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LARGE INTESTINE (B CASH, SECTION EDITOR)

# Update on the Medical Management of Crohn's Disease

**Parakkal Deepak**[1] · **David H. Bruining**[1]

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**Abstract** The medical management of Crohn's disease is a rapidly evolving field with expanding therapeutic drug options and treatment strategies. In addition to corticosteroids, immunomodulators, and anti-tumor necrosis (anti-TNF) agents, a new anti-adhesion medication (vedolizumab) has been approved. Individualized patient-based dosing of immunomodulators and biologic agents is now possible with therapeutic drug monitoring (TDM). There is a changing paradigm in treatment goals to achieve deeper remission identified by composite clinical and endoscopic endpoints. More aggressive treatment strategies in the postoperative setting have been proposed due to emerging data on medication efficacy in this setting. Management algorithms that stratify CD patients into risk groups to balance treatment benefit against adverse events and costs are being developed to translate research into clinical practice. This review provides an update on these new developments for practicing gastroenterologists.

**Keywords** Crohn's disease management · Tumor necrosis factor-alpha/antagonists and inhibitors · Antibodies · Monoclonal · Humanized/therapeutic use · Drug monitoring

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✉ David H. Bruining
bruining.david@mayo.edu

Parakkal Deepak
deepak.parakkal@mayo.edu

[1] Division of Gastroenterology and Hepatology, Mayo Clinic College of Medicine, 200 First Street SW, Rochester, MN 55905, USA

## Introduction

Crohn's disease (CD) is a chronic idiopathic transmural inflammatory process involving the gastrointestinal tract, often characterized by periods of clinical remission alternating with episodes of active and symptomatic disease [1]. The natural history of CD, as defined by population-based cohort studies, is one of progression from inflammatory lesions to the development of penetrating and fibrostenotic complications such as stricture(s), fistula(s), and abscess(es) [1]. Uncontrolled inflammation can lead to disability and other adverse outcomes such as surgical resections and hospitalizations [1].

The medical management of CD and the treatment goals that were initially based on symptom control using corticosteroids has been revolutionized since the introduction of immunomodulators (azathioprine, 6-mercaptopurine, and methotrexate) and anti-tumor necrosis factor (anti-TNF) therapies into clinical practice. Therapeutic strategies have emerged that can reduce complications and thus modify the disease course [2••]. Growing data now supports the use of drug levels in CD management algorithms [3]. Furthermore, in patients who have achieved treatment goals on these medications, protocols are being explored to potentially identify patients for de-escalation of therapy [4•]. An anti-adhesion molecule, vedolizumab, has been recently approved for the management of CD [5••]. These changes make CD management a truly dynamic arena of medicine.

## Medications

### Aminosalicylates

The therapeutic efficacy of 5-aminosalicylates (5-ASAs) is now widely disputed in CD. In a Swiss IBD cohort of 1420

CD patients, 835 (59 %) individuals were reported to have been treated with 5-ASA agents, successfully (physician global assessment) in 46 % [6]. This report is in contrast to a meta-analysis analysis of 23 randomized controlled trials (RCTs) of CD (7 in active, 13 in quiescent, and 3 in active and quiescent CD) [7]. There was a trend towards a benefit with sulfasalazine over placebo in inducing remission (two RCTs, relative risk (RR)=0.83; 95 % confidence interval (CI)=0.69–1.00), but no definite benefit of mesalamine over placebo (four RCTs, RR=0.91; 95 % CI=0.77–1.06). Neither sulfasalazine (four RCTs, RR=0.98; 95 % CI=0.82–1.17) nor mesalamine (RR=0.94; 95 % CI=0.87– 1.01) were effective in preventing quiescent CD relapse. In patients in surgical remission, the role of 5-ASAs is also controversial. A meta-analysis of 11 RCTs evaluated the risk of relapse of CD in remission after surgery with 5-ASA vs. placebo or no therapy [8]. Overall, mesalamine was more effective than placebo or no therapy (RR=0.80; 95 % CI=0.70–0.92) with a number need to treat (NNT) of 10. In total, there is very little robust data to support the use of 5-ASA therapy in Crohn's disease.

Corticosteroids (CS) have been a mainstay in the acute treatment of CD for several decades [9]. They have been used in topical, oral, and parenteral formulations. Oral forms include prednisone and more recently, budesonide (a controlled-ileal release medication). Budesonide (9 mg/day) has been shown to be numerically, but not statistically, more effective than Eudragit-L-coated mesalamine (4.5 g/day) in patients with mildly to moderately active CD [10]. Furthermore, once daily (9 mg) dosing has been shown to be equivalent to three times a day dosing both in achieving clinical remission, mucosal healing (MH), and deep remission [11]. No benefit, however, was shown in a meta-analysis analysis of 12 studies for maintenance of remission with budesonide in CD, particularly when used beyond 3 months following induction of remission [12].

## Thiopurines

Azathioprine (AZA) and 6-mercaptopuine (6-MP) are thiopurine analogs that have been used for several decades in the management of steroid-dependent moderate-to-severe inflammatory bowel disease (IBD). A recent Cochrane review analyzed 13 RCTs of AZA and 6-MP therapy for CD: 9 compared to placebo and 6 included active comparators [13]. Compared to placebo, thiopurines demonstrated a steroid-sparing effect (64 vs. 46 %; RR=1.34; 95 % CI=1.02–1.77), but were not statistically significant in achieving clinical remission (48 vs. 37 %; RR=1.23; 95 % CI=0.97–1.55). The 3-year, randomized, parallel, open-label RAPID (Résultat de l'Adjonction Précoce d'ImmunoDépresseurs) trial compared early (within the first 6 months after diagnosis) AZA at 2.5 mg/kg/day ($n$=65) with conventional step-care treatment ($n$=67) in patients at high risk for disabling CD [14•]. This study did not demonstrate a difference between the groups in terms of proportion of trimesters spent in corticosteroid-free and anti-TNF-free remission during the first 3 years after inclusion (67 vs. 56 %, $p$=0.69). In another prospective double-blind trial, AZathioprine for Treatment or Early CD in adults (AZTEC) with a recent (<8 weeks) CD diagnosis, patients were randomly assigned to AZA (2.5 mg/day, $n$=68) or placebo ($n$=63) [15•]. Early AZA therapy was no more effective than placebo in achieving sustained corticosteroid-free remission at week 76 (44.1 vs. 36.5 %, respectively, $p$=0.48). However, a meta-analysis analysis of 10 retrospective observational studies ($n$=12,586 CD patients) demonstrated a significant reduction in the need for a surgical resection (hazard ratio (HR)=0.59; 95 % CI=0.48–0.73) [16]. These studies raise questions regarding the efficacy of thiopurines for the induction of remission as monotherapy and whether corticosteroid-free clinical remission is an ideal endpoint for CD assessment [17].

## Methotrexate

Methotrexate (MTX) is often used as a second-line immunomodulator or as an alternative to thiopurine analogs in the treatment of patients with CD. A recent Cochrane meta-analysis identified a single large randomized trial that suggested benefit for induction of remission (and steroid sparing effect) in refractory CD with intramuscular MTX (25 mg/week) and maintenance of remission at a dose of 15 mg/week, compared to placebo [18, 19]. Combination therapy with MTX and infliximab (IFX) was assessed in the COMMIT trial [20•]. In this double-blind, placebo-controlled trial, MTX, in combination with IFX, was compared with IFX monotherapy in 126 CD who had initiated prednisone induction therapy within the preceding 6 weeks. MTX was started at an initial weekly subcutaneous dose of 10 mg, escalating to 25 mg/week ($n$=63), or placebo ($n$=63). No difference was detected between the groups for the primary endpoint of maintaining prednisone-free clinical remission (Crohn's Disease Activity Index (CDAI) <150) through week 50 (30.6 vs. 29.8 %, HR=1.16; 95 % CI=0.62–2.17). However, this trial enrolled CD patients without a minimum threshold CDAI or endoscopy criteria, and nearly 30 % of the patients in each arm had a CDAI score <150, potentially impacting achievement of the primary end-point [21]. The clinical benefit and tolerability of MTX monotherapy after thiopurine therapy discontinuation (lack of response or adverse event) studied in 174 consecutive CD patients demonstrated sustained clinical benefits in 98 (86 %), 50 (63 %), 27 (47 %), and 3 (20 %), at 6, 12, 24, and 60 months, respectively [22].

## Tumor Necrosis Factor-Alpha Inhibitors

Approved TNF inhibitors in the management of CD include infliximab (IFX), adalimumab (ADA), and certolizumab

pegol (CZP) [23••]. Recent guidelines from the American Gastroenterological Association (AGA) have recommended the use of these agents either as monotherapy or in combination with thiopurines for the induction and maintenance of remission in moderate to severe CD [23••]. Long-term data on the efficacy of the TNF inhibitors is accumulating. In a tertiary center experience among 469 CD patients treated with IFX maintenance therapy for a median 4.5 years, the estimated 5-year sustained benefit was 55.7 % [24]. Similar data was reported at 4 years follow-up among ADA-treated patients with moderately to severely active CD enrolled in the CHARM and ADHERE clinical trials with 54 % of those in remission at 1-year maintaining remission [25]. The long-term efficacy of CZP was demonstrated in an open-label extension trial (PRECiSE 3) for up to 7 years, where remission rates (by last observation carried forward) were 56 % at year 3 and 55 % at year 7 [26].

Several studies have evaluated predictors of long-term response on these agents. In a prospective study of 42 CD patients treated for at least 3 months with TNF inhibitors (52 % ADA and 48 % IFX), endoscopic remission at 1 year (11/33, 33 %) was significantly more common among those who had been in endoscopic remission at 3 months, compared with those with endoscopically active disease at 3 months (7/10, 70 % vs. 4/23, 17 %, $p$=0.01) [27]. In a post hoc analysis of the ACCENT I trial, a higher baseline CRP was associated with a higher probability of maintained remission, and CRP normalization (<0.5 mg/dL) at week 14 resulted in a higher probability of maintained response ($p$<0.001) or remission ($p$=0.052) through 54 weeks of IFX therapy [28]. Young age at the start of IFX and colonic CD are additional factors that have been found to be associated with a beneficial long-term (>5 years) use of IFX [29]. Studies have also shown that IFX can be reinstituted in patients who have previously received IFX or ADA [30]. In the absence of head-to-head trials of the three approved TNF antagonists, studies have attempted to address this issue using either clinical trial data or US Medicare data [31•, 32, 33•] with divergent conclusions. This includes network meta-analyses that have demonstrated greater effectiveness for ADA and IFX plus AZA, [31•] IFX [32] or equally effectiveness for IFX and ADA [33•].

### Vedolizumab

Vedolizumab (VDZ) is a humanized, anti-$\alpha_4\beta_7$ integrin, immunoglobulin G1 monoclonal antibody that has recently been approved for the induction and maintenance of remission in patients with moderate to severe active CD [34]. This is dosed as 300 mg infused intravenously at 0, 2, and 6 weeks, then every 8 weeks thereafter. The safety and efficacy of vedolizumab was studied in two pivotal Phase-3 trials, GEMINI 2 and 3 in CD [5••, 35•]. In GEMINI 2, CD patients with moderate to severe active disease (CRP >2.87 mg/L, colonoscopic ulceration, or a fecal calprotectin (FC) >250 mcg/g plus evidence of ulcers on imaging) were enrolled [5••]. One of the primary endpoints in the induction phase of clinical remission (CDAI≤150 points) at week 6 was achieved in 14.5 % on VDZ vs. 6.8 % on placebo ($p$=0.02). At week 52, the primary maintenance phase endpoint of clinical remission was achieved in 39 % receiving VDZ every 8 weeks, 36.4 % receiving VDZ every 4 weeks, and 21.6 % receiving placebo ($p$<0.001 and $p$=0.004; Q4weekly and Q8weekly compared to placebo, respectively). GEMINI 3 enrolled patients with moderate to severe active CD, most of whom (76 %) had failed anti-TNF therapy [35•]. The primary endpoint of clinical remission at week 6 in the anti-TNF failure sub-group was not achieved (15.2 % on VDZ vs. 12.1 % on placebo, $p$=0.43). However, the secondary endpoint of clinical remission at week 10 was higher among those treated with VDZ compared to placebo (26.6 vs. 12.1 %, RR=2.2; 95 % CI=1.3-3.6). Summarizing the two trials, VDZ appears to be efficacious in moderate-to-severe active CD, including in patients refractory to conventional therapy including anti-TNF agents.

The safety profile of vedolizumab has been explored [36]. Drug-related adverse events (AEs) include headache, 6 %; nasopharyngitis, 4 %; nausea, 4 %; arthralgia, 4 %; upper respiratory infection, 3 %; and fatigue, 3 %. Gastrointestinal disorders were the most frequently reported serious AEs and included disease exacerbation in both ulcerative colitis (8 %) and CD patients (11 %). Except for anal abscess in CD (2 %), all serious infection incidence rates were <1 %, both overall and by indication. No cases of progressive multifocal leukoencephalopathy have been reported. Malignancies were observed in <1 % of patients (two cases each of colon cancer and malignant melanoma).

## Therapeutic Strategies

### Treat-to-Target

Mucosal healing (MH) has been proposed as a treatment target as it is associated with improved clinical outcomes (reductions in hospitalizations, surgeries, and corticosteroid use) in CD patients [2••, 37]. The feasibility of treating to a target of MH was demonstrated in a study of 67 CD patients with a median follow-up period of 62 weeks [38•]. In this study, a short time (<26 weeks) between endoscopic procedures (HR=2.35; 95 % CI=1.15–4.97) and adjustment of medical therapy when MH was not observed (HR=4.28; 95 % CI=1.9–11.5) were predictive of MH. A newer proposed strategy is treating to a target of deep remission (a composite of symptom control and endoscopic mucosal healing) [39•, 40]. At week 52 of the EXTEND trial involving ADA, patients who achieved deep remission (at week 12) required significantly fewer ADA

treatment adjustments, hospitalizations, and CD-related surgeries; they had significantly less activity impairment; and had better quality of life and physical function compared with patients not achieving deep remission. This was also associated with estimated total cost savings of US$10,360 (from weeks 12 through 52) compared with lack of deep remission [41•]. This concept will likely continue to expand, potentially to include radiologic targets as well.

### Step Up vs. Top Down Algorithms

Management algorithms for CD have evolved over time into two broad strategies. These have either been the conventional or accelerated step up care (differentiated on the timing of immunomodulator and anti-TNF usage) versus the early top-down therapy (initial aggressive therapy with anti-TNF agents in combination with an immunomodulator) [42•]. The step-up approach has been associated with lower efficacy, disease progression, and repeated corticosteroid use (with higher risk of infections) [42•]. In comparison, the early top-down therapy has been associated with a lower rate of disease-related complications, higher rates of mucosal healing, and decreased rates of surgery and hospitalization [42•]. The strongest evidence for early treatment with combination of anti-TNF agents and an immunomodulator comes from the SONIC trial [43••]. In this study performed in CD patients with no prior anti-TNF or immunomodulator exposure, more patients in the combination arm (IFX plus AZA) were in corticosteroid-free remission at week 26 than in the IFX monotherapy group (56.8 vs. 44.4 %, $p=0.02$) or the AZA monotherapy group (30.0 %, $p<0.001$). Similar results were shown after 1 year of follow-up. Despite the concerns of higher costs associated with the top-down approach, a recent Markov model simulating a 5-year duration of step-up vs. top-down using IFX, AZA, and corticosteroids demonstrated the cost-effectiveness of the top-down approach [44]. Given the potentially higher risk of drug-related serious adverse events, utilizing a shared decision making process in partnership with patients is ideal [45•]. An algorithmic approach has been proposed (Fig. 1) for the selection of treatment strategy in patients with an early diagnosis (<2 years) of CD naïve to prior use of immunomodulator therapy or anti-TNF agents and the absence of pre-existing transmural complications [40].

### De-Escalation of Medical Therapy

Reduction of medical therapy remains a controversial topic among clinicians. The infliximab diSconTinuation in CrOhn's disease patients in stable Remission on combined therapy with Immunosuppressors trial (STORI) included 115 CD patients in remission on IFX and AZA for at least 1 year (more than 6 months of corticosteroid-free remission) whose IFX was stopped and were followed for at least 1 year [46•]. After a median follow-up period of 28 months, 52 (45.2 %) patients experienced a relapse with a 1-year rate of 43.9 %. Risk factors for relapse included male sex, the absence of surgical resection, leukocyte counts >6.0×109/L, hemoglobin ≤145 g/L, CRP ≥5.0 mg/L, and fecal calprotectin ≥300 mcg/g. Patients with no more than two of these risk factors (~29 % of the study population) had a 15 % risk of relapse within 1 year. Another prospective observational cohort, the Relapse After Stopping biologicals in Hungary (RASH), studied the predictors of relapse after discontinuation of anti-TNF agents in 121 patients (87 on IFX, 34 on ADA) with CD in remission after 1 year of anti-TNF therapy [47]. In this study, previous biological therapy and elevated CRP level at week 52 (when the biological therapy was discontinued) were independently associated with the time to re-initiation of infliximab therapy, with smoking being borderline-significant. Within 1 year of discontinuation of biological therapy (despite concomitant thiopurine usage in 77.7 %), resumption of therapy was necessary in 55 (45 %) patients with another 43 % of the untreated patients requiring restarting of biologic therapy over the next 18–24 months. In another observational, single-center, retrospective study of all CD patients with a primary response to IFX, 53 discontinued IFX while in clinical steroid-free remission [48]. Of these, 36 (68 %) had a relapse within 1 year after discontinuation.

The strategy of discontinuing the immunomodulator during combination therapy with IFX has also been explored. One clear concern with this approach is the risk of immunogenicity and lower anti-TNF concentrations after immunomodulator withdrawal. A retrospective study of immunomodulator withdrawal during combination therapy with IFX was performed in 117 CD patients in durable response for greater than 6 months (ongoing clinical benefit with CRP below 10 mg/L and persistent improvement in symptoms such as abdominal pain, liquid stools, or blood in stools). During the follow-up after withdrawal (median 29 months), 45/117 patients (38 %) experienced a disease flare necessitating IFX dose escalation, though the median levels of IFX remained stable after immunomodulators were withdrawn (before: 3.2 mcg/mL; 95 % CI=1.6–5.8 mcg/mL and after: 3.7 mcg/mL; 95 % CI=1.3–6.3 mcg/mL) [49•]. At the time of immunomodulator withdrawal, trough levels of IFX (<5 mcg/mL) and CRP (>5 mg/L) were predictive of the need for IFX dose escalation, IBD surgery, and discontinuation of IFX due to loss of response.

These studies indicate that there may be a subset of patients on combination therapy with a biologic agent and an immunomodulator who can be maintained on monotherapy. If that is to be attempted, most clinicians favor immunomodulator withdrawal based on the limited data available. Various authors have proposed algorithms where patients may be risk stratified and de-escalation avoided in patients who have a younger age of onset, perianal disease, internal penetrating

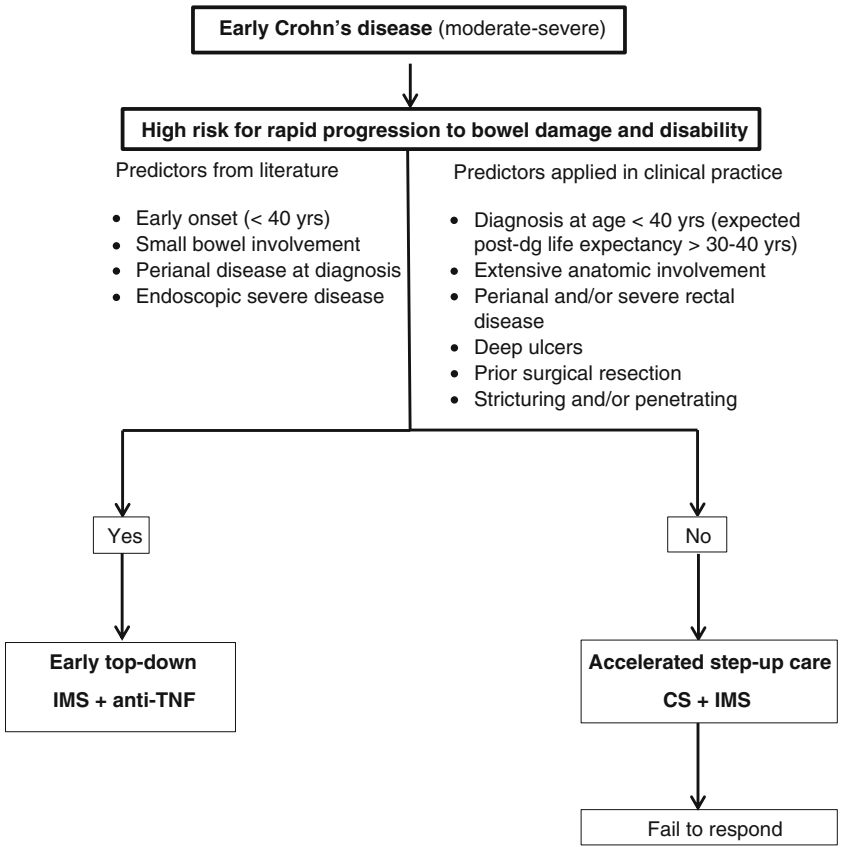


**Fig. 1** Proposed algorithm for treatment of early Crohn's disease (disease duration less than 2 years and no prior exposure to immunomodulators or anti-TNF therapies). In this algorithm, patients with predictors for rapid progression to bowel damage and disability should be treated with a top-down approach with immunomodulators and anti-TNF therapies. *IMS* immunomodulators; *CS* corticosteroids; *TNF* tumor necrosis factor; *Dg* diagnosis. Figure adapted and reproduced from Ordás et al., [42•] with permission from BMJ Publishing Group. ©2011

disease, or have required more than one biologic to achieve remission [4•, 50]. The duration of therapy and depth of remission prior to de-escalation remain a matter of debate and further prospective studies are required to clarify this treatment strategy. Most experts also recommend obtaining drug levels prior to de-escalating to monotherapy.

## Therapeutic Drug Concentration Monitoring

Therapeutic drug concentration monitoring (TDM) is a new focus in CD management algorithms, commercially available for both infliximab and adalimumab. In luminal CD, primary non-response (PNR) was noted at week 4 in placebo-controlled trials at 71 % for CZP, 40 % for IFX, and 41 % for ADA [51]. Additionally, there is an annual risk for loss of response at 13 % per patient-year with IFX and 24 % per patient-year with ADA [52, 53]. The relationship between IFX drug levels and disease activity was explored using 2021 samples from 532 participants in four prospective CD RCTs or cohort maintenance studies of IFX [54]. An IFX trough concentration (TC) ≥3 mcg/mL was predictive of lower CRP with an area under the curve (AUC) of 0.74. In another prospective study of 84 CD patients, week 14 or 22 IFX TC >3 mcg/mL was associated with a decreased risk of treatment failure at 1 year (HR=0.34; 95 % CI=0.16–0.75) [55]. The role of TDM in ADA treatment was studied in a cross-sectional study of 59 CD patients, where an ADA ≤5 mcg/mL predicted elevation of CRP levels [56]. Similar results were demonstrated in another cross-sectional study, where an ADA TC>4.85 mcg/mL was predictive for clinical remission (likelihood ratio (LR), 2.5; sensitivity, 81 %; specificity, 67 %) and a TC<4.9 mcg/mL for absence of MH (LR, 4.3; sensitivity, 66 %; specificity, 85 %) [57•].

## Anti-Drug Antibodies

Anti-drug antibodies (ADAs) are also assessed as part of the commonly available commercial assays used in TDM. In a meta-analysis of 1378 patients with IBD (1077 CD), those who developed antibodies to infliximab (ATI) compared to those without, had a risk ratio of 3.2 (95 % CI=2.0–4.9) to lose clinical response to IFX and also resulted in lower IFX TC [58]. Antibodies to infliximab mostly develop within the first 12 months of therapy [59]. Sustained ATI are ADAs detected at more than one time point and maybe of greater concern than transient ATI (detected at a single time point). In a study involving retrospective testing of 1232 consecutive samples from 90 IBD patients (64 CD), 68 % of those with sustained ATI discontinued IFX treatment compared to 13 % of patients with transient ATI [60•]. With scheduled IFX, combination with an immunomodulator results in longer ATI-free survival vs. IFX monotherapy ($p$=0.003) [59]. Addition of

immunomodulators to treatment regimens in patients with ATI may restore response [61•]. Dose escalation to overcome low-level ATA is also being explored as a mechanism to regain clinical response [62].

### Testing at Loss of Response

There are several potential advantages to a reactive strategy of TDM at the time of loss of response to anti-TNF agents including identifying a non-TNF driven inflammatory cascade, dose intensification in those with low concentrations of the drug, avoiding dose intensification in patients with high ADAs, and potentially reducing overall healthcare costs [63]. In a randomized, single-blinded, multicenter study of 69 CD patients with loss of response to IFX, 36 underwent empiric intensification (5 mg/kg every 4 weeks) while 33 underwent an algorithmic intervention using an IFX level drawn at the time of the loss of response [64••]. A level of ≥0.5 mcg/mL was considered to be therapeutic. In an intention-to-treat analysis, algorithmic treatment cost was lower compared with empiric intensification (€6038 vs. €9178, $p<0.001$) with similar clinical efficacy at week 12. In a decision-analytic model, incremental cost-effectiveness of a TDM-based approach vs. empiric strategy was examined over 1 year in two simulated CD cohorts [65]. Similar quality adjusted life years (QALYs) gains were seen with the TDM strategy compared to the empiric strategy, but at lower cost (US$31,870 vs. US$37,266, respectively) with similar rates of remission and response.

### Dose Optimization Strategy

There are several potential advantages to TDM with a goal of optimizing the dose based on drug concentration in the serum rather than waiting to check levels at the time of loss of response. These include early disease control with sustained response, reducing loss of response and consequent drug discontinuation during the maintenance phase, and avoiding adverse events associated with supratherapeutic drug concentrations [66•]. In a post hoc analysis of A Crohn's Disease Clinical Trial Evaluating Infliximab in a New Long-term Treatment Regimen I (ACCENT I) trial, median week 14 IFX TC among those with durable sustained response (week 54) to the 5 mg/kg dose was significantly higher compared to those without [67]. Additionally, a week 14 IFX TC ≥3.5 mcg/mL predicted durable sustained response on 5 mg/kg (OR=3.5). The strategy of concentration-based dosing was compared to clinically based dosing of IFX in a 1 year, randomized, controlled trial of a cohort of 263 IBD patients (178 with CD) with stable responses to maintenance IFX therapy, the Trough concentration Adapted infliXImab Treatment (TAXIT) trial [68••]. After dose escalation or reduction using an algorithm to reach a target TC of 3–7 mcg/mL in all patients (optimization phase), 251 IBD patients were randomized 1:1 to either receive IFX dosing based on their clinical features ($n=123$) or dosing based on TDM ($n=128$) (maintenance phase). Overall, the primary endpoint of clinical and biochemical remission at 1 year after the optimization phase was similar, whether dosed based on clinical features or TDM (66 vs. 69 %, $p=0.69$). However, a significantly higher proportion of CD patients who underwent dose escalation for a low TC in the optimization phase went into clinical remission (88 % post versus 64 % pre-optimization, $p=0.02$). Additionally, among the 72 IBD patients with TC >7 mcg/mL, 67 patients (93 %) achieved TC of 3–7 mg/mL after dose reduction, resulting in a 28 % reduction in drug cost than before dose reduction ($p<0.001$). Finally, fewer flares were reported in the TDM group compared to clinically based dosing (7 vs. 17 %, $p=0.02$). Continued TDM strategy after achieving TC optimization, however, was not superior to dosing based on clinical features.

### Prevention of Postoperative Recurrence

The prevention of postoperative CD recurrence (POR) remains a critical aspect of CD care. Several therapies have been assessed for this purpose, including aminosalicylates, thiopurines, imidazole antibiotics, and anti-TNF agents [69•]. Both aminosalicylates and imidazole antibiotics have been shown to have a modest benefit, with safety and tolerability issues with long-term antibiotic usage [69•]. A meta-analysis of four RCTs (three with AZA and one with 6-MP) involving 433 CD patients demonstrated that thiopurines were more effective than placebo in preventing both clinical and endoscopic postoperative recurrence in CD (at 1 and 2 years), but with a higher rate of AEs leading to drug withdrawal [70]. Several studies have recently evaluated the efficacy of IFX ([71, 72•, 73] and ADA [74, 75, 76•] for preventing POR. In an open-label extension of an RCT with follow-up for 5 years, patients assigned to the IFX group in the first year after surgery (compared to placebo) were more likely to stay in endoscopic remission and had a lower rate of POR requiring additional resections (20.0 vs. 64.3 %, $p=0.047$) [72•]. Similar results were seen with ADA in a prospective, randomized unblinded trial ($n=51$) after ileocolonic resection. After 2 years of follow-up, a significantly lower proportion of patients demonstrated endoscopic POR with ADA (6.3 %) compared with the AZA (64.7 %) and mesalamine groups (83.3 %).

Evolving algorithms on postoperative management of CD have highlighted the importance of risk stratification of patients to decide initial choice of medications. These risk factors have varied and often include smoking, prior penetrating disease, perianal disease, and prior resections [69•, 77]. There is often agreement on the need to treat high-risk groups for postoperative CD with an anti-TNF agent. Experts, however, have varied in their recommended approach in classifying the

remaining patients as moderate and low risk. Key questions that remain to be answered in the postoperative setting include dose optimization strategies using low-dose IFX (3 mg/kg) and titrating the dose based on level of fecal biomarkers such as fecal calprotectin [78, 79•].

## Conclusions

The medical management of CD is a rapidly evolving field. New medications continue to emerge and expand the armamentarium available to clinicians. Strategies to improve drug efficacy and limit AEs using treat-to-target approaches, TDM, and de-escalation protocols are being refined.

**Compliance with Ethics Guidelines**

**Conflict of Interest** Parakkal Deepak and David H. Bruining declare that they have no conflict of interest.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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