



Key Concepts

- Antibiotics, probiotics, diets, and fecal transplant do not appear offer clinically significant benefit for treatment of Crohn's disease.
- Exclusive enteral nutrition is beneficial in children but has not yet be shown to be of benefit in adults.
- 5-Aminosalicylates are widely recognized to have role in treatment of mucosal ulcerative colitis, but have a very limited role in the treatment of CD.
- Budesonide is efficacious for induction of clinical remission for CD patients when compared with placebo.
- Systemic steroids are indicated for induction of remission, but not for maintenance of remission due to its side effects; steroid dependency is an indication for surgery.
- Thiopurine and methotrexate monotherapy is not efficacious for induction of remission, but for maintenance of remission as a steroid-sparing agent; these medications are most commonly used in combination with biologics to decrease immunogenicity to the biologic agent.
- Biologic agents are indicated for induction and maintenance of remission in patients with moderate-to-severe Crohn's disease.
- Biosimilars present no differences in efficacy or safety compared to their originator compounds and have the advantage of lower cost.
- Therapeutic drug monitoring (TDM) of drug levels and anti-drug antibodies (ADA) allows more precise management of patients with Crohn's disease.

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History

The first case series describing regional enteritis was published in 1932 by a group of physicians at Mount Sinai Medical Center in New York City [1–3]. A senior surgeon, Dr. A.A. Berg, operated on 12 patients with terminal ileitis, and Drs. Leon Ginzburg and Gordon Oppenheimer wrote the initial manuscript. Of note, after Dr. Berg declined to be involved as a coauthor, Dr. Burrill Crohn was brought in as a third contributing author with two additional patients. At that time, the journal's publication policy was to order the authors alphabetically – thus Dr. Crohn was the first author, and regional enteritis subsequently became known as Crohn's disease, not Berg's disease, nor Ginzburg-Oppenheimer disease [3, 4].

Introduction

As surgeons who care for patients with inflammatory bowel diseases (IBD), just as we expect IBD-gastroenterologists (GI) to be facile with surgical treatment options, it is their expectation that we be facile with the medical therapies to which our patients are exposed. The treating colorectal surgeon should be able to manage these medications in the perioperative period, and may be called upon as part of the multidisciplinary team to provide perspective on initiation, continuation, or escalation of medical therapies as part of surgical decision-making. The types and timing of medical therapy may also have implications for the type and timing of surgical intervention. In this chapter, we will review the profiles of the most commonly prescribed medical therapies for Crohn's disease (CD). We will focus the role of each class of medications has in the induction and maintenance of remission, efficacy, commonly prescribed forms and dosing schedules, side-effect profiles, and perioperative management for these complex patients. Interested readers are referred to the recommendations of the American

Gastroenterology Association (AGA) 2013 Guideline on Medical Management in Crohn's [5], the American College of Gastroenterology (ACG) 2018 Crohn's Guideline [6, 7], and the European Crohn's and Colitis Organization (ECCO) 2020 Crohn's Guideline [8]. A summary of the treatment recommendations for these guidelines is shown in Table 46.1.

The AGA guideline [5], which is now the oldest and due to be updated, was limited to 9 recommendations on the use of thiopurines, methotrexate (MTX), and TNF inhibitors (TNFi's) for the induction of remission and maintenance of remission, while the ACG guideline is the most comprehensive and made a total of 60 recommendations which were stratified based on the severity of illness; mild-to-moderately severe disease/low-risk disease vs. moderate-to-severe disease/moderate-to-high-risk disease vs. severe fulminant disease vs. perianal disease. The ACG guideline also made recommendations regarding postoperative prophylaxis including smoking cessation and that intra-abdominal abscesses should be treated with antibiotics and either radiologic or surgical drainage [2]. Finally, the recently updated ECCO guideline recommendations were stratified in a manner similar to the AGA's based on induction (10 recommendations) and maintenance (13 recommendations) of

remission, plus perianal disease (7 recommendations) for a total of 30 recommendations.

In contrast to ulcerative colitis (UC), for which surgery is curative for the colonic and rectal manifestations of disease, patients with CD have a life-long disease for which surgery only manages the complications of the inflammatory, fibrostenotic, penetrating, and neoplastic manifestations of disease. Surgery will often "reset the clock," and many patients will be able to be managed expectantly without ongoing medical therapy and a colonoscopy 6 months after ileocolic resection to assess disease activity. However, those with high-risk phenotypes (Table 46.2) will require active postoperative medical therapy to prevent or delay post-operative recurrence (POR).

Table 46.2 Example of high-risk features as indications for more aggressive medical therapy in luminal CD

Male sex	Short-interval recurrence(s)
Young onset of disease	Multifocal disease (<i>i.e.</i> , diffuse jejunoileitis)
Active smokers	Granulomas
Penetrating phenotype	Perianal disease

Table 46.1 Summary of medication treatment recommendations by the various society guidelines. Note AGA and ECCO recommendations based on induction vs. maintenance, ACG based on severity.

Medication	Induction of remission in CD			Maintenance of remission in CD			Notes
	AGA ⁵	ACG ⁶	ECCO ⁸	AGA ⁵	ACG ⁶	ECCO ⁸	
Antibiotics	--	No*	No	--	--	No	* Role limited to treatment of intra-abdominal abscesses, perianal cellulitis, or to decrease perianal fistula drainage amount
Oral 5-ASA	--	No*	No	--	No	No	*For mild colonic symptoms
Rectal 5-ASA	--	--	No	--	--	No	--
Antimotility, diet, etc.	--	Yes	--	--	--	--	--
Topical steroids (budesonide)	--	Yes	Yes	--	No (>4 mo.)	Yes	Ileal or right colonic disease
Systemic steroids	--	Yes	Yes	--	No	No	Short-term only
TPMT testing	--	Yes	--	--	--	--	Before TP initiation
TP monotherapy	No	No	No	Yes	Yes +/-TNFi	Yes*	*For steroid sparing/fistulae otherwise recommend <i>against</i> early introduction in new patients; recommend continuation in those already on TP in remission due to risk of relapse
MTX monotherapy	No	Yes	--	Yes	Yes +/-TNFi	Yes*	*Steroid sparing; parenteral recommended
TNFi monotherapy	Yes	Yes	Yes	Yes	Yes	Yes	Steroid and IMM resistance; severe disease; fistulae; perianal disease
TNFi combo-therapy	Yes	Yes, if naïve to both	Yes	Yes	Yes, over monotherapy	Yes	TPs or MTX; see SONIC trial [70]
Vedolizumab	--	Yes	Yes	--	Yes	Yes	+/- IMM
Ustekinumab	--	Yes*	Yes	--	Yes	Yes	*In TNFi exposed or naïve
Cyclosporine	--	No	--	--	--	--	--
Tofacitinib	--	--	No	--	--	No	Not yet FDA-approved for CD

Microbiome Therapies

Antibiotics

Overall, antibiotics are probably not efficacious for induction or maintenance of remission in CD [9–11]. A systematic review with meta-analysis from 2011 found that in active CD, compared to placebo, antibiotics may be efficacious (RR 0.85, 95% CI 0.73–0.99, $p = 0.03$); however this pooled analysis combined a number of different antibiotics, and the excessive heterogeneity precluded definitive conclusions. The Cochrane collaboration updated their review in 2019 and found 13 randomized controlled trials (RCT) examining the role of antibiotics for the induction and maintenance of remission [12]. They concluded that although antibiotics may be modestly beneficial, this may not be clinically significant based on moderate- to high-quality evidence. Although there was high-quality evidence that antibiotics are safe, efficacy for maintenance of remission was not demonstrated and remains uncertain. Therefore, the ACG and ECCO guidelines do not recommend them for induction or maintenance of remission, nor for maintenance of remission, consistent with North American practice [11].

Although antibiotics likely do not have a definitive role in the induction or maintenance of remission for luminal or perianal CD, they obviously have a role in the management of septic complications of penetrating CD; aspirates from percutaneously or intraoperatively drained abdominopelvic abscesses should be sent for aerobic, anaerobic, and fungal cultures with sensitivities to guide optimal management [6, 13]. The Toronto Consensus statement concluded that antibiotics only have a role in initial symptomatic control of perianal disease [14]. Of note, ciprofloxacin has recently had a black box warning for tendinopathy, especially in older patients also receiving corticosteroids [15]. Low-dose metronidazole may be used to decrease drainage. The principles of management of perianal CD are covered in another chapter.

Probiotics

Probiotics are beneficial microorganisms that can alter the gut's microbiota, metabolic activity, and immunomodulation to confer patient benefit. These bacteria and fungi alter microbial diversity through competitive inhibition of other microbes, enhance mucosal barrier function via the production of short-chain fatty acids, and interact with intestinal dendritic cells to instigate an anti-inflammatory response. The microorganisms must be of human origin, nonpathogenic, and able to survive the gastrointestinal transit in order to be beneficial. Unfortunately, multiple meta-analyses suggest that probiotics are ineffective for induction and maintenance of remission in patients with CD and may not be without risks [16–18].

Dietary Interventions

Similarly, dietary interventions have failed to demonstrate efficacy for the induction and maintenance of remission [19]. The Cochrane group performed a meta-analysis of 18 RCTs including 1,878 patients who received dietary intervention. Interventions included high-fiber, low-refined carbohydrate diets, low-microparticle diets, low-calcium diets, symptom-guided diets, and highly restricted organic diets. In general, efficacy was suggested by several of the diets, particularly the symptom-based and several restrictive diets; but overall the studies were heterogenous, prone to bias, and of low- or very-low quality of evidence. The authors made no firm conclusions but did note that there are several well-designed ongoing RCTs in over 500 patients examining this topic, and that the meta-analysis would be updated subsequently.

Fecal Transplant

The other manner in which a patient's microbiota can be altered is via fecal microbiota transplant (FMT). This management has proven useful in treating recurrent *Clostridium difficile* infections (CDI), but has not been adequately studied nor shown efficacy in CD. A recent small pilot RCT of 17 patients with CD who achieved remission with steroids and underwent FMT did not demonstrate the primary efficacy endpoint, although endoscopic scores and C-reactive protein (CRP) levels were significantly better in the FMT-treated patients [20]. A meta-analysis suggested FMT may have efficacy in UC but not Crohn's; no safety concerns were raised by this study [21]. The Cochrane groups meta-analysis on this topic suggested a lack of available studies of FMT for CD, with no studies examining the role of FMT for induction of remission in CD [22]. Interestingly, a separate meta-analysis of FMT for CDI in IBD patients demonstrated efficacy, just as in the non-IBD population [23]. Of note, on March 12, 2020 the Food & Drug Administration (FDA) released a Safety Alert after 2 patients with chronic medical conditions who received FMT for CDI died of complications related to FMT-related transmission of enteropathogenic and/or shigatoxin-releasing *E. coli*.

Exclusive Enteral Nutrition

A promising form of nutritional intervention specific to CD is exclusive enteral nutrition (EEN). EEN is a nutritional intervention where patients are placed on a full-liquid monodiet with a commercially available nutritional supplementation [24]. In pediatric CD patients, EEN has been shown to

be more effective than steroids for induction of remission, but this has not yet been replicated in adult CD patients [25]. Presently, some centers use EEN in adults while they are tapered off steroids as they await elective surgery [26].

5-ASA Therapy

5-Aminosalicylate (5-ASA) moieties, which have a large role in the medical treatment of UC, are widely recognized to have a limited role in the treatment of CD. The indication for this class of medications is for the induction and maintenance of remission in mild-to-moderate UC. These medications are covered more fully in the Medical Therapy of UC chapter. The mechanism of action of 5-ASAs is as topical anti-inflammatory agents, which explains their efficacy in mucosal UC as opposed to CD, which is a full-thickness bowel disease.

Multiple well-designed double-blinded placebo-controlled RCTs of oral formulations with varying dosages and meta-analyses have concluded that oral 5-ASAs lack efficacy for the induction of clinical remission for ileal, ileocolic, or colonic CD. In addition, as noted in the meta-analysis within the ECCO CD guidelines, oral 5-ASAs also lack efficacy for the maintenance of remission (RR 1.03, 95% CO 0.92, 1.16) [8].

Isolated Colonic Crohn's

Nonetheless, the question remains if there is a role for 5-ASAs in isolated colonic CD. The largest trials of 5-ASAs for colonic disease were the National Cooperative Crohn's Disease Study (NCCDS) and the European Cooperative Crohn's Disease Study (ECCDS) [27, 28]. There were mixed results in the early clinical trials with mild-to-moderate disease, but these studies also lacked endoscopic or biochemical data [29]. Thus, a need exists to replace this older data with new studies which include modern assessments tools [30]. Some providers will use 5-ASAs in patients with mild colonic CD and assess response, in a treat-to-target manner with mucosal healing as the endpoint. 5-ASAs are not approved for CD in the USA but are approved in Europe, Canada, Australia, and Japan. Of note, the ACG and ECCO treatment guidelines also concluded that 5-ASAs lack efficacy for induction of remission in CD [6, 8].

Crohn's Proctitis

Despite the overall lack of efficacy for the induction or maintenance of remission of CD, there may be a role for 5-ASA rectal formulations for patients with proctitis [31]. Proctitis may result in disabling fecal urgency, tenesmus, and agora-

phobia. 5-ASA enemas and suppositories may have a role in palliating these symptoms as adjuncts to primary medical therapy. Mesalamine suppositories are typically prescribed at doses of 500–1000 mg per rectum at bedtime, with mesalamine enemas at 4 grams/60 cc enemas 1–2 times per day. These formulations are typically well-tolerated but often require prior authorization and/or may be non-formulary for many commercial insurance plans.

Side-Effects and Perioperative Management

5-ASA medications have an excellent safety profile and may be resumed postoperatively. The most common side-effects of these medications include gastrointestinal (GI) upset, headaches, and skin hypersensitivity to sun [29]. Rare side-effects include bone marrow suppression, fever, hemolytic anemia, hepatitis, hypersensitivity reactions, pancreatitis, pneumonitis, and rash. Patients who take sulfasalazine must also take folic acid (1 mg daily) because the medication depletes folic acid stores [29, 31].

Corticosteroids

Topical Corticosteroids

Budesonide is a synthetic glucocorticoid which is administered as an oral enteric-coated capsule which resists gastric degradation. Budesonide has high first-pass metabolism and very limited systemic absorption and is generally well-tolerated [32]. It comes in 3 mg capsule and is dosed up to 9 mg per day. Of note, budesonide is the mainstay of therapy for induction of remission in microscopic and collagenous colitis. In order to target small bowel proximal to the terminal ileum, the "open-capsule technique" may be chosen for administration; half of the daily dose (one full 3 mg capsule and half of one 3 mg capsule) is opened and sprinkled on food. The Multimatrix® (MMX®) formulation allows for controlled release for use in the colon [33].

A Cochrane meta-analysis found that budesonide was efficacious in the induction of clinical remission for CD patients, when compared with placebo [34]. This meta-analysis also stated that budesonide was not as effective as conventional steroids but was significantly safer. They also found a lack of efficacy for maintenance of remission. The ACG and ECCO guidelines recommend budesonide for the induction of remission in mild-to-moderate ileal or right-sided colonic disease [6, 8]. For maintenance of remission, the ACG guidelines suggest it not be used for more than 4 months, but the ECCO guidelines allow for maintenance therapy with budesonide [6, 8].

Table 46.3 Side-effects of budesonide with long-term use

Frequency	Organ system	Effect
Common	Endocrine	Cushingoid features, hypokalemia
	Psychiatric	Mood changes
	Optic	Blurry vision
	Cardiac	Palpitations
	GI	Dyspepsia
	Skin	Skin reactions
	Reproductive	Altered menses
Uncommon	Nervous system	Tremor
Rare	Musculoskeletal	Reduced growth velocity
	Systemic	Anaphylaxis

Adapted with permission from: O'Donnell and O'Morain [32]. Copyright © 2010 Sage Publications

Side-Effects and Perioperative Management

Although well-tolerated and safer than traditional steroids, budesonide may have side effects (Table 46.3), especially when used for prolonged periods of time. When used for less than 1 year, the side-effect profile is similar to that of placebo with rare occurrences of the clinically important side effects typically associated with traditional glucocorticoids [35]. Given the excellent safety profile of budesonide with its limited systemic absorption, budesonide may be safely held immediately before and after surgery, stress-dose steroids are *not* needed, and resumption postoperatively may not be necessary.

Systemic Corticosteroids

Traditional corticosteroids are powerful systemic anti-inflammatory drugs which were first used by Truelove and Witt for the treatment of IBD in 1955 [36, 37]. Although they are extremely efficacious as anti-inflammatories, they have an unfavorable side-effect profile which limits their clinical utility to induction of remission in otherwise medically refractory disease. A meta-analysis limited to randomized controlled trials identified 2 trials including 267 patients using standard oral glucocorticoids to induce remission in active Crohn's disease [38]. Overall, 79 of 132 patients (60%) assigned to oral glucocorticoids achieved remission compared with 42 of 135 (31%) prescribed placebo. Moreover, the number needed to treat to achieve remission in one patient with standard glucocorticoids was 3 (95% CI, 2–11), which is very low and associated with high efficacy. Both the ACG and ECCO guidelines recommend systemic steroids for induction of remission, but not for maintenance of remission [6, 8]. Steroids should not be used chronically as long-term use carries a high risk of serious adverse events. The need for systemic steroids represents a “bad omen” or “tipping point” for patients with CD, as it is associated with a more complicated disease course. Steroid dependency is an indication for surgery.

For outpatient induction of remission, prednisone is typically prescribed at 40 mg by mouth daily and tapered by

Table 46.4 Glucocorticoid conversion table

Class (T _{1/2} in hours)	Corticosteroid	Equivalent dose in mg	Potency relative to hydrocortisone (anti-inflammatory/mineralocorticoid)
Short-acting (8–12)	Cortisone	25	1/1
	Hydrocortisone	20	0.8/0.8
Intermediate-acting (18–36)	Prednisone	5	4/0.8
	Prednisolone	5	4/0.8
	Methylprednisolone	4	5/0.5
Long-acting (36–54)	Triamcinolone	4	5/0
	Betamethasone	0.6	30/0
	Dexamethasone	0.75	30/0

Modified from: Nicolaides *et al.* [37]

5–10 mg per week; but this depends on what other medical or surgical options the patient, gastroenterologist, and colorectal surgeon are contemplating. Steroid conversion calculators and tables (Table 46.4) [37], widely available on the Internet, allow for conversion between enteral, parenteral, and various formulations.

Safety

Despite the substantial efficacy for induction of remission in CD, chronic corticosteroid treatment is among the most significant risk factors for postoperative infectious and/or wound complications. A summary of the toxicity of corticosteroid therapy is shown in Table 46.5 [37]. The side effects are organ-based and wide-ranging and for the most part dose- and duration-dependent. Cessation of steroid therapy will ameliorate some, but not all, of the risks of exposure to these medications. The side effects would not likely be considered acceptable, if not for the wide therapeutic effect across a wide range of human auto-inflammatory and auto-immune diseases. Many of these diseases lacked any efficacious therapy other than corticosteroids until recently. Chronic steroid use, loosely defined as more than several months, has largely fallen by the wayside as new biologic treatments with better short- and long-term safety profiles continue to be developed and marketed.

Stress-Dose Steroids and Tapering

Of note, several publications have examined the role of stress-dose steroids in the perioperative period for IBD [39–42]. In a series of steroid-dependent UC patients, only one patient developed postoperative adrenal insufficiency [39]. The authors concluded that stress-dosing was not beneficial, but all steroid-dependent patients should be monitored after surgery for symptoms of adrenal insufficiency. Two studies from Cedars Sinai had similarly questioned the utility of stress-dose steroids at the time of surgery for IBD [41, 42]. In the era of enhanced recovery, many patients receive 8 mg of intraoperative dexamethasone for postoperative nausea and vomiting prophylaxis which effectively replaces the

Table 46.5 Toxicity of chronic corticosteroid treatment

Organ system	Unwanted Effect	Notes
Systemic	Cushingoid appearance, weight gain	Occurs in >70%, 4–8% mean increase in body weight Adipose redistribution: truncal, facial, dorsocervical; occurs in ~25% \geq 7.5 mg prednisone/day
	Immunosuppression	Mainly by sequestration of CD4+ T-lymphocytes in the reticuloendothelial system, and by inhibiting the transcription of cytokines; profoundly inhibits lymphocyte migration into lymph nodes
	Impaired wound healing	Decreased collagen synthesis and maturation, inhibited leukocyte/macrophage infiltration Potentially maybe overcome by epidermal-derived growth factor, TGF-beta, platelet-derived growth factor, tetrachlorodecaoxygen, and retinoic acid (vitamin A)
Endocrine	HPA-axis suppression	Wide-ranging, non-specific, symptoms may overlap with Crohn's (see Table 46.6). Avoid abrupt cessation of therapy
	Hyperglycemia/diabetes	Increased insulin resistance; +risk of persistent diabetes
Musculoskeletal	Osteoporosis, avascular necrosis, fractures	Osteoblast and osteocyte suppression and apoptosis Reduced bone mineral density Osteonecrosis develops in 9–40% of adults, often misdiagnosed as lumbar symptoms
	Myopathy	Catabolic effect on skeletal muscle
Optic	Cataracts, glaucoma	Cataracts (reduced acuity) which require earlier surgical treatment -Painless glaucoma (decreased visual field) can cause permanent optic nerve damage
Cardiovascular	Hypertension, obesity, dyslipidemia, arrhythmias	Higher CV event risk with \geq 7.5 mg prednisone/day Risk of sudden death even with pulse therapy if pre-existing kidney/heart disease
GI	Gastroesophageal ulceration, acute pancreatitis	Ulcer/hemorrhage risk increased if concurrent NSAID use pancreatitis may be secondary to systemic lupus erythematosus (SLE), or TP treatment, rather than drug effect
Psychiatric/ Cognitive	Various	Wide range: memory impairment, agitation, anxiety, fear, hypomania, insomnia, irritability, lethargy, mood lability, frank psychosis Heightened if concomitant pre-existing conditions
Skin	Various	Atrophic skin changes, thin fragile skin; purpura; red striae

Modified from: Nicolaides et al. [37]

Table 46.6 Signs and symptoms of adrenal suppression and Addisonian crisis

Adrenal suppression	Addisonian crisis
Malaise/weakness/fatigue	Hypotension, fluid-refractory and otherwise un-explained
Nausea/vomiting/diarrhea	Hyponatremia
Abdominal pain	Unexplained hypoglycemia
Morning headache	Lethargy
Fever	Decreased consciousness/seizure/coma
Anorexia/weight loss	
Myalgia/arthralgia	
Psychiatric symptoms	
Growth suppression (in children)	

Modified from: Nicolaides et al. [37]

need for stress-dose steroids [26]. For patients who received a short-term (1–2 weeks) of steroids preoperatively, it is our practice to simply stop them postoperatively, and for those on chronic steroids to continue post-operative corticosteroids at the same dose, or dose-equivalent, the patient was receiving preoperatively [43–45].

Chronic steroid therapy must not be stopped abruptly lest patients develop severe Addisonian crisis with circulatory collapse (Table 46.6). On the other hand, no evidence-based

guidelines for steroid tapering exist [46]. When patients do present to surgery receiving corticosteroids, the rapidity with which they may be tapered depends on the chronicity of treatment. We typically reduce the dose by 50% every 5–7 days. Sometimes a slow taper with several additional weeks is required if the patient has been on steroids for a prolonged period to avoid withdrawal symptoms such as fatigue, lethargy, and depression. Testing for adrenal suppression in such cases is typically not needed; the patients can either be counseled that these uncomfortable symptoms will eventually pass, or their corticosteroid dose can be increased with a more prolonged tapering schedule. Readers are referred to the an excellent resource *Glucocorticoid Therapy and Adrenal Suppression in the Internet book Endotext* for further reading at www.endotext.org.

Immunomodulators

Thiopurines

Thiopurines (TPs), namely 6-mercaptopurine (6MP) and azathioprine (AZA), along with methotrexate (MTX), are known as immunomodulators (IMM) [5, 6, 9]. TPs are purine analogs and thus antimetabolites, which inhibit DNA and

have antiproliferative properties and proapoptotic action on activated T-lymphocytes [31]. The typical dose of AZA is 2 mg/kg daily, while 6MP is typically 1 mg/kg daily. AZA and 6MP are typically started at low doses (50 mg and 10 mg, respectively) with biweekly complete blood counts and liver function testing and given normal labs dose escalation every 2 weeks to the desired dose. Of note, the clinical effect of TP therapy takes several months, so patients are typically re-evaluated after 3 months of therapy [31].

TP Pharmacokinetics

AZA is a prodrug of 6MP, and both AZA and 6MP are prodrugs of 6-thioguanine (6TG). AZA and 6MP are converted by intracellular thiopurine methyltransferase (TPMT) to 6TG (Fig. 46.1) [47]. Clinical TPMT activity testing is critically important for patients prior to being placed on TG treatment [48]. While 80% of the population has normal TPMT metabolism, ~10% have hyperactive TPMT metabolic activity ("shunters") which leads to the accumulation of toxic secondary metabolite, increasing the likelihood of drug side-effects such as hepatotoxicity [49]. Shunters, as the name implies, also shunt drug away from the normal metabolic pathway, resulting in less clinical activity. The shunting can be overcome by using allopurinol, which inhibits secondary metabolite production, and prescribing 25% of the usual TG dose [49].

In addition to the shunters, 10% of the population are heterozygous for TPMT and have intermediate (lower than average) metabolic activity, and 0.3% of the population are TPMT deficient (homozygous). The intermediate activity patients require a higher than average dose to acquire the desired effect, while the deficient population will not be clinically responsive to TP treatment [48, 49].

Monotherapy

Current guidelines agree that TP are efficacious at the maintenance of remission of luminal CD obtained by other means and that they are *not* efficacious for the *induction* of remission in mild-to-moderate luminal CD [5, 6, 9]. This is mainly due to their onset of action; thus they may be started concomitantly with other medications for the induction of remis-

sion, which can then be weaned (in the case of steroids) while the TPs take effect. Thus, TPs have traditionally served a role as monotherapy for the maintenance of remission in CD as a steroid-sparing agent.

Specifically, when patients were unable to be weaned off steroids, TP therapy would provide an exit strategy from the steroid dependency in patients who were able to achieve but not maintain remission without continued steroids. In a meta-analysis of placebo-controlled randomized trial in steroid-dependent patients, AZA was shown to be superior to placebo (RR 1.19, 95% CI 1.05–1.34) for maintenance of remission as a steroid-sparing agent [5]. Combination therapy will be covered below in the section on biologics.

Relative contraindications include patients with neoplasia or hematologic comorbidities [49]. MTX is a relatively safe and more widely acceptable alternative in older patients and especially in young men. The EBV status in young males is important, as young men with +EBV status are at a very small but demonstrable risk of developing hepatocellular T-cell lymphoma, a universally-fatal condition, thus TGs are avoided in these at-risk patients. In addition, EBV naïve patients are at risks of developing hemaphagocytosis.

Side Effects and Perioperative Management

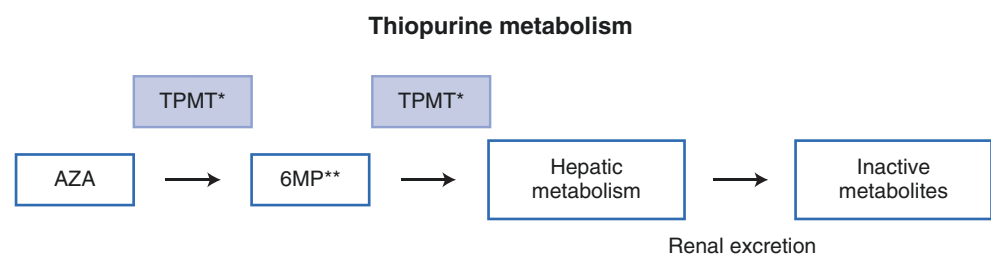
The side effects of TG therapy can be significant and are shown in Table 46.7. Idiosyncratic pancreatitis is the most common dose-independent side effect; hepatitis, which is

Table 46.7 Side effects of TG therapy

Type	Toxicity	Frequency	Testing
Dose-independent	Pancreatitis	<15%	Lipase
	Flu-like symptoms	5%	Patient-reported
	Rash	4%	Patient-reported
Dose-dependent	Hepatitis	<30%	LFTs, TPMT testing
	GI intolerance	<20%	Patient-reported
	Leukopenia	10%	CBC, TPMT testing
	Agranulocytosis	0.3%	CBC, TPMT testing

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Fig. 46.1 Thiopurine metabolism



* TPMT enzymatic activity, found in RBC's is deficient in 1 in 300 patients and will predictably result in severe myelosuppression, thus TPMT activity must be assessed prior to initiation of therapy with AZA/6MP

**Purine analog, becomes false base in RNA/DNA

dose-dependent and whose risk increases with ongoing therapy, is the most common overall. Many patients have GI side-effects from TG therapy; CBCs are used to assess for hematologic consequences. It is controversial whether long-term use has been associated with malignancy. The best available population-based cohort data comes from the CESAME – Cancer and Increased Risk Associated with Inflammatory Bowel Disease in France study group. They suggest risk is increased in IBD patients receiving TP therapy for hematologic neoplasia including leukemia and lymphoma, non-melanoma skin cancer, cervical cancer, and urinary tract cancer. The risk of colorectal adenocarcinoma may actually be lower due to control of intestinal inflammation [50–52]. TG therapy also have a number of drug-drug interactions to be aware of including ACE inhibitors, allopurinol, anticoagulants, sulfamethoxazole/trimethoprim, and other immunomodulators including MTX and cyclosporine A [49].

TP may be safely used in the perioperative period. Although therapeutic efficacy takes several months to be observed, the half-life of these medications is very short. In addition, TPs have not been shown to be associated with postoperative complications in IBD patients [53]. Thus, most surgeons hold TP therapy in the immediate postoperative period and allow the referring gastroenterologist to reassess the need for ongoing IMM therapy.

Methotrexate

The other drug in the immunomodulator class is MTX, which is also an antimetabolite, similar to the TGs. The discovery of MTX as a powerful inhibitor of cellular metabolism and mitosis was honored with a Nobel Prize in 1988, and the first trial demonstrating a benefit of MTX in CD was in 1989 [54, 55]. MTX has efficacy in the maintenance of remission of luminal CD obtained by other means and is not recommended for the induction of remission [5, 6, 9]. MTX inhibits TNF, MMPs, JAK 1/2, and IL-23 pathways [56]. It is typically prescribed at a dose of 25 mg subcutaneously (SC) or intramuscular (IM) weekly for active CD, and 15 mg PO/SC weekly for maintenance therapy, both with 5 mg of folic acid PO weekly.

Side-Effects and Perioperative Management

Similar to TPs, MTX may have dose-limiting toxicity (Table 46.8). For fertile young couples, pregnancy must be avoided as MTX is a known teratogenic agent and abortifacient, and abstinence and/or high-quality contraceptives should be used [57–60]. An effect of MTX on sperm counts and quality has also been described.

MTX inhibits dividing cells and thus may interfere with wound healing. However, it has a very short half-life. MTX

Table 46.8 Side effects of MTX

Organ	Symptoms	Mitigation strategy
Gastrointestinal	Mucositis, diarrhea	5 mg folate weekly, switch from PO to SC/IM route
Bone marrow	Anemia, leukopenia	5 mg folate weekly
Hepatic	Steatosis, fibrosis, cirrhosis	Avoid dose >1 g
Pulmonary	Pneumonitis, PCP pneumonia	Monitor symptoms
Renal	Renal insufficiency (rare)	Monitor GFR/reduce dose
Reproductive	Teratogenic	Abstinence/contraceptive

Adapted from Bedou et al. [56]. No permission required <https://www.mdpi.com/openaccess>

Table 46.9 Summary of biologic medications for CD

Medication	Route	Dose	
		induction	Maintenance
Infliximab	Intravenous	5 mg/kg at weeks 0, 2, and 6	5–10 mg/kg every 8 weeks
Adalimumab	Subcutaneous	160 mg at week 0, 80 mg at week 0	40 mg every 2 weeks
Certolizumab pegol	Subcutaneous	400 mg at weeks 0, 2, and 4	400 mg every 4 weeks
Natalizumab	Intravenous	None	300 mg every 4 weeks
Vedolizumab	Intravenous	300 mg at weeks 0, 2, and 6	300 mg every 8 weeks

does not appear to be associated with postoperative complications [61]. Thus, the perioperative management of MTX is the same as for TPs mentioned above; they may be safely discontinued prior to surgery and held in the postoperative period, and their ongoing therapeutics need to be reassessed by the GI team after recovery.

Biologic Therapy

Since the FDA approval of infliximab in 1998, biologic agents (summarized in Table 46.9) have revolutionized the treatment of CD. Rather than indiscriminate immunosuppression, biologic medications are monoclonal antibodies directed at particular proteins that drive the inflammatory cascade of IBD. They are approved to induce and maintain remission in moderate-to-severe CD. This is defined using clinical and endoscopic factors and typically includes a Crohn's disease activity index (CDAI) >220, a Crohn's disease endoscopic index of severity (CDEIS) >8, or a simple endoscopic score (SES-CD) >6. At present, there are three categories of biologic agents with six commonly used medications that are FDA-approved for this indication:

1. *Tumor Necrosis Factor inhibitor (TNFi) agents*
 - Infliximab
 - Adalimumab
 - Certolizumab pegol
2. *Anti-integrin agents*
 - Natalizumab
 - Vedolizumab
3. *Anti-interleukin agents*
 - Ustekinumab

Selection of biologic therapy should be driven by patient and physician preference; but in reality, insurance approval and cost are often factors into which agent is ultimately chosen. A 2017 review of insurance policies regarding biologic use for IBD reported that 90% of policies are inconsistent with AGA guidelines [62].

The positioning of biologic agents in the therapeutic algorithm is a matter of debate. Historically, a “step-up” strategy starting with 5-ASA compounds, IMM, and corticosteroids with escalation to biological therapy after failure to maintain remission has been employed. The top-down approach (early utilization of biologics) has been suggested for patients presenting with poor prognostic factors suggesting a complicated phenotype (Table 46.2). The goal of this approach is to optimally control disease and prevent complications such as fistula or stricture, where medical therapy is less or ineffective. Factors such as early age of diagnosis, stricturing or fistulizing disease, perianal or severe rectal disease, extensive involvement of the GI tract, deep ulcerations, prior surgical resection, or rapid onset should be considered for early biologic therapy. High-risk patients have shown benefit from the early use of TNFi's for an overall risk reduction of surgery, hospitalization, loss of response, and the development of disease-related complications [63].

Before initiation of biologic therapy, routine assessment for tuberculosis (typically using QuantiFERON-TB Gold) and viral hepatitis and selective assessment for histoplasmosis and blastomycosis should be initiated. Patients should be vaccinated against pneumococcus, varicella, human papilloma virus, influenza vaccine, hepatitis A vaccine, and herpes zoster.

Antitumor Necrosis Factor Agents

The TNFi agents are infliximab, adalimumab, and certolizumab pegol. These medications successfully modulate the immune system by binding to tumor necrosis factor alpha (TNF-alpha) and inhibiting signal transduction and limiting inflammation. These agents are proven to induce remission and provide maintenance therapy in patients with moderate-to-severe CD and are supported by the AGA, ACG, and ECCO guidelines [5, 6, 8]. Several meta-analyses of RCTs

support their use in those who failed therapy with steroids or other forms of immunosuppression [64–66]. TNFi's are particularly useful in the management of perianal or rectal disease, fistulizing CD, patients at high-risk for postoperative recurrence, and those with pyoderma. Response may be seen within the first few weeks after starting therapy, but maybe delayed up to 6 weeks after initiation.

Infliximab (IFX) is a chimeric mouse-human immunoglobulin (Ig) monoclonal antibody. This is typically administered with intravenous induction dosing at 5 mg/kg at weeks zero, two, and six followed by maintenance therapy every 8 weeks thereafter. IFX is the only agent with a phase 3 study demonstrating efficacy for the treatment of fistulizing disease, particularly perianal disease [67]. There are some data suggesting that infliximab is also associated with fewer hospitalizations, surgeries, and steroid use when compared with other TNFi agents for CD [68].

Adalimumab (ADA) is a fully human Ig monoclonal antibody given subcutaneously. This is started with induction dosing of 160 mg at week zero, followed by 80 mg at week 2, and then 40 mg every 2 weeks thereafter.

Certolizumab pegol is a PEG-ylated Fab fragment. This medication is self-administered subcutaneously at a dose of 400 mg at weeks 0, 2, and 4, followed by 400 mg every 4 weeks thereafter.

Adverse events with TNFi drugs include psoriasis, arthritis, hepatotoxicity, rarely cytopenia, and an increased risk of melanoma and lymphoma formation [69]. Patients on combination therapy with immunomodulators may also have an increased risk of non-melanoma skin cancers and lymphoma [69]. Patients are also at risk for opportunistic infections.

Combination Therapy

The use of combination therapy with immunomodulators has been shown to increase TNFi serum concentrations while minimizing the risk of adverse drug reactions [70]. Unfortunately, combination therapy has also been associated with an increased risk of opportunistic infections [71, 72].

When starting IFX, combination therapy with a TP is generally recommended. The SONIC (Study Of Biologic and Immunomodulator Naïve Patients In Crohn's Disease) trial compared IFX with AZA to each therapy alone in treatment naïve patients [70]. Combination therapy was more likely to result in mucosal healing [RR: 1.82; 95% CI: 1.01–3.26] and clinical remission at 26 weeks. The authors also found significantly lower rates of serious adverse events in those on combination therapy [RR: 0.56; 95% CI: 0.32–0.97]. No controlled trial has addressed whether to continue immunomodulators (IMM) when starting a TNFi after failure of IMM monotherapy. A post hoc subgroup meta-analysis of controlled trials of these types of patients showed no added benefit for the continued use of IMM with TNFi regarding 6 month remission [OR: 1.02; 95% CI: 0.80–1.31], induction

of complete response [OR: 1.08; 95% CI: 0.79–1.4] or partial response [OR, 1.25; 95% CI, 0.84–1.88], maintenance therapy [OR: 1.53; 95% CI, 0.67–3.49], or fistula closure [OR: 1.10; 95% CI, 0.68–1.78] [73]. However, TNFi and other biologic agents are intrinsically antigenic, although the non-TNFi's are less antigenic and combination therapy is most commonly used with the TNFi's. The development of anti-drug antibodies (ADA) leading to loss of response is an important consideration; in the absence of direct evidence, an individualized approach to combination therapy seems appropriate [73].

The REACT [Early Combined Immunosuppression for the Management of Crohn's Disease] trial showed that the early use of biologic therapy combined with IMMs as compared with a more conventional stepwise management was associated with significantly lower rates of complications including need for hospitalization, serious disease-related outcomes, or surgery in patients with early CD [63]. Of note, there was no significant difference between the two groups of patients in steroid-free remission, the trial's primary outcome. The "Enhanced Algorithm for Crohn's Treatment Incorporating Early Combination Therapy [REACT2]" is currently enrolling with a primary endpoint based on mucosal healing.

The DIAMOND [Deep Remission of Immunomodulator and Adalimumab Combination Therapy for Crohn's Disease] trial is the only RCT that studied the use of combination therapy of adalimumab with thiopurines versus monotherapy for inducing remission [74]. Combination therapy was not superior for remission [RR: 0.95; 95% CI: 0.78–1.15]. While combination therapy was associated with endoscopic improvement at week 26 [RR: 1.32; 95% CI: 1.06–1.65], this benefit was lost at 1 year. There was no increase in adverse events associated with combination therapy [RR: 1.03; 95% CI: 0.60–1.78], but the dose of AZA used in this trial was lower than what is typically used in CD. Given the ability of immunomodulators to reduce the rate of ADA formation, long-term combination therapy in ADA may very well have a benefit outside of short-term clinical remission or maintenance.

Leukocyte-Trafficking Agents

Leukocyte-trafficking agents, or integrin receptor antagonists, prevent margination of leukocytes by blocking the surface integrins and preventing adhesion to endothelial cells. Natalizumab inhibits the $\alpha 4$ integrin, while vedolizumab blocks the $\alpha 4\beta 7$ heterodimer and is gut selective.

Natalizumab is an infusional drug dosed at 300 mg every 4 weeks and is effective in the treatment of CD [75]. Because this medication is not specific to the GI tract, there is a rare but increased risk of progressive multifocal leukoencepha-

lopathy (PML) resulting from infection with the John Cunningham (JC) virus [76]. This risk is reported to be as high as 1 in 100 who are antibody positive for JC virus, so patients should be surveilled for infection before starting treatment and at every 6 months after. Fear of this dreaded complication, combined with the demonstrated efficacy of novel biologics, has largely led to the abandonment of this medication for CD.

Vedolizumab is also an intravenous medication, with a 300 mg dose at 0, 2, and 6 weeks followed by maintenance every 8 weeks thereafter. The onset of action is quite slow, and initial response is typically seen within 12 weeks of starting the drug [77]. Vedolizumab has historically been used in those patients who have had an inadequate response, lost response, or could not tolerate anti-TNF, corticosteroids or IMM therapy. Failure of other therapies is not a requirement, however, and it can be positioned as first-line agent in patients with active disease. Vedolizumab has been shown to achieve clinical response, clinical remission, and steroid-free remission, and use is supported by the ACG and ECCO guidelines [6, 8, 77–79]. Because it is selective to the GI tract, there is no known risk for PML, unlike natalizumab. Patients who have received prior treatment with TNFi agents may require longer treatment to reach efficacy [80]. Those patients appear to have the same efficacy at 10 weeks that TNFi-naïve patients experience at 6 weeks. Prospective clinical trials comparing vedolizumab monotherapy with combination therapy has not been reported.

A recent network meta-analysis suggests that ADA or combination therapy with IFX and AZA is more effective than vedolizumab in inducing and maintaining remission in CD [81].

Interleukin-12 and -23 Antagonist

In 2016, the FDA-approved ustekinumab for use in moderate-to-severe CD. This drug targets the p40 subunit of interleukin-23 and interleukin-12. Induction should be given intravenously usually at 6 mg/kg followed by maintenance dosing of 90 mg subcutaneously every 8 weeks. The onset of action is usually seen within 6 weeks.

Ustekinumab is efficacious in treating patients with moderate-to-severe CD who have failed both conventional non-biologic therapy and TNFi medications but also can be positioned as a first-line agent [82]. Consistent with clinical trials, a large database study of patients undergoing treatment for psoriasis demonstrated an excellent safety profile without a significant increase in infections or malignancies [83]. There have been no trials directly comparing ustekinumab to integrin receptor antagonists or TNFi agents, and the choice of first biologic is at the discretion of the patient and provider. Ustekinumab may be less effective in

patients who have failed TNFi therapy [84]. Both the ACG and ECCO guidelines support its use for both induction and maintenance of remission [6, 8].

Biosimilars

Biosimilar medications are highly structurally and clinically similar to an already FDA-approved originator product, and they undergo an accelerated and abbreviated FDA-approval pathway. These medications should present no differences in efficacy or safety compared to their originator compounds and have the advantage of lower cost. Biosimilars were approved for the treatment of IBD in September 2013 in Europe and in April 2016 in the USA.

Biosimilar TNFi agents are effective treatments for patients with moderate-to-severe CD and can be used for *de novo* induction and maintenance therapy. The major advantage of biosimilar therapy is cost. Five agents have gained approval for infliximab and adalimumab, with many more expected in coming years:

- Infliximab-abda
- Infliximab-dyyb
- Infliximab-qbtx
- Adalimumab-atto
- Adalimumab-adbm

While other generic small-molecule drugs are exact replicas, the same is not true for TNFi biosimilars. Exact replicas cannot be made of biologics because of their structural complexity and complicated manufacturing process. Their amino acid sequences remain the same, but they may differ in their glycosylation patterns. This influences a molecular solubility, stability, clearance, immunogenicity, and immune effector function [6, 55]. At present, there is not sufficient data to support the safety and efficacy of switching patients with stable disease from one biosimilar to another.

A large randomized, non-inferiority phase 3 clinical trial of patients with CD compared IFX to the biosimilar infliximab-dyyb in biologic naïve patients [85]. Patients were randomly assigned to receive infliximab-dyyb then infliximab-dyyb, infliximab-dyyb then IFX, IFX then IFX, or IFX then infliximab-dyyb; the medication switch occurring at week 30. A total of 220 patients were enrolled, and response rates at week 6 were similar for infliximab-dyyb [69.4%, 95% CI 59.9–77.8] and IFX [74.3%, 95% CI 65.1–82.2], establishing non-inferiority. Adverse events were similar in each group. There is still a significant paucity of data around interchangeability, limiting adoption at this time despite cost savings.

Induction and Maintenance of Remission

Principles of Induction Therapy

Mild Disease

Mild disease limited to the terminal ileum may be managed with symptom control and dietary changes or by using budesonide. Mesalamine and antibiotics have not been associated with significant benefit. For mild disease involving the colon, 5-ASA compounds or steroids can be used. Mild disease with upper gastrointestinal involvement should be treated initially with steroids and immunomodulators; for those with clinical features suggestive of a more aggressive phenotype, consideration should be given for early biologic therapy.

Moderate Disease

Moderate ileal disease should be treated with budesonide or steroids. If indicated for complications of local sepsis, antibiotics can also be added. Alternative strategies can include steroids plus an immunomodulator, early biologic therapy, or surgery. The LIR!C trial demonstrated that early laparoscopic resection may be considered a reasonable, cost-effective alternative to upfront infliximab therapy in patients with limited (< 30 cm), inflammatory (non-stricturing/non-penetrating) ileocecal Crohn's disease [86, 87].

Colonic disease should be treated with steroids or biologic therapy. In the setting of relapse, combination therapy with biologics and an IMM or an IMM with steroids (if relapses are infrequent) may be considered.

Severe Disease

Severe disease of the terminal ileum should be managed with biologic therapy with or without an IMM. Those with infrequent relapse may be treated with an IMM and steroids at the time of disease exacerbation. Early resection should also be considered. Colonic disease may be treated with steroids. Extensive upper gastrointestinal Crohn's disease should be managed with steroids and IMM. For patients who have relapsed, biologic therapy with or without combination therapy is an option.

Principles of Maintenance Therapy

Target to Treat

Recently, there has been a paradigm shift in the medical management of patients with IBD. Classically, treatment has focused on controlling symptoms with escalation of therapy and a "step-up" approach as the disease progresses or therapies fail. This escalation of therapy appears suboptimal with

respect prevention of disease progression. “Target to treat” is a shift toward to a more nuanced strategy, focusing on both control of symptoms and the objective signs of inflammation, that may occur before symptoms or complications develop. Inflammation can be assessed through blood and stool biomarkers such as fecal calprotectin and C-reactive protein (CRP), cross-sectional imaging, and endoscopy. Goals of care are built on minimizing disease activity in the early stages of IBD to avoid progressive bowel damage such as fibrostenotic or penetrating disease.

The goals for target to treat are a combination of patient-reported and clinical outcomes as described by the “Selecting Therapeutic Targets in Inflammatory Bowel Disease” [STRIDE] International Organization for the Study of Inflammatory Bowel Diseases. These outcomes are defined as resolution of abdominal pain and diarrhea or altered bowel habit, endoscopic remission defined absent ulceration at endoscopy, or findings of inflammation on magnetic resonance enterography (MRE) or CT-enterography. The patient-reported endpoints should be assessed at a minimum of 3 month intervals during active disease, and the endoscopic endpoints should be assessed at 6–9 month intervals [88]. Other adjunctive measures include histological remission, and biomarker remission defined as a normal CRP and fecal calprotectin; mucosal healing is inversely associated with risk of relapse, surgery, hospitalization, and inability to wean steroids [88–93].

The “Effect of Tight Control Management on Crohn’s Disease” [CALM] was a phase 3 multicenter study comparing a “tight control strategy” to symptom-driven care [93]. In the tight control arm, treatment was escalated with a CDAI >150, fecal calprotectin >250, CRP > 5, and prednisone use within the previous week. In the standard care cohort, treatment was escalated if there was not a decrease in the CDAI >70 or 100 (at randomization or post-randomization, respectively), a CDAI >200, or steroid use within the previous week. Tight control was associated with superior endoscopic remission and a lower rate of Crohn’s disease-related hospitalizations when compared to symptom-driven care.

General Principles of Maintenance Therapy

If maintenance was initially achieved with steroids that have been successfully weaned, consideration may be given to no therapy with close observation typically by a 6-month follow-up endoscopic reassessment looking for inflammation. Additionally, isolated disease in the appropriate patient can also be managed by surgical resection followed by a surveillance colonoscopy 6 months post-resection.

IMM monotherapy may also be considered, but oral 5-ASA compounds have not been consistently shown to be effective in maintenance of remission. If induction was achieved with biologic agents, maintenance should be

offered. However, combination therapy of biologics and IMM tend to have the best results. Annual endoscopy should be considered for those on biologic agents.

If patients experience a flair while taking a TNFi agent, drug concentrations and ADAs may be checked. Those with low drug level and low levels or absent ADAs may require higher dosing; those with high ADAs typically need to be switched to a different TNFi. Those with normal drug levels and no ADAs typically need to change to a new class of biologics for lack of response.

Therapeutic Drug Monitoring

Therapeutic drug monitoring (TDM) is the measurement of circulating levels of medications and ADA to inform therapy. The role of TDM in the management of transplant recipients has been well established; however, its role in patients with CD is emerging. While there is no definitive evidence to support routine TDM, there are clear theoretical advantages. Goals of care are based on maintaining medical remission while avoiding immunogenicity or loss of response. TDM would seemingly help in these endeavors as the trough concentrations of IMM and biologic therapy can vary. Factors effecting drug levels include disease severity, phenotype, degree of inflammation, combination therapy, patient sex, body mass index, and variability in drug clearance.

TDM can be done reactively following clinical evidence of active disease such as symptoms, endoscopic changes, elevation of CRP or fecal calprotectin, or proactively based on routine measurement done at set timepoints.

Patients usually become refractory to medical therapy for one of three reasons: lack of response, low drug concentrations, or development of ADAs. The AGA has clear guidelines for those on TNFi’s for maintenance therapy in the setting of disease recurrence (Fig. 46.2). Adequate trough levels are defined as $\geq 5\mu\text{g/mL}$ for IFX, $\geq 7.5\mu\text{g/mL}$ for ADA, and $\geq 20\mu\text{g/mL}$ for certolizumab pegol. However, there is no consensus of optimal trough concentrations, and those with perianal disease may require higher concentrations for efficacy:

- If the drug level is *normal*, then the dose should be increased or the medication changed
- If the drug level is *absent* or *low*, check ADAs:
 - If ADAs are *absent* or *low* assure compliance, then consider:
 1. Shorten the dosing interval
 2. Increase the dose
 3. Combination therapy with an immunomodulator
 - If ADAs are *high* then switch medications

High serum trough levels have been shown to be associated with mucosal healing. A retrospective study of 145

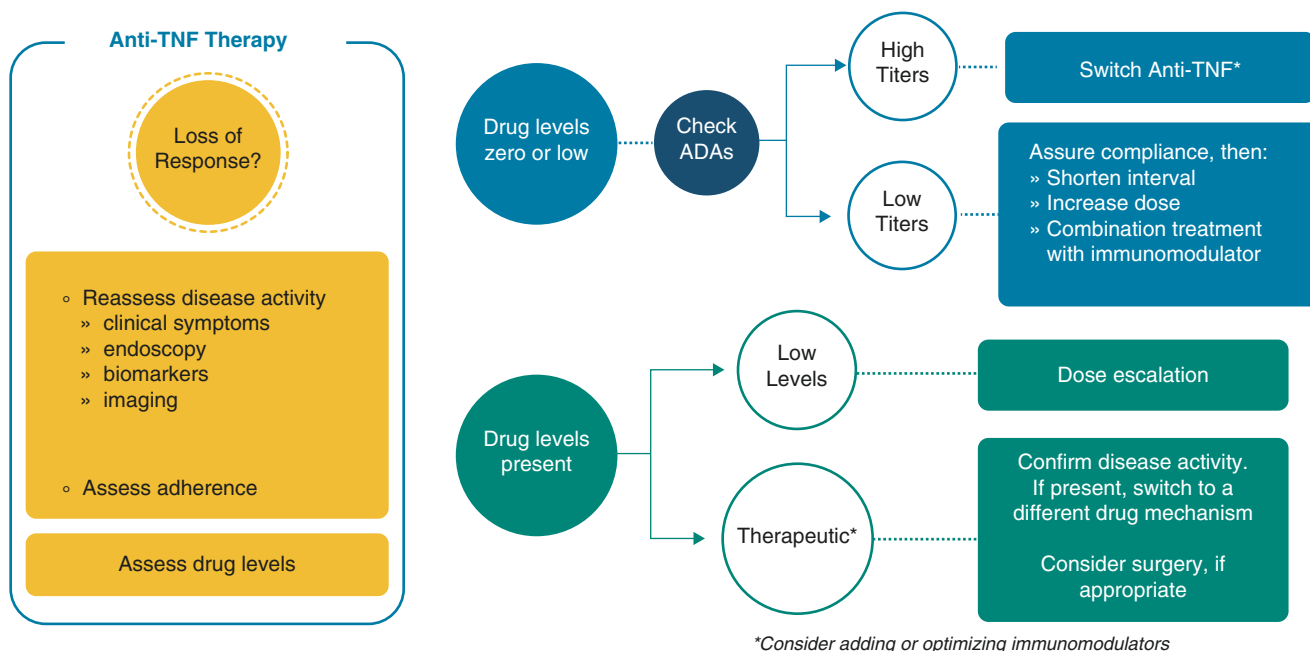


Fig. 46.2 Reactive therapeutic drug monitoring

patients over 5 years examined mucosal healing and associated this with trough levels of IFX and ADA at the same time points [94]. They found IFX levels $>5\mu\text{g/mL}$ and ADA levels $>7.1\mu\text{g/mL}$ identified patients with mucosal healing with 85% specificity. They also noted that higher levels of IFX and ADA beyond $8\mu\text{g/mL}$ and $12\mu\text{g/mL}$, respectively, conferred no significant additional benefit [7].

A post hoc analysis of ACCENT I [A Crohn's Disease Clinical Trial Evaluating Infliximab in a New Long-term Treatment Regimen I] evaluated the association between IFX trough concentrations and CRP at 14 weeks after induction treatment [95]. Patients with a durable sustained response had higher post-induction trough levels than patients without sustained response. Similarly, a study of 71 patients on ADA correlated high trough serum concentrations with remission [96].

Three large RCTs have been published on the role of TDM. Trough Concentration Adapted Infliximab [TAXIT] randomized 263 IBD patients on maintenance infliximab to dose adjustment for a target concentration of $3\text{--}7\mu\text{g/mL}$ versus empiric dosing [97]. All patients initially had a starting level of $3\text{--}7\mu\text{g/mL}$ and were dose adjusted if appropriate. The study found that those patients who required an increase in dosing to achieve target trough level had a higher rate of remission and a decrease in CRP. They also identified 67 patients who started at drug level $>7\mu\text{g/mL}$ and were able to be dose reduced. This translated to a 28% reduction in cost. TDM did not affect levels of clinical remission at 1 year, but patients did experience fewer flares.

A more recent double-blind RCT known as "Study Investigating Tailored Treatment with Infliximab for Active Crohn's Disease" [TAILORIX] included 122 biologic-naïve patients with active disease [98]. All patients underwent induction with combination therapy (immunomodulator plus IFX). At 14 weeks subjects were randomized to three groups: the control arm (dose increase 10 mg/kg based on clinical symptoms alone) or one of two dose intensification strategies based on clinical symptoms, biomarker analysis, and/or serum infliximab concentrations $<3\mu\text{g/mL}$. The authors found no benefit of TDM over symptom-guided management in achieving corticosteroid-free remission at 1 year. This study, however, was underpowered, and there was a very low threshold for dose escalation in the control arm.

The Pediatric Crohn's disease Adalimumab-Level-based Optimization Treatment [PAILOT] was a prospective study comparing proactive versus reactive TDM in pediatric patients [99]. The study included 78 biological-naïve children with CD who responded to adalimumab induction therapy and were then randomized to either proactive dose optimization (with a target of $5\text{--}10\text{ mg/mL}$) or reactive testing. They found that clinical improvement was significantly higher in the proactive group versus reactive TDM group.

De-escalation

When contemplating de-escalation of therapy, strong consideration should be given not only to disease control but also to the overall disease characteristics, prior treatment history,

tolerance to medications, and risk for adverse events. Some patients who are at lower risk for serious complications related to CD may benefit from de-escalation of medical therapy. This reduces the risk of immunosuppression and drug toxicity and can improve quality of life and provide for cost savings. De-escalation can mean moving from combination therapy to monotherapy or withdrawing medications completely. However, in the setting of subclinical inflammatory changes, de-escalation can increase the risk of flares, use of steroids, and hospitalizations and can lead to irreversible complications and surgery [100]. Patients discontinuing biologic therapy may develop drug resistance by producing ADAs, limiting future therapeutic options.

De-escalation of combination therapy can be considered in those with well-controlled disease with no prior Crohn's-related resections or significant complications related to their disease course (Fig. 46.3) or after surgical resetting of the clock. Those with upper GI tract CD, repeated penetrating complications, surgeries, or escalated dosing of TNFi's should not be considered for de-escalation. Once selected, patients have to be confirmed to be in deep remission defined by clinical symptoms, normal biomarkers, endoscopy with normal histology, or normal imaging of the small bowel for those with ileal disease. Surveillance after de-escalation includes clinical monitoring of inflammation every 12 weeks for a year with CRP and fecal calprotectin. Prior to de-escalation from biologics, consideration should be given to obtaining drug levels. If low, this suggests the biologic is probably not the source of remission and de-escalation is more likely to be successful.

If biomarkers start to rise, endoscopy or imaging should confirm recurrence, and other sources like infection should be ruled out. If recurrence of active Crohn's is confirmed, the previously successful maintenance medication should be restarted. If needed, budesonide or steroids can be provided as a bridge.

Postoperative Prophylaxis

Off medical therapy, the rate of endoscopic disease approaches 90% at 3 years, while clinical recurrence may reach 60% [101]. The goal of postoperative prophylaxis is medical maintenance of remission, as we know 50% of those who undergoing ileocolic resection will require additional surgery within 10 years [102].

After ileocolic resection, all patients should undergo endoscopic surveillance at 6–12 months [103]. Only one RCT has been performed pertaining to the timing of prophylaxis [104]. The study randomized patients to routine AZA starting early at 8 weeks or to endoscopically guided therapy at 6–12 months. This study found no difference in the two groups; however, potential flaws included mismatched cohorts, high attrition, low accrual, and the use of non-biologic therapy.

Many factors have been associated with the risk of postoperative recurrence, and more aggressive initiation of medication is recommended in these patients. Risk factors for early recurrence include younger patients, male gender, tobacco abuse, penetrating or fistulizing disease, prior operative intervention, and short disease duration. A recent meta-analysis demonstrated a significantly increased risk of postoperative recurrence (OR, 1.7; 95% CI, 1.3–2.1; $p < 0.001$) based on the presence of histopathologically positive margins or presence of plexitis (OR, 2.3; 95% CI, 1.1–4.9; $p = 0.02$) [105].

Numerous RCTs have examined which agent should be utilized for postoperative prophylaxis. Probiotics, 5-ASA, and budesonide show no benefit over placebo [67, 106–108]. Antibiotics may reduce recurrence; but the best evidence to prevent postoperative disease is monotherapy with either biologics or IMM. Early and aggressive prophylaxis is particularly important in patients with risk factors for recurrence. Those patients who are low risk for recurrence (e.g.,

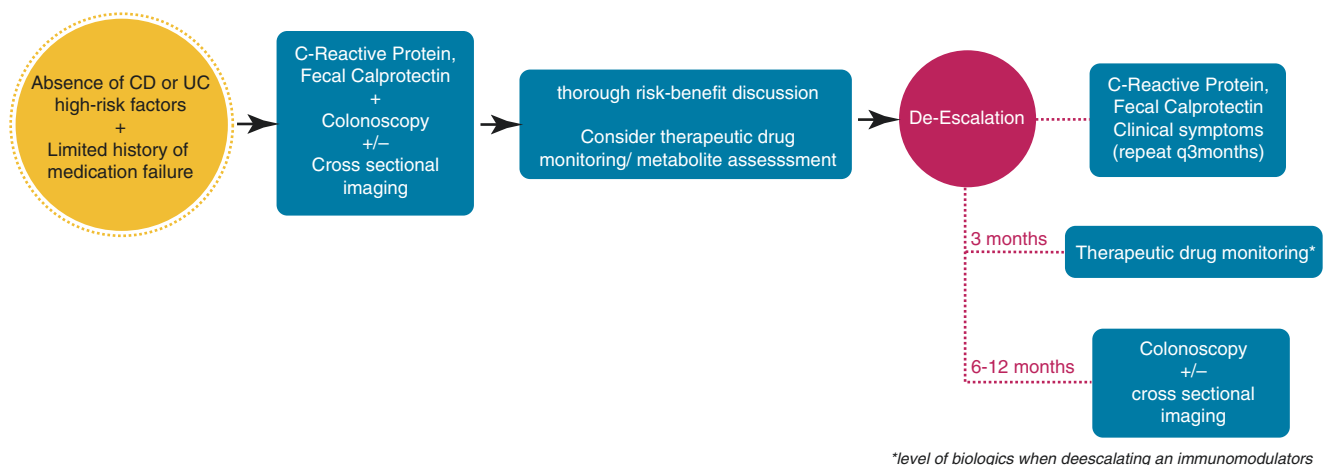


Fig. 46.3 De-escalation of therapy in IBD

isolated short segment ileocolic disease present for a long duration in an elderly non-smoker) can be surveilled 6–12 months after surgery off therapy.

Conclusions

The last two decades have seen unprecedented advances in the medical management of CD. All current strategies for therapy focus on symptom management and control of inflammation to prevent or slow bowel damage. As we improve our understanding of the disease, so too does the capacity to provide new, innovative, safer, and more effective therapies. The approach to medical management over the recent years has shifted to more proactive utilization of medications with targeted assessment to verify efficacy prior to the development of complications. The armamentarium of drug options has expanded considerably. However, the efficacy of these medications remains limited, and surgical intervention is still commonly required to manage complications and to improve or restore patient quality of life.

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