Chapter 10
Tricks of the Trade: Treating Your Patient with Moderate-to-Severe IBD

Rahul S. Dalal, Jan-Michael Klapproth, and Gary R. Lichtenstein

When Treating Patients with IBD Who Have Active Symptoms, Document the Presence of Active Disease

Appropriate management of inflammatory bowel disease (IBD) first requires objective evidence of active inflammation. Symptoms may suggest disease activity but are usually nonspecific. Diarrhea and abdominal discomfort, two of the most common symptoms in patients with active Crohn's disease (CD) and ulcerative colitis (UC), are not specific for IBD but may overlap with typical presentations of numerous other gastrointestinal disorders including lactose deficiency, irritable bowel syndrome, celiac disease, CMV colitis, *Clostridium difficile* colitis, and infections from enteric pathogens. Excluding alternative etiologies and confirmation of active IBD require laboratory evaluation and objective documentation of appropriately active disease findings on upper endoscopy, colonoscopy, and small bowel imaging.

Demonstration that a patient has objective evidence of inflammation in their bowel has important implications for predicting therapeutic response, as highlighted by the Study of Biologic and Immunomodulator Naïve Patients in Crohn's Disease (SONIC) study group [1]. The SONIC trial was a randomized, double-blind

R.S. Dalal, MD
Department of Internal Medicine, Hospital of the University of Pennsylvania, 3701 Market St 6th Floor, Philadelphia, PA 19104, USA

J.-M. Klapproth, MD
Division of Gastroenterology, Department of Medicine, Hospital of the University of Pennsylvania, Philadelphia, PA, USA

G.R. Lichtenstein, MD (✉)
Department of Internal Medicine/Division of Gastroenterology, Hospital of the University of Pennsylvania, Perelman Center for Advanced Medicine, 3400 Civic Center Blvd, 7th Floor – South Pavilion, Room 753, Philadelphia, PA 19104, USA
e-mail: Gary.Lichtenstein@uphs.upenn.edu; grl@uphs.upenn.edu

R.D. Cohen (ed.), *Inflammatory Bowel Disease*, Clinical Gastroenterology,
DOI 10.1007/978-3-319-53763-4_10

trial that evaluated the efficacy of infliximab monotherapy, azathioprine (AZA) monotherapy, or the two drugs combined in immunomodulator-naïve patients with moderate-to-severe Crohn's disease. Patients were eligible based on age and their Crohn's Disease Activity Index (CDAI), which utilizes subjective criteria such as patient-reported stool counts and symptoms [2]. Ileocolonoscopy was performed at baseline and again at 26 weeks for those patients found to have mucosal ulcers. The primary endpoint was the rate of corticosteroid-free clinical remission, which was defined by a CDAI score of less than 150 and no administration of systemic corticosteroids for 3 weeks. While the study concluded that therapy with infliximab resulted in significantly higher rates of corticosteroid-free clinical remission than AZA monotherapy, a post hoc analysis found that patients with elevated C-reactive protein (CRP), mucosal lesions, or a combination of both at baseline endoscopy had the best clinical response. Furthermore, there was no significant difference in the three therapy groups for subjects without these findings, suggesting that patients without objective evidence of mucosal inflammation are less likely to respond to immunomodulatory therapies.

After active disease is endoscopically confirmed, disease activity should be followed. The costs of invasive monitoring and the once prevailing view that clinical response is more relevant than endoscopic findings led to the development of several clinical disease activity indices. The CDAI, mentioned previously, is the most broadly utilized index in clinical trials of CD. It correlates the physician's evaluation of clinical status to eight variables, including hematocrit, body weight, extraintestinal manifestations, need for antidiarrheal medication, presence of an abdominal mass, general well-being, abdominal pain severity, and liquid stool counts [2]. The calculation requires a 7-day diary of patient-reported symptoms, and the final score relates to the severity of disease activity. However, the CDAI has been shown to be poorly correlated to endoscopic disease activity and is plagued by subjectivity and patient recall bias [3]. The ACCENT I trial, which evaluated infliximab as a long-term treatment regimen in Crohn's, showed that at 10 weeks, only 36% of patients with confirmed mucosal healing (MH) were in remission as calculated by the CDAI [4]. Conversely, 40% of those in clinical remission per the CDAI did not demonstrate endoscopic remission. The Harvey Bradshaw Index (HBI) is a simplification of the CDAI, using only five of its eight independent variables and no laboratory data [5]. While lauded for its simplicity relative to the CDAI, it too correlates poorly with the severity of endoscopic disease [6, 7]. The CDAI, although used in clinical trials in the past, has been cumbersome and not well accepted for use in clinical practice.

Recognizing the limitations of scoring systems that omit endoscopic assessment in CD, the French GETAID group developed the Crohn's Disease Endoscopic Index of Severity (CDEIS) [8]. The group evaluated the importance of mucosal lesions and the percentage involvement of the colon. The resulting CDEIS incorporates superficial and deep ulcerations, lesion surface area, and the number of colonic segments involved. The index was found to have relatively minimal interobserver variability, and lesion surface area assessment measured on a visual analog scale was highly reproducible. The tool is frequently used as an

endoscopic severity index in clinical trials. However, it requires careful training and is too difficult and cumbersome to employ clinically.

Fortunately in 2004, Daperno and coworkers proposed the Simplified Endoscopic Severity Index for Crohn's Disease (SES-CD) [9]. The SES-CD evaluates the size and penetration of ulcerations and also has strong interobserver agreement. Additionally, it is well correlated with the CDEIS, but does not require such precise measurements of lesion surface area [10]. Therefore, for routine clinical practice, the SES-CD may be the endoscopic index of choice to follow disease activity in CD. The SES-CD however is not a useful index for patients who have undergone ileocecal resection when assessing their risk for disease recurrence postoperatively.

In Crohn's patients who have undergone ileocecal resection, the Rutgeerts endoscopic score, which incorporates endoscopic lesions in the neoterminal ileum, is routinely used in randomized controlled trials (RCTs) and is the clinician's gold standard assessment tool for postoperative recurrence [11]. It grades the mucosa of the distal ileum from a range of i0 (no lesions) to i4 (diffuse inflammation with nodules, large ulcers, and/or narrowing). Patients with a score of i3 or i4 within 12 months of ileocecal resection have a higher rate of disease recurrence and more aggressive disease course than those with lesions of lesser severity. Therefore, patients should undergo ileocolonoscopy within 6–12 months after resection for risk stratification and to determine the need for additional therapy.

In UC, several indices have been developed to assess disease activity, many of which incorporate endoscopic evaluation. The role of endoscopic findings in UC has been appreciated for decades, and Truelove and Witts developed the first endoscopic score to evaluate UC activity in 1955 [12]. Today, the Mayo score prevails in clinical trials to describe disease activity [13]. It incorporates stool frequency, rectal bleeding, physician global assessment, and flexible sigmoidoscopy findings, known as the Mayo endoscopic subscore. This score ranges from 0 to 3. A score of 0 represents normal mucosa, 1 represents mild disease and friability, 2 represents moderate disease and market erythema and friability, and 3 represents severe disease with diffuse ulcerations and spontaneous bleeding. The main challenges with this scoring system however are the overlap between scores, particularly 1 and 2, the inability to discriminate superficial from deep ulcerations, and the evaluation of only the most severely affected mucosa with no consideration of disease extension. Additionally, interobserver agreement was recently found to be modest [14].

To address the need for increased interobserver agreement, the Ulcerative Colitis Endoscopic Index of Severity (UCEIS) was developed in 2012 [15]. The UCEIS is a validated index for UC endoscopic severity that incorporates a more detailed description of mucosal inflammation than the Mayo subscore. It is therefore felt to be more clinically useful by reducing variability between observers, though an improvement in interobserver agreement has yet to be established (see Table 10.1) [16].

More recently, Lobaton and colleagues recalculated and expanded the Mayo endoscopic subscore to include the evaluation of disease extension as the Modified Mayo Endoscopic Score (MMES) [17]. They multiplied the sum of Mayo scores in five colonic segments by the total extension of inflammation and divided the product by the number of actively inflamed segments (Mayo subscore >0). The

Table 10.1 Commonly used disease activity indices in IBD

Disease index	Disease	Independent variables	Score interpretation	Advantages	Disadvantages
Crohn's Disease Severity Index (CDAI) [2]	CD	Number of liquid/soft stools Abdominal pain General well-being Extraintestinal manifestations Antidiarrheal use Abdominal mass Hematocrit	Remission: <150 Severe: >450	Does not require endoscopy Extensively used in clinical trials	Subjective Relies on patient recall or diary over 7 days Correlates poorly with endoscopic findings Cumbersome for everyday practice
Harvey Bradshaw Index (HBI) [5]	CD	Number of liquid/soft stools Abdominal pain General well-being Extraintestinal manifestations	Remission: <5 Mild: 5–7 Moderate: 8–16 Severe: >16	Does not require endoscopy Does not require laboratory testing Fewer variables than the CDAI	Subjective Correlates poorly with endoscopic findings
Crohn's Disease Endoscopic Index of Severity (CDEIS) [8]	CD	Deep ulcerations Superficial ulcerations Surface area affected by disease Surface area with ulcerations	Range 0–44 (higher = more severe)	Reliable and reproducible	Elaborate and time consuming Requires visual analog scale Cumbersome for everyday practice Not useful after ileocecal resection
Simplified Endoscopic Severity Index for Crohn's Disease (SES-CD) [9]	CD	Presence and size of ulcers Extent of affected surface Extent of ulcerated surface Presence and type of narrowings	Remission: <2 Mild: 3–6 Moderate: 7–15 Severe: >15	Reliable and reproducible Correlates well with CDEIS and is less cumbersome	Still perhaps too cumbersome for everyday practice Not useful after ileocecal resection

Rutgeerts Score [11]	CD	Aphthous lesions Ulcers Inflammation Nodules Stenosis	Low recurrence risk: i0–i1 Intermediate: i2 High: i3–4	Extensively used in clinical trials Gold standard assessment for postoperative recurrence Cutoffs validated for recurrence	Only utility is after ileocecal resection
Mayo Score [13]	UC	Stool frequency Rectal bleeding Physician global assessment Endoscopic subscore: erythema, vascular patterns, friability, bleeding, ulcerations, and erosions	Overall range 0–12 (higher = more severe) Endoscopic subscore: Normal: 0 Mild: 1 Moderate: 2 Severe: 3	Combines clinical and endoscopic components Extensively used in clinical trials	Subjective Overlap between endoscopic subscore ratings
Modified Mayo Endoscopic Score [17]	UC	Sum of Mayo endoscopic subscore in five colonic segments × disease extent/ number of segment with active inflammation		Accounts for disease extension Has potential for use in clinical practice	Newly developed and requires further validation
Ulcerative Colitis Endoscopic Index of Severity [15]	UC	Vascular pattern Bleeding Lesions and ulcerations	Range 3–11 (higher = more severe)	Validated Does not require full colonoscopy High interobserver agreement	Does not consider disease extension No cutoff values for disease severity Unclear delineation between superficial and deep ulcers

MMES was shown to correlate significantly with fecal calprotectin (FC; $r = 0.73$) and clinical index ($r = 0.54$). It has potential for use in both clinical practice and research but will require further validation in clinical trials. A summary of the most commonly used clinical and endoscopic disease activity indices in IBD can be found in Table 10.1.

Employ a "Treat-to-Target" Strategy in Clinical Practice

With confirmation of disease activity, every gastroenterologist should identify a treatment target and a strategy to reach it. Management of rheumatoid arthritis (RA), another chronic disease characterized by ongoing inflammation, exemplifies the benefits of a treat-to-target approach. Newer biologic therapies including tumor necrosis factor (TNF) antagonists have allowed clinicians to achieve lower levels of disease activity in RA than ever before. The advent of feasible disease remission has prompted trials of drug combinations of TNF antagonists with older agents like methotrexate and newer approaches such as early therapy that have sought to suppress inflammation to the greatest degree [18]. This reflects a treat-to-target strategy that relies on regular assessment of disease activity and subsequent adjustments to the therapeutic plan to reduce disease activity further.

In RA, specific treatment targets such as the Disease Activity Score (DAS) rely on patient-reported outcomes as well as objective data. The traditional targets of therapy in IBD have similarly centered on patient symptoms, but it is now known that the correlation between symptoms and mucosal inflammation is poor. Patients may have no symptoms with the presence of active histological disease and vice versa [7, 19]. Consequently, a symptom-based treatment strategy undertreats a significant proportion of patients and predisposes many to the detriments of ongoing inflammation, including disease progression and dysplasia.

There is growing evidence that targeting mucosal healing (MH) in IBD leads to more favorable outcomes such as sustained remission and reduced rate of steroid use, hospitalization, and surgery [20–22]. MH is evaluated by endoscopy and is typically defined by the absence of mucosal ulceration. A Scandinavian prospective cohort study first established the importance of MH in 2007 [19]. Over 5 years, 227 CD patients were evaluated, and 141 were reevaluated by endoscopy up to 2 years after diagnosis. Of these, 38% demonstrated MH. After a 5-year follow-up period, the presence of MH was associated with significantly less endoscopic inflammation and steroid use. In a follow-up study of the step-up/top-down trial by D'Haens et al. [23], MH was defined as a SES-CD of 0 [22]. Patients that achieved this score 2 years into the trial had significantly more steroid-free remission at years 3 and 4.

The benefits of MH are similarly represented in UC. In the prospective Inflammatory Bowel South-Eastern Norway (IBSEN) study, about 50% of UC patients had MH 1 year after diagnosis [20]. Subsequent colectomy rates were significantly lower when compared to patients without MH. Additionally, the time to MH appears to have prognostic significance. Ferrante and colleagues conducted a

single-center cohort of UC patients treated with infliximab, where early MH negatively predicted colectomy [24]. Patients with early MH, defined by a Mayo endoscopic subscore of 0 or 1 at week 4 or 10 after infliximab initiation, had a significantly lower 5-year colectomy rate. Post hoc analysis of the Active Ulcerative Colitis (ACT) trials similarly showed that patients with a Mayo endoscopic subscore of 0 or 1 at 8 weeks had significantly lower colectomy rates after 1 year [25].

While the above studies underscore the utility of MH as a therapeutic target, several drawbacks exist. Most obvious is the lack of a universal definition for MH and the variability in its interpretation. In clinical trials, MH was typically defined using various endoscopic scoring systems including the Mayo endoscopic subscore (for patients with UC) and the SES-CD (or patients with CD); however, these indices were created only for the purpose of describing and quantifying disease severity, not for establishing disease remission. Additionally, using MH exclusively ignores important aspects of the disease in UC and CD that are not identified endoscopically. Healed mucosa seen only macroscopically in UC may harbor active histological disease and inflammation, which predisposes these patients to dysplasia and malignancy [26]. Similarly, CD often involves extracolonic segments that are not easily accessed (i.e., small intestinal disease), and exclusive attention to mucosal ulceration ignores the transmural disease that may be appreciated only by MR enterography. Also, from a practical perspective, patients may not be amenable to routine invasive monitoring, particularly when their symptoms are well controlled.

Reasonable alternates to invasive strategies include biomarkers of disease activity, such as the fecal calprotectin (FC) and C-reactive protein (CRP). Calprotectin is found primarily in neutrophils, and when the bowel is inflamed, neutrophil infiltration rises and the cells are then shed into the feces [27]. Therefore, the FC can reflect the severity of inflammation in IBD [28]. Multiple studies have shown the association between FC and both endoscopic and microscopic bowel inflammation [29–31]. A prospective study by Guidi et al. demonstrated that FC also has predictive functions in active IBD and can fulfill a noninvasive treat-to-target strategy [32]. They enrolled 63 IBD patients who received anti-TNF induction therapy. An FC $\leq$ 121 μg/g after therapy predicted mucosal healing, which occurred in 22% of patients, with a negative predictive value (NPV) of 90%. In UC patients with colonoscopic evidence of mucosal healing (defined by Mayo endoscopic subscore of 0 or 1), FC has been shown to correlate with active histological inflammation. Patients with histologically active disease had a significantly higher median FC (278 vs. 68 μg/g, $p = 0.002$) than patients with normal microscopic findings [33].

To facilitate a treat-to-target strategy, after remission in UC is achieved, FC can be used to modify therapy before clinical relapse ensues. After total colectomy and creation of an ileal pouch anal anastomosis (IPAA), FC has been significantly elevated 2 months before the clinical onset of pouchitis [34]. Additionally, DeVos and colleagues demonstrated that two consecutive FC >300 μg/g 1 month apart in UC patients treated with infliximab predicted relapse with 61.5% sensitivity and 100% specificity [35]. In a study by Falvey et al., the investigators sought to identify a relationship between biomarkers and endoscopic inflammation to establish potential

thresholds for IBD disease activity. Endoscopically active disease was assessed in 81 UC patients who submitted stool samples for FC just prior to their bowel prep [36]. Receiver operating curve (ROC) analysis determined that FC > 125 μg/g predicted endoscopic activity with 74% sensitivity and 80% specificity. Unfortunately, no threshold could be calculated to predict endoscopic remission.

Similar success for FC has been documented in CD. FC predicted endoscopic relapse after ileocecal resection in a post hoc analysis of the Post-Operative Crohn's Endoscopic Recurrence (POCER) trial [37]. Levels of FC were measured in 135 patients and decreased from 1347 to 166 μg/g 6 months after surgery and was significantly elevated (275 vs. 72 μg/g) in patients with endoscopic evidence of relapse (defined by Rutgeerts score ≥2) compared to those in remission. FC > 100 μg/g predicted endoscopic recurrence with 89% sensitivity, 59% specificity, and an NPV of 91%. Conversely, FC < 51 μg/g in patients with remission at 6 months predicted sustained remission with an NPV of 79%. Falvey and coworkers also assessed FC thresholds in CD and determined that FC > 125 μg/g predicted endoscopic inflammation with a sensitivity and specificity of 71% each [36]. But similar to the study's results in UC, no threshold could reliably predict mucosal healing. Larger-scale studies are desired to establish universal FC thresholds in CD and UC to predict both endoscopically active disease and mucosal healing. However, given that FC is often normal in patients with confirmed active disease, endoscopy will likely remain the clinician's test of choice to document mucosal healing. The use of FC in a treat-to-target strategy should not replace endoscopic evaluation.

While the CRP has also been associated with endoscopically active IBD, interpatient variability has precluded the establishment of universal thresholds for clinicians to target and adjust therapy [36, 38]. However, the CRP has some utility in predicting disease severity and morbidity. In a prospective UC cohort, elevated CRP was significantly associated with hospitalization [39]. Crohn's patients with "silent disease," or those with clinical remission but elevated CRP, had significantly more hospitalizations than those in remission with normal CRP levels [40]. Additionally, a Hungarian cohort study found that elevated high-sensitivity CRP was associated with relapse after 3 and 12 months in CD patients previously in remission [41]. Evidence also suggests that normalized CRP levels are associated with a favorable disease course. CRP < 10 mg/L 12 weeks after therapy with adalimumab was associated with endoscopic remission after 1 year in a multicenter Crohn's cohort [42]. Similarly, in a CD cohort treated with infliximab, early normalization of CRP was associated with sustained remission [43]. Furthermore, CRP levels measured after induction in these patients were correlated with the degree of MH.

Given the diversity of phenotypes and patient preferences in IBD, flexibility in therapeutic approach is essential. However, our general treat-to-target strategy centers on endoscopic evidence for disease activity or MH with interim measurements of serum and fecal biomarkers that may help predict disease recurrence (Fig. 10.1). Once a diagnosis is made, disease extent and prognostic factors should be considered when deciding the intensity of induction therapy. High-risk patients with severe and extensive inflammation should be treated both early and aggressively

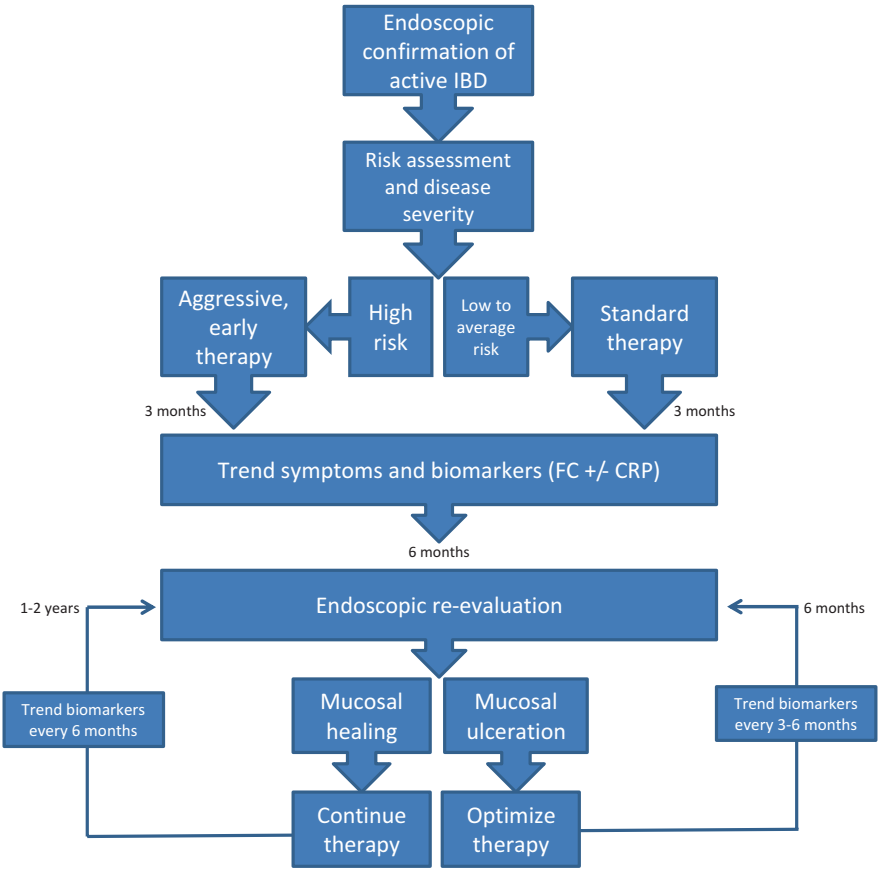

Fig. 10.1 A proposed treat-to-target strategy in IBD

with MH as a therapeutic target. While no widely accepted definition for MH exists, the absence of mucosal ulceration is a reasonable assumption. In the SONIC trial, 44% of patients who received early effective therapy achieved MH (defined by the absence of mucosal ulceration) [1]. Moreover, the step-up/top-down trial demonstrated that 73% of patients with CD who were assigned to early dual therapy achieved MH within 2 years. However, for patients with only mild inflammation endoscopically, the risks of aggressive therapy will likely outweigh the benefits.

After risk stratification and initiating treatment in a step-down fashion, endoscopy should guide therapeutic adjustments to achieve MH. While prospective data supporting this approach is limited, a retrospective study by Bouguen and colleagues demonstrated that when endoscopic ulceration was present after a diagnosis of UC, subsequent treatment alterations over time were significantly associated with both MH (defined by Mayo endoscopic subscore of 0) and histological healing [44]. In a related study in CD, modifications to medical therapy after early endoscopic reevaluation (<26 weeks)

had revealed persistent ulceration were also strongly associated with MH [45]. While the literature available to guide endoscopic intervals is scarce, we suggest reevaluation after 6 months of initial therapy in both UC and CD. In patients with abnormal FC and/or CRP at diagnosis, levels should be checked after 3 months of therapy and twice yearly thereafter. Once the target of MH is achieved, de-escalation of therapy can be considered after at least one full year of remission. However, at this time there is inadequate data to recommend discontinuation of therapy after any duration of stable remission. In patients who refuse repeated endoscopies, the clinician should avoid pure reliance on biomarkers and may consider imaging modalities such as MR enterography or CT colonography in patients with CD and UC, respectively [46]. Thoughtful communication between the gastroenterologist and patient is essential at diagnosis to establish expectations and the most effective management plan.

Measure Therapeutic Drug Levels for Proactive Monitoring and for Patients with Secondary Loss of Response

CD and UC are chronic, systemic, and inflammatory conditions that are treated by blunting or modulating the immune response. Therapy traditionally consisted of systemic glucocorticoids and 5-aminosalicylate compounds. The detriments of long-term steroid use led to trials evaluating the efficacy of immunomodulators such as 6-mercaptopurine (6-MP) and AZA, both of which effectively maintain remission in many CD and UC patients and are widely utilized to this day [47, 48]. More recently, anti-TNF therapies including infliximab, adalimumab, certolizumab pegol, and golimumab have proven effective in IBD treatment and have transformed our expectations for disease remission [4, 49–54]. Recently, anti-integrin agents have been added as tools to treat patients with UC (vedolizumab) and CD (vedolizumab and natalizumab).

As TNF antagonists have become a mainstay of therapy in moderate-to-severe IBD, the importance of therapeutic drug monitoring has become apparent. In severe IBD, combined therapy with an anti-TNF agent and an immunomodulator is an effective induction strategy in part due to the synergistic effects that help reduce immunogenicity [55]. A similar mechanism justifies the maintenance of adequate serum drug levels, which helps minimize the generation of antidrug antibodies (ADAs) that promote early drug clearance. Baert and colleagues conducted one of the first studies that underscored the impact of immunogenicity on long-term drug efficacy. They demonstrated lower titers of anti-infliximab antibodies and increased duration of response to episodic dosing when drug levels were above 12 μg/mL at 4 weeks [56]. Further work has corroborated that low serum drug levels are associated with an increased risk for immunogenicity with both infliximab and adalimumab [57–59].

The clinical benefits of adequate drug concentrations have been confirmed by multiple studies that measured anti-TNF trough levels (TLs). TLs have been shown to correlate inversely with CRP and endoscopic scores and positively with MH and

remission [60, 61]. In a post hoc analysis of the ACCENT I trial, TLs of 3.5 μg/mL or greater 14 weeks after infliximab induction predicted remission through week 54 [62]. Similarly in the SONIC trial, infliximab TLs greater than 1.0 μg/mL were associated with increased remission rates (72.8 vs. 58.2%) at 30 weeks [1]. Undetectable infliximab levels have been associated with higher colectomy rates in UC, but detectable drug levels were associated with increased rates of MH [49, 63]. Increased remission rates with higher TLs of adalimumab have also been appreciated in an Israeli cohort study [64]. A more recent cross-sectional analysis by Ungar et al. investigated the influence of therapeutic drug levels on MH in 145 patients receiving either infliximab or adalimumab therapy. Patients demonstrating MH had more than twice the drug levels for both infliximab and adalimumab compared to those with inflammation. The authors also identified optimal therapeutic windows; infliximab and adalimumab levels greater than 5 and 7.1 μg/mL, respectively, were most predictive for MH, while there was no added benefit above 8 and 12 μg/mL [65].

In clinical practice, there are two scenarios in which therapeutic drug monitoring may be considered. Individuals who initially respond to the biologic agent but over time lose the response are known to have a secondary loss of response (LOR). Drug monitoring is also used proactively, which may entail drug dose escalation or lowering and measurement of trough levels and antibodies. If the presence of a strongly positive antibody is detected in a patient, then different biologic agents may be considered.

One of the most difficult aspects of IBD management is secondary LOR to previously effective therapy. In the ACCENT I trial, less than 40% of patients initially responsive to infliximab therapy maintained remission at 54 weeks [4]. Other study groups have estimated an annual LOR risk of 13% per patient-year with infliximab [66]. The presence of ADAs may contribute to this LOR. Since the work of Baert and colleagues, two episodic dosing trials have found a reduction in response duration in those who developed anti-infliximab antibodies [67, 68]. However, two scheduled dosing trials have not identified adverse outcomes with positive ADA titers [4, 69]. Interestingly, the Active Ulcerative Colitis (ACT) trials found an improved drug response in patients with positive anti-infliximab antibodies. The data for antibodies against adalimumab and certolizumab is similarly conflicting.

In practice, coupling serum TL drug concentrations with antibody titers can help guide management in patients with secondary LOR (Fig. 10.2). During an IBD flare with documented inflammation (i.e., active disease), if antibody titers are negative and TLs of the drug are therapeutic, the physician should consider switching to an entirely new class of medication [70]. If the drug is subtherapeutic, the dose or frequency of administration should be increased. If high antibody titers are detected, switching to another anti-TNF or an anti-integrin is recommended. If only low titers are present, the same agent can be used with the addition of an antimetabolite such as AZA, which may restore the clinical response by eradicating ADAs [71]. Switching therapeutic mechanisms to an anti-integrin is another option. The available clinical data supports this strategy. In a retrospective study of therapeutic

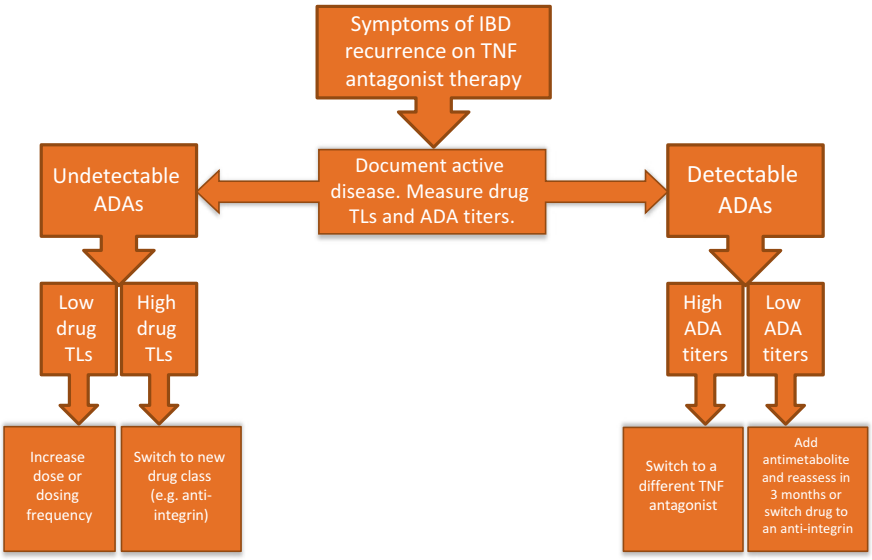

Fig. 10.2 Proposed use of anti-TNF trough levels (TLs) and antidrug antibodies (ADAs) during an IBD flare

infliximab monitoring, 83% of patients with subtherapeutic drug levels responded to dose escalation compared to a 33% response rate after switching to a different TNF antagonist. In patients with ADAs, 92% responded to switching anti-TNF agents compared to a 17% response rate with dose escalation [72].

A strategy to minimize LOR involves monitoring serum drug concentrations proactively. Drug levels are measured at prespecified time points followed by titration of the dose to achieve target concentrations. The benefits of this strategy were demonstrated by the *T*rough Level *A*dapted Infli*XI*mab *T*reatment (TAXIT) study group [73]. Higher rates of clinical remission were achieved when a threshold TL of 3–7 μg/mL was actively targeted. The study also demonstrated an economic benefit to this approach, as patients with TLs of ≥7 μg/mL could be safely dose de-escalated without affecting remission rates. After a successful dose optimization, there was no added benefit to continuing concentration-based dosing over clinically based dosing for the remainder of the first year of therapy [74]. In a recent cross-sectional study, Vaughn and colleagues investigated the impact of proactive drug concentration monitoring and titration of infliximab dosing to a target in patients with clinical remission. Patients who underwent proactive monitoring had a greater likelihood of remaining on infliximab therapy compared to controls (HR = 0.3, 95% CI 0.1–0.6), and those with a TL > 5 μg/mL saw the greatest benefit [75].

Measuring serum drug concentrations to guide therapy has also proven to be cost effective. Velayos and colleagues utilized a Markov model to compare simulated outcomes for a testing-based strategy vs. empirical dose escalation in Crohn's patients with LOR to infliximab [76]. The testing-based strategy had similar

quality-adjusted life-years and remission rates, but was significantly less expensive ($31,870 vs. $37,266) than empirical dose escalation over a 1-year period. Therefore, for both clinical and economic benefits, clinicians should consider incorporating drug concentration measurements into their therapeutic decision-making process.

When Treating Patients with Biologic Therapy, Optimize Therapy

The goals of therapy in IBD have focused on the achievement and maintenance of disease remission through treatment optimization. Traditionally, symptomatic remission was pursued using a "step-up" strategy involving medication and dose escalation as the severity of disease progressed. This strategy involves the use of the least effective and least potentially toxic medications initially, and if not beneficial, more aggressive and effective therapies with potentially greater toxicity are initiated. With the advent of biologic therapy, an effort to achieve resolution of both clinical symptoms and endoscopic inflammation is the focus of therapeutic intervention. The use of prognostication to predict which patients have the highest probability of aggressive disease has led to earlier introduction of biologic therapy in the medical therapeutic armamentarium. Since many patients do not initially respond to standard dosing, adjustments are needed to achieve optimized dosing.

The growing diversity of biologic agents alone has facilitated therapy optimization and remission even in severe disease. The TNF antagonists currently approved by the FDA for CD include infliximab, adalimumab, and certolizumab pegol, while those for UC include infliximab, adalimumab, and golimumab. All of the TNF antagonists have comparable clinical response rates, but switching between them is one potential optimization strategy after LOR [77]. Alternatives to anti-TNF therapy include the anti-integrin agents natalizumab (humanized monoclonal anti-alpha-4 integrin) and vedolizumab (humanized monoclonal anti-alpha-4-beta-7 integrin). However, use of natalizumab is restricted due to an increased risk for JC virus-associated progressive multifocal leukoencephalopathy (PML). The data for therapy optimization, however, is primarily based on the data from infliximab since this agent has been on the market for the longest of all biologics (FDA approved in 1998).

Optimization of therapy begins with an assessment of the risk of disease progression and assessment of the disease severity when considering the use of combination therapy (anti-TNF and immunomodulator). Certain clinical factors portend a higher risk of having complicated disease (poor prognosis), including early onset disease, early steroid requirement, perianal involvement, and severity of endoscopic inflammation [78]. Patients with these risk factors merit a "top-down" approach with early initiation of both a biologic and an antimetabolite. A randomized controlled trial by D'Haens et al. demonstrated that early treatment with dual therapy – infliximab and AZA – in patients with CD (who had no prior exposure to immunomodulators or biologic therapy) was associated with higher rates of MH compared to those receiving biologics later in their disease course [23]. The SONIC

trial also found a dual therapeutic approach in CD to be the most efficacious for steroid-free remission and MH [1]. Most recently, Khanna and colleagues conducted a cluster randomized trial to compare early combined immunosuppression with a conventional step-up approach in CD [79]. While there was no difference in remission rates as prior studies had shown, the risk of surgery, hospital admission, and disease-related complications was significantly lower with no increase in drug-related adverse events in patients receiving early combined therapy.

In UC, the benefits of combination therapy were also investigated in patients with frequent relapse and steroid dependence. Prior treatment guidelines have recommended a "step-up" approach in UC patients with antimetabolite monotherapy prior to a trial of a biologic agent [80]. The validity of this strategy was challenged by the UC SUCCESS trial [81]. Patients with moderate-to-severe UC who were refractory to steroids and naïve to TNF antagonists were treated with AZA monotherapy, infliximab monotherapy, or dual therapy. Those in the dual therapy group had significantly higher rates of corticosteroid-free remission at 16 weeks than patients receiving either monotherapy. Combined therapy also demonstrated significantly more MH than AZA monotherapy, further supporting a top-down approach for these high-risk patients.

In addition to implementing a "top-down" approach in high-risk patients, the clinician should have a strategy to optimize those with an inadequate initial response or secondary LOR to biologic therapy. Scheduled maintenance biologic dosing is preferred to episodic dosing to minimize immunogenicity, but is not 100% effective in preventing ADAs and subsequent LOR [72]. As discussed previously, therapeutic drug monitoring and ADA titers can be helpful in this regard (Fig. 10.2).

Dose escalation is appropriate in situations of negative ADAs and low drug levels, and the available data is most helpful for titrations of infliximab and adalimumab. With infliximab, dosing can be increased from 5 to 10 mg/kg every 4–8 weeks. The ACCENT I trial demonstrated an 80% response rate to this dose escalation in CD patients and the ACCENT II study showed a 50% response in more severe, fistulizing disease [82, 83]. Evidence also supports escalation of adalimumab from 40 mg every other week to weekly. In the CLASSIC II trial, 204 CD patients who were not in remission at weeks 0 and 4 after adalimumab induction entered an open-label cohort with 40 mg adalimumab given every other week [84]. With subsequent disease flares, doses could be escalated to 40 mg weekly. Forty-six percent of patients who completed 56 weeks of therapy required escalation to weekly dosing, among which 42% achieved clinical remission. In a post hoc analysis of the ULTRA 2 trial for UC, 29% of primary nonresponders to adalimumab demonstrated MH by week 52 with weekly dosing [85]. Similarly, weekly adalimumab led to clinical response and MH in 45% of patients with secondary LOR.

More data is needed to support dose escalation for the newer TNF antagonists – specifically certolizumab pegol and golimumab – given the lack of prospective, controlled blinded data. With certolizumab, the WELCOME and PRECISE 4 trials showed that reinduction doses or a single additional dose led to a maintained

clinical response in 50–60% of CD patients with relapse [86, 87]. For golimumab, higher drug levels were associated with greater clinical response in the PURSUIT-SC trial, suggesting a potential benefit to dose escalation that should prompt further investigation [54]. Recent data suggests there may be similar benefit for shortening the dosing frequency for patients with secondary LOR receiving vedolizumab for the treatment of IBD [88].

The diversity of patient and clinical factors in IBD presents challenges to therapeutic decision-making. However, the available data should provide a framework for achieving disease remission in a spectrum of disease manifestations. The greatest benefits are seen when a combination of biologic and antimetabolite therapy is initiated early in severe disease, and following drug levels and ADAs can positively influence dosing and medication adjustments to maintain MH. Future advancements in drug development and monitoring, individualized diagnostics, and risk stratification will promote a more robust approach to therapy optimization.

Dose Appropriately and Use the Correct Induction and Maintenance Doses

For treating IBD patients with active disease, we will review several clinical scenarios that require careful dosing considerations. First, it is important to give appropriate loading doses and appropriate maintenance dosing. Use of approved loading and maintenance doses are based upon pharmacokinetics and modeling. The standard induction and maintenance regimens for approved biologics are listed in Table 10.2.

(a) Prior to initiation of biologics and immunomodulators, vaccinate and screen for future potential infectious complications appropriately.

Table 10.2 Loading doses for biologics and immunomodulators

Biologic	Indication	Loading dose	Maintenance dose
Infliximab	CD, UC	5 mg/kg IV week 0, 2, 6	5 mg/kg IV every 8 weeks
Adalimumab	CD, UC	160 mg sc week 0; 80 mg sc week 2, 40 mg sc week 4	40 mg sc every 2 weeks
Certolizumab pegol	CD	400 mg sc week 0, 2, 4	400 mg sc every 4 weeks
Golimumab	UC	200 mg sc week 0, 100 mg sc week 2	100 mg every 4 weeks
Vedolizumab	CD, UC	300 mg IV week 0, 2, 6	300 mg IV every 8 weeks
Immunomodulator	**Indication**	**Dose**	**–**
Azathioprine	CD, UC	2.5 mg/kg/day	–
6-Mecaptopurine	CD, UC	1.5 mg/kg/day	–
Methotrexate	CD	25 mg sc/im/week	–

Table 10.3 Recommended testing and vaccination prior to initiation of therapy with immunomodulators and biologic agents

Infectious agent	Test	Treatment recommendation
HBV	HBcore Ab, HBsurface Ag, HBsurface Ab	Tenofovir, entecavir
Mycobacterium tuberculosis	Quantiferon TB Gold	INH
HIV	P24 antigen and antibody, PCR	N/A
Varicella	History, PCR	Two doses of varicella vaccine, repeat X 1
Human papilloma virus	Serology IgA, IgG	Bi/quadrivalent vaccine for both gender
Pneumococcus PCV13	N/A	Single vaccination
Influenza	N/A	Annual vaccination in autumn

It is well known that the use of immunomodulators and biologic therapy increases the risk of developing viral, fungal, parasitic, or bacterial infections (Table 10.3). Use of azathioprine/6-MP has been linked to an increased risk for viral infections, whereas biologic agents primarily increase the rate of fungal or mycobacterial infections [89].

Elderly patients with IBD are at an even greater risk for infectious complications. Specifically, patients over the age of 65 years have a 3- to 20-fold increased likelihood of developing urinary tract infection and community-acquired pneumonia while on immunomodulator therapy when compared to subjects 25 years and younger [90]. This argument also applies to elderly patients receiving biologics, as this population is more likely to develop severe infections and have an even higher mortality, making age an independent risk factor for hospitalization [91].

Prior to the initiation of immunosuppressive medications, all patients must be tested for hepatitis B (HBc antibody, HBs antigen, HBs antibody). In addition, vaccination is recommended for all HBc antibody-negative or hepatitis B surface antibody-negative individuals. HBs antigen-positive individuals who require immunosuppressive therapy for CD or UC should receive either entecavir or tenofovir 2 weeks prior to initiating immunosuppressive therapy. Reactivation of HBV in HBs antigen-positive patients has been shown to result in liver dysfunction ranging from 25 to 36% [92, 93]. Fulminant hepatic failure has also been described in this population. Currently, it is suggested that nucleotide/nucleoside analogs should be continued for a total of 12 months after completion of therapy for IBD in patients with a high viral load (HBV DNA > 2000 IU/mL) [94, 95]. The most recent suggestion is to continue nucleotide/nucleoside analogs until reaching endpoints that apply to immunocompetent patients [94, 95].

Besides HBV, serious consideration has to be given to latent Mycobacterium tuberculosis (TB) infection. TB should be excluded prior to the treatment of IBD in all patients with testing that includes an interferon-γ release assay, chest X-ray, and tuberculin skin test. This practice is mandatory, since it has been well recognized that TB reactivation can lead to serious complications and even death in patients treated with anti-TNF medications [96, 97]. Tuberculin skin test results have to be

interpreted with caution, as false-positive results (injection site induration ≥5 mm at 48 h) occur in patients that have received immunization with Bacillus Calmette–Guerin in the past, whereas false-negative findings are associated with active treatment with steroids, immunomodulators, and even active IBD by itself.

Treatment for latent tuberculosis consists of isoniazid and vitamin B6 [98]. Studies on the length of therapy with isoniazid have shown that medication for 9 months is associated with 90% protection, and treatment for 6 months resulted in 60–80% protection from tuberculosis reactivation [99]. Only a fraction of patients on isoniazid will develop liver biochemical abnormalities, and these should be monitored periodically. For patients with IBD and latent tuberculosis, a delay of at least 2 months for treatment prior to initiation of anti-TNF medications has been recommended [100].

Infection of immunocompromised IBD patients with varicella zoster virus (VZV) is a potentially fatal complication in up to one out of four subjects, resulting in disseminated intravascular coagulopathy, encephalitis, and/or hepatitis [101, 102]. In addition, postherpetic neuralgia is more severe in IBD patients treated with immunomodulatory medications with evidence of systemic dissemination in more than 20% [102, 103]. Therefore, IBD subjects without a definite history of chickenpox or varicella zoster should be tested for VZV-specific IgG and if negative, receive two doses of the VZV vaccine at least 3 weeks prior to initiation of biologic therapy [104].

Recommendations for the live zoster vaccine are more complex. In contrast to VZV, immunization with the zoster vaccine can be given while on immunosuppressive therapy, according the United States Center for Disease Control, as long as current medical therapy does not exceed the following dosing schedules: azathioprine ≤3 mg/kg, 6-mercaptopurine ≤1.5 mg/kg, methotrexate ≤0.4 mg/kg [105]. The zoster vaccine appears to be safe even in IBD patients on anti-TNF therapy [106]; however, it is not currently suggested to be given to patients on current anti-TNF therapy.

Female patients with IBD being treated with immunosuppressive medications should receive an annual pelvic examination. The screening for cervical cancer and its precursors in immunocompromised patients is now a standard recommendation. In addition to and regardless of medical therapy, the quadrivalent vaccine directed against human papilloma virus (HPV) L1-virus-like particles should be given to sexually active women and men from 11 to 26 years of age (Advisory committee on immunization practices CDC 2013).

(b) Optimize therapy – dose escalate when appropriate.

Patients who have persistent clinically significant inflammation despite biologic (anti-TNF or anti-integrin) therapy with therapeutic drug levels are considered as a therapeutic primary failure. However, patients initially responding who lose their response over time (termed secondary loss of response) should be considered for dose escalation before switching to an alternative agent. In general, the concept involves targeting higher biologic trough levels of the prescribed biologic agent. Table 10.4 summarizes relevant studies of dose escalation and factors that influence response and remission to biologic agents.

Table 10.4 Dose escalation and factors that influence response and remission to biologics

Study	Endpoint	Result	Remarks
ACCENT I (2002) [4] Maintenance of remission for CD	Rate of remission at week 30	Placebo 21%, IFX 5 mg/kg 39%*, IFX 10 mg/kg 45%*	*: Statistically significant in comparison to placebo 28.5% of patients developed worsening symptoms on IFX
	Median time to loss of response at week 54 (CDAI decrease >70 points, or 25% reduction total score)	Placebo 19 weeks, IFX 5 mg/kg 38 weeks*, IFX 10 mg/kg > 54 weeks*	
	Discontinuation of steroids at week 54	Placebo 9%, combined IFX 5/10 mg/kg 29%*	
GAIN (2007) [107] Adalimumab for the treatment of CD patients who failed IFX	Rate of remission at week 4 (CDAI decrease >70 points)	Placebo 7% vs. adalimumab 21%*	*: Statistically significant in comparison to placebo Switching to adalimumab after failure of IFX does not result in regain of anti-TNF responsiveness
PRECISE 4 (2010) [86] Dose escalation in CD patients with secondary failure to certolizumab	Rate of response at week 4	Group A (reintroduction dosing) 63%, group B (maintenance dosing) 65%	
	Rate of response at week 54	Group A (reintroduction dosing) 55%, group B (maintenance dosing) 59%	Addition of a single dose of certolizumab results in regain of anti-TNF responsiveness
Identification of variables that influence IFX dose intensification in CD (2007) [108]	Rate of event-free (flare) at month 30 time period from first infusion	Interval decrease 69%, dose increase 49%, interval decrease and dose increase 46%	Patients becoming symptomatic with IFX every 8 weeks should be tried on an increased infusion frequency schedule, first

Adalimumab dose intensification in CD patients with secondary loss of response (2013) [109]	Change in CDAI at months 3 and 12 while on adalimumab every week	Rate of patients with a decrease in CDAI >100 64% at 3 months, and 57% at 12 months	After secondary loss of response, dose escalation with weekly adalimumab injections induces response and remission
Effect of serum albumin concentration on the effectiveness of vedolizumab in patients with CD (2016) [88]	Assessment of Harvey Bradshaw Index score at weeks 0 and 14, subdivided by quartile serum albumin concentration	Response to vedolizumab was independent of albumin serum concentration	Vedolizumab might provide an alternative first choice of biologic in patients with below normal serum albumin concentrations

(c) Check TPMT prior to treatment with antimetabolite therapy. Consider the toxicities associated with thiopurine use.

Thiopurine methyltransferase (TPMT) genotype or phenotype (i.e., enzyme activity) testing prior to initiating immunomodulatory therapy with AZA or 6-MP can help to predict drug response and is now standard of practice [110–112]. In the general population and in patients with IBD, enzyme activity in Caucasians is divided into low (0.3%), intermediate (11%), and normal levels (89%). In general, patients with intermediate enzyme activity are started on a lower dose of 6-mercaptopurine and azathioprine, as opposed to patients with normal TPMT activity, usually receiving a regular maximal dose at 1.5 mg/kg and 2.5 mg/kg, respectively. The rare patient with a low TPMT enzyme activity should not receive immunomodulatory therapy with AZA or 6-MP due to increased toxicities.

Thiopurines for the maintenance of remission are not tolerated by approximately 20% of patients beyond 1 month. Most commonly encountered side effects including headache, diarrhea, nausea, vomiting, abdominal pain, and fatigue [113]. Complications encountered for the duration of thiopurine treatment include myelosuppression with ensuing leukopenia in about 5% of patients, even after patients stop medication for 6 months [114, 115]. In addition, 2.3% of patients may develop pancreatitis, and more rarely, hepatitis may occur.

A more recent concern is the increased risk for lymphoma with thiopurine use. Kotlyar and colleagues conducted a meta-analysis to determine how this risk varied with patient age and gender and found that the risk was greatest in individuals older than 50 and men younger than 30 [116]. Weighing the risks and benefits of antimetabolite therapy therefore merits further attention in individuals from either of these groups.

(d) Prior to conception, it is important to ensure the mother is in remission.

Pregnancy in patients with IBD poses a special challenge to the mother, fetus, and provider. Besides general recommendations, including adequate nutrition, supplemental folate and vitamin D, and smoking cessation, specific attention has to be paid to medical therapy for induction and maintenance of remission. Prognostically, female patients that conceive during a flare of IBD have an approximately 70% chance of continued or worsening activity of intestinal inflammation during pregnancy [117–119]. Therefore, it is of paramount importance to achieve clinical remission prior to considering pregnancy. Continuation of appropriate medication during pregnancy is currently the standard to consider for patients in remission.

(e) Anti-TNF therapy is perceived to be safe in pregnancy to the mother and fetus. However, there is limited data for the safety of anti-integrin therapy.

Anti-TNF agents are used for induction and maintenance of remission during pregnancy and are considered low risk to the fetus and mother [120]. Transplacental traffic of IgG1 increases and accumulates in the fetus with gestational age [121], and the increase in anti-TNF medications might lead to modification and suppression of

the fetal enteric immune system, as clearance of anti-TNFs has been shown to take between 2 and 7 months to become undetectable postpartum. Infliximab, adalimumab, golimumab, and vedolizumab are composed of IgG1 Fc segments and cross transplacentally, whereas certolizumab pegol is IgG4 and has low transplacental transfer. To this date, preterm birth, infections, or developmental differences have not been identified in comparison to unexposed infants [122]. Biologic agents can be safely sustained for the first two trimesters until weeks 24–26, but due to a lack of prospective trial data, firm recommendations whether to stop, decrease the dose, or maintain the medication at full strength depend on the individual provider and the patient. However, prior to any decision, disease activity should be assessed [123].

Vedolizumab has limited data available in abstract form only [124]. A small study showed that of 16 documented exposures to vedolizumab during pregnancy, nine resulted in live births, two in spontaneous abortions, two in elective abortions, and three were lost to follow-up.

(f) AZA and 6-MP use during pregnancy is not associated with any systematic birth defect but has been associated with infants who are premature or small for gestational age.

AZA and 6-MP are categorized as class D drugs in pregnancy, as there is positive evidence of human fetal risk, based on adverse reaction data from investigational and marketing experience, as well as human studies. However, potential benefits may warrant use of the drug in pregnant women despite the potential risks, as there is no systematic birth defect that has been described with its use. A recent meta-analysis [125] has demonstrated that thiopurine exposure in women with IBD was not associated with low birth weight or congenital abnormalities, but was associated with preterm birth. Exposure in men at the time of conception was not associated with congenital abnormalities.

Data from the PIANO registry noted that adverse outcomes for women and their newborn were not significantly different from control populations, but this study noted a few exceptions to this finding [126]. First, besides an increased rate of spontaneous abortions and Cesarean sections, infants born to mothers with IBD were more likely to deliver early and require postpartum intensive care. Second, mothers treated with anti-TNF agents for UC had a fivefold increased rate of spontaneous abortion, which was not the case for CD pregnancies. Third, combination therapy with anti-TNF and immunomodulatory agents resulted in postpartum complications of any kind, adjusted for disease activity.

Additionally, 6-thioguanine nucleotide (6-TGN), a metabolite of 6-MP and AZA, is detectable in newborns of mothers treated with immunomodulators and usually mirrors the mother's 6-TGN serum concentrations. In contrast, 6-methylmercaptopurine nucleotide (6-MMP) does not traverse the placental barrier and is not found in fetal peripheral blood. Despite these findings, increased congenital abnormalities have not been described [125, 127, 128]. Among providers there is agreement to not start immunomodulators during pregnancy out of concern for bone marrow suppression and pancreatitis.

(g) For infants born to mothers on anti-TNF therapy, avoidance of live vaccines for 6 months after birth is suggested. Certolizumab pegol crosses the placenta in very low concentrations.

Experts from the United States Centers for Disease Control and Prevention, Public Health Agent of Canada, European Crohn's and Colitis Organization, and World Congress of Gastroenterology, all currently recommend that infants exposed to biologics in utero should receive the same nonlive vaccines given to unexposed individuals. However, live attenuated vaccines, like rotavirus, intranasal influenza, and BCG, should not be given until 6 months of age. This recommendation is based upon the observation that biologics for the treatment of the mother's inflammatory bowel disease in some cases are not cleared by the infant until that time, raising the concern for disseminated infections. If concern regarding a lack of clearance of biologics in infants beyond 6 months exists, serum titers can be obtained to guide the administration of live attenuated vaccines.

Therefore, it is advisable to weigh risks and benefits carefully, tailored to each individual pregnancy, taking into consideration the past and present behavior and severity of disease, as well as successful and unsuccessful medications used to maintain remission. A multidisciplinary approach is advisable, managing these complex patients with advice from obstetrics, nutrition, pharmacy, and possibly surgery.

(h) Serum albumin is one of the most important predictors of response to biologic therapy.

When evaluating patients in the office or hospital setting, it is important to assess the response that an individual patient may have to medical therapy. Biomarkers that enable practitioners to successfully predict a patient's response to biologic agents are now beginning to emerge. Serum albumin concentration is one of the most well-studied biomarkers for this purpose. Combining data from two study populations with over 700 UC subjects, patients with a normal range of serum albumin demonstrated a lower clearance rate, longer half-life, and significantly higher serum trough levels of infliximab, translating into a more favorable clinical response rate to therapy [129]. In particular, a retrospective pharmacokinetic analysis of two Phase III trials by the same group (REACH, ACCENT I) found that low serum albumin was associated with significantly increased infliximab clearance [130]. Interestingly, even within the range from high (4.8 mg/dL) to low-normal (3.1 mg/dL) albumin levels, infliximab clearance increased by approximately 45%, speculating that a normal albumin concentration improves the function of the neonatal Fc receptor, ergo recycling infliximab more efficiently, and accounting for more than 80% of infliximab efficacy. When investigating CD patients with a loss of response to anti-TNF therapy at 5 mg/kg, after a dose adjustment to 10 mg/kg, remission rates at 40 weeks were significantly higher in subjects with trough infliximab concentrations $\geq$1 μg/mL and albumin levels $\geq$3.5 g/dL [131].

While treating with certolizumab pegol, univariant analysis short-term recurrence is significantly higher in patients with an albumin concentration below

3.5 mg/dL [132]. Further, multivariant analysis has shown that for every unit increase in albumin and single percent of hematocrit, the probability of losing remission at a given time is reduced (HR 0.944 and HR 0.736, respectively). In reverse, when data was subjected to logistic regression analysis, maintenance of remission with certolizumab was shown to be associated with, among others, a normal serum albumin concentration (OR 1.07, 95% CI 1.01–1.13). These findings suggest that serum albumin concentrations should be closely monitored for the prediction of long-term outcome in UC and CD, and dose escalation should be considered in patients with low serum albumin.

Promote Medication Adherence in All Patients

While successful IBD management requires a thoughtful and personalized treatment approach, suboptimal medication adherence remains a significant and often overlooked barrier to remission. Nonadherence occurs in greater than 30% of IBD patients, and as many as 60% of adults do not take their oral 5-ASA medications consistently [133, 134]. This lack of adherence increases the risk of IBD flares by more than fivefold while also escalating healthcare costs [135]. Unfortunately, recognition of nonadherence is challenging, and evidence for the use of disease characteristics and demographics to screen for nonadherence is lacking [136, 137]. The clinician's efforts should therefore focus on methods to promote medication adherence in all patients.

Current evidence supports the use of education and dose simplification to maximize adherence. Gastroenterologists should aim to expand their patients' knowledge regarding IBD and associated symptoms, purpose and mechanisms of specific medications, potential adverse effects of therapy, and the consequences of nonadherence. The most commonly reported reasons for intentional treatment discontinuation are adverse effects and symptom resolution (removing the perceived need for therapy), which may reflect a fundamental misunderstanding of the disease process [138]. Many patients outwardly express a desire to learn more about their disease and endorse fear related to knowledge deficits [139, 140]. Prior studies have demonstrated that disease-specific education can mitigate these concerns and bolster adherence [141–143]. An RCT by Waters et al. corroborated that formal IBD education successfully improves patient knowledge, perceived knowledge, and satisfaction [144]. While underpowered, the study also found a nonsignificant reduction in nonadherence in the patient education group. In a recent cohort study, Selinger and colleagues investigated modifiable risk factors associated with nonadherence to IBD therapy. The belief of necessity of medication was associated with significantly better adherence, suggesting a valuable role for a patient's understanding of specific treatments and their functions.

Simplification of the dosing regimen has also been shown to improve medication adherence in adults. Kane et al. randomized UC patients to either conventional mesalamine dosing (two or three times daily) or once-daily dosing. At 3 months,

once-daily dosing resulted in full adherence, while conventional dosing yielded only 70% adherence [145]. Further work by Dignass and colleagues found the remission rate of UC to be higher with once-daily compared to twice-daily mesalamine [146]. Additionally, both once- and twice-daily MMX mesalamine effectively induced clinical and endoscopic remission when compared to placebo in patients with mild to moderate UC, affirming that simplified dosing is also a therapeutically sound option [147]. This strategy may be most beneficial in cases of accidental nonadherence due to the complexity of treatment regimens.

Several more specialized adherence strategies may be considered based on patient preferences and characteristics. In pediatric populations, cognitive behavioral therapy (CBT) aimed at problem solving has been effective. Greenley and colleagues found that two family-centered problem-solving training sessions improved adherence by 18% among patients who were previously nonadherent to oral medication [148]. For more challenging cases, a multifaceted and tailored approach that combines education, behavioral therapy, and support may be preferred. Moshkovska et al. demonstrated significantly greater adherence to mesalamine in UC patients who underwent motivational training, education, and three additional patient-chosen tactics including simplified dosing, pill organizers, and various medication alarms and reminders [149]. Given the many potentially effective interventions, it is worthwhile for every gastroenterologist to discuss adherence in the clinic and identify any modifiable barriers prior to optimizing therapy.

Prognosticate to Predict Which Patients Will Have the Highest Probability of Having Aggressive Disease. Treat Aggressive Disease Aggressively

One of the most important challenges in IBD management is identifying high-risk patients to whom a top-down therapeutic approach should be applied. The risk of structural bowel damage leading to intestinal resection in CD is nearly 80%, and 10% of UC patients will have a colectomy within 10 years of diagnosis [150, 151]. Implementing early aggressive therapy that combines a thiopurine and TNF antagonist can reduce the incidence of these tragic outcomes in select patients [1]. But those destined for a more benign disease course may instead suffer from the complications of unnecessary immunosuppression if their risk is incorrectly stratified. There is therefore an obvious need for reliable predictors of disease course and severity to be applied in clinical practice.

In CD, clinical findings at diagnosis can predict disease severity. Wolters et al. found that age <40 years and the presence of upper gastrointestinal lesions on endoscopy predicted recurrence, while Solbert and colleagues identified age <40 years, perianal fistulas and abscesses, and involvement of the terminal ileum as predictive factors for surgery within 10 years of diagnosis [152, 153]. The need for steroids in treating the first IBD flare also predicted disabling disease (e.g., steroid dependence, hospitalization, surgery, disabling symptoms) within 5 years of diagnosis in a

referral center cohort [154]. Smoking has been established as a risk factor for transient worsening in CD, while nonsmoking status and higher educational level were independently associated with a nonsevere 15-year course in a 600-patient cohort [148, 155]. For postoperative CD recurrence, smoking is associated with a twofold increased risk that grows further according to the number of cigarettes smoked daily [156].

Serologic factors can also provide useful prognostic information in CD. Several studies have assessed serum markers, and antibodies against *Saccharomyces cerevisiae* antibody (ASCA), *Escherichia coli* outer-membrane porin C (OmpC), anti-CD-related bacterial sequence (anti-I2), and CBir1 flagellin (CBir1) are associated with early disease onset, penetrating disease, and need for early surgical intervention [157–159]. ASCA may also predict pouchitis after ileal-anal anastomosis [160]. Unlike in UC, perinuclear antineutrophil cytoplasmic antibody (p-ANCA) has been associated with less severe disease and fewer small bowel complications in CD [158, 161].

The utility of genetic predisposition is more limited in prognosis, given that a family history of CD (which increased risk for CD) does not predict disease severity [162]. However, a select few genetic polymorphisms may help predict clinical outcomes. The NOD2 polymorphism has been associated with an increased risk for stricture, early surgical intervention, and postoperative recurrence [163]. Additionally, multidrug resistant 1 (MDR1), migration inhibitory factor (MIF), and TNF genetic polymorphisms may help predict steroid refractory disease [164–166]. More recent work has identified apoptosis gene polymorphisms that may help predict anti-TNF responsiveness in CD [167].

In UC, clinical predictors for disease severity were evaluated in population-based cohorts. Female gender and young age at diagnosis were associated with frequent relapses in two studies, and significant systemic symptoms such as fever and weight loss increased the risk for colectomy in a Danish cohort [168–170]. The data for smoking, however, is somewhat more conflicting; one cohort study associated smoking with reduced relapses, while others have found a less active disease course in nonsmokers [155, 169]. Nonetheless, smoking is never advised in IBD patients.

Less data exists for serologic and genetic markers for disease severity in UC. However, multiple studies, including a recent prospective Australian cohort, have associated colectomy with elevated CRP at diagnosis [171]. And while genetic factors are not yet applied in clinical practice, Iliev and colleagues found that a haplotype of the gene CLEC7A predicts treatment-refractory UC and shorter time to colectomy [172].

A global assessment of prognostic factors should be used to guide therapy in IBD. Siegel and colleagues recently developed a Web-based tool that combines clinical, serologic, and genetic variables to predict outcomes that can help providers make personalized treatment decisions in CD [173]. The variables incorporated into the model are readily available through standard IBD evaluation and include the location of disease in the bowel, ASCA, CBir1, ANCA, and NOD2 frameshift mutation. These characteristics are inputted in an online interface that then calculates and plots the patient's percentage risk for complications

against time. This is the first validated predictive model that facilitates shared decision-making between the patient and the provider that will hopefully see extensive use by gastroenterologists in the coming years. With additional prospective data on predictors of disease course, we hope that similar models will be developed for practical use in UC as well.

Conclusions

We hope that this chapter provides a helpful framework for approaching patients with moderate-to-severe IBD. While no single therapeutic plan can benefit all patients, we feel that a general strategy that involves documenting active disease, treating to objective targets, optimizing therapy, and promoting adherence will lead to the best outcomes. High-risk patients now warrant a top-down approach, and achieving mucosal healing has become a feasible goal in the biologic era. With the growing diversity of immunomodulatory agents and improvement in our prognostic capabilities, we hope to be able to tailor therapy with even greater precision to individual patients' needs.

References

1. Colombel JF, Sandborn WJ, Reinisch W, Mantzaris GJ, Kornbluth A, Rachmilewitz D, et al. Infliximab, azathioprine, or combination therapy for Crohn's disease. N Engl J Med. 2010;362(15):1383–95.
2. Best WR, Bechtel JM, Singleton JW, Kern Jr F. Development of a Crohn's disease activity index. National Cooperative Crohn's Disease Study. Gastroenterology. 1976;70(3):439–44.
3. Cellier C, Mahmoud T, Froue E, Adénies A, Be laiche J, Bretagne JF, et al. Correlations between clinical activity, endoscopic severity, and biological parameters in colonic or ileocolonic Crohn's disease. A prospective multicentre study of 121 cases. The Groupe d'Etudes Therapeutiques des Affections Inflammatoires Digestives. Gut. 1994;35(2):231–5.
4. Hanauer SB, Feagan BG, Lichtenstein GR, Mayer LF, Schreiber S, Colombel JF, et al. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. Lancet. 2002;359(9317):1541–9.
5. Harvey RF, Bradshaw JM. A simple index of Crohn's-disease activity. Lancet. 1980; 1(8167):514.
6. Stjernman H, Tysk C, Almer S, Strom M, Hjortswang H. Factors predicting the outcome of disease activity assessment in Crohn's disease. Inflamm Bowel Dis. 2009;15(12):1859–66.
7. af Bjorkesten CG, Nieminen U, Turunen U, Arkkila P, Sipponen T, Farkkila M. Surrogate markers and clinical indices, alone or combined, as indicators for endoscopic remission in anti-TNF-treated luminal Crohn's disease. Scand J Gastroenterol. 2012;47(5):528–37.
8. Mary JY, Modigliani R. Development and validation of an endoscopic index of the severity for Crohn's disease: a prospective multicentre study. Groupe d'Etudes Therapeutiques des Affections Inflammatoires du Tube Digestif (GETAID). Gut. 1989;30(7):983–9.
9. Daperno M, D'Haens G, Van Assche G, Baert F, Bulois P, Maunoury V, et al. Development and validation of a new, simplified endoscopic activity score for Crohn's disease: the SES-CD. Gastrointest Endosc. 2004;60(4):505–12.

10. Sipponen T, Nuutinen H, Turunen U, Farkkila M. Endoscopic evaluation of Crohn's disease activity: comparison of the CDEIS and the SES-CD. Inflamm Bowel Dis. 2010;16(12):2131–6.
11. Rutgeerts P, Geboes K, Vantrappen G, Beyls J, Kerremans R, Hiele M. Predictability of the postoperative course of Crohn's disease. Gastroenterology. 1990;99(4):956–63.
12. Truelove SC, Witts LJ. Cortisone and corticotrophin in ulcerative colitis. Br Med J. 1959;1(5119):387–94.
13. Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. N Engl J Med. 1987;317(26):1625–9.
14. Daperno M, Comberlato M, Bossa F, Biancone L, Bonanomi AG, Cassinotti A, et al. Inter-observer agreement in endoscopic scoring systems: preliminary report of an ongoing study from the Italian Group for Inflammatory Bowel Disease (IG-IBD). Dig Liver Dis. 2014;46(11):969–73.
15. Travis SP, Schnell D, Krzeski P, Abreu MT, Altman DG, Colombel JF, et al. Developing an instrument to assess the endoscopic severity of ulcerative colitis: the Ulcerative Colitis Endoscopic Index of Severity (UCEIS). Gut. 2012;61(4):535–42.
16. Feagan BG, Sandborn WJ, D'Haens G, Pola S, McDonald JW, Rutgeerts P, et al. The role of centralized reading of endoscopy in a randomized controlled trial of mesalamine for ulcerative colitis. Gastroenterology. 2013;145(1):149–57. e2
17. Lobaton T, Bessissow T, De Hertogh G, Lemmens B, Maedler C, Van Assche G, et al. The Modified Mayo Endoscopic Score (MMES): a new index for the assessment of extension and severity of endoscopic activity in ulcerative colitis patients. J Crohns Colitis. 2015;9(10):846–52.
18. Allaart CF, Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Breedveld FC, Dijkmans BA, FARR study group. Aiming at low disease activity in rheumatoid arthritis with initial combination therapy or initial monotherapy strategies: the BeSt study. Clin Exp Rheumatol. 2006;24(6 Suppl 43):S-77-82.
19. Peyrin-Biroulet L, Reinisch W, Colombel JF, Mantzaris GJ, Kornbluth A, Diamond R, et al. Clinical disease activity, C-reactive protein normalisation and mucosal healing in Crohn's disease in the SONIC trial. Gut. 2014;63(1):88–95.
20. Froslie KF, Jahnsen J, Moum BA, Vatn MH, Group I. Mucosal healing in inflammatory bowel disease: results from a Norwegian population-based cohort. Gastroenterology. 2007;133(2):412–22.
21. Schnitzler F, Fidder H, Ferrante M, Noman M, Arijs I, Van Assche G, et al. Mucosal healing predicts long-term outcome of maintenance therapy with infliximab in Crohn's disease. Inflamm Bowel Dis. 2009;15(9):1295–301.
22. Baert F, Moortgat L, Van Assche G, Caenepeel P, Vergauwe P, De Vos M, et al. Mucosal healing predicts sustained clinical remission in patients with early-stage Crohn's disease. Gastroenterology. 2010;138(2):463–8. quiz e10-1
23. D'Haens G, Baert F, van Assche G, Caenepeel P, Vergauwe P, Tuynman H, et al. Early combined immunosuppression or conventional management in patients with newly diagnosed Crohn's disease: an open randomised trial. Lancet. 2008;371(9613):660–7.
24. Ferrante M, Vermeire S, Fidder H, Schnitzler F, Noman M, Van Assche G, et al. Long-term outcome after infliximab for refractory ulcerative colitis. J Crohns Colitis. 2008;2(3):219–25.
25. Colombel JF, Rutgeerts P, Reinisch W, Esser D, Wang Y, Lang Y, et al. Early mucosal healing with infliximab is associated with improved long-term clinical outcomes in ulcerative colitis. Gastroenterology. 2011;141(4):1194–201.
26. Korelitz BI, Sultan K, Kothari M, Arapos L, Schneider J, Panagopoulos G. Histological healing favors lower risk of colon carcinoma in extensive ulcerative colitis. World J Gastroenterol. 2014;20(17):4980–6.
27. Roseth AG, Fagerhol MK, Aadland E, Schjonsby H. Assessment of the neutrophil dominating protein calprotectin in feces. A methodologic study. Scand J Gastroenterol. 1992;27(9):793–8.

28. Roseth AG, Aadland E, Jahnsen J, Raknerud N. Assessment of disease activity in ulcerative colitis by faecal calprotectin, a novel granulocyte marker protein. Digestion. 1997; 58(2):176–80.
29. D'Haens G, Ferrante M, Vermeire S, Baert F, Noman M, Moortgat L, et al. Fecal calprotectin is a surrogate marker for endoscopic lesions in inflammatory bowel disease. Inflamm Bowel Dis. 2012;18(12):2218–24.
30. Sandborn WJ, Panes J, Zhang H, Yu D, Niezychowski W, Su C. Correlation between concentrations of fecal calprotectin and outcomes of patients with ulcerative colitis in a phase 2 trial. Gastroenterology. 2016;150(1):96–102.
31. Theede K, Holck S, Ibsen P, Ladelund S, Nordgaard-Lassen I, Nielsen AM. Level of fecal calprotectin correlates with endoscopic and histologic inflammation and identifies patients with mucosal healing in ulcerative colitis. Clin Gastroenterol Hepatol. 2015;13(11):1929–36. e1
32. Guidi L, Marzo M, Andrisani G, Felice C, Pugliese D, Mocci G, et al. Faecal calprotectin assay after induction with anti-Tumour Necrosis Factor alpha agents in inflammatory bowel disease: prediction of clinical response and mucosal healing at one year. Dig Liver Dis. 2014;46(11):974–9.
33. Guardiola J, Lobaton T, Rodriguez-Alonso L, Ruiz-Cerulla A, Arajol C, Loayza C, et al. Fecal level of calprotectin identifies histologic inflammation in patients with ulcerative colitis in clinical and endoscopic remission. Clin Gastroenterol Hepatol. 2014;12(11):1865–70.
34. Yamamoto T, Shimoyama T, Bamba T, Matsumoto K. Consecutive monitoring of fecal calprotectin and lactoferrin for the early diagnosis and prediction of pouchitis after restorative proctocolectomy for ulcerative colitis. Am J Gastroenterol. 2015;110(6):881–7.
35. De Vos M, Louis EJ, Jahnsen J, Vandervoort JG, Noman M, Dewit O, et al. Consecutive fecal calprotectin measurements to predict relapse in patients with ulcerative colitis receiving infliximab maintenance therapy. Inflamm Bowel Dis. 2013;19(10):2111–7.
36. Falvey JD, Hoskin T, Meijer B, Ashcroft A, Walmsley R, Day AS, et al. Disease activity assessment in IBD: clinical indices and biomarkers fail to predict endoscopic remission. Inflamm Bowel Dis. 2015;21(4):824–31.
37. Wright EK, Kamm MA, De Cruz P, Hamilton AL, Ritchie KJ, Krejany EO, et al. Measurement of fecal calprotectin improves monitoring and detection of recurrence of Crohn's disease after surgery. Gastroenterology. 2015;148(5):938–47. e1
38. Yoon JY, Park SJ, Hong SP, Kim TI, Kim WH, Cheon JH. Correlations of C-reactive protein levels and erythrocyte sedimentation rates with endoscopic activity indices in patients with ulcerative colitis. Dig Dis Sci. 2014;59(4):829–37.
39. Sulz MC, Siebert U, Arvandi M, Gothe RM, Wurm J, von Kanel R, et al. Predictors for hospitalization and outpatient visits in patients with inflammatory bowel disease: results from the Swiss Inflammatory Bowel Disease Cohort Study. Eur J Gastroenterol Hepatol. 2013;25(7):790–7.
40. Click B, Vargas EJ, Anderson AM, Proksell S, Koutroubakis IE, Ramos Rivers C, et al. Silent Crohn's disease: asymptomatic patients with elevated C-reactive protein are at risk for subsequent hospitalization. Inflamm Bowel Dis. 2015;21(10):2254–61.
41. Kiss LS, Papp M, Lovasz BD, Vegh Z, Golovics PA, Janka E, et al. High-sensitivity C-reactive protein for identification of disease phenotype, active disease, and clinical relapses in Crohn's disease: a marker for patient classification? Inflamm Bowel Dis. 2012;18(9):1647–54.
42. Kiss LS, Szamosi T, Molnar T, Miheller P, Lakatos L, Vincze A, et al. Early clinical remission and normalisation of CRP are the strongest predictors of efficacy, mucosal healing and dose escalation during the first year of adalimumab therapy in Crohn's disease. Aliment Pharmacol Ther. 2011;34(8):911–22.
43. Jurgens M, Mahachie John JM, Cleynen I, Schnitzler F, Fidder H, van Moerkercke W, et al. Levels of C-reactive protein are associated with response to infliximab therapy in patients with Crohn's disease. Clin Gastroenterol Hepatol. 2011;9(5):421–7. e1

44. Bouguen G, Levesque BG, Pola S, Evans E, Sandborn WJ. Feasibility of endoscopic assessment and treating to target to achieve mucosal healing in ulcerative colitis. Inflamm Bowel Dis. 2014;20(2):231–9.
45. Bouguen G, Levesque BG, Pola S, Evans E, Sandborn WJ. Endoscopic assessment and treating to target increase the likelihood of mucosal healing in patients with Crohn's disease. Clin Gastroenterol Hepatol. 2014;12(6):978–85.
46. Prabhakar N, Kalra N, Bhasin DK, Rana SS, Gupta V, Singh R, et al. Comparison of CT colonography with conventional colonoscopy in patients with ulcerative colitis. Acad Radiol. 2015;22(3):296–302.
47. Timmer A, McDonald JW, Tsoulis DJ, Macdonald JK. Azathioprine and 6-mercaptopurine for maintenance of remission in ulcerative colitis. Cochrane Database Syst Rev. 2012;9:CD000478.
48. Chande N, Tsoulis DJ, MacDonald JK. Azathioprine or 6-mercaptopurine for induction of remission in Crohn's disease. Cochrane Database Syst Rev. 2013;4:CD000545.
49. Rutgeerts P, Sandborn WJ, Feagan BG, Reinisch W, Olson A, Johanns J, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2005;353(23):2462–76.
50. Colombel JF, Sandborn WJ, Rutgeerts P, Enns R, Hanauer SB, Panaccione R, et al. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. Gastroenterology. 2007;132(1):52–65.
51. Sandborn WJ, van Assche G, Reinisch W, Colombel JF, D'Haens G, Wolf DC, et al. Adalimumab induces and maintains clinical remission in patients with moderate-to-severe ulcerative colitis. Gastroenterology. 2012;142(2):257-65 e1-3.
52. Sandborn WJ, Abreu MT, D'Haens G, Colombel JF, Vermeire S, Mitchev K, et al. Certolizumab pegol in patients with moderate to severe Crohn's disease and secondary failure to infliximab. Clin Gastroenterol Hepatol. 2010;8(8):688–95. e2
53. Sandborn WJ, Feagan BG, Marano C, Zhang H, Strauss R, Johanns J, et al. Subcutaneous golimumab induces clinical response and remission in patients with moderate-to-severe ulcerative colitis. Gastroenterology. 2014;146(1):85–95. quiz e14-5
54. Sandborn WJ, Feagan BG, Marano C, Zhang H, Strauss R, Johanns J, et al. Subcutaneous golimumab maintains clinical response in patients with moderate-to-severe ulcerative colitis. Gastroenterology. 2014;146(1):96-109 e1.
55. van Schaik T, Maljaars JP, Roopram RK, Verwey MH, Ipenburg N, Hardwick JC, et al. Influence of combination therapy with immune modulators on anti-TNF trough levels and antibodies in patients with IBD. Inflamm Bowel Dis. 2014;20(12):2292–8.
56. Baert F, Noman M, Vermeire S, Van Assche G, D'Haens G, Carbonez A, et al. Influence of immunogenicity on the long-term efficacy of infliximab in Crohn's disease. N Engl J Med. 2003;348(7):601–8.
57. Nanda KS, Cheifetz AS, Moss AC. Impact of antibodies to infliximab on clinical outcomes and serum infliximab levels in patients with inflammatory bowel disease (IBD): a meta-analysis. Am J Gastroenterol. 2013;108(1):40–7. quiz 8
58. Karmiris K, Paintaud G, Noman M, Magdelaine-Beuzelin C, Ferrante M, Degenne D, et al. Influence of trough serum levels and immunogenicity on long-term outcome of adalimumab therapy in Crohn's disease. Gastroenterology. 2009;137(5):1628–40.
59. Radstake TR, Svenson M, Eijsbouts AM, van den Hoogen FH, Enevold C, van Riel PL, et al. Formation of antibodies against infliximab and adalimumab strongly correlates with functional drug levels and clinical responses in rheumatoid arthritis. Ann Rheum Dis. 2009;68(11):1739–45.
60. Roblin X, Marotte H, Rinaudo M, Del Tedesco E, Moreau A, Phelip JM, et al. Association between pharmacokinetics of adalimumab and mucosal healing in patients with inflammatory bowel diseases. Clin Gastroenterol Hepatol. 2014;12(1):80–4. e2

61. Maser EA, Villela R, Silverberg MS, Greenberg GR. Association of trough serum infliximab to clinical outcome after scheduled maintenance treatment for Crohn's disease. Clin Gastroenterol Hepatol. 2006;4(10):1248–54.
62. Cornillie F, Hanauer SB, Diamond RH, Wang J, Tang KL, Xu Z, et al. Postinduction serum infliximab trough level and decrease of C-reactive protein level are associated with durable sustained response to infliximab: a retrospective analysis of the ACCENT I trial. Gut. 2014;63(11):1721–7.
63. Reinisch W, Feagan BG, Rutgeerts PJ, Adedokun OJ, Cornillie FJ, Diamond R, Marano CW, Sandborn WJ. 566 infliximab concentration and clinical outcome in patients with ulcerative colitis. Gastroenterology. 2012;142(5):S-114.
64. Mazor Y, Almog R, Kopylov U, Ben Hur D, Blatt A, Dahan A, et al. Adalimumab drug and antibody levels as predictors of clinical and laboratory response in patients with Crohn's disease. Aliment Pharmacol Ther. 2014;40(6):620–8.
65. Ungar B, Levy I, Yavne Y, Yavzori M, Picard O, Fudim E, et al. Optimizing anti-TNF-alpha therapy: serum levels of infliximab and adalimumab are associated with mucosal healing in patients with inflammatory bowel diseases. Clin Gastroenterol Hepatol. 2016;14(4):550–7. e2
66. Gisbert JP, Panes J. Loss of response and requirement of infliximab dose intensification in Crohn's disease: a review. Am J Gastroenterol. 2009;104(3):760–7.
67. Farrell RJ, Alsahli M, Jeen YT, Falchuk KR, Peppercorn MA, Michetti P. Intravenous hydrocortisone premedication reduces antibodies to infliximab in Crohn's disease: a randomized controlled trial. Gastroenterology. 2003;124(4):917–24.
68. Vermeire S, Noman M, Van Assche G, Baert F, D'Haens G, Rutgeerts P. Effectiveness of concomitant immunosuppressive therapy in suppressing the formation of antibodies to infliximab in Crohn's disease. Gut. 2007;56(9):1226–31.
69. Hanauer SB, Wagner CL, Bala M, Mayer L, Travers S, Diamond RH, et al. Incidence and importance of antibody responses to infliximab after maintenance or episodic treatment in Crohn's disease. Clin Gastroenterol Hepatol. 2004;2(7):542–53.
70. Khanna R, Sattin BD, Afif W, Benchimol EI, Bernard EJ, Bitton A, et al. Review article: a clinician's guide for therapeutic drug monitoring of infliximab in inflammatory bowel disease. Aliment Pharmacol Ther. 2013;38(5):447–59.
71. Ben-Horin S, Waterman M, Kopylov U, Yavzori M, Picard O, Fudim E, et al. Addition of an immunomodulator to infliximab therapy eliminates antidrug antibodies in serum and restores clinical response of patients with inflammatory bowel disease. Clin Gastroenterol Hepatol. 2013;11(4):444–7.
72. Afif W, Loftus Jr EV, Faubion WA, Kane SV, Bruining DH, Hanson KA, et al. Clinical utility of measuring infliximab and human anti-chimeric antibody concentrations in patients with inflammatory bowel disease. Am J Gastroenterol. 2010;105(5):1133–9.
73. Vande Casteele NC, Compernolle G, Ballet V, Van Assche G, Gils A, Vermeire S, Rutgeerts P. OP11 individualised infliximab treatment using therapeutic drug monitoring: a prospective controlled Trough level Adapted infliXImab Treatment (TAXIT) trial. J Crohns Colitis. 2012;6:S6.
74. Vande Casteele NG, Gils A, Ballet V, Compernolle G, Peeters M, Van Steen K, Simoens S, Ferrante M, Van Assche G, Vermeire S, Rutgeerts P. OP001 randomised controlled trial of drug level versus clinically based dosing of infliximab maintenance therapy in IBD: final results of the TAXIT study. United European Gastroenterol J. 2013;1:A1.
75. Vaughn BP, Martinez-Vazquez M, Patwardhan VR, Moss AC, Sandborn WJ, Cheifetz AS. Proactive therapeutic concentration monitoring of infliximab may improve outcomes for patients with inflammatory bowel disease: results from a pilot observational study. Inflamm Bowel Dis. 2014;20(11):1996–2003.
76. Velayos FS, Kahn JG, Sandborn WJ, Feagan BG. A test-based strategy is more cost effective than empiric dose escalation for patients with Crohn's disease who lose responsiveness to infliximab. Clin Gastroenterol Hepatol. 2013;11(6):654–66.

77. Patil SA, Rustgi A, Langenberg P, Cross RK. Comparative effectiveness of anti-TNF agents for Crohn's disease in a tertiary referral IBD practice. Dig Dis Sci. 2013;58(1):209–15.
78. Peyrin-Biroulet L, Fiorino G, Buisson A, Danese S. First-line therapy in adult Crohn's disease: who should receive anti-TNF agents? Nat Rev Gastroenterol Hepatol. 2013;10(6):345–51.
79. Khanna RL, Levesque BG, Bressler B, Zou G, Stitt L, Greenberg GR, Panaccione R, Bitton A, Pare P, Vermeire S, D'Haens GR, Macintosh DG, Sandborn W, Vandervoot MK, Morris JC, Veagan BG. Early combined immunosuppression for the management of Crohn's disease: a community-based cluster randomized trial. J Crohns Colitis. 2014;8:S2.
80. Kornbluth A, Sachar DB, Practice Parameters Committee of the American College of Gastroenterology. Ulcerative colitis practice guidelines in adults: American College of Gastroenterology, Practice Parameters Committee. Am J Gastroenterol. 2010;105(3):501–23. quiz 24
81. Panaccione RG, Ghosh S, Middleton S, Marques JR, Khalif I, Flint L, Hoogstraten HV, Zheng H, Danese S, Rutgeerts PJ. Infliximab, azathioprine, or infliximab + azathioprine for treatment of moderate to severe ulcerative colitis: the UC success trial. Gastroenterology. 2011;140:S134.
82. Kopylov U, Mantzaris GJ, Katsanos KH, Reenaers C, Ellul P, Rahier JF, et al. The efficacy of shortening the dosing interval to once every six weeks in Crohn's patients losing response to maintenance dose of infliximab. Aliment Pharmacol Ther. 2011;33(3):349–57.
83. Dignass A, Van Assche G, Lindsay JO, Lemann M, Soderholm J, Colombel JF, et al. The second European evidence-based consensus on the diagnosis and management of Crohn's disease: current management. J Crohns Colitis. 2010;4(1):28–62.
84. Sandborn WJ, Hanauer SB, Rutgeerts P, Fedorak RN, Lukas M, MacIntosh DG, et al. Adalimumab for maintenance treatment of Crohn's disease: results of the CLASSIC II trial. Gut. 2007;56(9):1232–9.
85. Wolf D, D'Haens G, Sandborn WJ, Colombel JF, Van Assche G, Robinson AM, et al. Escalation to weekly dosing recaptures response in adalimumab-treated patients with moderately to severely active ulcerative colitis. Aliment Pharmacol Ther. 2014;40(5):486–97.
86. Sandborn WJ, Schreiber S, Hanauer SB, Colombel JF, Bloomfield R, Lichtenstein GR, et al. Reinduction with certolizumab pegol in patients with relapsed Crohn's disease: results from the PRECiSE 4 study. Clin Gastroenterol Hepatol. 2010;8(8):696–702. e1
87. Sandborn WH, Hanauer SB, Pierre-Louis B, Lichtenstein GR. Su2079 certolizumab pegol plasma concentration and clinical remission in Crohn's disease. Gastroenterology. 2012;142(5):S-563.
88. Mendoza Ladd AH, Scott FI, Grace R, Bownik H, Lichtenstein GR. Sa1086 dose escalation of vedolizumab from every 8 weeks to every 4 or 6 weeks enables patients with inflammatory bowel disease to recapture response. Gastroenterology. 2016;150(4):S235–6.
89. Toruner M, Loftus Jr EV, Harmsen WS, Zinsmeister AR, Orenstein R, Sandborn WJ, et al. Risk factors for opportunistic infections in patients with inflammatory bowel disease. Gastroenterology. 2008;134(4):929–36.
90. Gavazzi G, Krause KH. Ageing and infection. Lancet Infect Dis. 2002;2(11):659–66.
91. Cottone M, Kohn A, Daperno M, Armuzzi A, Guidi L, D'Inca R, et al. Advanced age is an independent risk factor for severe infections and mortality in patients given anti-tumor necrosis factor therapy for inflammatory bowel disease. Clin Gastroenterol Hepatol. 2011;9(1):30–5.
92. Loras C, Gisbert JP, Minguez M, Merino O, Bujanda L, Saro C, et al. Liver dysfunction related to hepatitis B and C in patients with inflammatory bowel disease treated with immunosuppressive therapy. Gut. 2010;59(10):1340–6.
93. Park SH, Yang SK, Lim YS, Shim JH, Yang DH, Jung KW, et al. Clinical courses of chronic hepatitis B virus infection and inflammatory bowel disease in patients with both diseases. Inflamm Bowel Dis. 2012;18(11):2004–10.

94. European Association for the Study of the Liver. EASL clinical practice guidelines: management of chronic hepatitis B virus infection. J Hepatol. 2012;57(1):167–85.
95. Ayoub WS, Keeffe EB. Review article: current antiviral therapy of chronic hepatitis B. Aliment Pharmacol Ther. 2011;34(10):1145–58.
96. Aberra FN, Stettler N, Brensinger C, Lichtenstein GR, Lewis JD. Risk for active tuberculosis in inflammatory bowel disease patients. Clin Gastroenterol Hepatol. 2007;5(9):1070–5.
97. Keane J, Gershon S, Wise RP, Mirabile-Levens E, Kasznica J, Schwieterman WD, et al. Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent. N Engl J Med. 2001;345(15):1098–104.
98. Jasmer RM, Nahid P, Hopewell PC. Clinical practice. Latent tuberculosis infection. N Engl J Med. 2002;347(23):1860–6.
99. American Thoracic Society. Targeted tuberculin testing and treatment of latent tuberculosis infection. MMWR Recomm Rep. 2000;49(RR-6):1–51.
100. Theis VS, Rhodes JM. Review article: minimizing tuberculosis during anti-tumour necrosis factor-alpha treatment of inflammatory bowel disease. Aliment Pharmacol Ther. 2008;27(1):19–30.
101. Gilden D, Cohrs RJ, Mahalingam R, Nagel MA. Varicella zoster virus vasculopathies: diverse clinical manifestations, laboratory features, pathogenesis, and treatment. Lancet Neurol. 2009;8(8):731–40.
102. Hambleton S, Gershon AA. The impact of varicella vaccination in the United States. Semin Pediatr Infect Dis. 2005;16(1):38–43.
103. Cullen G, Baden RP, Cheifetz AS. Varicella zoster virus infection in inflammatory bowel disease. Inflamm Bowel Dis. 2012;18(12):2392–403.
104. Marin M, Guris D, Chaves SS, Schmid S, Seward JF, Advisory Committee on Immunization Practices, CDC, et al. Prevention of varicella: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 2007;56(RR-4):1–40.
105. Harpaz R, Ortega-Sanchez IR, Seward JF, Advisory Committee on Immunization Practices, Centers for Disease Control and Prevention. Prevention of herpes zoster: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 2008;57(RR-5):1–30. quiz CE2-4
106. Zhang J, Xie F, Delzell E, Chen L, Winthrop KL, Lewis JD, et al. Association between vaccination for herpes zoster and risk of herpes zoster infection among older patients with selected immune-mediated diseases. JAMA. 2012;308(1):43–9.
107. Sandborn WJ, Rutgeerts P, Enns R, Hanauer SB, Colombel JF, Panaccione R, et al. Adalimumab induction therapy for Crohn disease previously treated with infliximab: a randomized trial. Ann Intern Med. 2007b;146(12):829–38.
108. Regueiro M, Siemanowski B, Kip KE, Plevy S. Infliximab dose intensification in Crohn's disease. Inflamm Bowel Dis. 2007;13(9):1093–9.
109. Sutharshan K, Gearry RB. Temporary adalimumab dose escalation is effective in Crohn's disease patients with secondary non-response. J Crohns Colitis. 2013;7(7):e277–8.
110. Ford LT, Berg JD. Determination of thiopurine S-methyltransferase activity in erythrocytes using 6-thioguanine as substrate and a non-extraction liquid chromatographic technique. J Chromatogr B Analyt Technol Biomed Life Sci. 2003;798(1):111–5.
111. Ford LT, Cooper SC, Lewis MJ, Berg JD. Reference intervals for thiopurine S-methyltransferase activity in red blood cells using 6-thioguanine as substrate and rapid non-extraction liquid chromatography. Ann Clin Biochem. 2004;41(Pt 4):303–8.
112. Ford L, Graham V, Berg J. Whole-blood thiopurine S-methyltransferase activity with genotype concordance: a new, simplified phenotyping assay. Ann Clin Biochem. 2006;43(Pt 5):354–60.
113. Gisbert JP, Nino P, Rodrigo L, Cara C, Guijarro LG. Thiopurine methyltransferase (TPMT) activity and adverse effects of azathioprine in inflammatory bowel disease: long-term follow-up study of 394 patients. Am J Gastroenterol. 2006;101(12):2769–76.
114. Timmer A, Patton PH, Chande N, McDonald JW, MacDonald JK. Azathioprine and 6-mercaptopurine for maintenance of remission in ulcerative colitis. Cochrane Database Syst Rev. 2016;5:CD000478.

115. Chande N, Patton PH, Tsoulis DJ, Thomas BS, MacDonald JK. Azathioprine or 6-mercaptopurine for maintenance of remission in Crohn's disease. Cochrane Database Syst Rev. 2015;10:CD000067.
116. Kotlyar DS, Lewis JD, Beaugerie L, Tierney A, Brensinger CM, Gisbert JP, et al. Risk of lymphoma in patients with inflammatory bowel disease treated with azathioprine and 6-mercaptopurine: a meta-analysis. Clin Gastroenterol Hepatol. 2015;13(5):847–58 e4. quiz e48-50
117. Cornish J, Tan E, Teare J, Teoh TG, Rai R, Clark SK, et al. A meta-analysis on the influence of inflammatory bowel disease on pregnancy. Gut. 2007;56(6):830–7.
118. Caprilli R, Gassull MA, Escher JC, Moser G, Munkholm P, Forbes A, et al. European evidence based consensus on the diagnosis and management of Crohn's disease: special situations. Gut. 2006;55(Suppl 1):i36–58.
119. Keller J, Frederking D, Layer P. The spectrum and treatment of gastrointestinal disorders during pregnancy. Nat Clin Pract Gastroenterol Hepatol. 2008;5(8):430–43.
120. Mahadevan U, Cucchiara S, Hyams JS, Steinwurz F, Nuti F, Travis SP, et al. The London Position Statement of the World Congress of Gastroenterology on Biological Therapy for IBD with the European Crohn's and Colitis Organisation: pregnancy and pediatrics. Am J Gastroenterol. 2011;106(2):214–23. quiz 24
121. Kane SV, Acquah LA. Placental transport of immunoglobulins: a clinical review for gastroenterologists who prescribe therapeutic monoclonal antibodies to women during conception and pregnancy. Am J Gastroenterol. 2009;104(1):228–33.
122. Mahadevan UM, Martin CF, Chambers C, Kane SV, Dubinsky M, Sandborn W, Sands BE. Achievement of developmental milestones among offspring of women with inflammatory bowel disease: the PIANO registry. Gastroenterology. 2014;146(5):S-1.
123. Leung Y, Panaccione R, Ghosh S, Seow CH. Management of the pregnant inflammatory bowel disease patient on anti-tumour necrosis factor: state of the art and future directions. Can J Gastroenterol Hepatol. 2014;28(9):505–9.
124. Dubinsky M, Mahadevan U, Vermeire S, Abhyankar B, Lasch K. P563 vedolizumab exposure in pregnancy: outcomes from clinical studies in inflammatory bowel disease. J Crohns Colitis. 2015;9(suppl 1):S361–2.
125. Akbari M, Shah S, Velayos FS, Mahadevan U, Cheifetz AS. Systematic review and meta-analysis on the effects of thiopurines on birth outcomes from female and male patients with inflammatory bowel disease. Inflamm Bowel Dis. 2013;19(1):15–22.
126. Mahadevan U, Martin CF, Sandler RS, Kane VS, Dubinsky M, Lewis JD, Sandborn W, Sands BE. 865 PIANO: a 1000 patient prospective registry of pregnancy outcomes in women with IBD exposed to immunomodulators and biologic therapy. Gastroenterology. 2012;142(5):S-149.
127. Jharap B, de Boer NK, Stokkers P, Hommes DW, Oldenburg B, Dijkstra G, et al. Intrauterine exposure and pharmacology of conventional thiopurine therapy in pregnant patients with inflammatory bowel disease. Gut. 2014;63(3):451–7.
128. Baiocco PJ, Korelitz BI. The influence of inflammatory bowel disease and its treatment on pregnancy and fetal outcome. J Clin Gastroenterol. 1984;6(3):211–6.
129. Fasanmade AA, Adedokun OJ, Olson A, Strauss R, Davis HM. Serum albumin concentration: a predictive factor of infliximab pharmacokinetics and clinical response in patients with ulcerative colitis. Int J Clin Pharmacol Ther. 2010;48(5):297–308.
130. Fasanmade AA, Adedokun OJ, Blank M, Zhou H, Davis HM. Pharmacokinetic properties of infliximab in children and adults with Crohn's disease: a retrospective analysis of data from 2 phase III clinical trials. Clin Ther. 2011;33(7):946–64.
131. Suzuki Y, Matsui T, Ito H, Ashida T, Nakamura S, Motoya S, et al. Circulating interleukin 6 and albumin, and infliximab levels are good predictors of recovering efficacy after dose escalation infliximab therapy in patients with loss of response to treatment for Crohn's disease: a prospective clinical trial. Inflamm Bowel Dis. 2015;21(9):2114–22.
132. Sandborn WJ, Melmed GY, McGovern DP, Loftus Jr EV, Choi JM, Cho JH, et al. Clinical and demographic characteristics predictive of treatment outcomes for certolizumab pegol in

moderate to severe Crohn's disease: analyses from the 7-year PRECiSE 3 study. Aliment Pharmacol Ther. 2015;42(3):330–42.
133. Jackson CA, Clatworthy J, Robinson A, Horne R. Factors associated with non-adherence to oral medication for inflammatory bowel disease: a systematic review. Am J Gastroenterol. 2010;105(3):525–39.
134. Kane S, Huo D, Aikens J, Hanauer S. Medication nonadherence and the outcomes of patients with quiescent ulcerative colitis. Am J Med. 2003;114(1):39–43.
135. Kane S, Shaya F. Medication non-adherence is associated with increased medical health care costs. Dig Dis Sci. 2008;53(4):1020–4.
136. Trindade AJ, Morisky DE, Ehrlich AC, Tinsley A, Ullman TA. Current practice and perception of screening for medication adherence in inflammatory bowel disease. J Clin Gastroenterol. 2011;45(10):878–82.
137. Selinger CP, Robinson A, Leong RW. Clinical impact and drivers of non-adherence to maintenance medication for inflammatory bowel disease. Expert Opin Drug Saf. 2011;10(6):863–70.
138. Sood A, Midha V, Sood N, Kaushal V. Self-reported disease awareness--a questionnaire survey of ulcerative colitis patients. Indian J Gastroenterol. 2001;20(1):6–8.
139. Scholmerich J, Sedlak P, Hoppe-Seyler P, Gerok W. The information needs and fears of patients with inflammatory bowel disease. Hepato-Gastroenterology. 1987;34(4):182–5.
140. Casati J, Toner BB, de Rooy EC, Drossman DA, Maunder RG. Concerns of patients with inflammatory bowel disease: a review of emerging themes. Dig Dis Sci. 2000;45(1):26–31.
141. Hawthorne AB, Rubin G, Ghosh S. Review article: medication non-adherence in ulcerative colitis--strategies to improve adherence with mesalazine and other maintenance therapies. Aliment Pharmacol Ther. 2008;27(12):1157–66.
142. Mazzuca SA. Does patient education in chronic disease have therapeutic value? J Chronic Dis. 1982;35(7):521–9.
143. Quan H, Present JW, Sutherland LR. Evaluation of educational programs in inflammatory bowel disease. Inflamm Bowel Dis. 2003;9(6):356–62.
144. Waters BM, Jensen L, Fedorak RN. Effects of formal education for patients with inflammatory bowel disease: a randomized controlled trial. Can J Gastroenterol. 2005;19(4):235–44.
145. Kane S, Huo D, Magnanti K. A pilot feasibility study of once daily versus conventional dosing mesalamine for maintenance of ulcerative colitis. Clin Gastroenterol Hepatol. 2003b;1(3):170–3.
146. Dignass A, Veerman H. Once versus twice daily mesalazine (Pentasa) granules for the maintenance of remission in ulcerative colitis: results from a multi-national randomized controlled trial. Gut. 2008;57(supple 1):A1.
147. Lichtenstein GR, Kamm MA, Boddu P, Gubergrits N, Lyne A, Butler T, et al. Effect of once- or twice-daily MMX mesalamine (SPD476) for the induction of remission of mild to moderately active ulcerative colitis. Clin Gastroenterol Hepatol. 2007;5(1):95–102.
148. Greenley R, Nguyen E, Kunz JH, Biank J, Blank E, Miranda A, Noe J, Werlin S, Stephens M. Phone intervention to improve pediatric oral medication adherence: preliminary acceptability and feasibility: P-148. Inflamm Bowel Dis. 2011;17(S12):S57.
149. Moshkovska T, Stone MA, Smith RM, Bankart J, Baker R, Mayberry JF. Impact of a tailored patient preference intervention in adherence to 5-aminosalicylic acid medication in ulcerative colitis: results from an exploratory randomized controlled trial. Inflamm Bowel Dis. 2011;17(9):1874–81.
150. Cosnes J, Gower-Rousseau C, Seksik P, Cortot A. Epidemiology and natural history of inflammatory bowel diseases. Gastroenterology. 2011;140(6):1785–94.
151. Targownik LE, Singh H, Nugent Z, Bernstein CN. The epidemiology of colectomy in ulcerative colitis: results from a population-based cohort. Am J Gastroenterol. 2012; 107(8):1228–35.
152. Wolters FL, Russel MG, Sijbrandij J, Ambergen T, Odes S, Riis L, et al. Phenotype at diagnosis predicts recurrence rates in Crohn's disease. Gut. 2006;55(8):1124–30.

153. Solberg IC, Vatn MH, Hoie O, Stray N, Sauar J, Jahnsen J, et al. Clinical course in Crohn's disease: results of a Norwegian population-based ten-year follow-up study. Clin Gastroenterol Hepatol. 2007;5(12):1430–8.
154. Beaugerie L, Seksik P, Nion-Larmurier I, Gendre JP, Cosnes J. Predictors of Crohn's disease. Gastroenterology. 2006;130(3):650–6.
155. Cosnes J, Carbonnel F, Beaugerie L, Le Quintrec Y, Gendre JP. Effects of cigarette smoking on the long-term course of Crohn's disease. Gastroenterology. 1996;110(2):424–31.
156. Faubion Jr WA, Loftus EV, Sandborn WJ, Freese DK, Perrault J. Pediatric "PSC-IBD": a descriptive report of associated inflammatory bowel disease among pediatric patients with PSC. J Pediatr Gastroenterol Nutr. 2001;33(3):296–300.
157. Targan SR, Landers CJ, Yang H, Lodes MJ, Cong Y, Papadakis KA, et al. Antibodies to CBir1 flagellin define a unique response that is associated independently with complicated Crohn's disease. Gastroenterology. 2005;128(7):2020–8.
158. Vasiliauskas EA, Kam LY, Karp LC, Gaiennie J, Yang H, Targan SR. Marker antibody expression stratifies Crohn's disease into immunologically homogeneous subgroups with distinct clinical characteristics. Gut. 2000;47(4):487–96.
159. Arnott ID, Landers CJ, Nimmo EJ, Drummond HE, Smith BK, Targan SR, et al. Sero-reactivity to microbial components in Crohn's disease is associated with disease severity and progression, but not NOD2/CARD15 genotype. Am J Gastroenterol. 2004;99(12): 2376–84.
160. Melmed GY, Fleshner PR, Bardakcioglu O, Ippoliti A, Vasiliauskas EA, Papadakis KA, et al. Family history and serology predict Crohn's disease after ileal pouch-anal anastomosis for ulcerative colitis. Dis Colon Rectum. 2008;51(1):100–8.
161. Vasiliauskas EA, Plevy SE, Landers CJ, Binder SW, Ferguson DM, Yang H, et al. Perinuclear antineutrophil cytoplasmic antibodies in patients with Crohn's disease define a clinical subgroup. Gastroenterology. 1996;110(6):1810–9.
162. Carbonnel F, Macaigne G, Beaugerie L, Gendre JP, Cosnes J. Crohn's disease severity in familial and sporadic cases. Gut. 1999;44(1):91–5.
163. Alvarez-Lobos M, Arostegui JI, Sans M, Tassies D, Plaza S, Delgado S, et al. Crohn's disease patients carrying Nod2/CARD15 gene variants have an increased and early need for first surgery due to stricturing disease and higher rate of surgical recurrence. Ann Surg. 2005;242(5):693–700.
164. Cucchiara S, Latiano A, Palmieri O, Canani RB, D'Inca R, Guariso G, et al. Polymorphisms of tumor necrosis factor-alpha but not MDR1 influence response to medical therapy in pediatric-onset inflammatory bowel disease. J Pediatr Gastroenterol Nutr. 2007;44(2):171–9.
165. Farrell RJ, Kelleher D. Glucocorticoid resistance in inflammatory bowel disease. J Endocrinol. 2003;178(3):339–46.
166. Potocnik U, Ferkolj I, Glavac D, Dean M. Polymorphisms in multidrug resistance 1 (MDR1) gene are associated with refractory Crohn disease and ulcerative colitis. Genes Immun. 2004;5(7):530–9.
167. Hlavaty T, Pierik M, Henckaerts L, Ferrante M, Joossens S, van Schuerbeek N, et al. Polymorphisms in apoptosis genes predict response to infliximab therapy in luminal and fistulizing Crohn's disease. Aliment Pharmacol Ther. 2005;22(7):613–26.
168. Henriksen M, Jahnsen J, Lygren I, Vatn MH, Moum B, Group IS. Are there any differences in phenotype or disease course between familial and sporadic cases of inflammatory bowel disease? Results of a population-based follow-up study. Am J Gastroenterol. 2007;102(9):1955–63.
169. Hoie O, Wolters F, Riis L, Aamodt G, Solberg C, Bernklev T, et al. Ulcerative colitis: patient characteristics may predict 10-yr disease recurrence in a European-wide population-based cohort. Am J Gastroenterol. 2007;102(8):1692–701.
170. Langholz E, Munkholm P, Davidsen M, Binder V. Course of ulcerative colitis: analysis of changes in disease activity over years. Gastroenterology. 1994;107(1):3–11.

171. Niewiadomski O, Studd C, Hair C, Wilson J, Ding NS, Heerasing N, et al. Prospective population-based cohort of inflammatory bowel disease in the biologics era: disease course and predictors of severity. J Gastroenterol Hepatol. 2015;30(9):1346–53.
172. Iliev ID, Funari VA, Taylor KD, Nguyen Q, Reyes CN, Strom SP, et al. Interactions between commensal fungi and the C-type lectin receptor Dectin-1 influence colitis. Science. 2012;336(6086):1314–7.
173. Siegel CA, Horton H, Siegel LS, Thompson KD, Mackenzie T, Stewart SK, et al. A validated web-based tool to display individualised Crohn's disease predicted outcomes based on clinical, serologic and genetic variables. Aliment Pharmacol Ther. 2016;43(2):262–71.