Medical Therapy for Inflammatory Bowel Disease

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KEYWORDS

• Inflammatory bowel disease • Crohn's disease • Ulcerative colitis • Fistula
• Fulminant colitis • Perioperative management

KEY POINTS

- The goal of medical treatment in inflammatory bowel disease (IBD) is to suppress inflammation and induce mucosal healing.
- There are multiple different classes of medications that are effective in IBD, many of which can be used concomitantly.
- The perioperative medical management of IBD can be challenging, and physicians must weigh the possible increased risk of surgical complications versus the potential for recurrent disease without appropriate therapy.

INTRODUCTION

Surgeons often care for patients with inflammatory bowel disease (IBD) who are receiving therapies that can include 5-aminosalicylic acid (5-ASA) compounds, steroids, immunomodulators, and biologics. The goal of these agents is to suppress intestinal inflammation, ultimately improving the quality of life in patients afflicted with IBD. Conventional IBD treatment paradigms have followed a stepwise treatment approach, with intensified therapies used only when symptoms are not resolved with an earlier treatment (**Fig. 1**). However, more recent data suggest that initiation of higher-tiered disease modification therapies early in the course of disease can modify disease progression and thus alter the natural history of IBD.

Initial IBD treatment is aimed at inducing remission, whereas subsequent therapies are chosen to maintain remission. Traditionally, an acceptable therapeutic endpoint was the resolution of symptoms, defined as clinical remission. However, as a result

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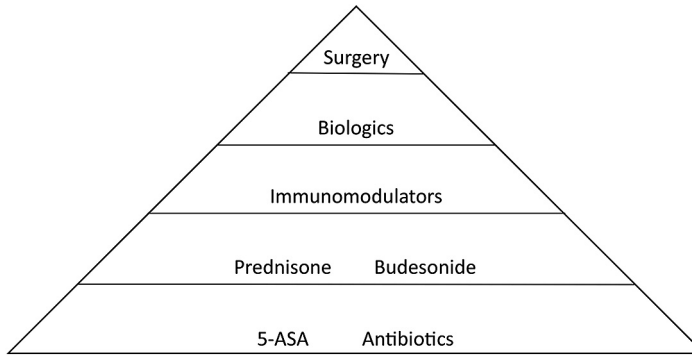

Fig. 1. A simplified approach to stepwise treatment of IBD.

of recent advances in therapy, clinicians can now strive to achieve more stringent endpoints, such as endoscopic and histologic remission. Although there is variability regarding the precise endoscopic and histologic criteria required to achieve mucosal healing, the concept of mucosal healing refers to the normalization of gut mucosa. Numerous studies have demonstrated that mucosal healing can reduce relapse rates as well as the need for corticosteroids, hospitalizations, and surgeries.[1–6] In addition, chronic colonic inflammation is a risk factor for colorectal cancer in patients with IBD.[7,8] Therefore, mucosal healing may also potentially decrease the risk for colorectal malignancy.

Many different classes of agents can be used, individually or in combination, to achieve mucosal healing. Treatment must be individualized based on the aggressive nature of a patient's disease, their treatment goals, and their tolerability of various medications. Recent data have illustrated a synergistic effect of combination therapy with biologics and immunomodulators,[9–12] which is used frequently for patients with more aggressive disease. Patients on advanced therapies require special care, counseling, and consideration with regards to not only efficacy of the drugs but also adverse effects as well as the perioperative and peripartum use of these medications.

INFLAMMATORY BOWEL DISEASE MEDICATIONS

5-Aminosalicyclic Acid Compounds

5-ASA compounds are a class of medication used for the induction and maintenance of remission in patients with IBD. They have been the traditional first-line therapy in the treatment of mild to moderate ulcerative colitis (UC); efficacy in Crohn's disease (CD) remains controversial.

Action and metabolism

Sulfasalazine, oral mesalamine (Pentasa, Asacol HD, Delzicol, Lialda, and Apriso), rectal mesalamine (Rowasa and Canasa), olsalazine, and balsalazide are drugs that deliver 5-ASA to various parts of the gut (**Table 1**). Sulfasalazine, the first drug developed in this class, is a prodrug composed of 5-ASA and sulfapyridine that was originally proposed as a treatment for rheumatoid arthritis. It was soon discovered to be effective in the treatment of IBD. Isolation of the active 5-ASA compound was undertaken because most adverse effects patients experienced were secondary to the sulfapyridine moiety. As a result, multiple other formulations have been developed for use in IBD, many of which target different areas of the gastrointestinal tract. The precise mechanism responsible for the clinical efficacy of the 5-ASA compounds is unknown,

Table 1
5-Aminosalicyclic acid compounds

Generic Name	Trade Name	Formulation	Sites of Delivery
Mesalamine	Rowasa	Enema suspension	Rectum to splenic flexure
	Canasa	Suppository	Rectum
	Pentasa	Ethylcellulose-coated granules	Duodenum, jejunum, ileum, colon
	Asacol HD	Eudragit-S-coated tablets (dissolves at pH $\geq$7)	Terminal ileum, colon
	Delzicol	Eudragit-S-coated tablets (dissolves at pH $\geq$7)	Terminal ileum, colon
	Apriso	Enteric coating around polymer matrix (dissolves at pH $\geq$6)	Terminal ileum, colon
	Lialda	Enteric coating around polymer matrix (dissolves at pH $\geq$7)	Terminal ileum, colon
Olsalazine	Dipentum	5-ASA dimer linked by azo bond	Colon
Sulfasalazine	Azulfidine	5-ASA dimer linked to sulfapyridine by azo bond	Colon
Balsalazide	Colazal	5-ASA dimer linked to inert carrier by azo bond	Colon
	Giazo	5-ASA dimer linked to inert carrier by azo bond	Colon

although they are thought to act topically. One proposed mechanism is the inhibition of cytokine synthesis by upregulating peroxisome proliferator activated receptor-$\gamma$and its target genes, which in turn suppresses the activation of Nuclear factor-kappa beta (NFkB) and toll-like receptors. It is also thought to inhibit the biologic functions of proinflammatory cytokines interleukin (IL)-1, tumor necrosis factor-α (TNF-α), IL-2, IL-8, and NFkB.[13–15] 5-ASA compounds have also been shown to inhibit both cyclo-oxygenase and lipoxygenase enzymes in arachidonic acid metabolism, thereby preventing formation of proinflammatory prostaglandins and leukotrienes.[16–20] Other proposed mechanisms of action include antioxidant activity, immunosuppressive activity, and impairment of white cell adhesion and function.[21–26]

Efficacy

A large, systemic review of 11 randomized controlled trials (RCTs) revealed 5-ASA compounds to be effective at both inducing and maintaining remission in mildly to moderately active UC, especially when doses of 2.0 g/d or greater were used.[27] In contrast, the role of 5-ASA compounds in the induction or maintenance of remission CD remains uncertain, as the preponderance of data does not show benefit.[28]

Safety

Adverse reactions and toxicity are common with sulfasalazine, with about 20% to 25% of patients discontinuing the drug secondary to side effects. Most common dose-related adverse reactions include headache, epigastric pain, nausea and vomiting, and rash. Rare idiosyncratic reactions include hepatitis, fever, autoimmune hemolysis, aplastic anemia, agranulocytosis, and pancreatitis. These reactions should result in immediate discontinuation of the drug. Patients on sulfasalazine should be supplemented with folic acid because it can cause a deficiency resulting in megaloblastic anemia. It is also known to cause reversible oligospermia, but is safe in pregnancy

and breast-feeding.[29,30] Mesalamine, olsalazine, and balsalazide are generally better tolerated that sulfasalazine. Headache, nausea, and abdominal pain are the most common side effects. The 5-ASA compounds can also rarely cause a paradoxic worsening of colitis, which would warrant drug discontinuation. In addition, olsalazine can induce a secretory diarrhea that can be controlled with gradual dose titration or administration with food.[31] Serious adverse events, such as hepatitis, pancreatitis, or interstitial nephritis, can also occur.[32,33] Like sulfasalazine, mesalamine, olsalazine, and balsalazide are safe in pregnancy and breast-feeding.

IMMUNOMODULATOR THERAPY

Thiopurines and methotrexate are commonly used immunomodulator therapies. Cyclosporine has a role in fulminant colitis.

Thiopurines

Action and metabolism

The thiopurine analogues azathioprine and 6-mercaptopurine (6-MP) gained widespread acceptance as established treatments for IBD in the early 1980s. These medications work through multiple mechanisms to control the dysregulated immune response in IBD. The thiopurine metabolite 6-thioguanine is a purine antagonist and therefore interferes with DNA and RNA synthesis. The reduction in DNA and RNA synthesis inhibits the proliferation of T and B lymphocytes.

Azathioprine is converted to 6-MP by a nonenzymatic reaction occurring within erythrocytes. There is significant genetic variation in thiopurine S-methyltransferase (TPMT) enzymatic activity and determining enzyme activity before initiation can help guide dosing (**Fig. 2**). TPMT testing, however, does not preclude the need for

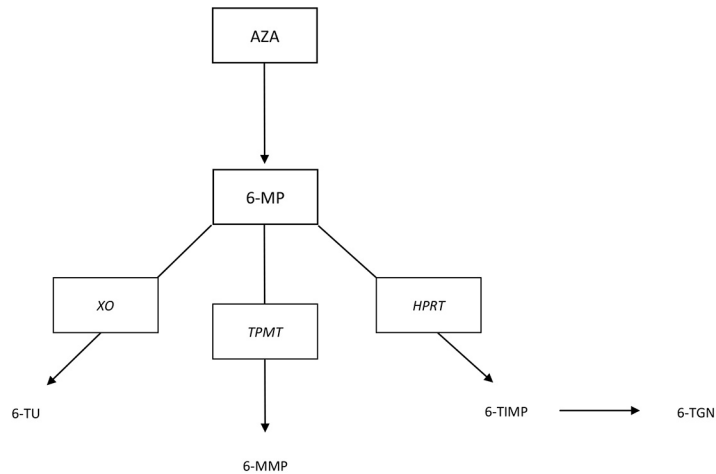

Fig. 2. A simplified approach to azathioprine (AZA) metabolism. TPMT breaks down 6-MP into the hepatotoxic metabolite 6-methylmercaptopurine (6-MMP). Besides TPMT metabolism, there are 2 other major pathways from 6-MP that should be considered. One is driven by the hypoxanthine phosphoribosyl transferase (HPRT) enzyme, leading to 6-thioguanine nucleotide (6-TGN), the metabolite responsible for the therapeutic benefit in inflammatory bowel disease and myelosuppression. The other pathway is driven by xanthine oxidase (XO), leading to production of 6-thiouric acid (6-TU), an inactive metabolite. 6-TIMP, 6-thioinosine monophosphate.

monitoring for hepatotoxicity or leukopenia. Although enzyme testing is expensive, it has been shown to reduce long-term costs from inappropriate dosing.[34,35]

Efficacy

Azathioprine and 6-MP promote clinical remission and steroid sparing in patients with IBD.[36] A recent *Cochrane Database Systemic Review* showed an odds ratio (OR) of 2.43 (95% confidence interval [CI], 1.62–3.64) for response in patients with CD who were treated with azathioprine or 6-MP compared with placebo. The steroid-sparing effect was also significant, with an OR of 3.69 (95% CI, 2.12–6.42).[37] Earlier data estimated that one-half to two-thirds of patients will respond to thiopurine treatment. Thiopurines have a delayed onset of action, requiring at least 3 to 4 months for a clinical benefit.[36]

Side effects

The side-effect profiles of azathioprine and 6-MP are significant, and 9.3% of patients develop adverse effects serious enough to stop therapy.[36] Allergic reactions include fever, rash, arthralgias, and pancreatitis; these are dose independent and resolve with discontinuation of the drug. Acute pancreatitis can be seen in 3% to 7% of patients, typically during the first month of treatment. Chronic pancreatitis attributable to azathioprine or 6-MP has not been reported.[38,39] Switching between azathioprine and 6-MP may help obviate side effects. However, patients who develop acute pancreatitis while taking either agent should be considered intolerant to both medications.

Myelosuppression is an important and potentially lethal complication of thiopurine therapy, and the white cell line is most commonly affected. Although typically associated with low TPMT enzyme activity, myelosuppression can also occur with normal enzymatic activity. Hepatotoxicity can be seen in up to 2% of patients and is typically caused by increased synthesis of 6-methylmercaptopurine.[40] Both myelosuppression and hepatotoxicity are dose-dependent responses, and management consists of dose reduction and possibly drug cessation.

For many patients and physicians, the most alarming adverse effect associated with thiopurine therapy is the potential risk of malignancy; the strongest associations have been linked with lymphoma and nonmelanoma skin cancer. A recent analysis of almost 20,000 French patients suggested that the risk of lymphoma in patients with IBD who were receiving thiopurines increased from 0.26 to 0.9 per 1000 patient-years, with a multivariate hazard ratio of 5.28 (95% CI, 2.01–13.9).[41] Furthermore, there have been 36 case reports of hepatosplenic T-cell lymphoma associated with thiopurine use, which most commonly occurs in young men and is usually fatal. Twenty of these cases were associated with the concomitant use of biologic therapy, and 16 involved thiopurine use alone.[42] A study of patients taking thiopurines for greater than 1 year showed a relative risk of 4.27 (95% CI, 3.08–5.92) for the development of nonmelanoma skin cancer. This risk further increased in those taking dual therapy with thiopurines and anti-TNF biologics.[43] Patients should ensure regular use of sunscreen during sun exposure and have annual skin examinations by their primary care provider or dermatologist.

Methotrexate

Action

Methotrexate was pioneered for the treatment of rheumatoid arthritis in the 1950s. It should be considered an alternative to thiopurines. Methotrexate has numerous anti-inflammatory effects, including blocking production of IL-1, IL-2, IL-6, and IL-8.[44]

Efficacy

RCTs have shown the efficacy of methotrexate in the induction and maintenance of remission in CD.[45–47] Based solely on existing data, methotrexate cannot be considered a major treatment of UC. For active UC, a single RCT including 67 patients showed similar remission rates after 4 months between the oral methotrexate group and the placebo group.[48] However, this study was limited in size and its use of oral methotrexate. In clinical practice, methotrexate is frequently successful in treating UC. A large RCT is currently ongoing to determine the efficacy of high-dose subcutaneous methotrexate in patients with UC. A clinical response can be expected within 8 weeks of starting therapy.[45]

Side effects

Although usually well-tolerated, the side-effect profile of methotrexate includes nausea, stomatitis, diarrhea, hair loss, leukopenia, interstitial pneumonitis, and hepatic fibrosis. Nausea is the most common side effect and usually improves with time. It is frequently managed supportively with ondansetron. Furthermore, daily folic acid can reduce nausea as well as stomatitis. Although the risk of hepatic fibrosis is low in patients with IBD, cirrhosis is the most worrisome adverse effect of methotrexate. The risk of cirrhosis is directly related both to the cumulative exposure to methotrexate and to the presence of other risk factors for liver disease. Therefore, patients with a history of excessive alcohol use and nonalcoholic fatty liver risk factors (eg, diabetes, obesity, hyperlipidemia) should avoid methotrexate. Elevated aminotransferase levels do not always correlate with the presence of hepatic fibrosis, and a liver biopsy should be considered if there is reasonable clinical suspicion for hepatic fibrosis, particularly if the cumulative dose has exceeded 1.5 g.[49] Methotrexate has high abortifacient and teratogenic effects, and patients should be counseled appropriately.

In general, potentially hepatotoxic and myelosuppressive medications should be avoided with methotrexate. Furthermore, the concurrent use of nonsteroidal anti-inflammatory drugs can increase methotrexate concentrations, thus increasing the risk of methotrexate toxicity.

Cyclosporine

Actions and characteristics

The development of cyclosporine greatly improved the success of solid organ transplantation. Cyclosporine selectively inhibits calcineurin, thus downregulating the transcription of many inflammatory cytokines (most notably IL-2) and reducing the proliferation of lymphocytes. The dramatic success of cyclosporine in organ transplantation has led investigators to explore its use in the treatment of immune-related disease. Over the last 2 decades, cyclosporine has been used in UC for the treatment of severe or fulminant colitis refractory to corticosteroids.

Efficacy

Cyclosporine was first shown to be an effective rescue or salvage therapy in corticosteroid-refractory UC in 1994 when a small, randomized placebo controlled trial showed that 9 of 11 patients treated with cyclosporine 4 mg/kg responded well enough to avoid colectomy, compared with 0 of 9 patients in the placebo arm. A comparison of 4 mg/kg versus 2 mg/kg continuous infusion showed that there was no difference in the response rate (approximately 85%) in each group.[50] Overall, studies have shown short-term response rates ranging from 64% to 100% and colectomy-free survival rates of 14% to 55% within 3 to 7 years.[51] A systematic review and meta-analysis in 2013 showed that cyclosporine and infliximab were comparable in

3-month and 12-month colectomy rates, adverse drug reactions, and postoperative complications in patients with fulminant colitis.[52]

In contrast to UC, the data do not support its efficacy in CD. Three large controlled trials illustrated that low-dose (5 mg/kg/d) oral cyclosporine is ineffective for both induction and maintenance of remission in CD.[53–55] Although there are no controlled trials with intravenous cyclosporine in CD, these trials are unlikely to be performed in the era of biologic therapy.

Safety

The side effects of cyclosporine can be significant. Trough levels between 150 and 250 ng/mL are recommended. Patients' renal function, magnesium levels, and cholesterol should be assessed before starting therapy. Patients should be carefully monitored for cyclosporine-induced hypertension, tremor, seizures, renal insufficiency, hypercholesterolemia, hypomagnesemia, and opportunistic infections.[56]

BIOLOGIC THERAPY

Tumor Necrosis Factor Antagonists

Actions and characteristics

Infliximab, adalimumab, golimumab, and certolizumab pegol are biologic agents that target TNF activity, decreasing mucosal inflammation through multiple mechanisms. Infliximab is a chimeric immunoglobulin (Ig) G1 antibody that binds to TNF, and in the late 1990s, it was the first biologic approved for use in IBD. It is administered intravenously. Adalimumab and golimumab are humanized IgG1 antibodies that bind to TNF and are administered subcutaneously. Certolizumab pegol is a pegylated Fab fragment an anti-TNF monoclonal antibody and also is given as a subcutaneous injection.

Efficacy

Sixty percent of patients will clinically respond to anti-TNF treatment within 2 to 6 weeks of initiation.[57] Multiple trials have shown that induction dosing with regular maintenance dosing, compared with intermittent dosing based on symptoms, ensures the highest efficacy and prevents loss of response. Nonetheless, response declines in 30% to 50% of initial responders while on maintenance therapy within 1 to 3 years. Loss of response can be attributed to the formation of antibodies, altered pharmacokinetics, or changes in the dominant mechanism of inflammation.[57] Antibody and metabolite testing of anti-TNF agents can better characterize loss of response and guide further management. When patients decompensate clinically without evidence of active inflammation on endoscopy, other processes such as a stricture, enteric infection (eg, *Clostridium difficile*), and concomitant irritable bowel syndrome should be considered. Anti-TNF treatment also has been found to be efficacious in the long-term treatment of fistulas associated with CD.[58–60]

Side effects

Reactions at the sites of subcutaneous injection (adalimumab, certolizumab, and golimumab) and intravenous infusion (infliximab) can occur during biologic therapy. Patients who have developed anti-infliximab antibodies are most prone to infusion reactions and can present with a syndrome of chest pain, dyspnea, rash, and hypotension.[58,61] A delayed hypersensitivity reaction, occurring within a few days to 2 weeks after infusion, can also occur. Symptoms include severe polyarthralgia, myalgia, facial edema, urticaria, and rash.[62] General management includes supportive care and a short course of oral steroids. Infections are a dreaded complication of anti-TNF therapy, and the use of concomitant immunosuppressants can increase infection risk.

There is an overall 2% to 4% risk of serious infection in the major trials of the anti-TNF agents.[62–64] Fungal, atypical, and mycobacterial (eg, reactivation of tuberculosis) infections should be considered in the workup of these patients. A chest radiograph along with hepatitis B and tuberculosis testing are mandatory before beginning treatment. Data on whether biologic therapy poses an increased risk for lymphoma are conflicting, but the preponderance of the data suggests that the increased risk for lymphoma from IBD therapy is principally attributable to thiopurines.[65,66] The formation of antinuclear antibodies and anti-double-stranded DNA can also occur with the use of anti-TNF biologic therapy over the long term.[11] Although drug-induced lupus is a possible side effect, the mere presence of antibodies is not pathogenic. Central and peripheral demyelination and polyneuropathy are uncommon neurologic side effects of anti-TNF biologic therapy.[67]

Anti-adhesion Molecules

Actions, characteristics, and efficacy

Natalizumab is a humanized monoclonal antibody that antagonizes both the α-4 β-1 and the α-4-β-7 integrins, blocking leukocyte adhesion and migration into areas of inflammation in both the central nervous system and the gastrointestinal tract. Data have shown efficacy for moderate to severe CD.[68,69] Natalizumab is US Food and Drug Administration–approved for inducing and maintaining clinical remission in adult patients with moderate to severe CD after failure of anti-TNF inhibitors.

Vedolizumab is also a humanized monoclonal antibody that targets only the α-4 β-7 integrin, which is limited to the gastrointestinal and nasopharyngeal mucosa.[70] It was found to be effective in both induction and remission therapy for UC and CD.[70–74] It also demonstrated efficacy for inducing clinical remission and mucosal healing. Vedolizumab is approved for the treatment of adult patients with moderate to severe IBD after failure of one or more standard therapies (corticosteroids, immunomodulators, or TNF antagonist). Given its impressive efficacy in UC, it is also being used as first-line therapy for maintenance of remission in patients with moderate to severe UC.

Side effects

Concerns over progressive multifocal leukoencephalopathy (PML) due to John Cunningham (JC) virus reactivation have prevented routine use of natalizumab as a therapy for IBD. Although the α-4 β-7 integrin subunit is relatively gut-specific, the α-4 β-1 subunit is present in numerous tissues, including the central nervous system. As a result, natalizumab affects leukocyte trafficking into the central nervous system, thereby increasing the risk of PML. This risk, along with hepatotoxicity, has reserved use of this biologic for only specific cases. Antibody testing for JC virus before initiating therapy, as well as during therapy, is recommended.[75]

In contrast, vedolizumab has been well tolerated in patients with either UC or CD, with no cases of PML in more 3000 patients.[76] As one could surmise based on the mechanism, the incidence of gastrointestinal and nasopharyngeal infections was higher with vedolizumab than with placebo.[74]

Overall, biologic therapies have few absolute drug-drug interactions. However, the risks and benefits of concomitant immunosuppressant use should be carefully considered.

CORTICOSTEROIDS

Actions and Characteristics

Corticosteroids, like many of the other drugs used in the treatment of IBD, were first developed to treat rheumatoid arthritis. Corticosteroids work by inhibiting almost

every aspect of the immune response. They inhibit expression of adhesion molecules and trafficking of inflammatory cells of all target tissues, including the intestines. They also induce apoptosis of activated lymphocytes and decrease expression of inflammatory cytokines.[77–81] As early as 1954, an RCT demonstrated efficacy of cortisone in UC. Because of this, systemic corticosteroids continue to remain widely used for the induction of remission and treatment of acute exacerbations of UC and CD. However, their long-term use has been limited by their adverse effects. The side-effect profile associated with systemic corticosteroids prompted the development of 2 oral preparations of budesonide: the controlled ileal-release preparation (Entocort), and multimatrix system colonic delivery form known as budesonide multi-matrix system (MMX) (Uceris). Budesonide has an extensive first-pass hepatic metabolism, and therefore, a lower systemic bioavailability compared with prednisone.[82] Given their targeted delivery, budesonide and budesonide MMX may be able to achieve many of the beneficial effects of systemic corticosteroids with a lower adverse event profile.[83–85]

Efficacy

A large systematic review of 5 RCTs involving 445 patients found that both oral systemic corticosteroids and budesonide were effective at inducing remission in active UC with a number needed to treat of 3. In the corticosteroid arm, 46% of patients achieved remission, compared with 21% with placebo.[86] For the induction of remission in active CD, an analysis of 2 RCTs showed the efficacy of oral corticosteroids, with remission rates of 60% compared with 31% with placebo.[87,88] In a systematic review comparing traditional corticosteroids to budesonide in the treatment of active CD, budesonide was not quite as effective as standard corticosteroids at inducing remission, but had a better adverse event profile.[86] Despite efficacy in the induction of remission, there are no data to support the use of either traditional or second-generation corticosteroids for the maintenance of remission in IBD.

Safety

The side effects of corticosteroids have been well described. Short-term adverse effects include immunosuppression, glaucoma, fluid retention, hypertension, hyperglycemia, weight gain, and psychiatric illness.[89–92] Long-term consequences can also include decreased bone mineral density, cataracts, adrenal insufficiency, impaired wound healing, and diabetes mellitus.[93] Patients who have had long-term exposure to corticosteroids should be screened with a dual-energy radiograph absorptiometry scan. Second-generation corticosteroids, such as budesonide and budesonide MMX, have less systemic bioavailability than systemic steroids and are generally well-tolerated with minimal corticosteroid-related clinical effects.[94–96] However, caution should be exercised in patients with cirrhosis, where systemic bioavailability is increased by 2.5-fold,[97] as well as those on prolonged courses of budesonide.[98]

FISTULIZING CROHN'S DISEASE

The transmural inflammatory nature of CD predisposes to the formation of fistulae, a complication indicating a more aggressive and refractory disease phenotype.[99] Neither oral nor topical 5-ASA compounds have any utility in the treatment of fistulizing CD. Antibiotics (most commonly ciprofloxacin and metronidazole) have commonly been used in the treatment of enterocutaneous and perianal fistulae and are often effective at improving symptoms.[100,101] However, there are no placebo-controlled studies of oral antibiotics to demonstrate fistula closure. In addition, discontinuation

of antibiotics leads to a high rate of recurrence.[102] A randomized placebo-controlled trial of topical metronidazole did not show a significant improvement in fistula closure, but did improve perianal discharge and pain.[103]

The data also suggest that azathioprine and 6-MP are effective in perianal fistula closure. This effectiveness has only been examined as a secondary endpoint,[38] and the advent of biologic therapy has resulted in a scarcity of clinical trials examining the efficacy of thiopurine therapy for fistulizing CD.[104] There are minimal data evaluating the efficacy of methotrexate for fistulizing CD.

TNF antagonists are the mainstay of medical therapy in fistulizing CD. The first RCT to demonstrate their efficacy randomized 94 CD patients with either abdominal or perianal fistulas to 3 months of treatment with placebo, 5 mg/kg, or 10 mg/kg of infliximab with standard dosing intervals. Reduction of draining fistulae by at least 50% was seen in 26% in the placebo group, compared with 68% and 56% in the infliximab 5 mg/kg and 10 mg/kg groups ($P = .002$ and $P = .02$). Complete closure of all fistulas was seen in 55% in the 5 mg/kg and 38% in the 10 mg/kg infliximab groups, compared with only 13% in the placebo group.[105] Follow-up studies confirmed the greater than 50% efficacy noted in this landmark trial.[106,107] Efficacy of adalimumab for perianal fistula closure, even in patients that are refractory to infliximab, has also been demonstrated.[59,108–110] Although limited data suggest a possible benefit for fistula closure with vedolizumab and natalizumab,[74,111] there is not enough evidence to recommend integrin inhibitors for fistulizing CD.

In summary, fistulizing CD is an aggressive phenotype, and medical therapy should involve a TNF inhibitor with strong consideration of concomitant treatment with a thiopurine. Metronidazole and ciprofloxacin can provide temporary benefit until combination therapy takes full effect.

FULMINANT COLITIS

Fulminant colitis secondary to IBD is a clinical scenario in which the surgeon should be intimately involved. It is more commonly described in UC, but can occur in CD as well. Despite the complexities and challenges that these patients present, the approach is simple: aggressive medical management, and early surgery in nonresponders.[112]

The cornerstone of initial therapy is intravenous corticosteroids with a dose equivalent to 60 mg methylprednisolone daily (which can be given either as a continuous infusion or in separate doses). Studies investigating higher doses have failed to show additional benefit with an increased risk of adverse effects.[113] The time period that one could be considered a nonresponder to corticosteroids is debated among experts, but generally ranges between 5 and 10 days.[112,114,115] Between 30% and 40% of patients with fulminant colitis do not respond to intravenous corticosteroids. For this group of patients, the decision to intensify medical treatment or proceed with surgery should be a joint discussion between the patient, gastroenterologist, and surgeon.[112]

For those patients who do not respond to corticosteroids, rescue therapy with infliximab or cyclosporine should at least be considered before surgery. The one open-label RCT directly comparing infliximab (5 mg/kg on days 0, 14, 42) and cyclosporine (2 mg/kg/d for 1 week, followed by oral medication until day 98) showed them to be similar in efficacy and adverse event profile. Despite some success, treatment failure (defined by the absence of a clinical response at day 7, a relapse between day 7 and day 98, absence of steroid-free remission at day 98, severe adverse event leading to treatment interruption, colectomy, or death) occurred in 54% and 60% of patients on infliximab and cyclosporine, respectively.[116] A systemic review and meta-analysis

comparing cyclosporine and infliximab for the treatment of fulminant colitis showed a comparable 3-month colectomy rate (OR = 0.86, 95% CI = 0.31–2.41, P = .775), 12-month colectomy rate (OR = 0.60, 95% CI = 0.19–1.89, P = .381), rate of adverse events (OR = 0.76, 95% CI = 0.34–1.70, P = .508), and postoperative complication rate (OR = 1.66, 95% CI = 0.26–10.50, P = .591).[52] A recent retrospective study, however, found the colectomy rates at 1, 2, and 3 years to be higher in the cyclosporine group. Predictive factors for cyclosporine failure included extensive disease, elevated C-reactive protein, and lack of azathioprine treatment.[117] One small series of 19 patients showed that initial failure of either infliximab or cyclosporine followed by treatment with the other drug resulted in approximately 70% of patients undergoing colectomy in 12 months.[118] Thus, it is generally advisable to proceed to colectomy after failure of either cyclosporine or infliximab.

Despite the inclusion of broad-spectrum antibiotics in many treatment protocols for fulminant colitis, controlled trials investigating oral vancomycin, intravenous metronidazole, and intravenous ciprofloxacin in the absence of proven infection have failed to show therapeutic benefit.[119–121] However, given the rising prevalence of *C difficile* in IBD patients,[122] and the variable sensitivity of available diagnostic modalities,[123] empiric treatment can be considered if clinical suspicion exists.

PERIOPERATIVE CONSIDERATIONS

Despite advances in medical management, surgical intervention is still necessary in many patients with IBD. The operative management of CD is generally reserved for patients who have an obstructing fibrotic stricture, perforation, cancer, or fistulae or active luminal inflammation refractory to medical management. Indications for surgery in UC include fulminant colitis, dysplasia, neoplasia, medically intractable disease, and patient preference. The perioperative medical management of IBD has become especially challenging as the paradigm of treatment of IBD has shifted to more advanced immunosuppressive therapies.

Patients who are malnourished, are greater than 60 years of age, require emergent surgery, or have penetrating disease have increased perioperative morbidity.[124] The nature of the surgical procedure is also an important factor in perioperative morbidity. For example, total proctocolectomy (TPC) with J pouch is more likely to result in postoperative infection when compared with TPC with ileostomy. Laparoscopic surgery has consistently been associated with decreased postoperative length of stay and complication rate when compared with open procedures.[125]

Consideration should also be given to whether UC or CD is the underlying disease process. In UC, the most common surgery, TPC with ileal pouch-anal anastomosis (IPAA), is theoretically curative, which tends to simplify postoperative medical therapy. Conversely, when CD patients progress to surgery, decisions regarding perioperative and postoperative medical therapies pose more of a challenge. Most patients with CD who progress to surgery will require continued immunosuppressive therapy postoperatively. Perioperative management of immunosuppressive therapy needs to be individualized. Physicians must weigh the possible increased risk of surgical complications versus the potential for recurrent disease without appropriate therapy.

Immunomodulators

The data for perioperative use of azathioprine and 6-MP are sparse and unfortunately conflicting in regards to postoperative infectious complications. A retrospective cohort study of 159 patients with IBD undergoing elective bowel surgery evaluated the risk of postoperative infections in 3 groups of patients: corticosteroids alone,

thiopurines (with or without corticosteroids), and neither thiopurines nor corticosteroids. Although the preoperative use of corticosteroids was associated with increased risk of postoperative infections (OR 3.69, 95% CI 1.24–10.97), the use of thiopurines was not (OR 1.68, 95% CI 0.65–4.27).[126] Conversely, prospective data from 343 consecutive patients with CD who underwent abdominal operations at a single tertiary referral center showed that thiopurine therapy was associated with an increase in intra-abdominal septic complications.[127]

Both azathioprine and 6-MP have some renal elimination, which harbors the potential for toxic metabolite accumulation in patients with decreased glomerular filtration. In rare circumstances, this could lead to severe myelotoxicity.[128] The authors recommend discontinuing thiopurines a day before surgery with resumption no sooner than 3 days after surgery.[124] The limited data investigating perioperative infectious complications on methotrexate are focused on orthopedic surgery in the rheumatoid arthritis population, not patients with IBD. Moreover, these data are conflicting, are of poor quality, and do not sufficiently address the risks of myelosuppression, pneumonitis, hepatotoxicity, and nephrotoxicity during the perioperative period. Therefore, the authors recommend that in patients with a history severe septic complication, it may be reasonable to discontinue methotrexate 1 week before surgery and resume it no sooner than 1 week after surgery.[124]

Cyclosporine is most typically used in patients with corticosteroid-refractory UC as a rescue therapy before colectomy. The most worrisome adverse effects of cyclosporine in the perioperative setting are nephrotoxicity and opportunistic infections. Mortalities secondary to opportunistic infections as high as 3.5% have been reported,[129] and prophylaxis of *Pneumocystis jiroveci* with trimethoprim-sulfamethoxazole should be considered.[124] Multiple small case series exploring the use of preoperative cyclosporine in UC have not shown an increase in adverse events during and after surgery.[130–132] Unfortunately, current clinical data are insufficient for further recommendations regarding cyclosporine in the perioperative period in CD; however, patients being treated should be closely monitored for deterioration in renal function and opportunistic infections.[124]

Biologics

Infliximab is the most widely studied biologic therapy for IBD. Although there is some conflicting evidence, the vast majority of data suggest that infliximab (and by extension the other TNF-α inhibitors adalimumab, certolizumab pegol, and golimumab) does not seem to increase peri-postoperative complications in IBD.

One study evaluated 45 patients who were randomized to infliximab or placebo after a failed trial of corticosteroids for severe or fulminant UC. Seven of the patients in the infliximab group and 14 in the placebo group required a colectomy within 3 months. There was no increase in the postoperative complication rate in the infliximab arm. In fact, 3 patients in the placebo group (compared with none of the infliximab-treated patients) required operation for septic complications.[133]

Although infliximab has decreased the rates of surgeries in patients with UC,[106] many were concerned that it merely delayed (but did not prevent) surgical intervention. Postponing surgery in this manner would lead to performing surgeries in patients who are more chronically ill, therefore increasing the risk of emergent procedures with associated greater morbidity and mortality.[134,135] To answer this question, Bordeianou and colleagues[136] retrospectively compared outcomes in 44 patients on infliximab with medically refractory UC undergoing a TPC or subtotal colectomy with 127 patients with a similar disease severity without exposure to biologic therapy. Infliximab exposure did not seem to affect the rate of emergent surgery (4.5% vs 4.4%, $P = .98$),

rate of subtotal colectomy (19.2% vs 18.0%, $P = .99$), or rate of ileoanal J-pouch reconstruction (53.8% vs 62%, $P = .98$). Intraoperative findings such as perforation, toxic megacolon, and active disease were similar in both groups. Furthermore, short-term postoperative complications, defined as within 30 days of loop ileostomy closure in TPC and IPAA, have been shown to be comparable in perioperative infliximab and non-infliximab-treated patients.[137] Thus, the preoperative use of infliximab does not seem to increase surgical morbidity or mortality in UC.

Most of the data in CD show a similar safety profile. A cohort study compared 40 patients with CD on infliximab before intestinal resection (more than 75% within 12 weeks) to 39 biologic-naïve patients adjusted for age, gender, and surgical procedure. Early (10 days) and late (3 months) major or minor complications were identified. The incidence of early minor (15.0% vs 12.8%) and major (12.5% vs 7.7%) and late minor (2.5% vs 5.1%) and major (17.5% vs 12.8%) complications and the mean hospital stay after surgery (10.3 $\pm$ 4.0 days vs 9.9 $\pm$ 5.5 days) were similar in both groups.[138]

However, some studies indicate that biologic therapy during the perioperative period can increase the rate of perioperative complications. A large retrospective study showed that patients with CD who received infliximab within 12 weeks of ileocolonic resection had increased rates of postoperative sepsis, intra-abdominal abscess, and 30-day hospital readmissions. However, the presence of a diverting stoma in patients with infliximab seemed to decrease the risk of these complications.[139] Similarly, much of the data that seem to indicate a higher complication rate with infliximab when performing a TPC with IPAA in UC suggest that this risk may be mitigated with a 2- or 3-stage surgery.[134,140,141] Although it is likely that much of the data suggesting an increase in perioperative complications with infliximab reflect the higher burden of comorbidities in patients on biologic therapies,[124,142] the data are limited by the lack of RCTs.

Based on the available data, the authors generally recommend continuing anti-TNF therapy during the perioperative period. Although data are not available for natalizumab and vedolizumab in the perioperative period, the authors generally recommend continuing anti-integrin therapy. However, as with all immunosuppressive therapy in the perioperative period, decisions regarding the continuation of biologic therapy should be based on a comprehensive discussion between the patient, gastroenterologist, and surgeon.

POSTOPERATIVE RECURRENCE OF CROHN'S DISEASE

Greater than 75% of patients diagnosed with CD will eventually require surgical intervention.[143] Unfortunately, recurrence is very common. After ileal or ileocolonic resection, there is a 20% to 30% symptomatic recurrence rate in the first year after surgery, with a 10% increase each subsequent year. Most patients will eventually suffer recurrence, and a reoperation rate of 50% to 60% is generally reported.[144] Most evidence-based assessments of postoperative CD to date have focused on symptom recurrence, which grossly underestimates the true rate of postoperative recurrence. Thus, the goal of endoscopic remission is of particular importance in postoperative CD.[145,146]

Rutgeerts and colleagues[147] illustrated the importance of endoscopic assessment when they followed a cohort of 89 patients after ileocolonic resection (**Table 2**). Endoscopic disease severity 1 year after surgery was a strong predictor of future clinical symptoms and reoperation. Patients with mild or inactive disease (i0, i1) rarely had symptoms at 1 year, and 80% of these patients continued to have mild or absent

Table 2
Rutgeert's grading system for postoperative Crohn's disease

Endoscopic Findings	Rutgeert's Score
Normal mucosa	i0
<5 Aphthous lesions	i1
≥5 Aphthous lesions with normal mucosa between the lesions, or skip areas of larger lesions, or lesions confined to the ileocolonic anastomosis	i2
Diffuse aphthous ileitis with diffusely inflamed mucosa	i3
Diffuse inflammation with ulcers that are already larger, nodules, and/or narrowing	i4

From Rutgeerts P, Geboes K, Vantrappen G, et al. Predictability of the postoperative course of Crohn's disease. Gastroenterology 1990;99(4):956–63; with permission.

endoscopic recurrence at 3 years. Thirty-three percent of patients in the intermediate group (i2) progressed to i4 lesions at 3 years. Patients with severe endoscopic disease (i3 or i4) were more likely to have clinical recurrence at 1 year; 92% of these patients had progressive, severe endoscopic disease at 3 years with a high likelihood for reoperation.

In addition to Rutgeert's grading system, there are well-established risk factors (**Table 3**) that predict disease recurrence.[145,148] Given the high likelihood of postsurgical recurrence in CD, appropriate medical treatment based on risk factors for disease recurrence should be started soon after surgery. Medical therapy should be intensified if endoscopic assessment shows moderate (i2) or severe (i3 or i4) disease. Aggressive postoperative treatment of CD may be able to avert or delay future surgeries. Therefore, individualized care with frequent endoscopic disease assessments is particularly important in the postoperative setting.

Both metronidazole and ornidazole have been shown to be effective in reducing the severity of endoscopic recurrence. A placebo-controlled trial compared patients who received metronidazole (20 mg/kg body weight) daily for 3 months after curative ileal resection and primary anastomosis to patients receiving placebo. At 12 weeks, 21 of 28 patients (75%) in the placebo group had recurrent lesions in the neoterminal ileum compared with 12 of 23 patients (52%) in the metronidazole group ($P = .09$). The incidence of severe endoscopic recurrence was significantly reduced by metronidazole (3 of 23; 13%) as compared with placebo (12 of 28; 43%; $P = .02$). Metronidazole therapy also reduced the clinical recurrence rates at 1 year (4% vs 25%). However,

Table 3
Predictors of recurrence

Strong Risk Factors	Inconclusive Risk Factors
Smoking[a]	Family history of IBD
Penetrating disease[a]	Anastomotic site of disease
History of prior resection[a]	Type of anastomosis
Short duration of disease (<10 y)	Gender
Small bowel and colon involvement	Disease extent (length of diseased intestine)
Progress to surgery despite immunomodulator and biologic therapy	Young age at disease onset

[a] Strongest risk factors.

reductions at 2 years (26% vs 43%) and 3 years (30% vs 50%) were not significant, suggesting that metronidazole may merely delay disease recurrence.[149] Ornidazole 1 g daily for 1 year after ileal or ileocolonic resection also reduced clinical and endoscopic recurrence compared with placebo at 1 year.[150] Unfortunately, adverse effects (neuropathy and gastrointestinal intolerance) preclude long-term use of both antibiotics. Nonetheless, nitroimidazole antibiotics should be considered after ileal or ileocolonic resection to reduce or delay recurrence.

A study of 81 patients undergoing ileal or ileocolonic resection with at least one risk factor for CD recurrence (age <30 years, active smoking, prior resection, penetrating disease) supports the benefit of thiopurines. In this study, all patients received 3 months of metronidazole 750 mg daily and either azathioprine or placebo for 12 months immediately after surgical resection. The primary endpoint was endoscopic recurrence at 3 and 12 months. After 3 months, moderate ($\geq$i2) endoscopic recurrence was evident in 53% of patients receiving placebo, but only in 34% on azathioprine ($P = .11$). At 12 months, the rate of moderate ($\geq$i2) endoscopic recurrence was significantly lower in the azathioprine group (44%) compared with placebo (69%; $P = .05$). Only 3% of patients receiving metronidazole/placebo had complete mucosal remission (i0) compared with 22% of those receiving metronidazole/azathioprine.[151] A recent study comparing azathioprine to mesalazine in patients who had undergone an ileocolonic anastomosis in the preceding 6 to 24 months and had developed moderate or severe ($\geq$i2) endoscopic recurrence before initiation of the study showed a superior endoscopic response with azathioprine. The proportion of patients showing a 1 point or greater reduction in Rutgeert's score between baseline and month 12 was 63.3% and 34.4% in the azathioprine and mesalazine groups, respectively ($P = .023$).[152] There are no studies currently that assess methotrexate monotherapy as prophylaxis for postoperative recurrence.

The ability of TNF-α antagonist therapy to induce mucosal healing in IBD has led to trials evaluating their use in postoperative CD. An early RCT comparing infliximab (5 mg/kg) to placebo illustrates the efficacy of infliximab in the postoperative setting. The rate of endoscopic recurrence at 1 year was 9.1% in the infliximab group, compared with 84.6% with placebo ($P = .0006$).[153] The data for adalimumab for postoperative CD seem equally promising.[154,155] Unfortunately, there are no data available for the use of natalizumab or vedolizumab in the postoperative setting (although there are ongoing trials for vedolizumab).

In summary, there are currently no formal guidelines for the medical prophylaxis of postoperative CD recurrence. Despite the lack of current guidelines, the natural progression of CD after surgery is toward recurrence. Thus, medical management should be strongly considered in all postoperative patients. Patients with aggressive risk factors for recurrence should generally be treated with immunomodulator or biologic therapy soon after surgery. Endoscopic recurrence is predictive of long-term outcomes, and endoscopy should therefore be performed at frequent intervals starting 3 to 6 months after surgery. Medication adjustments should be individualized and based on endoscopic findings.

REFERENCES

1. Dave M, Loftus EV Jr. Mucosal healing in inflammatory bowel disease—a true paradigm of success? Gastroenterol Hepatol (N Y) 2012;8(1):29–38.
2. Papi C, Fasci-Spurio F, Rogai F, et al. Mucosal healing in inflammatory bowel disease: treatment efficacy and predictive factors. Dig Liver Dis 2013;45(12):978–85.

3. Froslie KF, Jahnsen J, Moum BA, et al. Mucosal healing in inflammatory bowel disease: results from a Norwegian population-based cohort. Gastroenterology 2007;133(2):412–22.
4. Colombel JF, Rutgeerts PJ, Sandborn WJ, et al. Adalimumab induces deep remission in patients with Crohn's disease. Clin Gastroenterol Hepatol 2014; 12(3):414–22.e5.
5. Schnitzler F, Fidder H, Ferrante M, et al. Mucosal healing predicts long-term outcome of maintenance therapy with infliximab in Crohn's disease. Inflamm Bowel Dis 2009;15(9):1295–301.
6. Rutgeerts P, Van Assche G, Sandborn WJ, et al. Adalimumab induces and maintains mucosal healing in patients with Crohn's disease: data from the EXTEND trial. Gastroenterology 2012;142(5):1102–11.e2.
7. Herrinton LJ, Liu L, Levin TR, et al. Incidence and mortality of colorectal adenocarcinoma in persons with inflammatory bowel disease from 1998 to 2010. Gastroenterology 2012;143(2):382–9.
8. Ullman TA, Itzkowitz SH. Intestinal inflammation and cancer. Gastroenterology 2011;140(6):1807–16.
9. Fasci Spurio F, Aratari A, Margagnoni G, et al. Early treatment in Crohn's disease: do we have enough evidence to reverse the therapeutic pyramid? J Gastrointestin Liver Dis 2012;21(1):67–73.
10. Maser EA, Villela R, Silverberg MS, et al. Association of trough serum infliximab to clinical outcome after scheduled maintenance treatment for Crohn's disease. Clin Gastroenterol Hepatol 2006;4(10):1248–54.
11. Vermeire S, Noman M, Van Assche G, et al. Effectiveness of concomitant immunosuppressive therapy in suppressing the formation of antibodies to infliximab in Crohn's disease. Gut 2007;56(9):1226–31.
12. Colombel JF, Sandborn WJ, Reinisch W, et al. Infliximab, azathioprine, or combination therapy for Crohn's disease. N Engl J Med 2010;362(15):1383–95.
13. Rousseaux C, Lefebvre B, Dubuquoy L, et al. Intestinal antiinflammatory effect of 5-aminosalicylic acid is dependent on peroxisome proliferator-activated receptor-gamma. J Exp Med 2005;201(8):1205–15.
14. Shanahan F, Niederlehner A, Carramanzana N, et al. Sulfasalazine inhibits the binding of TNF alpha to its receptor. Immunopharmacology 1990;20(3):217–24.
15. Bantel H, Berg C, Vieth M, et al. Mesalazine inhibits activation of transcription factor NF-kappaB in inflamed mucosa of patients with ulcerative colitis. Am J Gastroenterol 2000;95(12):3452–7.
16. Sharon P, Ligumsky M, Rachmilewitz D, et al. Role of prostaglandins in ulcerative colitis. Enhanced production during active disease and inhibition by sulfasalazine. Gastroenterology 1978;75(4):638–40.
17. Hawkey CJ, Boughton-Smith NK, Whittle BJ. Modulation of human colonic arachidonic acid metabolism by sulfasalazine. Dig Dis Sci 1985;30(12):1161–5.
18. Ligumsky M, Karmeli F, Sharon P, et al. Enhanced thromboxane A2 and prostacyclin production by cultured rectal mucosa in ulcerative colitis and its inhibition by steroids and sulfasalazine. Gastroenterology 1981;81(3):444–9.
19. Miller DK, Gillard JW, Vickers PJ, et al. Identification and isolation of a membrane protein necessary for leukotriene production. Nature 1990;343(6255):278–81.
20. Stenson WF, Lobos E. Sulfasalazine inhibits the synthesis of chemotactic lipids by neutrophils. J Clin Invest 1982;69(2):494–7.
21. Ahnfelt-Ronne I, Nielsen OH, Christensen A, et al. Clinical evidence supporting the radical scavenger mechanism of 5-aminosalicylic acid. Gastroenterology 1990;98(5 Pt 1):1162–9.

22. Stevens C, Lipman M, Fabry S, et al. 5-Aminosalicylic acid abrogates T-cell proliferation by blocking interleukin-2 production in peripheral blood mononuclear cells. J Pharmacol Exp Ther 1995;272(1):399–406.
23. MacDermott RP, Schloemann SR, Bertovich MJ, et al. Inhibition of antibody secretion by 5-aminosalicylic acid. Gastroenterology 1989;96(2 Pt 1):442–8.
24. Rhodes JM, Bartholomew TC, Jewell DP. Inhibition of leucocyte motility by drugs used in ulcerative colitis. Gut 1981;22(8):642–7.
25. Neal TM, Winterbourn CC, Vissers MC. Inhibition of neutrophil degranulation and superoxide production by sulfasalazine. Comparison with 5-aminosalicylic acid, sulfapyridine and olsalazine. Biochem Pharmacol 1987;36(17):2765–8.
26. Rubinstein A, Das KM, Melamed J, et al. Comparative analysis of systemic immunological parameters in ulcerative colitis and idiopathic proctitis: effects of sulfasalazine in vivo and in vitro. Clin Exp Immunol 1978;33(2):217–24.
27. Ford AC, Achkar JP, Khan KJ, et al. Efficacy of 5-aminosalicylates in ulcerative colitis: systematic review and meta-analysis. Am J Gastroenterol 2011;106(4): 601–16.
28. Ford AC, Kane SV, Khan KJ, et al. Efficacy of 5-aminosalicylates in Crohn's disease: systematic review and meta-analysis. Am J Gastroenterol 2011;106(4): 617–29.
29. Box SA, Pullar T. Sulphasalazine in the treatment of rheumatoid arthritis. Br J Rheumatol 1997;36(3):382–6.
30. Azulfidine, EN-Tabs. In: Physicians Desk Reference. 52nd edition. Montvale (NJ): Medical Economics Company; 1998. p. 2239.
31. Stein RB, Hanauer SB. Comparative tolerability of treatments for inflammatory bowel disease. Drug Saf 2000;23(5):429–48.
32. Woltsche M, Woltsche-Kahr I, Roeger GM, et al. Sulfasalazine-induced extrinsic allergic alveolitis in a patient with psoriatic arthritis. Eur J Med Res 2001;6(11): 495–7.
33. Gisbert JP, Gonzalez-Lama Y, Mate J. 5-Aminosalicylates and renal function in inflammatory bowel disease: a systematic review. Inflamm Bowel Dis 2007; 13(5):629–38.
34. Dubinsky MC, Reyes E, Ofman J, et al. A cost-effectiveness analysis of alternative disease management strategies in patients with Crohn's disease treated with azathioprine or 6-mercaptopurine. Am J Gastroenterol 2005;100(10): 2239–47.
35. Priest VL, Begg EJ, Gardiner SJ, et al. Pharmacoeconomic analyses of azathioprine, methotrexate and prospective pharmacogenetic testing for the management of inflammatory bowel disease. Pharmacoeconomics 2006;24(8):767–81.
36. Pearson DC, May GR, Fick G, et al. Azathioprine for maintaining remission of Crohn's disease. Cochrane Database Syst Rev 2000;(2):CD000067.
37. Prefontaine E, Macdonald JK, Sutherland LR. Azathioprine or 6-mercaptopurine for induction of remission in Crohn's disease. Cochrane Database Syst Rev 2010;(6):CD000545.
38. Pearson DC, May GR, Fick GH, et al. Azathioprine and 6-mercaptopurine in Crohn disease. A meta-analysis. Ann Intern Med 1995;123(2):132–42.
39. Su C, Lichtenstein GR. Treatment of inflammatory bowel disease with azathioprine and 6-mercaptopurine. Gastroenterol Clin North Am 2004;33(2): 209–34, viii.
40. Bouhnik Y, Lemann M, Mary JY, et al. Long-term follow-up of patients with Crohn's disease treated with azathioprine or 6-mercaptopurine. Lancet 1996; 347(8996):215–9.

41. Beaugerie L, Brousse N, Bouvier AM, et al. Lymphoproliferative disorders in patients receiving thiopurines for inflammatory bowel disease: a prospective observational cohort study. Lancet 2009;374(9701):1617–25.
42. Kotlyar DS, Osterman MT, Diamond RH, et al. A systematic review of factors that contribute to hepatosplenic T-cell lymphoma in patients with inflammatory bowel disease. Clin Gastroenterol Hepatol 2011;9(1):36–41.e1.
43. Peyrin-Biroulet L, Khosrotehrani K, Carrat F, et al. Increased risk for nonmelanoma skin cancers in patients who receive thiopurines for inflammatory bowel disease. Gastroenterology 2011;141(5):1621–8.e1–5.
44. Cronstein BN, Naime D, Ostad E. The antiinflammatory mechanism of methotrexate. Increased adenosine release at inflamed sites diminishes leukocyte accumulation in an in vivo model of inflammation. J Clin Invest 1993;92(6):2675–82.
45. Feagan BG, Rochon J, Fedorak RN, et al. Methotrexate for the treatment of Crohn's disease. The North American Crohn's Study Group Investigators. N Engl J Med 1995;332(5):292–7.
46. Feagan BG, Fedorak RN, Irvine EJ, et al. A comparison of methotrexate with placebo for the maintenance of remission in Crohn's disease. North American Crohn's Study Group Investigators. N Engl J Med 2000;342(22):1627–32.
47. Arora S, Katkov W, Cooley J, et al. Methotrexate in Crohn's disease: results of a randomized, double-blind, placebo-controlled trial. Hepatogastroenterology 1999;46(27):1724–9.
48. Oren R, Moshkowitz M, Odes S, et al. Methotrexate in chronic active Crohn's disease: a double-blind, randomized, Israeli multicenter trial. Am J Gastroenterol 1997;92(12):2203–9.
49. Te HS, Schiano TD, Kuan SF, et al. Hepatic effects of long-term methotrexate use in the treatment of inflammatory bowel disease. Am J Gastroenterol 2000;95(11):3150–6.
50. Van Assche G, D'Haens G, Noman M, et al. Randomized, double-blind comparison of 4 mg/kg versus 2 mg/kg intravenous cyclosporine in severe ulcerative colitis. Gastroenterology 2003;125(4):1025–31.
51. Naganuma M, Fujii T, Watanabe M. The use of traditional and newer calcineurin inhibitors in inflammatory bowel disease. J Gastroenterol 2011;46(2):129–37.
52. Chang KH, Burke JP, Coffey JC. Infliximab versus cyclosporine as rescue therapy in acute severe steroid-refractory ulcerative colitis: a systematic review and meta-analysis. Int J Colorectal Dis 2013;28(3):287–93.
53. Jewell DP, Lennard-Jones JE. Oral cyclosporin for chronic active Crohn's disease: a multicenter controlled trial. Eur J Gastroenterol Hepatol 1994;6:499–505.
54. Feagan BG, McDonald JW, Rochon J, et al. Low-dose cyclosporine for the treatment of Crohn's disease. The Canadian Crohn's Relapse Prevention Trial Investigators. N Engl J Med 1994;330(26):1846–51.
55. Stange EF, Modigliani R, Pena AS, et al. European trial of cyclosporine in chronic active Crohn's disease: a 12-month study. The European Study Group. Gastroenterology 1995;109(3):774–82.
56. Sternthal MB, Murphy SJ, George J, et al. Adverse events associated with the use of cyclosporine in patients with inflammatory bowel disease. Am J Gastroenterol 2008;103(4):937–43.
57. Dassopoulos T, Sninsky CA. Optimizing immunomodulators and anti-TNF agents in the therapy of Crohn disease. Gastroenterol Clin North Am 2012;41(2):393–409, ix.
58. Sands BE, Anderson FH, Bernstein CN, et al. Infliximab maintenance therapy for fistulizing Crohn's disease. N Engl J Med 2004;350(9):876–85.

59. Colombel JF, Schwartz DA, Sandborn WJ, et al. Adalimumab for the treatment of fistulas in patients with Crohn's disease. Gut 2009;58(7):940–8.
60. Ng SC, Plamondon S, Gupta A, et al. Prospective evaluation of anti-tumor necrosis factor therapy guided by magnetic resonance imaging for Crohn's perineal fistulas. Am J Gastroenterol 2009;104(12):2973–86.
61. Sandborn WJ, Hanauer SB, Rutgeerts P, et al. Adalimumab for maintenance treatment of Crohn's disease: results of the CLASSIC II trial. Gut 2007;56(9):1232–9.
62. Hanauer S, Rutgeerts P, Targan S, et al. Delayed hypersensitivity to infliximab (Remicade) re-infusion after 2–4 year interval without treatment. Gastroenterology 1999;116:A731.
63. Hanauer SB, Feagan BG, Lichtenstein GR, et al. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. Lancet 2002;359(9317):1541–9.
64. Sandborn WJ, Feagan BG, Stoinov S, et al. Certolizumab pegol for the treatment of Crohn's disease. N Engl J Med 2007;357(3):228–38.
65. Siegel CA, Marden SM, Persing SM, et al. Risk of lymphoma associated with combination anti-tumor necrosis factor and immunomodulator therapy for the treatment of Crohn's disease: a meta-analysis. Clin Gastroenterol Hepatol 2009;7(8):874–81.
66. Deepak P, Sifuentes H, Sherid M, et al. T-cell non-Hodgkin's lymphomas reported to the FDA AERS with tumor necrosis factor-alpha (TNF-alpha) inhibitors: results of the REFURBISH study. Am J Gastroenterol 2013;108(1):99–105.
67. Nozaki K, Silver RM, Stickler DE, et al. Neurological deficits during treatment with tumor necrosis factor-alpha antagonists. Am J Med Sci 2011;342(5):352–5.
68. Sandborn WJ, Colombel JF, Enns R, et al. Natalizumab induction and maintenance therapy for Crohn's disease. N Engl J Med 2005;353(18):1912–25.
69. Targan SR, Feagan BG, Fedorak RN, et al. Natalizumab for the treatment of active Crohn's disease: results of the ENCORE Trial. Gastroenterology 2007;132(5):1672–83.
70. Feagan BG, Greenberg GR, Wild G, et al. Treatment of ulcerative colitis with a humanized antibody to the alpha4beta7 integrin. N Engl J Med 2005;352(24):2499–507.
71. Feagan BG, Greenberg GR, Wild G, et al. Treatment of active Crohn's disease with MLN0002, a humanized antibody to the alpha4beta7 integrin. Clin Gastroenterol Hepatol 2008;6(12):1370–7.
72. Feagan BG, Rutgeerts P, Sands BE, et al. Vedolizumab as induction and maintenance therapy for ulcerative colitis. N Engl J Med 2013;369(8):699–710.
73. Parikh A, Leach T, Wyant T, et al. Vedolizumab for the treatment of active ulcerative colitis: a randomized controlled phase 2 dose-ranging study. Inflamm Bowel Dis 2012;18(8):1470–9.
74. Sandborn WJ, Feagan BG, Rutgeerts P, et al. Vedolizumab as induction and maintenance therapy for Crohn's disease. N Engl J Med 2013;369(8):711–21.
75. Thomas A, Lodhia N. Advanced therapy for inflammatory bowel disease: a guide for the primary care physician. J Am Board Fam Med 2014;27(3):411–20.
76. Amiot A, Peyrin-Biroulet L. Current, new and future biological agents on the horizon for the treatment of inflammatory bowel diseases. Therap Adv Gastroenterol 2015;8(2):66–82.
77. Goulding NJ. The molecular complexity of glucocorticoid actions in inflammation—a four-ring circus. Curr Opin Pharmacol 2004;4(6):629–36.

78. Hayashi R, Wada H, Ito K, et al. Effects of glucocorticoids on gene transcription. Eur J Pharmacol 2004;500(1–3):51–62.
79. De Bosscher K, Vanden Berghe W, Haegeman G. The interplay between the glucocorticoid receptor and nuclear factor-kappaB or activator protein-1: molecular mechanisms for gene repression. Endocr Rev 2003;24:488–522.
80. Kagoshima M, Ito K, Cosio B, et al. Glucocorticoid suppression of nuclear factor-kappa B: a role for histone modifications. Biochem Soc Trans 2003; 31(Pt 1):60–5.
81. Buttgereit F, Saag KG, Cutolo M, et al. The molecular basis for the effectiveness, toxicity, and resistance to glucocorticoids: focus on the treatment of rheumatoid arthritis. Scand J Rheumatol 2005;34(1):14–21.
82. Lundin PD, Edsbacker S, Bergstrand M, et al. Pharmacokinetics of budesonide controlled ileal release capsules in children and adults with active Crohn's disease. Aliment Pharmacol Ther 2003;17(1):85–92.
83. Seow CH, Benchimol EI, Steinhart AH, et al. Budesonide for Crohn's disease. Expert Opin Drug Metab Toxicol 2009;5(8):971–9.
84. Klotz U, Schwab M. Topical delivery of therapeutic agents in the treatment of inflammatory bowel disease. Adv Drug Deliv Rev 2005;57(2):267–79.
85. De Cassan C, Fiorino G, Danese S. Second-generation corticosteroids for the treatment of Crohn's disease and ulcerative colitis: more effective and less side effects? Dig Dis 2012;30(4):368–75.
86. Ford AC, Bernstein CN, Khan KJ, et al. Glucocorticosteroid therapy in inflammatory bowel disease: systematic review and meta-analysis. Am J Gastroenterol 2011;106(4):590–9 [quiz: 600].
87. Summers RW, Switz DM, Sessions JT Jr, et al. National Cooperative Crohn's Disease Study: results of drug treatment. Gastroenterology 1979;77(4 Pt 2):847–69.
88. Malchow H, Ewe K, Brandes JW, et al. European Cooperative Crohn's Disease Study (ECCDS): results of drug treatment. Gastroenterology 1984;86(2):249–66.
89. Toruner M, Loftus EV Jr, Harmsen WS, et al. Risk factors for opportunistic infections in patients with inflammatory bowel disease. Gastroenterology 2008; 134(4):929–36.
90. Hanauer SB, Present DH. The state of the art in the management of inflammatory bowel disease. Rev Gastroenterol Disord 2003;3(2):81–92.
91. Marehbian J, Arrighi HM, Hass S, et al. Adverse events associated with common therapy regimens for moderate-to-severe Crohn's disease. Am J Gastroenterol 2009;104(10):2524–33.
92. Lichtenstein GR, Feagan BG, Cohen RD, et al. Serious infections and mortality in association with therapies for Crohn's disease: TREAT registry. Clin Gastroenterol Hepatol 2006;4(5):621–30.
93. Irving PM, Gearry RB, Sparrow MP, et al. Review article: appropriate use of corticosteroids in Crohn's disease. Aliment Pharmacol Ther 2007;26(3):313–29.
94. Lyckegaart E, HK, Bengtsson B. Compassionate use of budesonide capsules (Entocort EC) in patients with Crohn's disease. Gastroenterology 2002; 122(T-1665) [abstract: 500].
95. Sandborn WJ, Travis S, Moro L, et al. Once-daily budesonide MMX(R) extended-release tablets induce remission in patients with mild to moderate ulcerative colitis: results from the CORE I study. Gastroenterology 2012; 143(5):1218–26.e1–2.
96. Travis SP, Danese S, Kupcinskas L, et al. Once-daily budesonide MMX in active, mild-to-moderate ulcerative colitis: results from the randomised CORE II study. Gut 2014;63(3):433–41.

97. Edsbacker S, Andersson T. Pharmacokinetics of budesonide (Entocort EC) capsules for Crohn's disease. Clin Pharmacokinet 2004;43(12):803–21.
98. Greenberg GR, Feagan BG, Martin F, et al. Oral budesonide for active Crohn's disease. Canadian Inflammatory Bowel Disease Study Group. N Engl J Med 1994;331(13):836–41.
99. Beaugerie L, Seksik P, Nion-Larmurier I, et al. Predictors of Crohn's disease. Gastroenterology 2006;130(3):650–6.
100. Jakobovits J, Schuster MM. Metronidazole therapy for Crohn's disease and associated fistulae. Am J Gastroenterol 1984;79(7):533–40.
101. Bernstein LH, Frank MS, Brandt LJ, et al. Healing of perineal Crohn's disease with metronidazole. Gastroenterology 1980;79(3):599.
102. Brandt LJ, Bernstein LH, Boley SJ, et al. Metronidazole therapy for perineal Crohn's disease: a follow-up study. Gastroenterology 1982;83(2):383–7.
103. Maeda Y, Ng SC, Durdey P, et al. Randomized clinical trial of metronidazole ointment versus placebo in perianal Crohn's disease. Br J Surg 2010;97(9):1340–7.
104. Wiese DM, Schwartz DA. Managing perianal Crohn's disease. Curr Gastroenterol Rep 2012;14(2):153–61.
105. Present DH, Rutgeerts P, Targan S, et al. Infliximab for the treatment of fistulas in patients with Crohn's disease. N Engl J Med 1999;340(18):1398–405.
106. Lichtenstein GR, Yan S, Bala M, et al. Infliximab maintenance treatment reduces hospitalizations, surgeries, and procedures in fistulizing Crohn's disease. Gastroenterology 2005;128(4):862–9.
107. Ng SC, Plamondon S, Gupta A, et al. Prospective assessment of the effect on quality of life of anti-tumour necrosis factor therapy for perineal Crohn's fistulas. Aliment Pharmacol Ther 2009;30(7):757–66.
108. Hanauer SB, Sandborn WJ, Rutgeerts P, et al. Human anti-tumor necrosis factor monoclonal antibody (adalimumab) in Crohn's disease: the CLASSIC-I trial. Gastroenterology 2006;130(2):323–33 [quiz: 591].
109. Jilani NZ, Akobeng AK. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. Colombel JF, Sandborn WJ, Rutgeerts P, et al. Gastroenterology 2007;132:52–65. J Pediatr Gastroenterol Nutr 2008;46(2):226–7.
110. Lichtiger S, Binion DG, Wolf DC, et al. The CHOICE trial: adalimumab demonstrates safety, fistula healing, improved quality of life and increased work productivity in patients with Crohn's disease who failed prior infliximab therapy. Aliment Pharmacol Ther 2010;32(10):1228–39.
111. Chen CH, Kularatna G, Stone CD, et al. Clinical experience of natalizumab in Crohn's disease patients in a restricted distribution program. Ann Gastroenterol 2013;26(3):189–90.
112. Portela F, Lago P. Fulminant colitis. Best Pract Res Clin Gastroenterol 2013;27(5):771–82.
113. Rosenberg W, Ireland A, Jewell DP. High-dose methylprednisolone in the treatment of active ulcerative colitis. J Clin Gastroenterol 1990;12(1):40–1.
114. Truelove SC, Jewell DP. Intensive intravenous regimen for severe attacks of ulcerative colitis. Lancet 1974;1(7866):1067–70.
115. Blomberg B, Jarnerot G. Clinical evaluation and management of acute severe colitis. Inflamm Bowel Dis 2000;6(3):214–27.
116. Laharie D, Bourreille A, Branche J, et al. Ciclosporin versus infliximab in patients with severe ulcerative colitis refractory to intravenous steroids: a parallel, open-label randomised controlled trial. Lancet 2012;380(9857):1909–15.

117. Mocciaro F, Renna S, Orlando A, et al. Cyclosporine or infliximab as rescue therapy in severe refractory ulcerative colitis: early and long-term data from a retrospective observational study. J Crohns Colitis 2012;6(6):681–6.
118. Maser EA, Deconda D, Lichtiger S, et al. Cyclosporine and infliximab as rescue therapy for each other in patients with steroid-refractory ulcerative colitis. Clin Gastroenterol Hepatol 2008;6(10):1112–6.
119. Dickinson RJ, O'Connor HJ, Pinder I, et al. Double blind controlled trial of oral vancomycin as adjunctive treatment in acute exacerbations of idiopathic colitis. Gut 1985;26(12):1380–4.
120. Chapman RW, Selby WS, Jewell DP. Controlled trial of intravenous metronidazole as an adjunct to corticosteroids in severe ulcerative colitis. Gut 1986;27(10):1210–2.
121. Mantzaris GJ, Petraki K, Archavlis E, et al. A prospective randomized controlled trial of intravenous ciprofloxacin as an adjunct to corticosteroids in acute, severe ulcerative colitis. Scand J Gastroenterol 2001;36(9):971–4.
122. Issa M, Ananthakrishnan AN, Binion DG. Clostridium difficile and inflammatory bowel disease. Inflamm Bowel Dis 2008;14(10):1432–42.
123. Deshpande A, Pasupuleti V, Rolston DD, et al. Diagnostic accuracy of real-time polymerase chain reaction in detection of Clostridium difficile in the stool samples of patients with suspected Clostridium difficile infection: a meta-analysis. Clin Infect Dis 2011;53(7):e81–90.
124. Kumar A, Auron M, Aneja A, et al. Inflammatory bowel disease: perioperative pharmacological considerations. Mayo Clin Proc 2011;86(8):748–57.
125. Ananthakrishnan AN, McGinley EL, Saeian K, et al. Laparoscopic resection for inflammatory bowel disease: outcomes from a nationwide sample. J Gastrointest Surg 2010;14(1):58–65.
126. Aberra FN, Lewis JD, Hass D, et al. Corticosteroids and immunomodulators: postoperative infectious complication risk in inflammatory bowel disease patients. Gastroenterology 2003;125(2):320–7.
127. Myrelid P, Olaison G, Sjodahl R, et al. Thiopurine therapy is associated with postoperative intra-abdominal septic complications in abdominal surgery for Crohn's disease. Dis Colon Rectum 2009;52(8):1387–94.
128. Connell WR, Kamm MA, Ritchie JK, et al. Bone marrow toxicity caused by azathioprine in inflammatory bowel disease: 27 years of experience. Gut 1993;34(8):1081–5.
129. Arts J, D'Haens G, Zeegers M, et al. Long-term outcome of treatment with intravenous cyclosporin in patients with severe ulcerative colitis. Inflamm Bowel Dis 2004;10(2):73–8.
130. Pinna-Pintor M, Arese P, Bona R, et al. Severe steroid-unresponsive ulcerative colitis: outcomes of restorative proctocolectomy in patients undergoing cyclosporin treatment. Dis Colon Rectum 2000;43(5):609–13 [discussion: 613–4].
131. Fleshner PR, Michelassi F, Rubin M, et al. Morbidity of subtotal colectomy in patients with severe ulcerative colitis unresponsive to cyclosporin. Dis Colon Rectum 1995;38(12):1241–5.
132. Hyde GM, Jewell DP, Kettlewell MG, et al. Cyclosporin for severe ulcerative colitis does not increase the rate of perioperative complications. Dis Colon Rectum 2001;44(10):1436–40.
133. Jarnerot G, Hertervig E, Friis-Liby I, et al. Infliximab as rescue therapy in severe to moderately severe ulcerative colitis: a randomized, placebo-controlled study. Gastroenterology 2005;128(7):1805–11.
134. Mor IJ, Vogel JD, da Luz Moreira A, et al. Infliximab in ulcerative colitis is associated with an increased risk of postoperative complications after

restorative proctocolectomy. Dis Colon Rectum 2008;51(8):1202–7 [discussion 1207–10].
135. Selvasekar CR, Cima RR, Larson DW, et al. Effect of infliximab on short-term complications in patients undergoing operation for chronic ulcerative colitis. J Am Coll Surg 2007;204(5):956–62 [discussion: 962–3].
136. Bordeianou L, Kunitake H, Shellito P, et al. Preoperative infliximab treatment in patients with ulcerative and indeterminate colitis does not increase rate of conversion to emergent and multistep abdominal surgery. Int J Colorectal Dis 2010; 25(3):401–4.
137. Gainsbury ML, Chu DI, Howard LA, et al. Preoperative infliximab is not associated with an increased risk of short-term postoperative complications after restorative proctocolectomy and ileal pouch-anal anastomosis. J Gastrointest Surg 2011;15(3):397–403.
138. Marchal L, D'Haens G, Van Assche G, et al. The risk of post-operative complications associated with infliximab therapy for Crohn's disease: a controlled cohort study. Aliment Pharmacol Ther 2004;19(7):749–54.
139. Appau KA, Fazio VW, Shen B, et al. Use of infliximab within 3 months of ileocolonic resection is associated with adverse postoperative outcomes in Crohn's patients. J Gastrointest Surg 2008;12(10):1738–44.
140. Gu J, Remzi FH, Shen B, et al. Operative strategy modifies risk of pouch-related outcomes in patients with ulcerative colitis on preoperative anti-tumor necrosis factor-alpha therapy. Dis Colon Rectum 2013;56(11):1243–52.
141. Hicks CW, Hodin RA, Bordeianou L. Possible overuse of 3-stage procedures for active ulcerative colitis. JAMA Surg 2013;148(7):658–64.
142. Narula N, Charleton D, Marshall JK. Meta-analysis: peri-operative anti-TNFalpha treatment and post-operative complications in patients with inflammatory bowel disease. Aliment Pharmacol Ther 2013;37(11):1057–64.
143. Achkar JP, Shen B. Medical management of postoperative complications of inflammatory bowel disease: pouchitis and Crohn's disease recurrence. Curr Gastroenterol Rep 2001;3(6):484–90.
144. Rutgeerts P. Protagonist: Crohn's disease recurrence can be prevented after ileal resection. Gut 2002;51(2):152–3.
145. Schwartz M, Regueiro M. Prevention and treatment of postoperative Crohn's disease recurrence: an update for a new decade. Curr Gastroenterol Rep 2011; 13(1):95–100.
146. Rutgeerts P, Feagan BG, Lichtenstein GR, et al. Comparison of scheduled and episodic treatment strategies of infliximab in Crohn's disease. Gastroenterology 2004;126(2):402–13.
147. Rutgeerts P, Geboes K, Vantrappen G, et al. Predictability of the postoperative course of Crohn disease. Gastroenterology 1990;99(4):956–63.
148. Cho SM, Cho SW, Regueiro M. Postoperative management of Crohn's disease. Med Clin North Am 2010;94(1):179–88.
149. Rutgeerts P, Hiele M, Geboes K, et al. Controlled trial of metronidazole treatment for prevention of Crohn's recurrence after ileal resection. Gastroenterology 1995; 108(6):1617–21.
150. Rutgeerts P, Van Assche G, Vermeire S, et al. Ornidazole for prophylaxis of postoperative Crohn's disease recurrence: a randomized, double-blind, placebo-controlled trial. Gastroenterology 2005;128(4):856–61.
151. D'Haens GR, Vermeire S, Van Assche G, et al. Therapy of metronidazole with azathioprine to prevent postoperative recurrence of Crohn's disease: a controlled randomized trial. Gastroenterology 2008;135(4):1123–9.

152. Reinisch W, Angelberger S, Petritsch W, et al. Azathioprine versus mesalazine for prevention of postoperative clinical recurrence in patients with Crohn's disease with endoscopic recurrence: efficacy and safety results of a randomised, double-blind, double-dummy, multicentre trial. Gut 2010;59(6):752–9.
153. Regueiro M, Schraut W, Baidoo L, et al. Infliximab prevents Crohn's disease recurrence after ileal resection. Gastroenterology 2009;136(2):441–50.e1 [quiz: 716].
154. Papamichael K, Archavlis E, Lariou C, et al. Adalimumab for the prevention and/or treatment of post-operative recurrence of Crohn's disease: a prospective, two-year, single center, pilot study. J Crohns Colitis 2012;6(9):924–31.
155. Kotze PG, Yamamoto T, Danese S, et al. Direct retrospective comparison of adalimumab and infliximab in preventing early postoperative endoscopic recurrence after ileocaecal resection for Crohn's disease: results from the MULTIPER database. J Crohns Colitis 2015;9(7):541–7.