deemed Unnecessary, as Each Treatment Alone Demonstrates Similar Efficacy

Pharmacokinetic research indicates that orally administered 5-ASA primarily targets the distal ileum and proximal large bowel, resulting in a higher concentration of the active compound in the right colon compared to the left colon. On the contrary, only minimal quantities of the drug are found in the rectal mucosa [123,124]. Conversely, when 5-ASA is administered topically, it ensures significant drug availability in the rectosigmoid sites and, to a lesser extent, in the descending colon [125,126]. Thus, it seems that to enhance the mucosal 5-ASA concentration throughout the entire length of the large bowel in UC

patients, besides oral dosage, topical treatment should be considered [111,127,128]. In fact, in left-sided UC (and in ulcerative proctitis), the efficacy profile of topical 5-ASA is superior to oral 5-ASA therapy (and to topical steroids) [129].

Only a few trials, including 322 patients and with a treatment duration of 3–8 weeks, have compared the use of oral 5-ASA combined with topical 5-ASA versus oral 5-ASA as a monotherapy for the induction of remission in patients with active UC [111]. In all of these studies, the desirable effects of 5-ASA combined therapy (compared with oral monotherapy) probably outweigh the undesirable effects of this intervention, although the level of uncertainty is high [130–133]. Moreover, another study reported that combined oral and topical mesalazine treatment significantly improved health-related quality of life in patients with active UC [134]. Two trials compared these two therapeutic strategies for clinical response in patients with disease of at least a rectosigmoid extent [130,132]. In the pooled analysis, no significant advantage of combined therapy over 5-ASA monotherapy in clinical response was observed [111]; however, these trials were heterogeneous in terms of study design, 5-ASA doses, the definition of clinical activity, and the definition of clinical improvement [111]. The only trial comparing combined versus oral 5-ASA therapy on endoscopic activity of UC showed a higher endoscopic remission rate with the combined regimen [132]; however, the difference was not statistically significant [111]. Finally, combined oral and topical 5-ASA therapy also seems to exhibit a favorable cost–benefit ratio in pharmacoeconomic analyses [135,136].

Based on the aforementioned data, the ECCO guidelines on medical treatment of UC suggest the use of oral 5-ASA ($\geq$2 g/d) combined with topical (rectal) 5-ASA over oral 5-ASA monotherapy for the induction of remission in adult patients with active UC of at least a rectosigmoid extent. While many authors have asserted that patients generally find long-term rectal treatment acceptable, a postal survey of British patients revealed that 80% preferred oral treatment alone [137]. Therefore, this form of combination treatment (aimed at maintaining remission) could be reserved for patients with a high likelihood of relapse [138]. Consequently, adding rectal therapy becomes a viable treatment option for patients who have experienced a relapse while on oral 5-ASA alone.

5.3. The Total Dose of Aminosalicylates Should Be Split into at Least Two Daily Administrations, as a Single Daily Dose Is Less Effective

Multiple-dose daily regimens can disrupt patients' normal daily activities and diminish their overall quality of life, leading to decreased treatment adherence and potentially worse long-term outcomes [139]. UC colitis patients often identify the treatment regimen's complexity, the number of tablets, and the frequency of doses as significant barriers to their adherence [139,140].

Pharmacokinetic studies conducted in healthy volunteers have indicated that once-daily dosing could be a viable option for patients with UC [141,142]. The response to 5-ASA is closely associated with tissue concentrations and is best anticipated by examining drug concentrations within the colon lumen. Some researchers have utilized computer simulations, supporting the notion of the once-daily administration of 5-ASA as the standard treatment for UC [143]. In fact, several meta-analyses have demonstrated that once-daily dosing with 5-ASA is as effective and safe as conventional dosing schedules both for induction and for maintenance treatment in UC [144–148]. Furthermore, some studies have reported that patients with UC who receive 5-ASA once daily demonstrate superior remission rates, levels of acceptability, and self-reported adherence to therapy compared to those given 5-ASA twice daily [149].

The collective evidence indicates that the effectiveness of once-daily dosing for all these compounds might be attributed to the pharmacodynamic properties of 5-ASA, rather than to the specific characteristics of the formulation determining drug delivery. In other words, the effect is likely to be generic rather than specific to a particular 5-ASA compound.

6. Corticosteroids

6.1. Corticosteroids Are Generally Used Appropriately (Only When Necessary)

Corticosteroids remain, at present, one of the most useful group of drugs for treating acute IBD flares. Their high potency and low cost are only offset by their significant side effects, especially if their use is prolonged [150,151]. Thus, despite the development and incorporation of new therapeutic strategies, such as biological agents and small molecules, corticosteroids still play an important role in inducing remission in patients with IBD.

A frequent and relevant mistake is to use corticosteroids as maintenance treatment, either because they are not discontinued or because they are often prescribed without a maintenance therapy strategy [151–153]. Various authors have suggested that the (lack of) use of corticosteroids should be a quality-of-care indicator for IBD programs [154–156]. Despite this, a significant percentage of patients are still inadequately treated with corticosteroids [150,151]. Some studies indicate that 30–50% of IBD patients are still being exposed to corticosteroids annually, with 10–20% exposed to excessive corticosteroids [157]. It is noteworthy that approximately half of these cases could potentially be avoided [158–162]. Indeed, the misuse of corticosteroids is probably one of the most common bases for malpractice suits in the treatment of IBD [13]. Thus, although there are contraindications for prolonged corticosteroid use, an analysis of US claims data revealed that 10–25% of UC patients had received corticosteroid treatment for over 3 months during the 12-month study period [163].

Suitable alternatives to corticosteroids should always be considered. The timely introduction of immunomodulators/biologic agents/small molecules is essential, as these therapies have demonstrated corticosteroid-sparing potential in IBD. However, timely escalation when a patient is either corticosteroid-refractory or -dependent is not performed in a significant proportion of cases, leading to inappropriate corticosteroid excess [150,151]. In this respect, when compared to immunomodulators and biological therapies, the prolonged use of corticosteroids remains the primary risk factor for increased morbidity and mortality in patients with IBD [164]. The use of anti-TNF agents and the presence of multidisciplinary IBD teams are both associated with reduced levels of inappropriate long-term corticosteroid use [165]. The chronic or repeated use of systemic corticosteroids, without attempting steroid-sparing strategies in patients with IBD, represents low-quality care [114], despite the relatively lower direct costs of the medication compared with the costs of advanced therapies with steroid-sparing and disease-modifying benefits [114].

In order to avoid common mistakes with corticosteroids, physicians need to educate and engage patients and general practitioners (and also gastroenterologists) regarding the proper role of corticosteroids in IBD treatment, including information about the potential short-term and long-term side effects of corticosteroids [150,151]. Corticosteroid-free remission should be a key therapeutic target [166].

6.2. Corticosteroids Are Effective in Patients Who Are Already Receiving Treatment with Immunomodulators or Biological Agents

A meta-analysis including more than 4000 patients suggested that the combination of corticosteroids and an anti-TNF would only increase morbidity due to the presence of adverse events [167]. In a recent study, after one course of steroids administered to IBD patients receiving immunosuppressive treatment, only 35% remained in remission without needing treatment escalation [161].

6.3. It Is Recommended to Start with Low or Intermediate Doses of Corticosteroids, and Only Use Full Doses if No Response Is Observed

The approach of starting with low doses of corticosteroids and increasing them if the desired response is not achieved, with the intention of reducing the incidence of adverse effects, lacks a scientific basis. Once the decision to administer steroids has been made, they should be prescribed at doses that have been shown to be effective, namely "full" doses. This assertion is based on several arguments as follows. (a) The cumulative dose

of steroids received by patients who are prescribed full doses from the beginning is often lower than that received when the treatment starts with low doses and gradually increases them. This latter strategy is frequently associated with an incomplete clinical response, necessitating dose escalation and ultimately resulting in a longer duration and higher total dose of steroids. (b) It has been suggested (though not clearly proven) that the gradual use of increasing doses of steroids may promote the development of corticosteroid resistance or dependence. (c) Employing full doses of steroids from the beginning facilitates defining a flare as refractory, because if a high-dose treatment fails to elicit a response, we can classify the patient as corticosteroid-resistant without doubts about using a dose that was possibly insufficient.

However, the optimal steroid dose for treating IBD is not well established. One study compared three doses of prednisone (20, 40, and 60 mg/day) in patients with UC and demonstrated that the two higher doses are more effective than 20 mg/day [168]. Nonetheless, the limited sample size of this study, and the consequent reduced statistical power, did not allow for a determination of differences in efficacy between the 40 and 60 mg/day doses of prednisone [168]. A meta-regression analysis did not find any correlation between increased corticosteroid dosing and a reduction in colectomy rate in patients with severe UC and concluded that doses beyond 60 mg per day of methylprednisolone or equivalent should not be used [169]. Most clinicians use these drugs at doses ranging from 0.75 to 1 mg/kg/day of prednisone (or equivalent) [128]. In a meta-analysis of 24 cohort studies in patients with acute severe UC, the mean dose of intravenous methylprednisolone was 68 mg, ranging from 40 to 100 mg/day [169]. Administering doses exceeding 1 mg/kg/day of prednisone does not increase efficacy and, conversely, is associated with a higher incidence of adverse effects [170].

6.4. At Least 10 Days Must Pass before Considering a Patient with Severe UC Treated with Intravenous Corticosteroids as Corticosteroid-Refractory

The determination of the period from which steroid refractoriness is defined is crucial, as over time, especially in patients who do not clearly worsen but do not improve either, serious complications can develop, sometimes masked by steroid administration. Furthermore, the categorization of a patient with UC as corticoresistant should be followed by the consideration of rescue therapy, either with cyclosporine/infliximab or surgery [171]. Corticosteroid resistance has traditionally been defined in severely ill UC patients (hospitalized) receiving intravenous corticosteroids as the absence of response after 7–10 days [172]. However, more recently, it has been suggested that corticosteroid response should be evaluated earlier. Thus, some authors have suggested that 3–5 days of treatment might be sufficient, while others consider that 5 days, or perhaps between 5 and 7 days at most, could be considered a reasonable period to assess steroid treatment response [27]. In any case, it has been shown that prolonging steroid treatment for more than 7–10 days in corticosteroid-resistant patients does not increase therapeutic response and, on the contrary, is detrimental because it increases adverse effects and delays the administration of other potentially effective rescue treatments [173,174]. It seems appropriate here to recall the sensible aphorism that urges us not to be obstinate when it comes to saving a patient's colon, but rather the patient themselves [175,176].

6.5. Faced with a Patient with Severe UC Resistant to Corticosteroids Who Has a CMV Infection and Has Started Antiviral Treatment, It Is Necessary to Immediately and Completely Discontinue the Steroids

When CMV infection is detected in the colonic biopsies of a patient with severe corticosteroid-resistant UC, the physician faces the difficult dilemma of whether to suspend (rapidly) the immunosuppressive treatment, which would favor the response of the infection to antivirals but could worsen the activity of UC due to the underlying inflammatory disease [70]. The recommendation to rapidly taper, albeit progressively, the dose of steroids and other immunosuppressors in patients with corticosteroid-resistant UC who have been diagnosed with CMV infection and have started treatment with ganciclovir is

widely followed. However, the benefit of this approach has never been demonstrated and is not as obvious as it might seem. It could also be argued that steroids may be useful for controlling concomitant inflammation, and therefore, combined treatment with steroids and ganciclovir would allow for action simultaneously on inflammation and infection. In this regard, it is unknown whether corticosteroid resistance is permanent in this situation of superinfection, but some indirect data indicate that steroid refractoriness is reversible in both experimental and clinical conditions [177]. Moreover, we do not know to what extent treating CMV infection reverses the inflammatory component perpetuated by viral reactivation. Lastly, we must recall the previously mentioned recommendation that, regardless of the decision to administer treatment against CMV, the underlying disease should not be left untreated. Therefore, an immediate or excessively rapid withdrawal of steroids in this situation does not seem prudent.

6.6. Since Bone Loss Does Not Begin to Occur until Several Months after the Start of Corticosteroid Treatment, It Is Not Necessary to Initially Administer Prophylactic Therapy for Osteopenia

Osteoporosis is characterized by a decrease in bone mass accompanied by a deterioration of bone tissue architecture, leading to increased bone fragility and consequently an increased risk of fractures. Corticosteroids decrease the amount of absorbed calcium and increase the amount excreted in urine [178]. It has been estimated that between 25% and 50% of patients receiving prolonged steroid treatment will suffer bone fractures [179]. Moreover, IBD itself is a significant risk factor for the development of osteopenia and osteoporosis [180,181].

The use of steroids in IBD is undoubtedly one of the most determining factors in the occurrence of bone metabolism alterations in these patients [180,182]. It has been calculated that very low doses of steroids (even 2.5 mg/day) are capable of inducing bone mass loss. Notably, the rate of bone mass loss is highest during the first 6–12 months of steroid treatment, and the detrimental effects of these drugs can be identified by bone densitometry at as early as 6 months [182,183]. Thus, during the first year of treatment, up to 15% of bone mineral mass can be lost. Moreover, the increase in the incidence of bone fractures may manifest as early as 3 months after starting steroid treatment [182].

It has been suggested that short-term steroid administration (approximately only for one month) is not associated with a decrease in bone mineral density. However, most IBD patients will need to take these drugs for several months (the duration of the usual steroid tapering regimen), and it is precisely at the beginning when bone loss will be greatest (among other things, because initially higher doses of steroids are used). Finally, it should be noted that, unfortunately, upon the discontinuation of steroids after a certain period of administration, the bone mass usually does not return to pre-treatment levels [178,180].

Taken altogether, the aforementioned evidence indicates that prophylactic treatment of osteopenia should begin early [184]. A practical option is to administer calcium and vitamin D from the beginning to all IBD patients requiring steroid treatment, including low-bioavailability oral corticosteroids. However, a study involving 131 gastroenterologists showed that only 38% prescribed vitamin D and calcium in this patient group [185].

7. Thiopurines

7.1. It Is Advisable to Split the Dose of Thiopurines into Several Intakes to Facilitate Gastric Tolerance

Thiopurine drugs, namely azathioprine and mercaptopurine, have demonstrated effectiveness in maintaining remission in IBD, mainly in the context of corticodependence [111,113,116,186]. A debated aspect has been whether to administer the drug daily as a single dose or divided into several doses. Divided doses have been described as a limiting factor for treatment adherence, particularly in the case of chronic medication, such as thiopurine therapy, which supports the administration of the full dose in a single daily intake from the start of treatment, as splitting the dose has not been shown to have any advantage [140]. Dividing the dose should only be considered in patients who experience certain side effects (mainly digestive intolerance) [187].

7.2. In Patients Who Develop Digestive Intolerance to Azathioprine, Thiopurine Drugs Should Be Permanently Discontinued

Azathioprine intolerance remains a significant clinical issue in patients with IBD, leading to therapy withdrawal in up to 30% of patients [187–189]. In particular, digestive intolerance to thiopurines limits their use in 10–15% of patients [188,189]. However, it has been suggested that azathioprine and mercaptopurine could be interchangeable. Thus, an alternative strategy for managing azathioprine intolerance, mainly due to nausea or vomiting, is to switch to mercaptopurine (or vice versa).

Kennedy et al. performed a meta-analysis to determine the tolerance rate when prescribing mercaptopurine in azathioprine-intolerant patients and demonstrated that transitioning to mercaptopurine was a safe treatment strategy for more than two-thirds of patients who were intolerant to azathioprine [190]. This was particularly evident when the reason for azathioprine intolerance was gastrointestinal disturbance or hepatotoxicity, two of the most common causes for discontinuing thiopurine therapy [190]. However, switching from one thiopurine to another is usually not a good option in the case of flu-like illness, acute pancreatitis, or bone marrow aplasia [191,192].

7.3. Thiopurines Should Always Be Stopped and Non-Thiopurine Therapy Used Instead if Liver Abnormalities Are Detected

Abnormalities such as acute hepatocellular and cholestatic hepatitis have both been observed during thiopurine therapy [193]. A small percentage of patients may exhibit slight alterations in liver tests without clinical implications, which often return to normal parameters during follow-up, indicating that a dose adjustment of the immunomodulator is not always necessary [194,195].

When abnormalities in liver tests are more marked but not accompanied by jaundice, the dose of azathioprine or mercaptopurine may be reduced by 50%. It is usually unnecessary to completely withdraw these medications; however, strict and frequent clinical and analytical monitoring should be performed after reducing the dose. With this strategy, liver tests often normalize, thus allowing a cautious reintroduction of the initial dose of azathioprine or mercaptopurine [196–198].

If liver tests do not return to normal values with thiopurine tapering, it is recommended that therapy be withdrawn, which is necessary in less than 5% of patients. However, if azathioprine was initially prescribed, an alternative approach is to use mercaptopurine instead [190,199–202].

Nevertheless, it should be noted that in rare cases, thiopurines may induce severe cholestatic jaundice, which, unlike acute hepatocellular hepatitis, may not regress and can even progress despite thiopurine withdrawal [193]. Therefore, these drugs should be completely withdrawn, not merely tapered, in patients who present with clinically significant jaundice during thiopurine treatment [193].

7.4. Thiopurines Should Always Be Discontinued if Myelotoxicity Is Detected

It has been reported that mild leukopenia can resolve spontaneously without a change in dosage; therefore, in this case, the previous azathioprine/mercaptopurine dosage may be maintained with close monitoring [203]. The precise cut-off values for leukocyte or neutrophil counts that indicate when to lower the dose or discontinue the drug are still unknown. Some conservative authors suggest reducing the thiopurine dose (e.g., by 50%) when the leukocyte count is $<4 \times 10^9$/L, while others recommend this reduction when the count is $<3 \times 10^9$/L [203]. However, the risk of myelotoxicity is more closely related to neutropenia than to the total leukocyte count. Neutropenia is generally defined as an absolute neutrophil count of less than 1.5×10^9/L [203]; thus, this figure appears to be a more appropriate cut-off for deciding on dose modification.

In cases of mild neutropenia, with an absolute neutrophil count between 1.0 and 1.5×10^9/L, a dose reduction (e.g., to 50%) may be sufficient to resolve leukopenia, as demonstrated in some studies [203,204]. Nonetheless, some authors have observed that

after reducing the thiopurine dose by 50%, it may be safely increased back to 100% once leukocyte values have normalized [205,206]. In cases of leukopenia relapse, the dose should be reduced permanently and individualized with great care. As the risk of infection increases significantly at an absolute neutrophil count below 1×10^9/L [193], it is prudent to stop thiopurine administration (rather than just decrease the dose) in patients with lower counts [204].

7.5. Withdrawal of Thiopurines (When Administered as Monotherapy) Should Be Strongly Recommended in All Patients after Several Years in Remission

Thiopurine immunomodulators are an effective maintenance therapy for both CD and UC [111,116]. However, some studies have underscored the risks associated with the long-term use of these drugs [82,207,208]. Therefore, the periodic re-evaluation of the risk/benefit ratio of continued treatment with thiopurines is crucial. With the acknowledgment that IBD is a chronic condition requiring long-term therapy, it is increasingly recommended to continue effective maintenance therapy [209]. However, considering the risk of significant adverse effects, along with the necessity for long-term therapy in patients who are frequently young, the idea of discontinuing thiopurines in a patient in remission remains attractive [209].

A small retrospective study published in 1996 suggested that the withdrawal of azathioprine might be considered in patients who had maintained complete remission without steroids for longer than 3.5 years, as the 2-year relapse rate appeared to be similar whether the treatment was continued or stopped after this time [210]. However, subsequently, a multicenter, randomized, double-blind withdrawal trial was conducted, in which patients who were in clinical remission on azathioprine for more than 42 months were randomized to continue azathioprine or receive an equivalent placebo for 18 months [211]. The relapse rates at 18 months were 8% and 21%, respectively, indicating that azathioprine withdrawal was not equivalent to continued therapy for maintaining remission in patients with CD who had been in remission on azathioprine for over 3.5 years. Therefore, the authors concluded that azathioprine maintenance therapy should be continued beyond this time period [211]. In fact, at 5 years post-withdrawal, the cumulative relapse risk in the withdrawal group was as high as 63% [212].

Three subsequent randomized controlled trials also showed higher relapse rates in the drug withdrawal arm, which ranged from 17% to 53% at 12 months and were 31% at 24 months [213–215]. A subsequent meta-analysis of CD studies showed that continuing thiopurines reduced the relapse risk at 1 and 5 years with pooled odds ratios of 0.25 and 0.53, respectively [216].

Only one multicenter double-blind randomized controlled trial of azathioprine withdrawal in UC patients has been reported. The one-year relapse rates were 59% with azathioprine withdrawal and 36% with continued therapy (a statistically significant difference) [217]. In a multicenter retrospective study, one-third of UC patients relapsed within 12 months after azathioprine withdrawal, and two-thirds relapsed within 5 years [218]. Cohort studies reported varied relapse rates after immunomodulator withdrawal: from 11% to 77% at 12 months, from 43% to 65% at 5 years, and up to 87% with longer follow-up periods [194,219].

In conclusion, even after a long duration of clinical remission under thiopurines, the withdrawal of these drugs is associated with a high risk of relapse [220]. Therefore, thiopurine indefinite maintenance therapy should be at least considered in patients with IBD once remission has been achieved. When balancing the overall risks and benefits of prolonged maintenance therapy with thiopurines, it is likely that some clinicians and patients will accept the relatively small risk of lymphoid malignancy and opportunistic infections to prevent the ongoing morbidity and impact on quality of life associated with the chronic symptomatic activity of IBD.

8. Anti-TNF Agents

8.1. Anti-TNFs Are Not Useful for Treating Stricturing CD, Which Will Always Require Endoscopic Dilation or Surgery

CD typically causes inflammatory lesions in the ileocolonic region, but up to half of patients will develop complications such as strictures over time [221]. Thus, many patients experience disease progression leading to stricturing lesions, as no current drugs effectively prevent or reverse established fibrosis. Consequently, these patients are often treated with surgery or endoscopic balloon dilation [221].

Although fibrotic lesions are (almost) always associated with some degree of inflammation, there is limited evidence supporting the use of medical therapy in this context. Initially, some studies (a small cases series published only as an abstract) suggested that the healing process of inflammatory lesions might result in the formation of strictures [221]. However, a later analysis based on the TREAT registry found that the risk of stricturing complications was similar between patients treated with infliximab and those who were not [222]. In fact, over the past two decades, data from several cohorts have been published, indicating a clinical benefit associated with anti-TNF drugs [221].

A prospective, open-label observational study, known as the CREOLE study, focused on the efficacy of anti-TNF treatment specifically for patients with established symptomatic stenosis [223]. In this landmark research, 97 patients were evaluated over a 24-week period to assess the success rate of adalimumab treatment. Nearly two-thirds of the strictures were located in the ileum, with 13% of lesions situated at the ileocolonic anastomosis. At 24 weeks, 64% of the patients achieved treatment success, which was sustained in 29% of the patients during the long-term 4-year observation period [223].

In a more recent study, 262 patients with symptomatic stricturing CD who were receiving their first anti-TNF therapy (infliximab or adalimumab) and had no prior history of biological, endoscopic, or surgical therapy were included [224]. Anti-TNF treatment was effective in 87% and 73% of the patients after 6 and 12 months, respectively, and remained effective in 26% after a median follow-up of 40 months.

8.2. De-Escalation of Anti-TNF Treatment (Either Reducing the Dose or Increasing the Administration Interval) in IBD Is Generally Recommendable

Biologic therapy stands as an effective treatment for IBD; however, due to potential cost and safety concerns, de-escalation strategies, primarily for anti-TNF agents, have been proposed, especially following previous dose intensification. In clinical practice, approximately one-third of patients in remission after dose intensification revert to standard dosing. Conversely, de-escalation from standard dosing of anti-TNF agents is generally uncommon [225].

Around one-third of patients subjected to anti-TNF de-escalation, either from previous dose intensification or from standard dosing, experience relapse [225]. However, interpreting these relapse rates accurately is challenging due to the absence of a control group in most cases, although it seems that for some patients, the risk indeed increases [225]. Notably, the first (and only) randomized controlled trial comparing extended dosing intervals of adalimumab with standard intervals in stable CD patients (the LADI trial) reported similar persistent flare incidence in both groups, although the de-escalated group exhibited less clinical and biochemical remission and required more rescue therapy [226].

Predictive factors for relapse post-de-escalation remain unclear, making decision making challenging. However, the risk of relapse appears to be lower for patients in clinical, biologic, and endoscopic/radiological remission at de-escalation. Conversely, de-escalation should be approached cautiously or avoided altogether in high-risk patient groups, such as those with perianal fistulae or multiple prior surgeries [225]. Finally, it should be taken into account that, even though re-intensification in relapsed patients is usually effective, re-achieving remission is not guaranteed [225].

The main theoretical arguments favoring dose de-escalation are improved safety and cost savings, yet except for some cases, it has not consistently demonstrated a safer profile.

Moreover, the cost-effectiveness of this strategy remains uncertain, with medication costs reduced but potential increases in non-medication healthcare costs. Additionally, the evolving landscape of biosimilars is altering the cost–benefit dynamic of de-escalation over time [225].

Prospective studies, preferably randomized controlled trials, with larger cohorts and longer follow-ups, are warranted to clarify the efficacy and safety of biologic de-escalation and identify optimal candidates for this strategy. Meanwhile, shared decision making with patients, weighing the pros and cons of de-escalation on a case-by-case basis, is paramount.

9. Extraintestinal Manifestations

9.1. In Hospitalized UC Patients, Thromboprophylaxis Is Not Indicated, as They Are Usually Young (and Therefore at Low Risk) and Have Rectal Bleeding (Which Could Worsen with Anticoagulation)

The extent and severity of intestinal involvement are related to the occurrence of thromboembolic complications, which often coincide with episodes of IBD activity [227,228]. Therefore, patients with IBD who are hospitalized for a flare are at a markedly increased risk of venous thromboembolism. This complication represents an important and preventable cause of morbidity and mortality in patients with IBD [229]. Therefore, systematic prophylaxis with low-molecular-weight heparin is recommended for all IBD patients admitted for a flare [184,230,231].

While UC typically manifests with rectal bleeding, initiating prophylactic treatment with low-molecular-weight heparin is also advisable in this case, even though this approach may seem counterintuitive. This concern leads to the lower utilization of pharmacological thromboprophylaxis, especially in patients with overt bleeding [232]. However, the use of prophylactic heparin has not been associated with an increased risk of major or minor bleeding or the need for blood transfusion in patients with IBD [233]. Nevertheless, it is evident that this medication should be used cautiously in patients with severe bleeding, as a case of massive bleeding in a patient with corticosteroid-refractory UC attributed to the administration of low-molecular-weight heparin has been reported [234].

9.2. Ocular Manifestations of IBD Are Never an Emergency, and Therefore, Patients Experiencing Them Should Be Referred to an Ophthalmologist for Deferred Outpatient Evaluation

Two fundamental types of ophthalmologic manifestations have been described in IBD [235]. The first is a "benign" involvement, which includes processes such as conjunctivitis, scleritis, or episcleritis. All of these present as the so-called "red eye" and clinically produce a sensation of a foreign body, but they are not accompanied by ocular pain or loss of vision [236]. These mild ocular manifestations usually respond favorably to the basic treatment of IBD and, if necessary, topical steroids can be administered [236]. Conversely, ophthalmologic manifestations can become severe, as is the case with uveitis, a complication described in 0.5–3% of patients with IBD [236]. Uveitis manifests as visual disturbances (blurry vision or decreased visual acuity), ocular pain, photophobia, and a headache [236]. Unlike conjunctivitis or episcleritis, the course of uveitis is usually independent of the activity of intestinal disease [236].

The early diagnosis and treatment of uveitis are essential, preventing complications such as irreversible vision loss, so this extraintestinal manifestation should be considered an ophthalmologic emergency. Uveitis can be difficult to differentiate from conjunctivitis or episcleritis by a nonspecialist physician. Therefore, a patient with IBD and ocular manifestations should be evaluated on an urgent basis by an ophthalmologist and should not be referred for deferred evaluation by this specialist [184].

10. Anemia

10.1. Anemia (i.e., Low Hemoglobin Levels), Not Iron Deficiency (i.e., Low Ferritin Levels), Is the Only Significant Laboratory Finding

The prevalence of anemia in patients with IBD is very high, although the reported figures vary significantly between 10% and 75% [237,238]. There are several types of

mechanisms involved in the development of anemia in patients with IBD, the most common being secondary iron deficiency due to continuous blood losses in the gastrointestinal tract [239].

Anemia is just one aspect of the condition, as iron deficiency can cause symptoms even when fully developed anemia is not yet present [237]. Iron deficiency, with or without anemia, is a relevant analytical parameter in IBD. In fact, it is quite common in everyday clinical practice to find iron deficiency as the only sign of disease activity in IBD patients [239].

The decision to supplement iron in patients with iron deficiency but without anemia is not entirely clear and may depend on the clinical scenario and individual preference. The arguments for treating isolated iron deficiency are based on the fact that iron is essential for all cells of the body, and symptoms of iron deficiency are not only anemia-specific (such as fatigue and shortness of breath). Iron deficiency also affects nail growth, skin health, and mucosal regeneration and may cause symptoms such as headaches, sleep disorders, decreased libido, erectile dysfunction, and many more, including deterioration in quality of life [240,241]. Furthermore, recent evidence suggests that body iron levels should also be within the normal range, after iron supplementation, to fully improve cognitive performance and quality of life [242–244]. Finally, it is important to note that untreated iron deficiency is likely to progress to iron deficiency anemia [237].

10.2. The Impact of Anemia on the Quality of Life of Patients with IBD Is Quite Limited

The impact of iron deficiency anemia on quality of life is often underestimated or even ignored. However, the truth is that the repercussion of anemia on the quality of life of both general patients [245,246] and, specifically, patients with IBD [247–251] is substantial. In fact, the impact of anemia on the quality of life of these patients can be similar to that of a cancerous disease [247]. In addition, chronic fatigue resulting from anemia can weaken, affect, and worry these patients as much as abdominal pain or diarrhea [248]; therefore, the beneficial impact on quality of life derived from correcting anemia in patients with IBD can be similar to that of controlling diarrhea [248,250,252]. Moreover, anemia may impair quality of life even in the absence of specific symptoms [250,253]. For a long time, it was thought that the clinical symptoms of anemia (such as fatigue, headache, dizziness, shortness of breath, or tachycardia) occurred only when hemoglobin levels dropped abruptly [247,248]. It had been argued that patients would adapt to low hemoglobin levels if anemia developed slowly. This has led to the concept of "asymptomatic" anemia. In truth, the term "asymptomatic" seems to reflect the fact that impairments in physical condition, quality of life, and cognitive function may be unrecognized by both patients and their doctors. Therefore, the process of adaptation to chronic anemia would be, in fact, an adaptation to a lower quality of life [247,248].

10.3. Since Mild Anemia Is Common in Patients with IBD and Its Clinical Impact Is Only Evident When the Anemia Is Severe, Iron Therapy Is Rarely Necessary

The high frequency of low, albeit not excessively low, hemoglobin levels in patients with IBD often leads to an underestimation of this analytical alteration by physicians. One should not make the mistake of assuming that a certain level of anemia is a normal finding in patients with IBD and therefore does not require treatment [237,247]. On the contrary, oral iron administration should begin as soon as anemia is detected, defined according to the World Health Organization (WHO) as hemoglobin < 13 g/dL in males and <12 g/dL in females. Similarly, the therapeutic goal of oral iron therapy should be to completely correct the anemia, not just partially raise hemoglobin levels [184,239]. In fact, it is important to remember that the most significant improvement in quality of life is observed, precisely, when hemoglobin levels rise from 11 to 13 g/dL [254].

10.4. When Administering Oral Iron Treatment, Higher-Than-Usual Doses Should Be Used Because Its Absorption Is Often Decreased in Patients with IBD

Although it has been suggested that up to 200 mg of elemental iron per day are necessary to correct iron deficiency anemia, this is likely incorrect [255]. Since only approximately 10 mg of oral iron can be absorbed daily, higher doses are questionable. There is no rationale for using high doses of iron to treat iron deficiency anemia, whether in IBD or other associated diseases [256]. In fact, controlled efficacy studies on oral iron treatment in iron deficiency anemia among adults, the elderly, pediatric patients, and pregnant women, support the use of low-dose oral iron supplements [255–258]. From a physiological perspective, the iron absorption process is highly efficient but saturable [255,259]. A single tablet of most ferrous salt preparations (e.g., sulfate) provides more iron than the intestine can absorb in one day [256,257]. Non-absorbed iron salts can be toxic to the intestinal mucosa and may potentially activate the disease [237,260,261]. Furthermore, high doses of iron can cause diarrhea, impairing quality of life and complicating differentiation from an IBD relapse [260,262]. Therefore, as the absorption and efficacy of oral iron do not increase with higher doses, oral iron should be recommended at low doses (e.g., 50–100 mg of elemental iron daily), and higher doses would only increase the risk of adverse gastrointestinal effects (e.g., nausea, vomiting, constipation, and diarrhea) [239].

10.5. In Patients with IBD, Intravenous Iron Administration Should Be Reserved for Cases of Severe Anemia (e.g., Hemoglobin < 8 g/dL)

Following a widely agreed-upon algorithm, the initial therapeutic strategy for iron deficiency anemia in IBD patients is based on hemoglobin levels. Patients with hemoglobin levels above 10 g/dL could start treatment with oral iron. Those with levels below 10 g/dL—generally considered as severe anemia—should receive intravenous iron as the treatment of choice [237,239,263]. Intravenous iron should also be prescribed to patients with hemoglobin levels above 10 g/dL if there is intolerance to oral iron, failure to respond to oral iron treatment, or clinically active IBD [239].

11. Elderly Patients

In Elderly Patients with IBD, the Use of Biological Drugs Should Be Avoided at All Costs

While IBD typically affects younger individuals, elderly patients are increasingly represented in the IBD population [264]. Managing IBD in older patients can pose challenges due to their potential increased vulnerability to adverse events [264,265]. Partly due to the perception of less severe disease and concerns about therapy-related complications, effective immunosuppressive treatments are—erroneously—utilized less often in older patients compared to their younger counterparts. Multiple prior studies have noted that older patients with IBD are less likely to be prescribed anti-TNF therapy [266–270]. This results in prolonged morbidity from active disease in the elderly [266,267], while disease activity itself might increase the likelihood of more adverse events in this population [271].

Furthermore, multiple studies have noted that older patients with IBD are more likely to discontinue anti-TNF therapy [266,267,272–276]. The main reasons for stopping treatment reported in these cohorts included a lack of response and adverse events [275]. Earlier smaller studies have shown a higher risk of infections, hospitalizations, neoplasms, and/or mortality with anti-TNF therapy among elderly patients compared to younger ones [277]. However, the majority of available data come from retrospective observational studies, which may be constrained by confounding bias. Cheng et al. conducted a pooled analysis of data from randomized trials to assess the impact of age on the safety of anti-TNF therapy, showing that treatment of older patients with these agents did not increase the risk of serious adverse events or infections, compared with younger patients [278]. Although older anti-TNF users had numerically higher rates of infections than younger patients, this difference was not specific to biologics, and a similar numeric difference was also noted among those on the placebo [278]. Furthermore, anti-TNF therapy was similarly effective in older and younger patients [278]. Finally, elderly patients with IBD have a similar risk

of developing infliximab-related immune-mediated adverse events and a loss of response compared with younger patients [279].

On the other hand, when deciding to start anti-TNF therapy in older individuals, clinicians should also consider the implications of untreated disease and the potential risks linked to alternative treatments like surgery, along with the probability of post-operative complications [264]. Furthermore, it is important to consider the risks of disease relapse from discontinuing biological treatment and that the acute use of corticosteroids in elderly patients is also associated with a higher risk of adverse events. Therefore, treatment strategies for older patients that minimize steroid exposure should be considered [280].

In summary, the principles of medical management of IBD in elderly patients should be generally the same as in other age groups [275] Thus, elderly IBD patients—a clinical distinction must be made between fit elderly patients and frail elderly patients—should be candidates for treatment with all of the therapeutic options available for younger IBD patients [264].

12. Pregnancy

12.1. During Pregnancy, Endoscopic Examinations Should Not Be Performed Even if They Are Clearly Indicated, Due to the Risk of Harming the Fetus

Theoretically, the insertion of a colonoscope in a pregnant woman could induce premature labor. However, although experience evaluating the safety of endoscopic examinations during pregnancy is very limited, it appears that this technique is well tolerated by both the mother and the fetus [281]. Specifically, flexible sigmoidoscopy does not induce labor or cause fetal malformations, so this technique is not contraindicated during pregnancy [281–283]. Furthermore, this safety seems to be independent of the gestational age [283,284]. In addition, a systematic review determined that a lower endoscopy carries a minimal risk for both the mother and child throughout any of the three trimesters of pregnancy [285].

Obviously, for any patient but especially in pregnant women, diagnostic tests should not be performed if their result will not change the therapeutic approach. However, sometimes the information derived from a rectosigmoidoscopy is useful for establishing the cause of symptoms and the corresponding treatment, as in pregnant women presenting with hematochezia or unexplained diarrhea, who, thanks to this technique, can be finally diagnosed with IBD. In this regard, a study involving a sigmoidoscopy during pregnancy demonstrated that the most frequent diagnosis was IBD and that this knowledge led to a substantial change in the treatment of these women [286]. Similarly, a rectosigmoidoscopy would be indicated in patients with a known diagnosis of IBD who do not improve with standard treatment. Accordingly, the ECCO guidelines on pregnancy state that "during pregnancy, endoscopy can be performed when needed to guide clinical decision making" [287].

12.2. In Pregnant Women, Due to the Risk that Medications Pose to Fetuses, Efforts Should Be Made to Administer the Minimum Possible Treatment for IBD, Even if It Means that Some Intestinal Activity Persists

Since IBD typically affects young patients during their reproductive years, issues related to pregnancy often arise for them. The use of medications during pregnancy is a common concern for both the patient and the treating physician.

In a study examining the views and perceptions of women with IBD regarding medication use during pregnancy, a substantial portion (36%) of the participants believed that all IBD medications could negatively impact the health of unborn children [288]. Contrary to established evidence, around 24% of participants endured their symptoms without taking medication, because of the misconception that IBD medications are harmful [288]. Another study highlighted the concerns of women with IBD regarding fertility, pregnancy management, and the postpartum period, even though they received regular obstetric and specialized IBD care [289]. The most significant worry among participants was the

potential impact of their medication on pregnancy and offspring. They specifically feared the effects of medication on the child's immune system [289].

On the contrary, since it is clearly demonstrated that IBD activity during pregnancy is associated with a higher risk for the newborn (such as a premature birth or a low birth weight), it is important to "aggressively" treat IBD flare-ups during pregnancy instead of adopting a falsely "conservative" approach by arguing that the medications used in treating this disease may be harmful to the fetus [290–294]. In summary, the best way to ensure the fetus's well-being is to effectively control the mother's IBD activity [287].

Pregnant women experiencing a flare should be managed according to current guidelines for non-pregnant patients, with 5-ASA, steroids, anti-TNF agents, ustekinumab, or vedolizumab. Initiating monotherapy with a thiopurine is generally not recommended due to the slow onset of action and the potential risk of adverse events. Current guidelines recommend avoiding JAK inhibitors and S1P receptor modulators during pregnancy [287].

12.3. Biological Agents Are Not Safe during Pregnancy, and Therefore, They Should Be Discontinued before the Third Trimester

Biologics for the treatment of IBD are immunoglobulin G1 (IgG1) full monoclonal antibodies. In early pregnancy, only insignificant amounts of IgG are transported by passive diffusion. However, the maternal transfer of IgG1 through placental Fc neonatal receptors starts at weeks 13–17 and significantly increases thereafter. This transfer can result in cord blood levels in infants that may be several times higher than those in maternal serum [295]. Furthermore, detectable biological agents may persist in the infant's blood for up to 12 months [296].

Acknowledging the active transfer of biologics and the potential exposure of infants in utero and in early life (a sensitive period for immune system programming and development), there is a theoretical concern that such exposure may disturb the child's immunity. Discontinuing a biologic drug before the third trimester would limit the fetus's exposure to the drug and therefore could be beneficial to reduce its detrimental effects. However, a follow-up of children exposed to anti-TNF agents in utero showed no differences in infection rates requiring hospital admission, milestone developments, or other negative outcomes between those exposed only during early trimesters and those exposed throughout all three trimesters [287,290–294].

Furthermore, stopping a biologic drug that has induced remission may increase the chances of relapse, with negative consequences for both the mother and fetus [297–299]. Additionally, a prolonged drug (anti-TNF) holiday may increase the likelihood of a secondary loss of response in the postpartum period [287]. Therefore, in clinical practice, for women in remission, it is advised to continue anti-TNF agents during pregnancy since the potential risks of active disease are likely greater than those associated with anti-TNF use [287]. However, if a pregnant patient in long-term remission wishes to discontinue anti-TNF prior to the third trimester, the resumption of anti-TNF use shortly after delivery is recommended [287].

Other biological agents besides anti-TNFs, such as vedolizumab and ustekinumab, are also IgG1 [292,293]. Consequently, when the mother is treated during pregnancy, the fetus is exposed to these drugs from the second trimester, because from this time onwards, they cross the placenta. The clearance time of these drugs in newborns varies, but generally, vedolizumab and ustekinumab are cleared faster than anti-TNFs [292,293]. Animal studies have not shown a risk of teratogenicity with these drugs, and data are increasingly suggesting that both vedolizumab and ustekinumab are safe during pregnancy in humans as well [292–294].

12.4. Breastfeeding Is Contraindicated While the Mother Is Undergoing Treatment with Biological Agents

Breastfeeding is generally considered low-risk for patients on currently approved biologic drugs (mainly anti-TNFs, vedolizumab, and ustekinumab), as IgA is the predominant immunoglobulin found in breast milk, while the biologic agents used to treat

IBD are IgG. Therefore, secretion and transfer in breast milk should be minimal [292]. Furthermore, due to degradation in the infant's digestive tract, exposure to these drugs is unlikely to have any clinical relevance [293]. In summary, drugs that are considered low-risk during pregnancy are also considered low-risk during breastfeeding and thus can be continued [287]. In particular, several studies have shown that breastfeeding during treatment with anti-TNF agents appears to be safe and should not be discouraged [287,293]. Regarding non-anti-TNF biologics, the most relevant data on their safety during breastfeeding are summarized below.

In a study on monkeys, vedolizumab was detected at low concentrations in the breast milk of 3 out of 11 animals 28 days after their birth [300]. The first data on humans were reported in a study involving five breastfeeding women with IBD [301]. Serum and breast milk samples were collected before infusion, 30 min later, and over the following 14 days. The lowest vedolizumab concentrations (ranging from 0.124 to 0.228 mg/mL) were detected in breast milk samples collected before the infusion, peaking at 0.318 mg/mL on days 3 through 7, a concentration estimated to be less than 1% of serum levels. Considering the amount of milk ingested by a baby, the maximum amount of vedolizumab received is estimated to be 0.048 mg/kg per day [301]. Another recent study found similar findings in five post-partum women on maintenance therapy with vedolizumab [302]. Serum and breast milk samples were collected after 1 h and on the following days after the infusion. The amount of vedolizumab detected in breast milk was about 1% of the corresponding serum sample, peaking 3–4 days after the infusion and then progressively declining [302]. More recent data from 11 nursing women showed an average milk concentration of approximately 0.13 μg/mL with a peak of up to 0.56 μg/mL 3–4 days after the infusion [303].

Studies in macaques have shown that ustekinumab concentrations in breast milk are about 1/1000 of the serum blood concentration, a level considered too low to result in the systemic immunosuppression of the child [293]. Matro et al. reported on the concentration of various biologics in breast milk from patients included in the PIANO registry [304]. In a cohort of 824 infants, breastfeeding while receiving biological therapy did not affect the rate of infection or developmental milestones compared with non-breastfeeding. Six patients treated with ustekinumab provided breast milk samples, and ustekinumab was detected in four (67%) samples, with peak concentrations between 12 and 72 h after injection (range: 0.72–1.57 μg/mL). The authors concluded that lactation is compatible with maternal biologic therapy, including ustekinumab, based on minimal transfer rates in breast milk and no association with infant infections or developmental milestones [304]. Finally, Saito et al. also analyzed ustekinumab concentrations in breast milk, finding levels at 1/1400 of maternal serum, similar to previous studies on macaques and other case studies with CD [305].

12.5. In Children Exposed In Utero to Biologics, Non-Live Inactivated Vaccines Are Less Effective and Safe

Some reports and a meta-analysis suggest that several non-live inactivated vaccines (hepatitis A, hepatitis B, influenza, and *Streptococcus pneumoniae*) may not elicit adequate seroprotection when administered to adult IBD patients treated with anti-TNF agents [83,306–309]. In contrast, vaccines administered to children with IBD generally achieve adequate immunogenicity, regardless of the treatment, including anti-TNF agents [310,311].

Studies evaluating the efficacy of inactivated vaccines given to infants exposed to biologics (mainly anti-TNF agents) in utero suggest that the response (seroprotection) to inactivated vaccines could be considered adequate in most infants, although the available information is limited [312]. A systematic review and meta-analysis of studies assessing pregnancy and neonatal outcomes of women with immune-mediated inflammatory diseases (including IBD, rheumatoid arthritis, and psoriasis) exposed to anti-TNF agents during pregnancy demonstrated an adequate immune response to tetanus, *Streptococcus pneumoniae*, diphtheria, and hepatitis B virus [313]. In summary, newborns

with a history of in utero exposure to anti-TNF agents should adhere to a standard vaccination schedule for inactivated vaccines, as their effectiveness appears to be adequate based on current evidence [312].

Regarding the safety of inactivated vaccines, a systematic review has confirmed their safety in children with chronic conditions treated with biologics [314]. Furthermore, immunizations against hepatitis B and pneumococcus are well tolerated both in children and adults with IBD who are prescribed anti-TNF therapy [310,315–317]. When the studies evaluating the safety of non-live inactivated vaccines administered to infants exposed to biologics in utero were reviewed [312], no or only minor adverse events were reported following vaccination against hepatitis B virus, *Haemophilus influenzae*, influenza, and diphtheria [318,319]. Similarly, a meta-analysis of studies involving children born to mothers with immune-mediated inflammatory diseases exposed to anti-TNF agents during pregnancy reported only minor adverse events related to vaccinations, including tetanus, *Streptococcus pneumoniae*, diphtheria, hepatitis B virus, and *Haemophilus influenzae* type B [313]. In summary, there is no recommendation to alter the vaccination schedule for inactivated vaccines in infants exposed to biologics in utero, as this population does not appear to experience significant adverse events related to these vaccinations [287,320].

12.6. In Children Exposed In Utero to Biologics, All Live-Attenuated Vaccines Are Safe

Due to the risk of disease from uncontrolled replication, severe immunosuppression is generally considered a contraindication for live-attenuated vaccines [312,321]. Live-attenuated vaccines commonly administered in clinical practice during the first 12 months of life (when serum levels of biological drugs in the child can be detected) include the rotavirus vaccine and, in some countries, the Bacillus Calmette–Guérin (BCG) vaccine. Since the trivalent MMR (measles, mumps, and rubella) vaccine dose is recommended between 12 and 15 months, there is generally no reason to delay vaccination [40]. Studies assessing the safety of live-attenuated vaccines administered to infants exposed to biologics in utero have generally reported no serious adverse events [312]. However, despite the lack of severe complications following rotavirus vaccination in this context, five fatal cases of disseminated BCG infection in infants exposed to anti-TNF agents in utero, including infliximab and adalimumab, have been reported [312].

In accordance with ECCO recommendations, in children exposed in utero to biologics, vaccines should be withheld within the first year of life or until the biologic is no longer detectable in the infant's blood [287]. While avoiding the BCG vaccine may not be critical in most developed countries, it poses a more difficult decision in countries with a high tuberculosis incidence, where determining the serum levels of biological drugs in the child may be challenging or impossible. Therefore, the decision should always be individualized and made on a case-by-case basis [312].

Regarding rotavirus vaccination, most recent studies suggest that the risk of vaccination in infants exposed to biological agents in utero appears to be minimal or nil [313,322,323]. Therefore, it is increasingly common to allow such vaccination if it is deemed necessary, especially in developing countries, where rotavirus-related mortality is significant. Nevertheless, the risk–benefit ratio must always be carefully considered [312].

12.7. Administration of a Live-Attenuated Vaccine to a Breastfed Infant While the Mother Is Receiving Anti-TNF Agents Is Not Recommended Unless Infant Anti-TNF Serum Levels Are Undetectable

In March 2022, the European Medicines Agency (EMA) issued a direct healthcare professional communication (DHPC) concerning the use of live vaccines in infants exposed to infliximab during breastfeeding. According to this DHPC, the marketing authorization holders of infliximab, in agreement with the EMA, conveyed controversial information. They stated that infliximab has been detected in breast milk at low levels and also in infant serum after exposure via breastfeeding. Consequently, the DHPC advised against administering live vaccines to breastfed infants unless the infant's serum levels of infliximab are undetectable [312]. This recommendation aroused significant concern among gas-

troenterologists specialized in IBD, pregnancy, and lactation, leading to several responses opposing it [312,324–326]. Key arguments against the EMA recommendation included the following [312]:

(a) Multiple studies have consistently demonstrated that peak levels of infliximab in breast milk are minimal, typically less than 1% of maternal serum levels (see corresponding section above);
(b) A fully breastfed infant is estimated to receive a maximum of 0.045 mg of infliximab per kilogram of bodyweight per day [327]. Notably, breastfeeding while the mother is receiving infliximab treatment did not affect the clearance of infliximab in infants exposed in utero to the drug [312];
(c) The EMA's recommendation was primarily based on a case report involving two mothers receiving infliximab while breastfeeding. One infant's infliximab serum levels were undetectable, whereas the second infant's levels were measured at 1.7 μg/L during maternal induction treatment, equivalent to approximately 2% of the maternal serum infliximab level at that time [328];
(d) The largest study on biological treatment during breastfeeding involved 29 women treated with infliximab. This study confirmed very low levels of infliximab in breast milk and demonstrated that breastfed infants of mothers using biologics, including infliximab, had similar risks of infection and rates of milestone achievement compared to non-breastfed infants or infants not exposed to biologics [304];
(e) In the most recent study evaluating the risk of serious adverse events associated with live-attenuated vaccines in children breastfed by mothers receiving biological therapies—the DUMBO registry [329]—a quarter of breastfeeding mothers were on biologics (mostly anti-TNF agents). Sixty-eight percent of these children breastfed for at least 6 months received the rotavirus vaccine, 97% received the first dose of the trivalent MMR (measles, mumps, rubella) vaccine if they were breastfed for at least 12 months, and 84% received the first dose of the varicella vaccine if they were breastfed for at least 15 months. No serious adverse events related to these live-attenuated vaccines were reported [330];
(f) The recommendation against administering live-attenuated vaccines during lactation if mothers are treated with infliximab can have significant adverse consequences [324–326]. Breastfeeding women may choose to forgo medical treatment, decide not to breastfeed, or delay infant immunization. Such decisions could result in missed or delayed crucial vaccinations during the early years of a child's life, potentially increasing the risk of serious infections [312].

In conclusion, based on the available literature regarding the safety of live vaccines in infants breastfed by women receiving anti-TNF therapies, the benefits of breastfeeding while on infliximab (or any other anti-TNF agent) and adhering to national infant immunization programs likely outweigh any hypothetical risks to the infant [312].

13. Surgery

13.1. In CD, Surgery Always Represents the Failure of Medicine and Is Only Indicated When Medical Treatments Fail

Advances in medical management, combined with concerns shared by patients and doctors about the irreversibility of bowel resection, may lead some to view surgery as a last resort, to be delayed or avoided whenever possible, except in well-recognized situations of multiple medical treatment failure [331].

However, the LIR!C randomized controlled trial suggested that laparoscopic ileocecal resection was a viable and reasonable alternative to infliximab for patients with limited (diseased terminal ileum < 40 cm), non-stricturing, ileocecal CD who do not respond to conventional therapy [332]. This study indicated that while laparoscopic ileocecal resection was not superior to infliximab treatment, it was comparable in terms of restoring quality of life and was not associated with more serious adverse events. A long-term follow-up revealed that over one-third of patients initially treated with infliximab required an ileocecal

resection within a few years, while only one in four patients who initially underwent resection needed subsequent anti-TNF therapy [333]. Furthermore, laparoscopic ileocecal resection was a cost-effective treatment option compared with infliximab [334]. Based on these findings, laparoscopic ileocecal resection should be offered as an alternative to anti-TNF therapy for patients with limited, non-stricturing ileocecal CD that does not respond to conventional therapy [332].

More recently, Agrawal et al. conducted a population cohort study to compare long-term outcomes in patients diagnosed with ileal and ileocecal CD who underwent either ileocolic resection or received anti-TNF therapy within one year from diagnosis [335]. They found that ileocolic resection was associated with a 33% reduced risk of systemic corticosteroid exposure and CD-related surgery compared to medical therapy. Additionally, 50% of patients who underwent ileocolic resection did not require any further medical therapy at 5 years [335].

13.2. In Patients with Acute Severe UC, Surgery Should Be Delayed as Much as Possible

Acute severe UC potentially carries a high risk of death [231]. However, the introduction of intravenous steroid treatment in 1955 reduced acute mortality from 24% to 7% [336]. Timely surgery combined with intensive medical therapy further decreased the mortality rate to less than 1% in specialized centers [337]. However, with the advent of rescue medical therapy for steroid failure—using cyclosporine or infliximab—the necessity of surgery is being re-evaluated [27].

At present, in patients with acute severe UC, surgery should be performed when clearly indicated (such as in cases of suspected perforation, a toxic megacolon, or refractory bleeding), when medical rescue therapy is contraindicated, or in cases of failure of medical rescue therapy [27]. However, surgery should be considered relatively early in the treatment process as a beneficial alternative, not just a fallback after unsuccessful medical management. Postponing surgery is linked to a higher risk of postoperative complications, making the timing of the surgery crucial. Therefore, surgery should preferably be performed in a semi-elective setting rather than an emergency one whenever possible, as the mortality rate following a colectomy for UC is higher in emergency situations [27].

Randall et al. evaluated the long-term outcomes following urgent colectomies for acute severe UC and investigated whether the duration of in-hospital medical therapy was related to postoperative outcomes [338]. Patients with a major complication at any time during their follow-up had a significantly longer duration of medical therapy before a colectomy was performed than patients with no major complications. Therefore, it was concluded that delayed surgery for acute severe UC was associated with an increased risk of postoperative complications. This result does not question the value of medical therapy, which should be pursued vigorously to avoid surgery [171]. However, if medical therapy is continued for too long, the complication rate increases if surgery becomes necessary. Therefore, the challenge for both physicians and surgeons is to monitor patients closely and make the decision to operate at an appropriate time. We should never forget that our primary aim should be to reduce patient mortality rather than save the colon [171].

13.3. Most Drugs Used in IBD Treatment (Corticosteroids, Thiopurines, Biologics, and Small Molecules) Equally Increase the Risk of Postoperative Complications

Treatment with corticosteroids represents a risk factor for the development of complications during and after surgery [339–341]. However, unlike steroids, treatment with thiopurines (or methotrexate) does not increase the risk of postoperative complications (infectious or otherwise) in patients undergoing surgery for IBD [342,343]. Currently, a significant number of patients undergoing surgery are receiving biological agents. Therefore, it is crucial to ascertain whether this treatment increases the risk of complications to make informed decisions regarding the scheduling of surgeries.

Initial findings from several meta-analyses suggested an increased risk of post-operative complications in IBD patients undergoing anti-TNF therapy, particularly in those with

CD [344,345]. However, in contrast with these findings, recent meta-analyses focusing on CD or UC suggest that the preoperative administration of biological agents is not linked to increased early postoperative complications [346–350]. Additionally, prospective studies assessing this effect found no association between preoperative anti-TNF administration or drug levels and postoperative complications in IBD patients. Finally, the largest cohort study that has evaluated the safety of preoperative anti-TNF, vedolizumab, or ustekinumab treatments in IBD patients concluded that none of these drugs increased the risk of post-operative complications [351]. Accordingly, current guidelines suggest that preoperative treatment with any biological therapy, including vedolizumab and ustekinumab, does not increase the risk of post-operative complications in patients with IBD undergoing abdominal surgery [352]. Hence, the withdrawal of biological therapy before surgery may not be necessary (i.e., it is not mandatory) to reduce the incidence of postoperative complications [353]. It is likely that this same recommendation can be applicable to small molecules [350].

13.4. Previous Failure with an Anti-TNF Agent Necessarily Warrants Switching to a Drug with a Different Mechanism of Action (Such as Vedolizumab or Ustekinumab) to Prevent Post-Operative Recurrence of CD after Surgery

Anti-TNF therapy is frequently used in the treatment of refractory CD. Unfortunately, primary or secondary treatment failure of anti-TNF treatment is not uncommon [354,355]. Therefore, in clinical practice, a substantial proportion of patients who receive anti-TNF agents after surgery—to prevent post-operative recurrence (POR)—have been exposed to these agents prior to surgery. As the number of patients who do not respond to multiple biologics/small molecules and require surgery increases, the decision regarding postoperative treatment will become more complex [356,357].

Some studies have reported that anti-TNF agents are less effective for the prevention of POR in patients with previous exposure to anti-TNFs, compared with those naïve to these agents [358–362], suggesting that a reasonable approach to prevent POR would be choosing a biologic with an alternative mechanism of action (non-TNF-related) for those who experienced treatment failure with an anti-TNF agent [356]. Noteworthy, the aforementioned studies have some relevant limitations (including their retrospective design). However, other investigators have reached opposite conclusions, that is, that anti-TNF remains an effective option to prevent POR for patients operated upon with previous anti-TNF failure [363–368].

As the presence of intestinal complications is known to be one of the risk factors for the lower efficacy of anti-TNF agents, the requirement for surgery early after the initiation of anti-TNF treatment may not indicate the primary ineffectiveness of the agent but insufficient effectiveness owing to the presence of intestinal complications, thereby explaining the favorable results in the post-operative scenario despite previous anti-TNF failure [369]. Therefore, in these patients, the removal of intestinal complications by surgery might "reconstitute" the efficacy of anti-TNF agents. Others have tried to explain this by arguing that anti-TNF treatment shortly after surgery, when there are still no signs of active disease, could interfere with the initial pathogenic mechanisms of tissue damage, changing the natural evolution of the disease. Based on these results, some authors have proposed maintaining the anti-TNF treatment if these agents were used preoperatively, and then performing early screening to evaluate and adjust medications. This strategy might spare further possible biological treatment options in the future.

Nevertheless, the main limitation of all previously mentioned studies is that a control group, treated with a different biological agent than an anti-TNF, was not included. A preoperative anti-TNF therapy requirement might simply be a surrogate marker of a more severe, refractory disease (to any treatment) before surgery, and therefore, it may not necessarily imply a worse response when readministering anti-TNF treatment (compared with non-anti-TNF biological agents). In fact, both vedolizumab and ustekinumab are also less effective in anti-TNF-exposed patients [355]. Unfortunately, the two main strategies used to treat a patient with primary non-response to an anti-TNF agent—switching to

a second anti-TNF or switching to vedolizumab/ustekinumab—have not been properly compared in randomized controlled trials [355].

Recently, some studies have compared, in a non-randomized manner, the efficacy of anti-TNFs with that of other biologics in preventing POR. Yanai et al. reported that the continuation of anti-TNF treatment after surgery resulted in a similar rate of endoscopic POR as switching to a different mechanism of action [370]. On the other hand, Le Cosquer et al. evaluated CD patients who underwent bowel resection after failure of at least one anti-TNF treatment [371]. The rates of POR at two years were lower (24%) in the patients treated with anti-TNFs than in those receiving other biologics such as ustekinumab or vedolizumab (45%).

14. Conclusions

Two facts seem clear on the subject of errors: they are very common in medical practice—and in particular, in the healthcare of IBD patients—and most of them can be prevented. Despite the existence of guidelines for both disease management and preventive aspects of IBD care, a considerable variation in clinical practice and a lack of adherence to clinical guidelines for IBD still remain. In the present review, we have identified some mistakes frequently observed in clinical practice in the management of patients with IBD, then we have reviewed the scientific evidence available on the subject, and finally we have proposed the most appropriate recommendations. There is a clear need for a greater dissemination of clinical practice guidelines among gastroenterologists and for the implementation of ongoing training activities supported by scientific societies. Finally, it is recommended that IBD patients be followed in specialized units, which will be associated with higher-quality healthcare and lower likelihood of errors in managing these patients.

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Abbreviations

Anti-tumor necrosis factor (anti-TNF), Bacillus Calmette–Guérin (BCG), European Crohn's and Colitis Organisation (ECCO), Clostridioides difficile (C. difficile), cytomegalovirus (CMV), Crohn's disease (CD), direct healthcare professional communication (DHPC), Epstein–Barr virus (EBV), European Medicines Agency (EMA), hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), inflammatory bowel disease (IBD), post-operative recurrence (POR), ulcerative colitis (UC).

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Study Protocol

Effectiveness of Telemedicine in Inflammatory Bowel Disease in Russia: TIGE-Rus (Telemonitoring for IBD Goodness Examination in Russia) Study Protocol of a Randomized Controlled Trial

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Abstract: Background: Inflammatory bowel diseases (IBD), associated with a significant burden on patients' lives, are becoming increasingly common. Patients with IBD need continuous treatment and lifelong monitoring, which could be achieved by telemonitoring. Telemonitoring has been shown to be effective in improving outcomes for patients with IBD, and can provide a more convenient and accessible way for patients to receive care. However, the certainty of evidence remains low. This article outlines the methodology of a randomized control study that aims to assess the efficacy of telemonitoring compared to face-to-face follow-up for patients with IBD in Russia, hypothesizing that the implementation of telemonitoring will lead to improvement in clinical, social, and organizational areas. **Methods:** The TIGE-Rus study is a randomized controlled trial. The study consists of three stages, including selection of patients and random assignment into two groups with a ratio of 1:1, follow-up care using telemonitoring or face-to-face appointments, and evaluation and comparison of follow-up efficacy in both groups. In the first stage, all patients will undergo laboratory tests and instrumental examinations, and fill out questionnaires to measure disease activity, quality of life, medication adherence, psychological well-being, and satisfaction with medical care. In the second stage, the control group will receive standard care while the telemonitoring group will have access to a web platform where they can report their clinical activity, fill out questionnaires, and have online consultations with gastroenterologists. The gastroenterologists will also make monthly phone calls to each patient in the telemonitoring group to monitor their progress. In the third stage of the study, both the telemonitoring group and the control group will be re-hospitalized after six months of monitoring. IBD activity will be evaluated through laboratory and instrumental examinations. Additionally, all the participants will complete questionnaires to assess the disease activity, medication adherence, quality of life, psychological well-being, and satisfaction with medical care in both groups. **Conclusions**: The trial will explore whether telemonitoring is effective in improving clinical, social, and organizational aspects in the management of patients with IBD in the setting of the Russian healthcare system.

Keywords: inflammatory bowel disease; ulcerative colitis; Crohn's disease; mHealth; telemonitoring

1. Introduction

Inflammatory bowel diseases (IBD), such as Crohn's disease (CD) and ulcerative colitis (UC), are chronic conditions characterized by recurrent inflammation of various parts of the gastrointestinal tract. The increasing prevalence and incidence of IBD [1,2], combined with the nature of the disease course, creates a significant medical, social, and financial burden [3]. Even after achieving remission, patients may still experience symptoms such as stool disorders, abdominal pain, and weakness, leading to reduced ability to work and socialize, deterioration of quality of life, and psychological distress [4].

The Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE II) consensus in 2021 recommended that the endpoint for treatment should not only be clinical remission but also improvement in health-related quality of life (QoL), which could be achieved by continuous lifelong follow-up [5]. However, longitudinal face-to-face follow-up is resource-intensive [3], encouraging the development and implementation of innovative solutions and online tools, including telemedicine technologies (TMT) [6], large language models [7], artificial intelligence, and machine learning [8].

Telemonitoring has been shown to be effective in improving outcomes for patients with IBD [9]. Additionally, telemonitoring can provide a more convenient and accessible way for patients to receive care, as they can communicate with their healthcare provider from the comfort of their own homes. According to a systematic review by Al Khoury et al., IBD patients have a positive attitude towards the use of TMT and expect it to be included into their treatment program [10]. A meta-analysis by Pang et al. demonstrated that TMT significantly improved the QoL associated with IBD ($p = 0.002$) [11]. According to Cross et al., IBD patients in the telemonitoring group had a lower risk of hospitalization in comparison with the standard-care group [12]. However, previous studies estimated ad hoc endpoints that despite their value did not provide a complex assessment of social, organizational, and clinical aspects. To address this gap, before the start of the trial we defined the list of assessed parameters by the Delphi method [13]. In our study, we consider the individual with IBD not only as a patient but also as a person and a consumer of medical services.

Our study hypothesizes that the implementation of TMT in patient monitoring will lead to improvements in three key aspects:

(i) Clinical aspects: a reduction in the number of relapses and in disease activity;
(ii) Social aspects: improvements in QoL and psychological well-being;
(iii) Organizational aspects: higher adherence to treatment and satisfaction with medical care.

Additionally, the study hypothesizes that patients' QoL will be influenced by both the clinical course of the disease and their psychological well-being.

This article outlines the methodology of a randomized control study that aims to assess the efficacy of telemonitoring compared to face-to-face follow-up for patients with IBD in Russia.

Objectives

The primary objective of this study is to assess the impact of telemonitoring on quality of life (QoL) in patients with inflammatory bowel disease (IBD). Secondary objectives include evaluating disease activity, the incidence of IBD relapses, and the rate of leukopenia in patients receiving immunomodulatory treatments (e.g., thiopurines, cyclosporine, tacrolimus). Additionally, the study will investigate medication adherence, psychological well-being, and patient satisfaction with medical care in the telemedicine group, compared to the face-to-face follow-up group. Finally, we aim to explore the relationship between secondary outcomes and QoL.

2. Materials and Methods

This trial protocol follows the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) 2013 guidelines [14]. The trial will be conducted in compliance

with The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use Good Clinical Practice (ICH GCP). The trial is registered on Clinicaltrials.gov in August 2023, NCT05994716.

2.1. Study Design

The TIGE-Rus is designed as a prospective, parallel, two-armed, randomized controlled trial with a 1:1 allocation.

This study will consist of three stages (Figure 1).

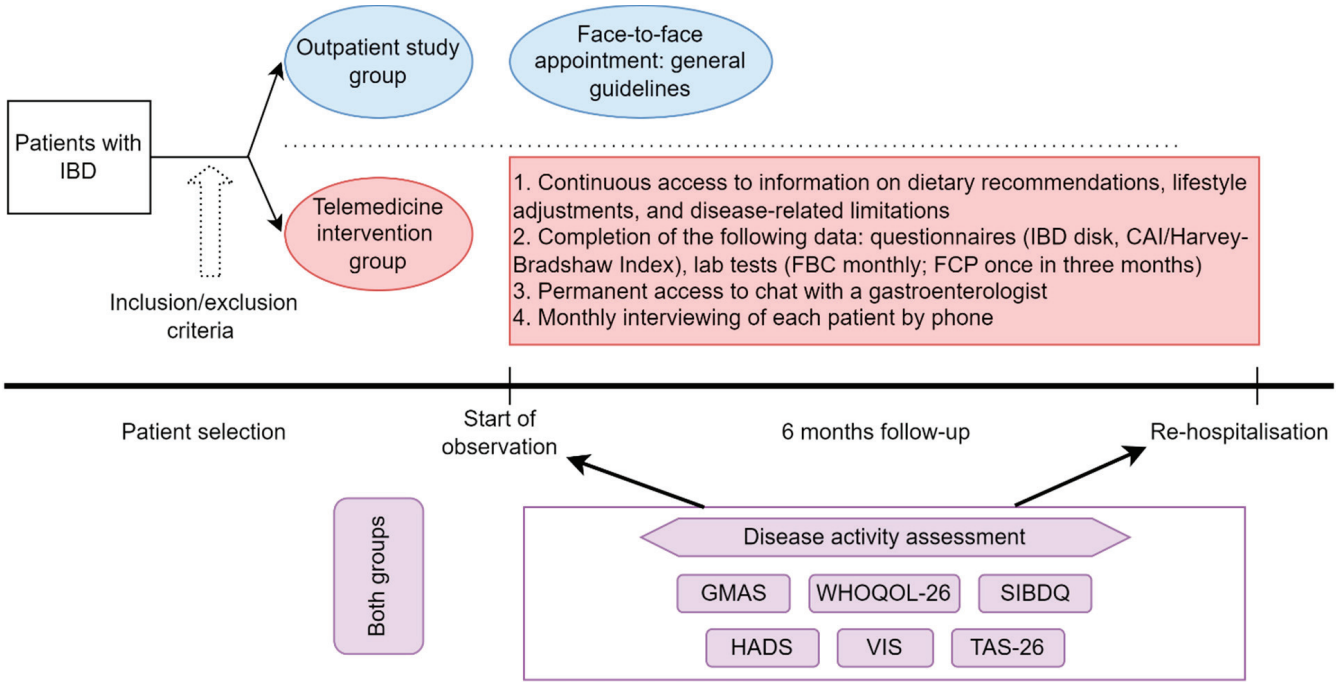

Figure 1. Study design.

The first stage will be a selection of patients with IBD after treatment in the Gastroenterology Department of the Sechenov University Hospital and random assignment of participants to two groups: face-to-face outpatient observation (control group) and observation using telemedicine technologies (intervention group). For every included patient, evaluation of disease activity, QoL, medication adherence, psychological well-being, and satisfaction with medical care will be performed (Figure 1).

The second stage consists of the follow-up care. For the control group, the follow-up scheme includes face-to-face appointment and follow-up recommendations on treatment, post-discharge care plan, and diet. They will be provided with the recommendations on discharge from the hospital and then on the patient's request. The follow-up for the intervention group consists of the following: monthly completion of questionnaires on the specialized web platform by the patient; the possibility of contacting the gastroenterologist via chat or phone call on the patient's request; and access to educational information about IBD, psychological well-being, lifestyle, diet, sexual life, pregnancy (examples in Multimedia Appendix A), posted on the web platform. In addition, patients in the intervention group will receive a monthly phone call to address any questions or concerns they may have. During these calls, they will also be interviewed using a predefined checklist (Multimedia Appendix B).

The third stage of the study will be evaluation and comparison of follow-up efficacy in the control and intervention groups. All patients will be re-hospitalized to the Gastroenterology Department after 6 months of follow-up, where the QoL, disease activity, number of IBD relapses, frequency of leukopenia in patients receiving immunomodulators,

medication adherence, psychological well-being, and satisfaction with medical care will be assessed (Figure 1).

2.2. Study Setting and Eligibility Criteria

The study will be conducted in the Gastroenterology Department of the Sechenov University Hospital in Moscow, Russia. It is a national center where patients from all Russian regions are treated. Thus, the study results can be extrapolated to the entire Russian population.

2.2.1. Inclusion Criteria:

(1) Age $\geq$ 18 years old. Under Russian law, age 18 is the point at which patients transition from the pediatric to the adult population. The aim of our study is to assess the effectiveness of telemonitoring in adult patients with inflammatory bowel disease. There is no upper age limit in our study because, as long as the patient does not meet any exclusion criteria, age will not influence the study outcomes;
(2) Signed informed consent;
(3) Diagnosis: Crohn's disease and ulcerative colitis (the diagnostic criteria for Crohn's disease and ulcerative colitis are detailed in Multimedia Appendix C);

2.2.2. Exclusion Criteria:

(1) Severe cognitive dysfunction;
(2) Severe mental illness;
(3) Oncological diseases requiring active treatment;
(4) Decompensation of a comorbid condition that has worsened to the point of posing serious health risks or complicating the assessment of the trial's outcomes;
(5) Pregnant individuals;
(6) Participation in other clinical studies;
(7) Lack of technical skills to take part in telemedicine intervention (e.g., difficulty using a smartphone, computer, or tablet) or the absence of appropriate technology;
(8) Inability to understand written Russian.

2.3. Consent

Every patient with IBD will receive an information brochure. A trained researcher will introduce the TIGE-Rus details to participants and discuss the trial with them. If the patient agrees to participate, they will have to sign informed consent (Multimedia Appendix D).

Patients who will be allocated to the telemonitoring group will also receive an Addendum to the informed consent containing information on health conditions requiring emergency or urgent care (Multimedia Appendix E).

2.4. Randomization

Randomization will be performed in 1:1 ratio between control and experimental groups using the envelope method.

2.5. Trial Interventions and Participant Timeline

2.5.1. Stage 1

All participants will undergo a series of laboratory tests, including a complete blood count, C-reactive protein levels, and fecal calprotectin. They will also receive instrumental evaluations such as a colonoscopy with biopsy. For patients with severe IBD or jejunoileitis, a contrast-enhanced abdominal and pelvic CT scan or magnetic resonance enterography will be conducted (Table 1).

Table 1. Summarizes the trial interventions and participant timeline.

	Study Period						
	Enrolment/Baseline 0 Weeks	Follow-Up					End of the Study (6 Months)
		1 Month	2 Months	3 Months	4 Months	5 Months	
Informed consent	X						
Eligibility criteria	X						
Demographic data	X						
Treatment in the Gastroenterology Department	X						X
Adverse events		X	X	X	X	X	X
Treatment	X	X	X	X	X	X	X
Face-to-face consultation for both groups	X						X
Observation using telemedicine technologies for the intervention group (including web-platform, phone calls)		X	X	X	X	X	
Clinical parameters							
Haemoglobin concentration	X	X	X	X	X	X	X
White blood cells concentration	X	X	X	X	X	X	X
C-reactive protein concentration	X			X			X
Fecal calprotectin concentration	X			X			X
IBD disk		X	X	X	X	X	
HBI/SCCAI questionnaire	X	X	X	X	X	X	X
Disease severity according to laboratory and instrumental data	X						X
Disease severity according to CDAI/UCDAI	X						X
Social parameters							
VSI questionnaire	X						X
TAS-26 questionnaire	X						X
HADS questionnaire	X						X
SIBDQ questionnaire	X						X
WHOQOL-26 questionnaire	X						X
Organizational parameters							
PSQ-18 questionnaire	X						X
GMAS questionnaire	X						X

After group assignment and signing informed consent, all participants will fill out the following questionnaires:

- Simple Clinical Colitis Activity Index (SCCAI) [15] questionnaire for patients with ulcerative colitis/Harvey-Bradshaw index (HBI) [16] questionnaire for patients with Crohn's disease;
- Short Inflammatory Bowel Disease Questionnaire (SIBDQ) [17];
- World Health Organization's QoL (WHOQOL-26) [18];
- General Medication Adherence Scale (GMAS) [19]
- Patient Satisfaction Questionnaire (PSQ-18) [20];
- Hospital Anxiety and Depression Scale (HADS) [21];
- Visceral Sensitivity Index (VSI) [22];
- Toronto Alexithymia Scale (TAS-26) [23].

The clinical activity of the disease will be measured by Disease Activity Index (DAI) for ulcerative colitis and Crohn's Disease Activity Index (CDAI) for Crohn's disease [24,25].

2.5.2. Stage 2

The patients in the control group will have a face-to-face consultation with a gastroenterologist, who will offer treatment recommendations, a post-discharge care plan, and dietary advice. Standard care for the control group will follow evidence-based guidelines, with outpatient visits available upon the patient's request [24,25].

The telemonitoring group patients will receive authorized access to the personal account on the web platform. The structure of the web platform is shown on the Figure 2. It includes educational content on IBD, necessary lifestyle adjustments, and dietary guidelines, all based on international standards and resources from the Crohn's and Colitis Foundation.

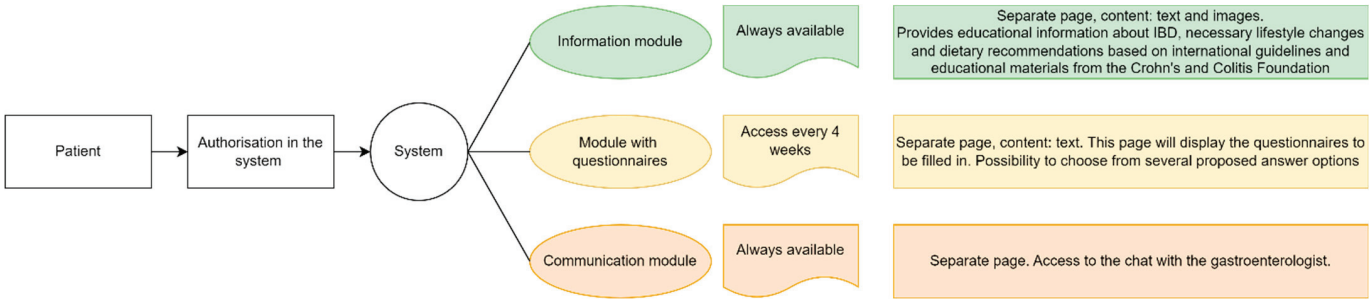

Figure 2. An online platform structure for patients in the intervention group.

Patients will be required to log in to the web platform at least once per month. Upon logging in, they will need to provide the following information: (1) SCCAI for ulcerative colitis and the Harvey-Bradshaw index for Crohn's disease to assess disease activity during monitoring; (2) the IBD disk questionnaire to track disease progression; and (3) results from laboratory tests (complete blood count, C-reactive protein, and fecal calprotectin). Both healthcare professionals and patients will have access to the test results. Additionally, patients can request an online consultation with a gastroenterologist via chat or phone call. They will be advised to contact a gastroenterologist if they experience disease recurrence.

Each month, gastroenterologists will call patients in the intervention group and ask questions based on a checklist (Multimedia Appendix A). They will be trained to provide immediate assistance if there are critical deviations in health indicators from the reference values (see Table 2) or complaints suggesting the onset of an acute condition.

Table 2. Limit values of the laboratory tests.

Laboratory Parameter	Critical Deviation from Reference Values
Haemoglobin concentration	Lower than 110 g/L; higher than 170 g/L
White blood cells concentration	Lower than 3×10^9 cells/L; higher than 11×10^9 cells/L
C-reactive protein concentration	Higher than 10 mg/L
Fecal calprotectin concentration	• Higher than 200 μg/g for patients included in the trial with initially normal levels. • Maintaining the level of more than 800 μg/g between two time points (Table 1) for patients included in the trial with initially high levels

Web Platform Description

Web platform http://ondoc.telemedai.ru/ provides access to a personal patient profile, a newsfeed with educational information (Appendix F, Figure A1), chat with the

gastroenterologist (Appendix F, Figure A2), a health parameters monitoring page (Appendix F, Figure A3), information about the gastroenterologist (Appendix F, Figure A4), and the questionnaires module (Appendix F, Figure A5).

2.5.3. Stage 3

After six months of monitoring, participants from both groups will be readmitted to the hospital. IBD activity will be assessed through laboratory and instrumental tests, including a complete blood count, C-reactive protein levels, fecal calprotectin, colonoscopy with biopsy, and computed tomography or MR-enterography (for patients with severe IBD or jejunoileitis). Both groups will also have to recomplete all the questionnaires to evaluate the study endpoints (see Table 1).

2.6. Adverse Event Reporting and Harms

An adverse event is defined as any untoward health-related occurrence in a study participant. It does not necessarily have a correlation with the allocated intervention. However, any adverse event will be recorded and reported at any study time point. Nevertheless, we developed an Addendum to the informed consent containing information on health conditions requiring emergency or urgent care for the intervention group (Multimedia Appendix D). We do not anticipate any harm related to participation in the study.

2.7. Outcome Measurements and Data Collection Methods

The assessment of the study outcome-related variables will take place at the baseline and at 6 months post–group assignment (Table 3).

Table 3. Study outcomes and data collection methods.

Item	Definition	Data Collection Method	Measure
Primary outcome			
Health-related quality of life (HRQol) in IBD	QoL specifically associated with bowel symptoms	SIBDQ score	Min score is 10, max score is 70. <50 means poor HRQol; >50 optimal HRQol Higher score means better outcome
Secondary outcomes			
Generic QoL	Generic QoL associated with several domains of life quality (physical and mental health, social relationships, and environment)	WHOQOL-26 score	Min score is 0%, max score is 100% for each domain. Higher score means better outcome.
Clinical activity of UC	Clinical activity of UC according to DAI with questions regarding clinical symptoms and endoscopic activity	DAI	0–2—remission; 3–6—mild activity; 7–10—moderate activity; >10—severe activity;
Clinical activity of CD	Clinical activity of CD according to CDAI, which is a 'gold standard' for trials. CDAI consists of questions regarding symptoms, lab tests, extraintestinal complications, general well-being	CDAI	<150—remission; 150–300—mild activity; 301–450—moderate activity; >450—severe activity;
General medication adherence	Adherence to the prescribed medications, patient compliance	GMAS score	0–26—non-adherent; 27–33—adherent [26];
Rate of leukopenia in patients taking immunomodulators (thiopurines, cyclosporine, tacrolimus)	Leukopenia that is associated with the intake of immunomodulators according to full blood count during the monitoring	Electronic health record, full blood count	Number of patients taking immunomodulators with onset of leukopenia
Satisfaction	Patient satisfaction with healthcare	PSQ-18 score	Min score is 18, max score is 90. Higher score means better outcome;

Table 3. *Cont.*

Item	Definition	Data Collection Method	Measure
Depression and anxiety	Levels of anxiety and depression in patients with chronic diseases	HADS	The HADS has two scales: for anxiety (HADS–A) and for depression (HADS–D), differentiating the two states. For each scale: 0–7—no depression or anxiety; 8–10—a doubtful case; 11–21—a definitive case;
Visceral sensitivity	Gastrointestinal (GI) symptom-specific anxiety causing bowel symptoms persistence	VSI score	0–10—no GI-specific anxiety; 11–30—moderate GI-specific anxiety; 31–75—severe GI-specific anxiety;
Alexithymia	Difficulty to perceive and express emotions	TAS-26 score	26–62—no alexithymia; 63–74—a doubtful case; 75–130—a definitive case;
Additional outcomes			
Endoscopic activity of UC	Endoscopic activity of UC assessed via colonoscopy	Mayo Endoscopic Score (MES)	0—normal or inactive disease; 1—mild disease with erythema, decreased vascular patterns and mild friability; 2—moderate disease with marked erythema, absence of vascular patterns, friability and erosions; 3—severe disease with spontaneous bleeding and ulceration
Endoscopic activity of CD	Endoscopic activity of CD assessed via colonoscopy	Simple Endoscopic Score for Crohn's Disease (SES-CD)	0–2—remission; 3–6—mild severity; 7–15—moderate severity; >15—severe;
Histological activity of IBD	Histological activity of IBD assessed via biopsy	Binary scale	No signs of inflammation in the histological material; Presence of signs of inflammation in the histological material
Laboratory tests	White blood cells concentration; Haemoglobin concentration; C-reactive protein concentration; Fecal calprotectin concentration;	Blood test and stool test	Normal values: 4–11 $\times$ 10^9 cells/L; 120–170 g/L; 0–5 mg/L; <200 μg/g for patients with initially normal levels. <800 μg/g in both time-points for patients included in the trial with initially high levels
General medication adherence differences	Adherence to the prescribed medications, interpreted in 5 levels of adherence	GMAS score	0–10—poor adherence; 11–16—low adherence; 17–26—partial adherence; 27–29—good adherence; 30–33—high adherence;
Rate of non-scheduled medical encounters *	Unplanned visits to the Physician for IBD symptoms	As recorded in electronic health record	Number of non-scheduled visits
Rate of surgical interventions *	Surgical interventions for IBD complications	As recorded in electronic health record	Number of surgical interventions
Rate of hospitalizations *	Unplanned hospital admissions for any reason	As recorded in electronic health record	Number of unplanned hospitalizations with specification of the reason

* we assume that telemonitoring will lead to decrease in these parameters.

2.8. Sample Size

The sample size was determined by the objective of estimating the primary outcome of the study. The standard deviation and expected difference in disease-related QoL between groups for the sample size were based on data from studies of IBD patients assessed with SIBDQ. The standard deviation was taken to be 12.52 points based on the study by Sun et al. [27]. The expected difference between the study groups was chosen to be smaller

than the clinically significant change in HRQoL according to Jowett et al. [28] and taken to be 10 points. Considering a potential loss and incomplete records of 20%, a total of at least 64 patients (32 patients in the control group and 32 patients in the intervention group) should be included in the study to detect a difference between groups with a statistical power of 80% (two-sided type I error of 0.05).

2.9. Statistical Methods

The results will be analyzed only after the follow-up of all the included patients has been completed. The questionnaire scores will be calculated based on scoring guides from the questionnaire developers. Missing questions will be processed according to these guidelines. Patients without completed SIBDQ at any study point will be excluded from the analysis. Patients who refused to participate at any point in the study will be excluded from the analysis. We plan to use the full analysis set and the per protocol set (for patients without completed SIBDQ at any study point or who refused to participate at any point in the study).

Continuous variables will be tested for normality using the Shapiro–Wilk test and presented as mean (SD) or median (IQR), as appropriate. Categorical variables will be presented as percentages. For demographic and clinical data, descriptive statistics will be used to characterize the study population and to identify erroneous values. Additionally, missing values will be analyzed to determine the randomness of these omissions.

Hypothesis testing will be conducted for primary and secondary outcomes (Table 4). Quantitative variables will be compared using the Student's T-test or the Mann–Whitney U test, as appropriate, and qualitative variables will be compared using the Fisher's exact test. Univariate analysis of variance and multiple linear regression will be performed to analyze the association of secondary outcomes with the primary outcome. The Benjami and Hochberg (BH) false discovery rate (FDR) approach will be used to correct for multiple comparisons ($p < 0.05$). For the variables with FDR $\leq$ 10%, the term "showing a trend" will be used to avoid confusion with statistically significant variables.

Table 4. Hypotheses proposed according to the primary and secondary study aims.

	H_0	H_a	
Hypothesis	6 months after the start of observation, there is no difference between the groups on the evaluated parameter	6 months after the start of observation, the values of the assessed parameter are higher in the telemonitoring group	6 months after the start of observation, the values of the estimated parameter are lower in the telemonitoring group
Outcomes	All primary and secondary outcomes	• HRQol • Generic QoL • General medication adherence • Satisfaction with medical care	• Clinical activity of UC/CD • Rate of leukopenia in patients taking immunomodulators (thiopurines, cyclosporine, tacrolimus) • Depression and anxiety • Visceral sensitivity • Alexithymia

H_0—null hypothesis; Ha—alternative hypothesis.

All the analysis will be performed using a Python version of at least 3.7.0 or an R version of at least 4.2.0. A value of $p < 0.05$ will be considered statistically significant.

3. Discussion

3.1. Overview

In this article, we describe the key elements of the design of a randomized control study aimed to evaluate telemonitoring efficacy for IBD in Russia.

The available evidence has shown that IBD patients have a lower quality of life compared to healthy individuals [29], even during periods of remission [30]. IBD is

characterized by a relapsing and remitting clinical course that requires lifelong monitoring. Telemonitoring offers a promising solution by enabling the continuous monitoring of a wide range of health-related parameters. A recent systematic review has indicated that telemonitoring improved the QoL for individuals with IBD [11]. However, the systematic review of Nguyen et al., which employed the GRADE (Grading of Recommendations, Assessment, Development, and Evaluations) approach, showed a reduction in healthcare utilization and costs, with no change in QoL, disease activity, or medical adherence (low or very low certainty of evidence) [31].

These results highlight the need for further studies to better understand the true impact of telemonitoring on IBD patients. The studies included in the reviews assessed various parameters and used different metrics, which shows the complexity of evaluating telemonitoring in IBD. To address this complexity, we decided to evaluate the impact of telemonitoring on a broad range of parameters, including clinical, social, and organizational aspects (see Table 1). Previously, we approached the issue systematically and surveyed gastroenterologists specializing in IBD treatment. Thus, we determined the parameters that should be monitored in IBD patients during telemonitoring [13]. It is important to note that this is the first trial in Russia aimed to evaluate telemonitoring efficacy in IBD.

When considering the scalability of an intervention, we can hypothesize that telemonitoring might be a suitable option for IBD patients in remote areas who do not have direct access to qualified face-to-face medical care. After the study completion, we plan to use the Intervention Scalability Assessment Tool (ISAT) [32] for the scalability assessment. In Russia, there are already examples of telemonitoring being implemented at the state level, such as the Federal project 'Personal Medical Assistants' https://ppma.ru/, which provides remote monitoring for patients with type 2 diabetes and arterial hypertension, funded by compulsory medical insurance.

3.2. Expected Findings

We anticipate that the implementation of TMT in monitoring patients with IBD will improve their QoL. This will be achieved through a reduction in overall and visceral anxiety, as well as constant, immediate access to medical care. Additionally, we expect an increase in satisfaction with medical care, improved psychological well-being, and a decrease in disease activity and relapse rate due to timely response and improved adherence to treatment.

3.3. Strengths

This study has been designed in close collaboration with patients to ensure that it addresses their specific needs and concerns. We discovered that there is a lack of standardized criteria for evaluating patients with IBD during monitoring except for objective markers of disease activity. We defined the list of assessed parameters by the Delphi method before the trial [13]. Another advantage of this trial is that the protocol has been developed in accordance with the SPIRIT guidelines, which will improve its transparency [14].

3.4. Limitations

The study has some limitations. One potential limitation is an uneven distribution of patients with UC and CD within the groups. Due to envelope randomization, there may be differences in the number of participants with UC or CD between the face-to-face and telemonitoring groups. Furthermore, the study does not intend to perform subgroup analysis based on a specific disease, such as UC or CD.

Another limitation of this study is that it is a single-center study. Different hospitals may have slightly different approaches to face-to-face management of patients. Additionally, patients in the groups may differ in the activity and severity of their IBD course, which could impact the therapy they receive during the study period.

Furthermore, the use of a website as a telemedicine intervention may also be a limitation. This approach requires patients to have certain technical equipment and computer literacy, which could reduce the number of study participants.

4. Conclusions

Our study aims to assess the effects of telemonitoring on patients with IBD in comparison to traditional face-to-face follow-up. Specifically, we will evaluate the impact on various aspects, such as QoL, frequency of disease relapses, medication adherence, adverse drug reaction of immunomodulators, and satisfaction with medical care.

Author Contributions: Conceptualization, D.A.A., Y.F.S., A.V.V., Y.A.A. and R.V.R.; methodology, D.A.A., Y.F.S., A.V.V., Y.A.A., R.V.R., M.G.M., Y.A.V., O.V.O.; formal analysis, Y.F.S., Y.A.A., R.V.R.; investigation, D.A.A., Y.F.S., M.G.M., A.S.P., O.V.T., I.V.K., M.V.Y., A.S.E.; resources, D.A.A., Y.F.S., Y.A.V., A.V.V., O.V.O.; data curation, D.A.A., Y.F.S., M.G.M., A.S.P., O.V.T., I.V.K., M.V.Y., A.S.E.; writing—original draft preparation, D.A.A., Y.F.S., Y.A.A., R.V.R.; writing—review and editing, D.A.A., Y.F.S., Y.A.A., R.V.R., M.G.M., Y.A.V., A.V.V., O.V.O.; supervision, R.V.R., M.G.M., Y.A.V., A.V.V., O.V.O.; project administration, A.V.V.; funding acquisition, Y.F.S., R.V.R., Y.A.V., A.V.V., O.V.O. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: The Local Ethics Committee of Sechenov University, Moscow, Russia approved the trial protocol with approval number 11-23 (16 June 2023).

Informed Consent Statement: Each patient will provide informed consent prior to the participation in the study.

Data Availability Statement: The datasets utilized and examined in this study can be obtained from the principal investigator (Akhmedzyanova Dina) upon reasonable request.

Conflicts of Interest: The authors declare no conflicts of interest.

Appendix A

Table A1. Educational information (Translated from Russian).

Topic	Example of Information
General information about IBD	Inflammatory bowel disease (IBD) is a term that covers diseases causing chronic inflammation of the gastrointestinal (GI) tract. The most common forms of IBD are ulcerative colitis (UC) and Crohn's disease (CD). Both CD and UC have similar symptoms; however, they are different disorders and affect different parts of the GI tract. The causes of IBD have not been studied enough. A combination of genetic factors (inherited) and environmental factors (acquired—a contact with animals, eating habits, etc.) is assumed. Normally, the immune system protects the body. However, in people with UC, the immune system may mistakenly take native microflora (bacteria that are normally in the intestines helping us absorb vitamins, food and other ordinary substances) for foreign agents. The body begins to attack them by sending leucocytes into the gut lining, where they cause inflammation and ulceration of the wall. The most common symptoms of CD are abdominal pain (often in the right lower abdomen) and diarrhea. There may also be rectal bleeding, decreased appetite, weight loss, and fever. The most common symptoms of UC are abdominal pain, diarrhea, blood in the stool and false urge to defecate. IBD symptoms most often tend to go through periods when they are more severe (relapse) and periods when they are much less pronounced or not present at all (remission). Both diseases are more common in Western countries; however, in recent years, increase in incidence in Russia, Asian countries, and Latin America has been noticed. For example, in North America, about 0.3% of the population has IBD, which means that approximately 2.2 million people have CD or UC. The path for a patient with IBD to remission can be long. From the onset of the disease to the moment of diagnosis, a patient usually visits many doctors, undergoes a lot of tests, examinations, and misdiagnoses. IBD is a difficult disease not only for patients, but for healthcare providers as well. Sometimes, patients feel that people around them treat them differently because of their disease. This leads to stress and attempts to isolate themselves from others. In fact, it is important to learn how to tell your loved ones and friends about your illness, how you cope with it, what difficulties you experience, and how you live a fulfilling life. After all, close people can provide invaluable support and help overcome many difficulties. Clinical symptoms of IBD can be painful, embarrassing, and debilitating. They interfere with your job, school, relationships, travels, and physical and emotional well-being. They can seriously affect a person's quality of life, causing stress, anxiety, and depression. In this case, you need to seek help from a mental health specialist and a psychological support. You cannot suffer in silence!

Table A1. *Cont.*

Topic	Example of Information
Psychological well-being in IBD	What is body image? Body image is our perceptions about our own body. It is not just a picture of how we look, but a set of components: What we think about our body What we feel about our body How we act in relation to it How we represent it in space How well we are able to recognize body signals Body image may not reflect how a person actually looks. In addition, ideas about your body may change throughout your life depending on what you are going through or doing. It is hardly possible to unequivocally answer the question of what exactly influences a perception of the particular person's body image. However, several main factors can be identified: interpersonal experience, culture, physical characteristics and their changes, and individual peculiarities. · The attitude towards the body is formed from early childhood from the experience interacting with parents and other close people. The following factors influence it: how it was customary for the family to treat your own body and the bodies of others, how physiological manifestations of the child's body and the features of his/her appearance were perceived by the close people. · Attitudes towards the body are also shaped by what is considered attractive in society. · Each person is born with specific features of appearance, and later it undergoes various changes throughout the life. Puberty, pregnancy, heredity, injuries and illnesses, age—all of these can increase a person's concern about his/her appearance. All of the above factors affect people in different ways. Some people manage not to be affected by this experience, while for someoneelse it turns out to be difficult to cope with its consequences. This is due to individual personality traits. For example: · Low self-esteem can become a basis for the formation of a negative body image, when a sense of inner inferiority extends to the perception of one's appearance. · A sense of insecurity in relationships can make a person feel that something is wrong with him/her, which, in turn, can contribute to a negative attitude towards one's own body. · Perfectionism influences the development of tension regarding one's body—in this case, a person needs to look impeccable for other people in his actions and appearance. One way or another, it is important to everyone how they look. At the same time, there is a difference between when a person "just doesn't like something" and when dissatisfaction with appearance acquires super-valuable significance. In the second case, it becomes a problem and seriously affects quality of life, and may be a sign of a mental disorder—dysmorphophobia or an eating disorder (ED). Body dysmorphic disorder is the obsessive preoccupation with one or more perceived physical defects. Usually these defects are invisible or slightly noticeable to others; however, they are much more significant for the person. A key pathology of an ED is the over-value of one's own body and a control over it. A negative body image does not lead to the eating disorder in every case; however, it contributes to developing and continuing this disorder in individuals predisposed to it. Normally, people's self-esteem is based on their achievements in various areas of their lives. People with an eating disorder base their self-esteem entirely or mainly on judgments about their weight and body shape and their ability to control them. This is why body image disorder therapy plays a significant role in recovery from an eating disorder.
Diet in IBD	What can you eat during a relapse? 1. Do not follow restrictive diets. Resist the urge to follow diets recommended to you by your friends, relatives, or people on the internet. Like medications, restrictive diets have potential side effects. They include nutritional deficiencies, unplanned weight loss, and the onset and/or progression of an eating disorder. All of these can negatively affect the disease outcome. Only your doctor or dietitian can prescribe you a correct diet. 2. Increase the amount of protein in your diet. During a relapse of IBD, the protein need is increased, so it is helpful to eat high-protein foods throughout the day. However, you should not exceed 80–100 g of protein a day. The following products are recommended: chicken, tofu, fish, turkey, eggs, cottage cheese, yogurt, beans, chia seeds, and nut butters. 3. Increase the amount of consumed liquid. If you have frequent loose stools or constipation, you need to increase the amount of consumed liquid, such as water, weak herbal teas, compotes, and hydrating solutions (for example, Rehydron). 4. High nutrient dense meals/snacks. If you have a decreased appetite, you have recently lost weight unintentionally, or you have diarrhea, then frequent eating of small portions of food can help you. You can also supplement your diet with enteral nutrition.

Appendix B

Table A2. Phone call checklist (Translated from Russian).

Item	Question	Clarifying Additional Question (If Necessary)	Answer Options			
Bowel frequency	How many times a day do you have bowel movements?	How many times a day do you have bowel movements during a disease remission?	The usual	1–2 times a day more than usual	3–4 times a day more than usual	5 times a day more than usual
Blood in the stool	Is there an admixture of blood in the stool?	Is there blood in the stool itself, at the end of defecation, or on a toilet paper?	Not	Blood streaks	Visible blood	Mostly blood

Question	Yes	No
Do you have constipation? (a need to strain during defecation, hard or sheep-like stools, a feeling of incomplete evacuation after defecation)		
Do you have painful urges to defecate?		
Have you lost more than 3 kg without any obvious reasons?		
Have you taken any antibiotics in the last month?		
Have you taken NSAIDs (non-steroidal anti-inflammatory drugs, painkillers) in the last month?		
Do you have joint pain?		
Have you had fever above 38 °C unrelated to a cold during the last month?		
Question	**Yes**	**No**
Do you remember to take all your medications?		
Are you sometimes careless about the time of taking your medications?		
Do you skip taking medications when you feel well?		
If you feel unwell after taking a medicine, do you skip the next dose?		

Appendix C. IBD Diagnostic Criteria According to Current Clinical Guidelines in Russia

Appendix C.1. Diagnostic Criteria for Crohn's Disease (CD) [25]

The Lennard-Jones criteria for a reliable diagnosis of CD include the following seven key features:

- Localization anywhere in the gastrointestinal (GI) tract, from the oral cavity to the anal canal, including chronic granulomatous lesions of the mucosa in the lips or cheeks, pyloroduodenal lesions, small intestine lesions, and chronic perianal lesions.
- Intermittent nature of the lesions.
- A transmural character of the lesions, which may present as fissure ulcers, abscesses, or fistulas.
- The presence of fibrosis, such as strictures.
- Lymphoid tissue findings (histology) that may include aphthoid ulcers or transmural lymphoid clusters.
- Mucin content (histology) showing normal levels in areas of active inflammation of the colonic mucosa.
- The presence of epithelioid granulomas.

A diagnosis of CD is considered reliable if three or more of these signs are present or if a granuloma is found in conjunction with any other sign.

The diagnosis must be confirmed using endoscopic and morphological methods and/or endoscopic and medical imaging techniques.

Endoscopic criteria for diagnosing CD include the presence of regional (intermittent) mucosal lesions, the 'cobblestone' appearance (characterized by deep longitudinal ulcers combined with transversely oriented ulcers and areas of edematous, hyperemic mucosa), linear ulcers (fissure ulcers), aphthae, and, in some cases, strictures and fistula openings.

Radiological findings associated with CD may include regional, intermittent lesions, strictures, cobblestone patterns, fistulas, and intra-abdominal or interintestinal abscesses.

Morphological features of CD include:

- Deep, slit-like ulcers that penetrate the submucosa or muscle layer.
- Epithelioid granulomas, which are clusters of epithelioid histiocytes without necrotic foci or giant cells. These are typically found in the wall of the resected area and are present in only 15–36% of cases in mucosal biopsies.
- Focal (discrete) lymphoplasmacytic infiltration of the intrinsic lamina of the mucosa.
- Transmural inflammatory infiltration with lymphoid hyperplasia affecting all layers of the intestinal wall.
- Lesions in the ileum characterized by structural changes in the villi, mucoid or pseudopyloric crypt metaplasia, and chronic active inflammation.
- Intermittent lesions, which involve the alternation of affected and healthy segments of the intestine when examining the resected portion.

Appendix C.2. Diagnostic Criteria for Ulcerative Colitis (UC) [24]

Criteria for establishing a diagnosis based on pathognomonic findings include:

- Anamnesis (medical history);
- Physical examination;
- Laboratory tests;
- Instrumental examinations.

There are no definitive diagnostic criteria for ulcerative colitis (UC). The diagnosis is established through a combination of the patient's history, clinical presentation, and characteristic endoscopic and histological findings.

Endoscopic examination of the colon is the primary method for diagnosing UC, although there are no specific endoscopic signs unique to the condition. The most characteristic features include diffuse inflammation confined to the mucosa, starting in the rectum and extending proximally, with a well-defined border of inflammation. The endoscopic activity of UC is best indicated by contact bleeding (the discharge of blood upon contact with the endoscope), a lack of vascularity, and the presence of erosions and ulcerations.

Microscopic signs of UC include crypt deformation, characterized by branching, multidirectional crypts of varying diameters, decreased crypt density, 'crypt shortening', and crypts that do not reach the underlying muscularis mucosa. Biopsies may reveal an 'uneven' surface of the mucosa, a reduced number of goblet cells, basal plasmacytosis, and infiltration of the lamina propria by mononuclear cells, along with a mixture of segmented neutrophils and eosinophils. Additionally, crypt abscesses and basal lymphoid aggregates may be present. Typically, the degree of inflammatory infiltration diminishes with increasing distance from the rectum.

Appendix D. Informed Consent (Translated from Russian)

Patient Information

Dear patient!

You are invited to participate in a study as a part of the research "Effectiveness of telemedicine technologies in monitoring patients with inflammatory bowel diseases".

Please read this document carefully; it contains information about the study and possible risks. You can discuss all your questions with a research physician and, if you wish, with the people you trust. Once you have read this document and decided to participate in the study, you will need to sign and date two copies of the informed consent form. You will keep a signed and dated copy of the information for a patient along with the informed consent form.

Participation in the study is voluntary. If you refuse, or having signed a consent change your decision at any time during the study without explaining the reasons, it will not affect the quality of the medical care provided to you.

You are invited to participate in this study because periodic monitoring of your condition is required to minimize the risk of a worsening of your disease. Our study compares telemedicine follow-ups with office visits.

A purpose of the study is to determine whether a provision of medical care using telemedicine technologies is effective compared with conventional face-to-face observation in patients with inflammatory bowel diseases (ulcerative colitis, Crohn's disease).

Sixty-four people are planned to participate in the study. Patients will be randomly assigned to two groups. The first group will be monitored on the outpatient basis according to the plan indicated by the attending physician in the discharge summary. Participants of the second group will be granted access to a website that will provide information about the disease, dietary recommendations, and rules of conduct. Also, the telemonitoring group will need to fill out a disease activity checklist and enter test results once a month. Patients in the telemedicine group will have the opportunity to chat with a gastroenterologist about any issues related to the disease. In addition, participants in the telemonitoring group will receive a phone call to assess their condition once a month.

On the day of your discharge from the hospital, we will ask you to complete anonymous questionnaires to achieve the following goals:

1. Clarification of your health status—the CAI questionnaire for patients with ulcerative colitis and the Harvey-Bradshaw Index questionnaire for patients with Crohn's disease.
2. Assessment of your Quality of life—a questionnaire developed by WHO (WHOQOL-26), as well as a special quality questionnaire for patients with IBD (SIBDQ).
3. Assessment of your psychological condition—the Hospital Anxiety and Depression Scale (HADS), the Toronto Alexithymia Scale (TAS-26), which reflects a risk factor for developing psychosomatic diseases, as well as a special gastroenterological questionnaire the Visceral Sensitivity Index (VSI) to determine how well and clearly you feel the signals from your gastrointestinal tract.
4. Evaluation of our work—the Patient Satisfaction Questionnaire (PSQ-18).

Completing the questionnaires takes about 10–15 min.

After 6 months, we will offer patients a re-hospitalization as part of the disease activity assessment, where we will again ask you to complete the above questionnaires.

The duration of the participation in the study is 6 months.

Possible benefits for the patient from participating in the study are an improved quality of life, a full control over IBD, and a contribution to the development of fundamental and practical medicine.

Possible or additional risks and inconveniences associated with participation in the study are a need to spend about 5 min of personal time once a month to fill out a checklist (in the case of being assigned to the telemedicine group).

Expenses on the part of participants are not expected.

You will be notified promptly if any additional information becomes available during the study that may affect your consent to continue participating in the study.

All information obtained from your medical records and medical history will be treated as confidential. You have the right to access your health information. The results of this study may be published without indicating your identity.

Appendix E. Addendum to the Informed Consent for a Telemonitoring Group (Translated from Russian)

A purpose of remote health monitoring as part of a study assessing the efficacy of telemedicine technologies in patients with inflammatory bowel diseases:

A procedure for remote monitoring of the patient's health status, and consultations using telemedicine technologies, are carried out in accordance with the Order of the Ministry of Health of the Russian Federation No 965N dated 30 November 2017 "On approval of the procedure for organizing and providing medical care using telemedicine technologies".

Remote monitoring of the patient's health status is aimed at timely detection and prevention of complications, exacerbations of diseases, increasing adherence to treatment and control, prevention, and developing skills to preserve and maintain health.

A clinical goal is to reduce a frequency of relapses in inflammatory bowel disease.

Program:

- Treatment regimen for the period of remote monitoring is prescribed by the attending physician upon discharge from the gastroenterological hospital
- Duration of remote monitoring is 6 months
- List of controlled parameters:
  (1) Body weight
  (2) Complete blood count
  (3) C-reactive protein
  (4) Fecal calprotectin
  (5) A total score of the IBD Disk questionnaire for all patients (results are interpreted by researchers)
  (6) Indicators of Simple Clinical Colitis Activity Index (SCCAI) for patients with ulcerative colitis and the Harvey-Bradshaw Index for patients with Crohn's disease (results are interpreted by researchers)
- Target parameters:
  - Hemoglobin—reference values 117–160 g/L
  - Leukocytes—reference values 4–11 $\times$ 10^9/L
  - CRP—reference values 0–5 mg/L
  - Fecal calprotectin—reference values up to 200 μg/g for patients enrolled in the trial with the initial normal level; for patients enrolled in the trial with the initial high level (more than 800 μg/g), the reference value is determined individually after 3 and 6 months of observation
  - IBD-disk score—reference values 0–40
  - Simple Clinical Colitis Activity Index (SCCAI)—a score of 0–4 during a remission
  - Harvey-Bradshaw Index—a score of 0–4 during a remission
- Critical levels of deviations in the values of monitored parameters (indicators for a patient and a doctor):
  - Hemoglobin—lower than 110 g/L, higher than 170 g/L
  - Leukocytes—lower than 3 $\times$ 10^9/L, higher than 11 $\times$ 10^9/L
  - CRP—higher than 10 mg/L
  - Fecal calprotectin—higher than 200 μg/g for patients enrolled in the trial with the initial normal level; maintaining the same values for patients enrolled in the trial with the initial high level (more than 800 μg/g).
- Critical levels of deviations in the values of monitored parameters (indicators only for a doctor):
  - IBD-disk score—higher than 40
  - Simple Clinical Colitis Activity Index (SCCAI) for patients with ulcerative colitis—a score is higher than 5

- Harvey-Bradshaw Index for patients with Crohn's disease—a score is higher than 5

Procedure:

Monitored parameters should be measured and entered into the patient's personal account with the following regularity:

(1) Complete blood count—once a month
(2) Fecal calprotectin, C-reactive protein—once every 3 month
(3) A total score of the IBD-disk questionnaire—once a month for all patients
(4) Simple Clinical Colitis Activity Index (SCCAI) for patients with ulcerative colitis and the Harvey-Bradshaw Index for patients with Crohn's disease—once a month.

A follow-up visit with a specialist is expected after 6 months of remote monitoring in the absence of critical deviations and situations requiring emergency medical care.

To provide telemonitoring, patients need to have access to electronic communications and the internet.

Consultations using telemedicine technologies are carried out on a planned basis or at the patient's request by exchanging messages from Monday to Friday from 9:00 to 17:30 in conditions that are not accompanied by a threat to the patient's life, do not require emergency and urgent medical care, if a delay in medical care for a certain period of time does not entail a worsening in the patient's condition, and if it is not a threat to his/her life and health.

A research physician conducting remote monitoring of the patient's health status reacts immediately if health indicators deviate from the limit values, or complaints indicate the development of an acute condition occurring during the period from Monday through Friday from 9:00 to 17:30. This emergency response covers a communication with the patient to clarify the condition and exclude unreasonable anxiety, informing an attending physician about the situation and measures taken, a supervision of the patient's call of an emergency ambulance for the hospitalization, or a communication with the attending physician about the emergency hospitalization.

In the case of conditions requiring an emergency response outside the above-mentioned time (Monday—Friday from 9:00 to 17:30), patients should call an emergency ambulance on their own and also inform an attending physician of the hospital about it.

List of conditions requiring emergency response (calling an emergency ambulance):

- Acute abdominal pain, not relieved by taking antispasmodics, lasting more than 30 min, for women—unrelated to menstruation
- Gastrointestinal bleeding
- Fever above 38.5 °C for 5 or more days in the absence of catarrhal symptoms (runny nose, cough, sore throat)
- Signs of intestinal obstruction—cramping abdominal pain, retention of stools and gases, bloating and asymmetrical abdomen, nausea and vomiting
- Signs of perforation of a hollow organ—severe diffuse abdominal pain, nausea, vomiting, moderate palpitations, decreased blood pressure

List of conditions requiring urgent response (communication with an attending physician of the hospital):

- Exacerbation of inflammatory bowel disease (increased stool frequency, abdominal pain (not meeting the emergency response criteria), blood in the stool)
- A fistula of the anterior abdominal wall, perianal, enterovesical, colorectal-vaginal (according to the results of self-examination or examination by a specialist)

Exacerbation of other chronic conditions, as well as the occurrence of emergency situations not related to IBD, require seeking emergency medical care outside of the ongoing study.

Appendix F. Sample Screenshots of the Website

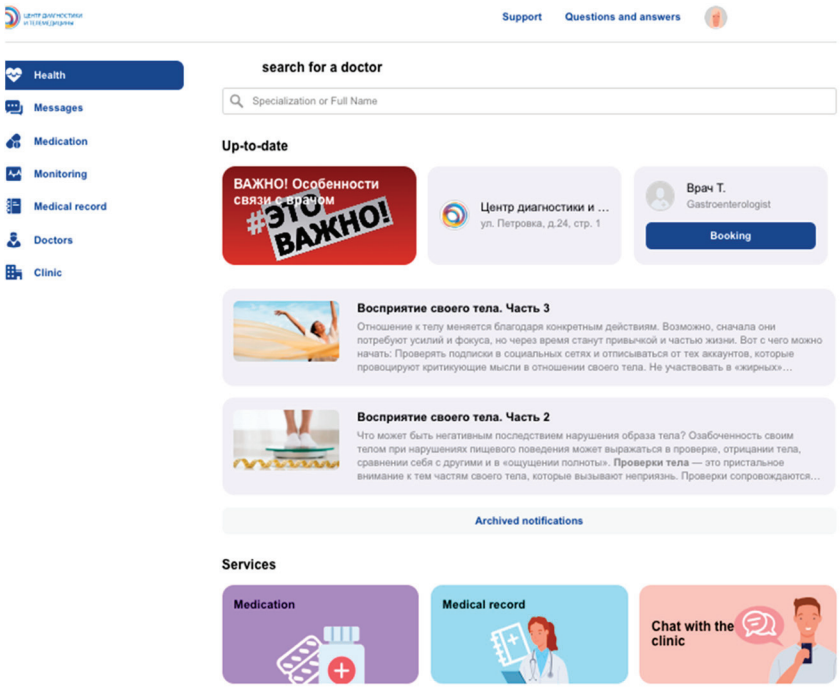

Figure A1. Personal patient profile, newsfeed with educational information.

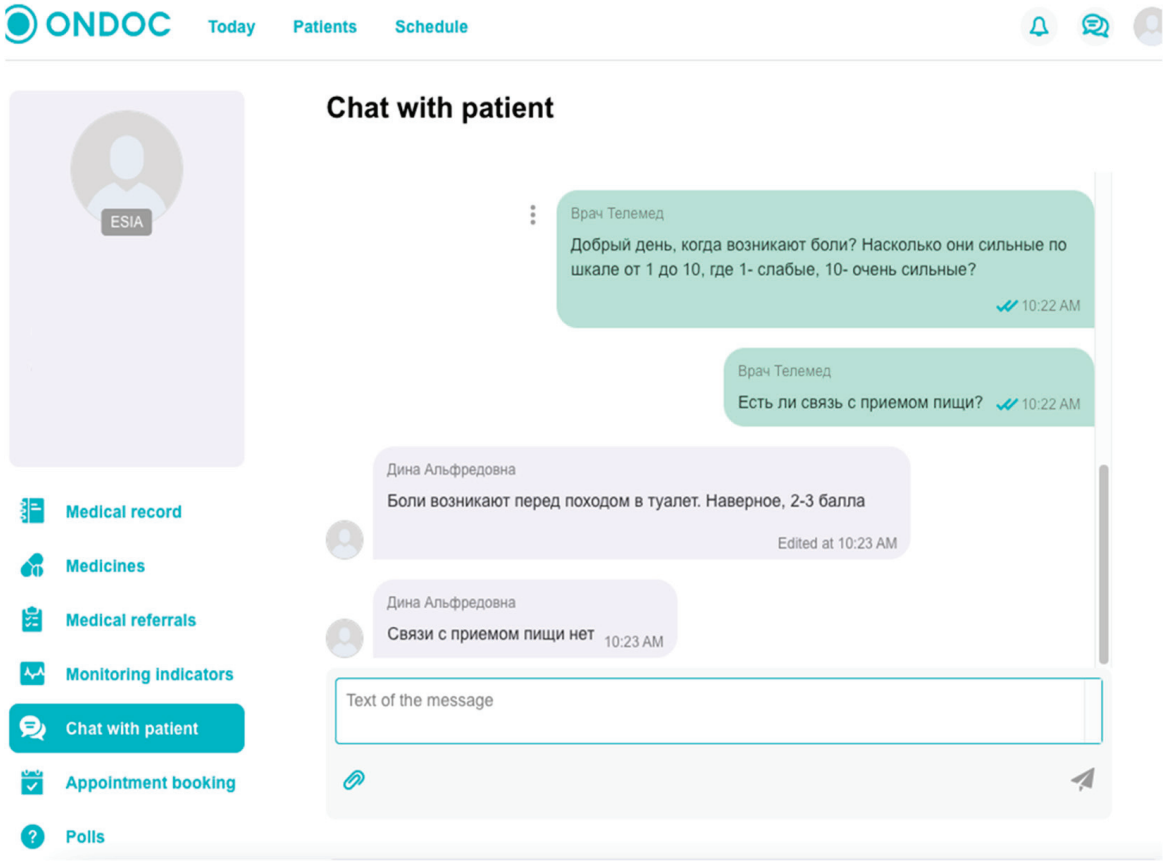

Figure A2. Chat with the gastroenterologist.

Figure A3. Health parameters monitoring page.

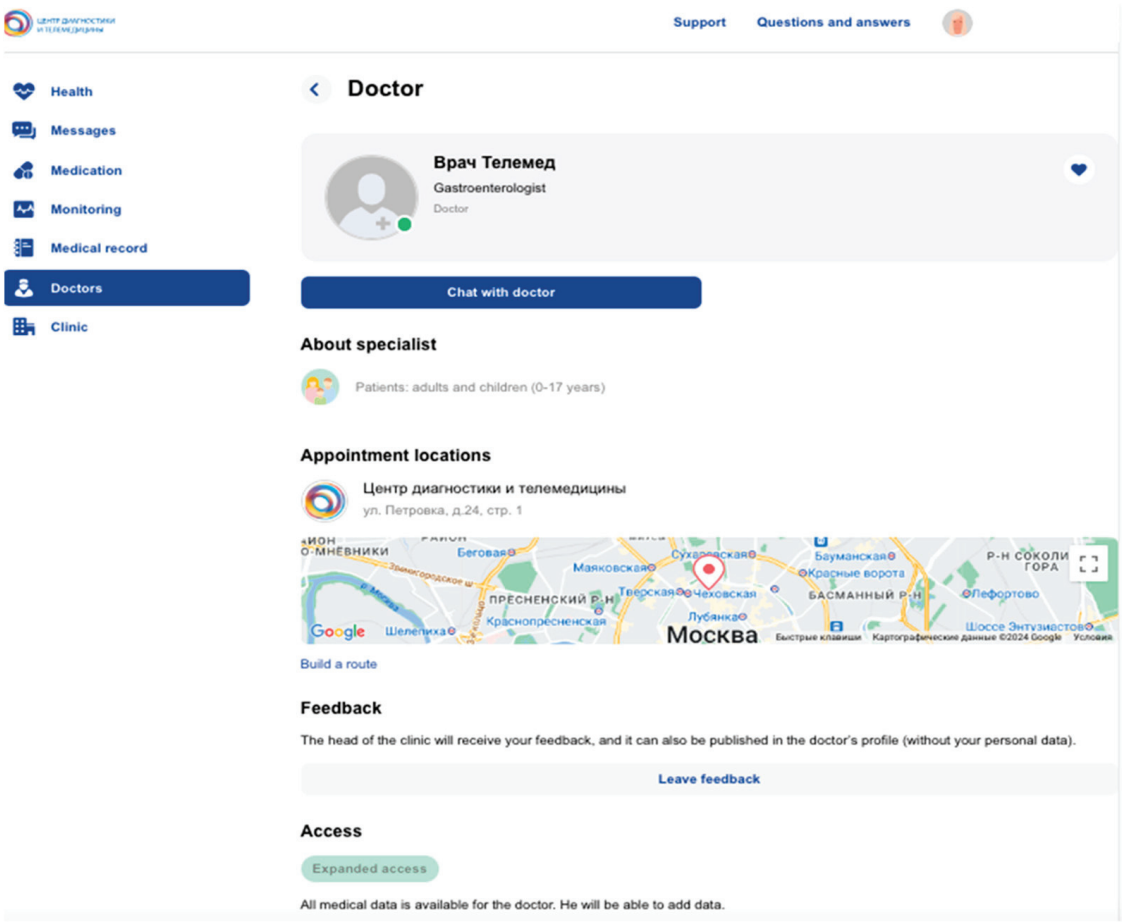

Figure A4. Information about the gastroenterologist.

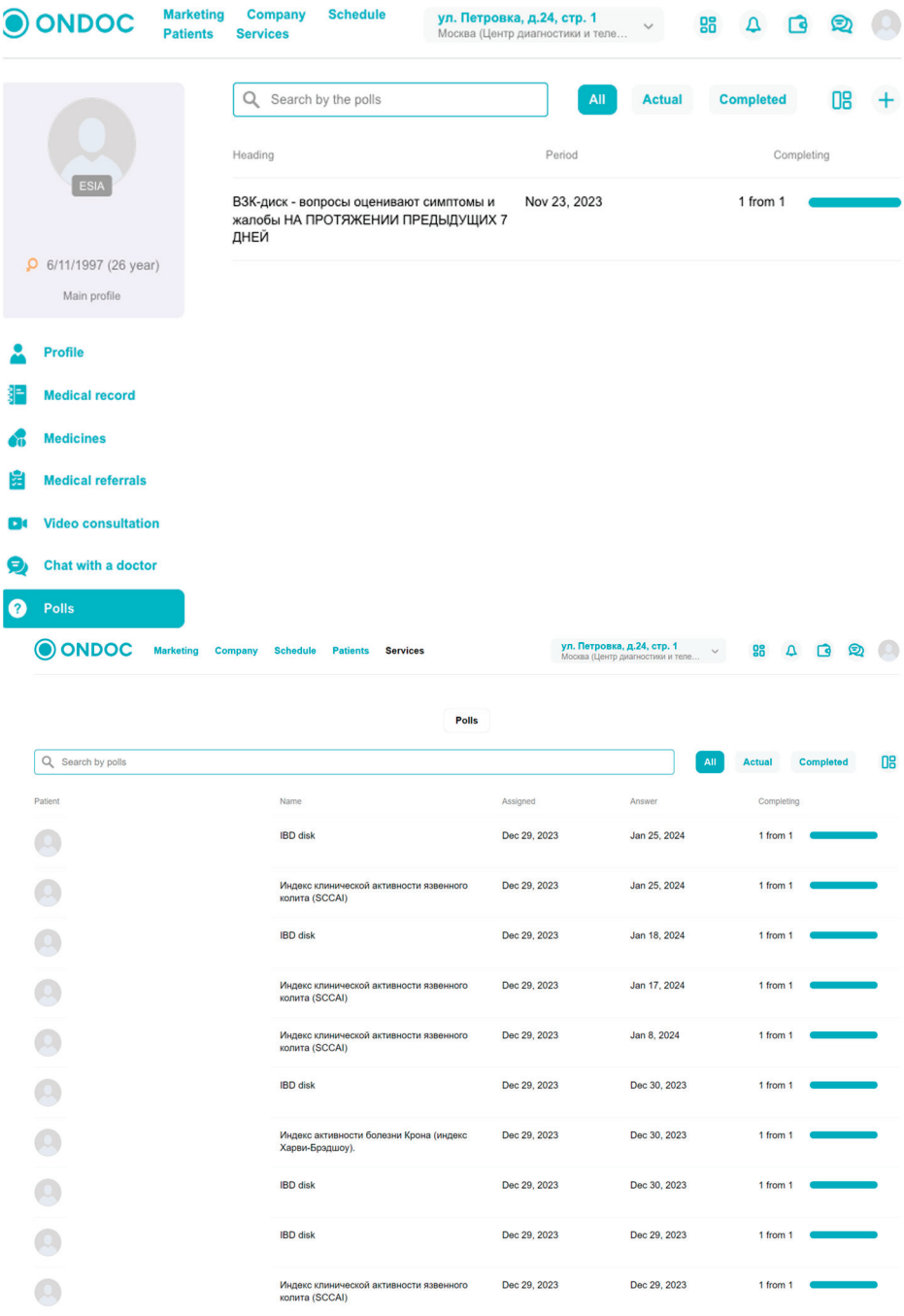

Figure A5. The questionnaires module.

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