REVIEW

Inflammatory Bowel Disease: Perioperative Pharmacological Considerations

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The perioperative management of patients with inflammatory bowel disease is challenging given the altered immune system that results from a variety of biologic and immunomodulator therapies. Clinicians are often faced with challenges and complicated equations when deciding on the type and dose of medication. To understand the effect of these medications and review the evidence regarding the management of these medications in the perioperative setting, a PubMed-based literature search (January 1, 1960, through April 1, 2011) was conducted using the following search terms: *perioperative management, risk, outcome, inflammatory bowel disease, ulcerative colitis, Crohn's disease, aminosalicylates, glucocorticoids, purine analogues, cyclosporine, methotrexate, biologic therapy, infliximab,* and *thromboembolism*. The 414 articles identified were manually sorted to exclude those that did not address perioperative risk, outcomes, and medications in the abstracts, yielding 84 articles for review. Additional references were obtained from the citations within the retrieved articles. This review surveys the findings of the selected articles and presents guidelines and resources for perioperative medication management for patients with inflammatory bowel disease undergoing surgery.

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ACTH = adrenocorticotropic hormone; 5-ASA = 5-aminosalicylic acid; CD = Crohn disease; CI = confidence interval; DVT = deep venous thrombosis; GI = gastrointestinal; HPA = hypothalamic-pituitary-adrenal; IBD = inflammatory bowel disease; LMWH = low-molecular-weight heparin; OR = odds ratio; PE = pulmonary embolism; TNF = tumor necrosis factor; TPC = total proctocolectomy; UC = ulcerative colitis; VTE = venous thromboembolism

The perioperative management of patients with Crohn disease (CD) and ulcerative colitis (UC) requires a multifaceted approach involving both traditional and disease-specific considerations. As is true of any surgical patient, a thorough preoperative evaluation is crucial. Of note, the proportion of older patients among those with inflammatory bowel disease (IBD) is increasing, with a consequent increase in the complexity of comorbid conditions that would require perioperative care. Recent data have shown worse outcomes among elderly patients treated with certain immunosuppressant agents such as anti–tumor necrosis factor (TNF) compared with a younger population.

Substantial morbidity is associated with IBD, especially among malnourished patients, those aged 60 to 80 years, those requiring emergency surgery, those with fistulizing disease, and those treated at low-volume surgical centers.

The perioperative morbidity is associated as well with the nature of the surgical procedure: a total proctocolectomy (TPC) with J pouch may result in higher postoperative infection rates than TPC with an ileostomy; a strictureplasty or stoma revision may have a decreased rate of postoperative cardiopulmonary or infectious complications compared with a complicated resection for fistulizing disease. Laparoscopic surgery also has been consistently associated with decreased postoperative length of stay and complication rate.[1,2]

One of the factors with the greatest effect on medical and surgical outcomes is the long-term immunosuppressant therapy that makes patients susceptible to infections and poor wound healing.[3]

The advent of immunomodulators and biological agents poses new challenges for practicing physicians, who are increasingly faced with making clinical recommendations with little evidence to support their decision. This review focuses on recommendations for perioperative management of immunosuppressant and immunomodulator agents in patients with IBD.

TIMING AND TYPE OF SURGERY

Patients undergoing urgent IBD-related surgery are at additional risk of cardiac complications. Various factors limit optimization of preoperative management of cardiovascular risk in such patients. Mangano[4] showed that cardiac complications were 2 to 5 times more likely to occur with emergent IBD and non–IBD-related surgical procedures than elective operations. Such increased risk might be expected, given the fact that these patients had chronically debilitating disease conditions.

The perioperative medication management in patients with IBD will vary depending on the clinical situation of the patient (UC vs CD; elective vs emergent surgery).

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ARTICLE HIGHLIGHTS

- Aminosalicylates (sulfasalazine and mesalamine) should be discontinued 1 day before surgery with resumption 3 days after surgery, especially in patients with susceptibility for decreased glomerular filtration
- For patients receiving glucocorticoids, the most relevant issue is to ensure adequate stress glucocorticoid supplementation if required
- Purine analogues (6-mercaptopurine/azathioprine) should be withheld on the day of surgery and resumed in the first 3 postoperative days when oral medications are resumed, if renal function remains normal
- Cyclosporine should be continued in the preoperative and immediate postoperative period, given the existing evidence
- Methotrexate should be discontinued 1 week before surgery until at least 1 week after surgery in patients with a history of infectious complications and resumed after successful wound healing
- Immunomodulator therapy with anti–tumor necrosis factor agents should be continued in the perioperative setting

In patients with UC, gastrointestinal (GI) surgery, most commonly elective TPC with ileoanal anastomosis, would be the recommended approach. However, emergency surgery can be required, especially in the setting of fulminant colitis with no opportunity for preoperative optimization. Patients with UC who have previously undergone proctocolectomy and require surgery will no longer require immunosuppressant therapy, allowing for more straightforward perioperative medication management. Similarly, for patients with CD, clinical decision making will depend on whether procedures are elective (eg, strictureplasty) or emergent (eg, alleviation of small bowel obstruction).

Perioperative morbidity is also associated with the nature of the surgical procedure: a TPC with J pouch may result in higher rates of postoperative infection than a TPC with an ileostomy; a strictureplasty or stoma revision may have a decreased rate of postoperative cardiopulmonary or infectious complications compared with a complicated resection for fistulizing disease.[5] Laparoscopic surgery has been consistently associated with decreased postoperative length of stay and complication rate.[1,2] Staged procedures also result in decreased short-term complications.[6,7]

The perioperative management of medication will not differ between patients with IBD undergoing GI vs non-GI surgeries (eg, orthopedic procedures) because, regardless of the type of procedure, the adequate control of IBD is paramount given its systemic implications.

Most of these patients who undergo surgery understand that it carries a perioperative cardiac risk but have reconciled themselves to the fact that the anticipated morbidity and mortality from not operating overrides that risk. Because most surgical procedures in these patients are intraperitoneal and are traditionally classified into the intermediate-risk category, case-by-case evaluation of risk factors should determine the use of perioperative β-blockers.[8-10]

Given the morbidity associated with the underlying disease, these patients may require emergency surgery, which poses the additional risk of postoperative complications and blood loss.[11]

One of the most important aspects of the perioperative care of patients with IBD, the correct and efficient management of medications, is summarized in Table 1 and discussed in detail in the section that follows.

PERIOPERATIVE MANAGEMENT OF MEDICATIONS USED IN IBD

AMINOSALICYLATES

5-Aminosalicylic acid (5-ASA) agents remain the mainstay of therapy for the induction of remission in mild to moderately active UC[12] and for the maintenance of remission in UC and possible CD.[13] Sulfasalazine, the prototype aminosalicylate, was developed to deliver both an antibacterial agent (sulfapyridine) and an anti-inflammatory agent (5-ASA, mesalamine, or mesalazine); the 5-ASA component of sulfasalazine is primarily responsible for the therapeutic benefit. It is poorly absorbed in the colon and partially absorbed in the small intestine. Several sulfa-free aminosalicylates have been developed in recent years[14] to target specific GI sites based on the assumption that the effects of 5-ASA are topical and not systemic. Sulfasalazine and mesalamine have multiple anti-inflammatory effects, including the inhibition of the arachidonic acid pathway along the cyclooxygenase, lipoxygenase, and platelet aggregation factor systems. These drugs are primarily eliminated by the kidneys. Important adverse effects include hypersensitivity reactions, bone marrow suppression, pneumonitis, pancreatitis, and hemolytic anemia. These compounds have a short half-life (6-10 hours) and are extensively metabolized. There is a paucity of clinical data for perioperative use of these medications.

In patients in whom decreased glomerular filtration is more likely (age, >65 years; American Society of Anesthesiologists physical status score, IV or V; revised cardiac risk index score, >2; chronic heart disease), a reasonable approach in the perioperative phase is to discontinue sulfasalazine and mesalamine a day before surgery with resumption 3 days after surgery.[15]

Patients undergoing proctocolectomy will not require postoperative resumption of these agents.

TABLE 1. **Medication Management During the Perioperative Period**[a]

Drug	Recommendation for practice	Evidence level[b]
Glucocorticoids	Continue; administer stress dose (see Table 2)	
5-ASA	Discontinue on day of surgery and resume 3 days after surgery if normal renal function	C
Azathioprine, 6-MP	Discontinue on day of surgery and resume 3 days after surgery if normal renal function	B, C
Methotrexate	Continue, unless previous poor wound healing or postoperative infections	B, C
Cyclosporine	Continue but carefully monitor for opportunistic infectious complications	B, C
Infliximab	Continue without interruption	B

[a] 5-ASA = 5-aminosalicylic acid; 6-MP = 6-mercaptopurine.
[b] Evidence level A = multiple populations evaluated (trials and clinical registries), multiple randomized clinical trials, or meta-analysis; evidence level B = limited populations evaluated; data derived from a single randomized trial or nonrandomized studies; evidence Level C = very limited populations evaluated or consensus opinion of experts, case studies, or standards of care.

GLUCOCORTICOIDS

Glucocorticoid use is common in IBD. The most relevant approach in the perioperative period is to ensure that adequate stress glucocorticoid supplementation is given. In patients with IBD, especially patients with active Crohn disease, glucocorticoids are highly effective in inducing clinical remission. However, the therapeutic role of glucocorticoids in the treatment of IBD is primarily to decrease the intensity of inflammation because they are ineffective in maintaining remission or healing mucosal lesions. Long-term use of glucocorticoids is associated with dependency as well as clinical relapses. In addition, long-term glucocorticoid use is associated with osteopenia and osteoporosis, glucose intolerance and diabetes mellitus, increased intraocular pressure and glaucoma, and severe infections.[16]

Adequate glucose control must be established in these patients in the perioperative setting because uncontrolled hyperglycemia is associated with worse outcome, including poor wound healing and increased infections.

The increased likelihood of infectious complications was demonstrated in the TREAT (The Crohn's Therapy, Resource, Evaluation, and Assessment Tool) registry, in which glucocorticoid use was an independent factor associated with serious infections (odds ratio [OR], 2.21; 95% confidence interval [CI], 1.46-3.34; $P<.001$).[17] In a series of 100 patients with IBD who developed opportunistic infections, Toruner et al[18] found that glucocorticoid use was significantly associated with the development of opportunistic infections (OR, 3.4; 95% CI, 1.8-6.2). In this series, in multivariate analysis, the risk for opportunistic infection increased substantially with the use of a single immunosuppressant (OR, 2.9; 95% CI, 1.5-5.3) vs a combination of 2 or 3 immunosuppressants (OR, 14.5; 95% CI, 4.9-43.0).

In an epidemiologic study in Olmsted County, Minnesota, glucocorticoid dependence at 1 year was found in 28% of patients with CD and 22% of patients with UC.[19]

The strategy to minimize adverse effects related to glucocorticoids in patients with IBD is to use the lowest effective dose to induce remission in patients with moderately to severely active CD and acute severe colitis,[16,20] along with the early use of other immunosuppressant glucocorticoid-sparing agents and biologic therapy.

In a 1952 article, Fraser et al[21] first reported iatrogenic adrenal insufficiency due to preoperative glucocorticoid withdrawal in a surgical patient. The publication of similar findings in a case report the following year led to recommendations for high-dose or "stress-dose" glucocorticoids in the perioperative period.[22] Since then, the overall practice has evolved, and currently the doses of glucocorticoid replacement are lower than initially espoused because of concerns about the adverse effects of glucocorticoids, including impaired wound healing, elevated risk of infections, GI bleeding, and hyperglycemia.[23] The entire practice of "stress-dose" glucocorticoid replacement, even in its current form, has been questioned by some investigators.[22-25] In a recent study, Bruewer et al[26] found that patients receiving high-dose and prolonged preoperative systemic glucocorticoid therapy who underwent bowel resection for CD experienced no more postoperative complications than did control patients.

In a series from the University of Tokyo, which analyzed data on all patients with UC from 1963 to 1994, those receiving high-dose glucocorticoids were more likely to undergo colectomy because they were more likely to have a refractory disease and to experience postoperative complications.[27]

Surgical stress is a potent stimulant of the hypothalamic-pituitary-adrenal (HPA) axis. Stress acts by stimulating the release of corticotropin-releasing hormone and arginine vasopressin that in turn causes adrenocorticotropic hormone (ACTH) release. In surgical patients, the highest ACTH levels are noted during the immediate postoperative recovery period and are likely triggered by trauma and pain. Elevated levels of ACTH are also seen during extubation and reversal of anesthesia and at the time of surgical incision.[27-29] Epidural or local anesthesia does not appear to stimulate the HPA axis.[30] In addition, plasma ACTH response during surgery is attenuated by opiate drugs.[28] Substantial variation exists in the degree of endogenous glucocorticoid release in response to surgical

TABLE 2. **Glucocorticoid Management During the Perioperative Period**

Axis suppression	Minor surgical stress (hernia)	Moderate surgical stress (articular replacement)	Major surgical stress (CABG)
No PDN <5 mg/d Glucocorticoids <3 wk Negative corticotropin test	Daily dose No supplementation	Daily dose No supplementation	Daily dose No supplementation

Documented or suspected
PDN >10 mg/d for >3 wk
Cushingoid
Positive corticotropin test
	Daily dose
	No supplementation
		Hydrocortisone
		50 mg IV (induction)
		25 mg IV every 8 h
		  for 24-48 h
			Hydrocortisone
			100 mg IV (induction)
			50 mg IV every 8 h
			  for 24 h
			25 mg IV every 8 h
			  for 24-48 h

Unknown
PDN 5-10 mg ≥3 wk
	Daily dose
	No supplementation
		Positive corticotropin test
		Hydrocortisone
		50 mg IV (induction)
		25 mg IV every 8 h
		  for 24-48 h
			Hydrocortisone
			100 mg IV (induction)
			50 mg IV every 8 h
			  for 24 h
			25 mg IV every 8 h
			  for 24-48 h

CABG = coronary artery bypass grafting; IV= intravenously; PDN = prednisone.
Adapted from *Med Clin North Am*,[36] with permission from Elsevier and *Perioperative Medicine: Just the Facts*,[37] with permission from McGraw-Hill.

stress. Important factors that may influence this variation include concomitant medication use, antecedent illnesses, and age. In general, patients receiving 5 mg or less of prednisone each day, alternate-day glucocorticoids, or any dose of glucocorticoids for less than 3 weeks are not considered to have a suppressed HPA axis and do not require "stress-dose" glucocorticoids.[31-34] In contrast, patients receiving less than 20 mg/d of prednisone (or its equivalent) for more than 3 weeks or with features of Cushing syndrome should be assumed to have a suppressed HPA axis and considered for "stress-dose" glucocorticoid supplementation perioperatively. For patients receiving between 5 and 10 mg of prednisone or its equivalent for more than 3 weeks, a clinical prediction rule cannot be implemented because, in this subset of patients, the HPA axis may or may not be suppressed. Generally speaking, rather than subjecting these patients to a corticotropin stimulation test, which may not reliably predict HPA axis suppression, it may be prudent to provide glucocorticoid supplementation in these patients. However, the administration of glucocorticoids in any patient who has been receiving prednisone doses of more than 5 mg/d for more than 1 week in the 6 to 12 months before surgery appears unnecessary.

The physician performing the preoperative assessment should bear in mind that patients receiving long-term high-dose inhaled or topical glucocorticoids for various conditions may have a suppressed HPA axis and may be candidates for "stress-dose" glucocorticoids. Although a healthy person is estimated to secrete between 20 and 30 mg of cortisol a day,[35] the requirement for patients undergoing a surgical procedure, while varying according to the degree of expected stress, rarely exceeds 200 mg of cortisol secretion in 24 hours.[22] Currently, expert consensus favors opti-

mizing the glucocorticoid replacement dose to the magnitude of stress posed by the surgery.

Patients receiving glucocorticoid therapy should receive their daily requirement throughout the perioperative period, along with supplementation as outlined in Table 2.[36,37]

PURINE ANALOGUES (6-MERCAPTOPURINE/AZATHIOPRINE)

These agents have been widely used as glucocorticoid-sparing agents for maintenance of remission. Both agents are oxidized or methylated in erythrocytes or the liver. The perioperative use of immunomodulators such as purine analogues does not affect surgical outcomes or morbidity. Early complications after proctocolectomy with ileal pouch-anal anastomosis were not found in patients using azathioprine/6-mercaptopurine but were observed in patients receiving high-dose glucocorticoids in a study by Mahadevan et al.[38] However, potential concerns related to purine analogues are pancreatitis, leukopenia, hepatitis, and bone marrow suppression.

Azathioprine is known to be antagonistic to neuromuscular blocking agents. Dretchen et al[39] described a reversal of neuromuscular blockage produced by D-tubocurarine but an increase of the neuromuscular blockade produced by succinylcholine. The effects of azathioprine on neuromuscular transmission are considered to be secondary to inhibition of phosphodiesterase in the motor nerve terminal. Gramstad[40] suggested that the initial dose of neuromuscular blocking drugs in renal transplant patients should be increased in the presence of azathioprine (atracurium by 37%, vecuronium by 20%, and pancuronium by 45%). In this study, the atracurium dose was unaffected by renal function, whereas dose requirements for vecuronium

and pancuronium were reduced by 23.2% and 61.5%, respectively, compared with patients not taking azathioprine. These findings suggest a transient antagonism of neuromuscular blockade in the presence of azathioprine.

Aberra et al[41] performed a retrospective cohort study in 159 patients with IBD who underwent elective bowel surgery, including 56 patients receiving glucocorticoids alone, 52 receiving 6-mercaptopurine/azathioprine with or without glucocorticoids, and 51 patients receiving neither glucocorticoids nor 6-mercaptopurine/azathioprine. The rate of postoperative infectious complications was not found to be significantly higher in the group receiving glucocorticoids or a combination of glucocorticoids and purine analogues. In an animal study conducted by Brokowski et al,[42] the regeneration of a ureter and renal pelvis from a transected and anastomosed strip of the ureteral wall was not associated with any adverse effect on wound healing in dogs receiving prednisone and azathioprine.

In a study by Colombel et al,[43] the rate of postoperative complications was not increased in 207 patients with CD who underwent intra-abdominal surgery while receiving glucocorticoids or immunosuppressive therapy with azathioprine, 6-mercaptopurine, methotrexate, or infliximab.

Myrelid et al[44] reported an 8% risk of postoperative intra-abdominal septic complications in 343 consecutive patients undergoing surgery for CD. Overall, thiopurine therapy was associated with an increased risk of intra-abdominal septic complications (16% vs 6% without therapy; P=.044). The use of thiopurines was associated with a 24% risk of septic complications in patients who had known risk factors (both preoperative intra-abdominal sepsis and use of colo-colonic anastomosis), 13% in patients with only 1 of these risk factors, and only 4% in patients with none of these risk factors (P<.001).

A potential association between the use of thiopurines and myelotoxicity has been reported.[45] It has been recommended, on the basis of weak evidence and physiologic considerations, that thiopurines be stopped on the day of surgery and resumed 3 days afterward because of their renal elimination and potential for toxic metabolite accumulation.[46] However, the incidence rate of severe myelotoxicity is less than 1% per patient and year of treatment, and the mortality risk is less than 0.1%[47]; therefore, although a theoretical risk for perioperative myelotoxicity exists, it is almost negligible. Therefore, our recommendation is to withhold thiopurines on the day of surgery and, if renal function remains normal, to resume within the first 3 postoperative days when oral medications are resumed.

CYCLOSPORINE

This potent immunosuppressive agent has been used in patients with glucocorticoid-refractory UC as rescue therapy before colectomy and occasionally in patients with CD. Cyclosporine, a potent inhibitor of T cells that is metabolized in the liver by CYP3A, is primarily excreted in bile; however, 6% of the drug is eliminated unchanged in urine. Major adverse effects include nephrotoxicity, seizures, and opportunistic infections. The mortality rate with opportunistic infections can be as high as 3.5%[48]; hence, patients receiving cyclosporine and glucocorticoid therapy should be carefully monitored for any signs of infection. These patients should also receive due consideration for *Pneumocystis jiroveci* prophylaxis with trimethoprim-sulfamethoxazole.

Preoperative cyclosporine has not been shown to have any detrimental effects during or after surgery. In a small case series of 25 patients, Pinna-Pintor et al[49] found no increased postoperative complications in patients treated with intravenous or oral cyclosporine. These findings were consistent with previous studies.[50,51]

We recommend careful observation of patients receiving cyclosporine for deterioration in renal function and opportunistic infections. At the same time, cyclosporine levels ought to be carefully monitored. Current clinical data are inadequate to support the discontinuation of this drug before and immediately after surgery.

METHOTREXATE

Methotrexate competitively inhibits the enzyme dihydrofolate reductase, impairing DNA synthesis and therefore cellular replication. Evidence to support its use in UC is minimal.[52] Methotrexate is excreted by the kidneys, and patients with renal impairment require dose adjustment. Major adverse effects include thrombocytopenia (up to 10%), pneumonitis, and hepatotoxicity. Perioperative considerations include, but are not limited to, an increase in infectious complications; in the setting of renal impairment, a toxic buildup of its metabolites can lead to bone marrow suppression.[53,54] In a 1997 study of a population of patients undergoing elective orthopedic surgery for rheumatoid arthritis, Bridges and Moreland[55] found increased perioperative complications in a small number of patients. Multiple subsequent studies in patients undergoing orthopedic surgery have suggested an increased risk of postoperative complications, consisting mainly of infections.[56-58] Grennan et al[59] published a retrospective study of 388 patients with rheumatoid arthritis who underwent surgery while receiving methotrexate and concluded that continuation of methotrexate does not increase the risk of either infections or surgical complications in patients within one year of elective orthopedic surgery. Most studies have not specifically addressed the effect of methotrexate in the perioperative period on renal function.

Concern has been raised about the potential interaction between nitrous oxide used for anesthesia and methotrex-

ate. A substantial interaction between nitrous oxide–based anesthesia and methotrexate in cancer patients undergoing surgery has been demonstrated by in vivo studies. According to these studies, patients who receive methotrexate during the immediate postoperative period (within 6 hours) after nitrous oxide–based anesthesia often develop severe bone marrow depression and mucositis.[60] However, no quantitative data for dose-effect interactions are available regarding the combined toxic effects of methotrexate and nitrous oxide.

Most published trials have included patients receiving low dosages of methotrexate (5-10 mg weekly). Only a paucity of data supports the currently recommended dosages of 15 mg weekly with escalation to 20 to 30 mg weekly depending on clinical response and tolerability.[61,62]

Existing data do not suggest a significant increase in the risk of perioperative infections or impaired wound healing. Given the lack of data, in patients with a history of previous or severe septic complications, it may be reasonable to discontinue methotrexate 1 week before surgery and resume it no sooner than 1 week after or when the wound has successfully healed. The risks vs the benefits of discontinuation should be discussed with the patient, and the potential for flare of the disease should be weighed against the potential of poor wound healing or infectious complications.[63]

BIOLOGIC THERAPY

Treatment for IBD has entered an era of biologic response modifiers. One such agent, infliximab, a chimeric monoclonal antibody targeting TNF-α, is the first drug approved by the US Food and Drug Administration for the treatment of CD. Its role in the treatment of refractory CD is well established,[64,65] and current data support its use in patients with moderately to severely active UC who have had an inadequate response to conventional therapy.[66] Infliximab has a long half-life of 8.0 to 9.5 days and has its own unique adverse effect profile. Several adverse effects have been reported for TNF-α–blocking agents, including reactivation of tuberculosis; an increased risk of sepsis, pneumonia, and fatal and opportunistic infections (eg, invasive fungal infections, listeriosis, *Pneumocystis* infections); reactivation of chronic hepatitis B in carriers; worsened chronic heart failure; optic neuritis; demyelination reactions; bone-marrow toxicity infusion reactions; acute and delayed hypersensitivity reactions; and formation of anti–double-stranded DNA.[67-70]

Despite its potent immunosuppressive effects, preoperative use of infliximab does not seem to increase postoperative complications in patients with UC or CD. In a cohort of 314 patients with CD, 40 of whom received 1 or more infusions of infliximab before intestinal resection, Marchal et al[71] found no increase in postoperative infections

or prolongation of hospital stay after infliximab infusion. In a study by Jarnerot et al[72] using infliximab as rescue therapy in patients with moderately severe UC, 7 patients who received infliximab underwent colectomy without any increase in the postoperative complication rate. On the basis of their retrospective study of 277 patients with CD who received infliximab within 8 weeks of surgery and 4 weeks after surgery in addition to other immunomodulators, Colombel et al[43] concluded that infliximab is safe in the perioperative setting. A 30-day postoperative follow-up showed no increase in septic and nonseptic complications.

In a cohort study by Kunitake et al[73] of 413 patients with IBD who underwent abdominal surgery, the rate of postoperative complications was similar in the 100 patients who had received infliximab 12 weeks or less before surgery vs those who had not.

Bordeianou et al[74] compared 44 patients with UC and symptoms of unremitting disease who were taking infliximab before TPC or a subtotal colectomy with 127 patients who were not using infliximab. The outcomes in both groups were similar: rate of emergent surgery (4.5% vs 0.4%; P=.98), rate of subtotal colectomy (19.2% vs 18.0%; P=.99), or rate of ileoanal J pouch reconstruction (53.8% vs 62.0%; P=.98). The authors concluded that infliximab contributed no increased surgical morbidity in patients with UC.

Kraemer et al[75] found that 16 of 19 patients who received 5 mg/kg of infliximab perioperatively during scheduled anal reconstructive surgery for complicated fistulizing anal CD had a favorable outcome, findings similar to those of other studies in the same population. In the TREAT registry study evaluating 6290 patients, Lichtenstein et al[76] found that infliximab was not independently associated with increased risk after adjustment for corticosteroid use and disease severity; however, both corticosteroids and disease severity were associated with adverse outcomes. In a recent study by Gainsbury et al,[77] infliximab was not associated with increased risk of short-term postoperative complications after proctocolectomy and ileoanal anastomosis.

A retrospective study of 389 patients with CD who underwent ileocolonic resection at the Cleveland Clinic, 60 of whom received infliximab within 3 months before surgery, found an increased rate of postoperative sepsis, abscess, and readmissions in the patients who received infliximab; the authors of this study suggested that these complications might have been prevented by a diverting stoma.[78] Of these patients, those using infliximab had an increased rate of early complications (OR, 3.54; 95% CI, 1.51-8.31; P=.004) or sepsis (OR, 13.8; 95% CI, 1.8-105.0; P=.011) and an increased need for a 3-stage procedure (OR, 2.07; 95% CI, 1.18-3.63; P=.011), leading Mor et al[79] to conclude that infliximab use has changed

the surgical approach to UC by increasing the number of operations. However, in response to an invited editorial comment, they acknowledged that 3-stage procedures are safe in these patients.

In a multivariate analysis of 301 patients with UC who underwent ileal pouch anal anastomosis, 47 of whom received infliximab preoperatively, Selvasekar et al[80] reported that infliximab was the only factor independently associated with infectious complications in this group of patients.

Toruner et al[18] described a substantial increase in the risk for opportunistic infection in patients taking a combination of 2 or 3 immunosuppressants (OR, 14.5; 95% CI, 4.9-43) vs those taking a single immunosuppressant (OR, 2.9; 95% CI, 1.5-5.3).

A recent study by Cottone et al[81] demonstrated a higher risk of severe infections (11%), neoplasms (3%), and mortality (10%) in patients older than 65 years who received TNF inhibitor therapy than in younger patients or in patients of the same age who did not receive such treatment.

Although new anti-TNFα drugs (eg, adalimumab and certolizumab pegol) are available for the treatment of CD, no data regarding their use in the perioperative setting have been reported. The safety profile of these medications appears to be similar to that of infliximab, especially for fistulizing CD.[82-88]

Another recently introduced agent that has been approved for the management of moderate to severe CD is natalizumab, a humanized monoclonal antibody against the α4 integrin subunit that inhibits leukocyte adhesion and migration to areas of inflammation. However, safety concerns regarding its association with progressive multifocal leukoencephalopathy have limited its use. Data regarding its use in the perioperative setting are unavailable.

Most evidence suggests that infliximab can be used safely in the perioperative period. Divergent data may reflect the higher burden of comorbidity (concomitant immunosuppressant use, increased severity of disease) in patients with adverse outcomes.

Practices being increasingly recommended to improve outcome include staged surgeries with temporary diverting stomas and the selection of 3- rather than 2-stage ileal pouch anal anastomosis.[7,89]

In a recent review, Beddy et al[5] questioned whether it was justifiable to delay surgery in patients who have recently been administered infliximab or to create a proximal diverting stoma purely to deliver biologic medications. Currently, we do not recommend the discontinuation of immunomodulator therapy with anti-TNF agents in the perioperative setting. However, the clinician should be aware of all possible complications, including serious infections, in surgical patients receiving these agents.

PERIOPERATIVE MEDICATION AND THROMBOEMBOLIC EVENTS IN IBD

Patients with IBD have long been known to be at increased risk of thromboembolism. In 1936, Bargen and Barker[90] at Mayo Clinic reported that 18 of 1500 patients with UC had evidence of extensive arterial and venous thrombosis. Since then, the association of these complications with IBD has been increasingly recognized. Thromboembolic complications in the cerebral and retinal vasculature,[91] the portal vein, and peripheral arteries[92] have been reported. In a case series of IBD-related thromboembolism from Mayo Clinic, the activity of disease and extent of colonic involvement in patients with UC were found to be associated with increased risk; however, 87% of patients in this study had another risk factor for venous thrombosis, such as hospitalization, immobilization, malignancy, or recent surgery.[93] These risk factors are common in patients who are undergoing surgery, and aggressive antivenous thrombosis prophylaxis should be considered in these patients. However, no guidelines for venous thrombosis prophylaxis specifically in IBD patients have been published. In a study by O'Connor et al,[94] the event rate of clinical thrombosis after major abdominal and pelvic surgery for patients with UC was noted to be similar to that in patients without UC undergoing similar surgery. The authors of that study concluded that standard prophylaxis in a patient with UC is acceptable to reduce the occurrence of thrombotic events in the perioperative period.

Inherited risk factors for thrombosis, such as the factor V Leiden mutation, the G20210A mutation in the prothrombin gene, and the homozygous C677T mutation in the methylenetetrahydrofolate reductase gene, have not been attributed to increased thrombosis in patients with IBD.[95] However, a thorough investigation of the coagulation profile and genetic testing is advisable in younger IBD patients with a first idiopathic thrombotic event.[96]

Hyperhomocysteinemia, which is considered a risk factor for arterial as well as venous thrombosis, has been found to be more prevalent in patients with IBD[97] but has not been found to be a major contributory factor in the development of venous or arterial thrombosis in patients with IBD.[98]

Using a large outpatient database (Manitoba Health database), Bernstein et al[99] demonstrated a 3-fold increased risk of developing deep venous thrombosis (DVT) or pulmonary embolism (PE) in patients with IBD, incidence rates of 31.4 per 10,000 person-years for DVT and 10.3 per 10,000 person-years for PE in patients with CD, and incidence rates of 30.0 per 10,000 person-years for DVT and 19.8 per 10,000 person-years for PE in patients with UC.[99]

In a more recent study among 13,756 patients with IBD and 71,672 matched controls, Grainge et al[100] found that

139 patients and 165 controls developed venous thromboembolism (VTE); patients with IBD had a higher risk of VTE compared with controls (hazard ratio, 3.4; 95% CI, 2.7-4.3; *P*<.001; absolute risk, 2.6 per 1000 person-years).

In the inpatient setting, Nguyen and Sam[101] evaluated a large national database of 522,704 discharges of non-IBD patients compared with 73,197 discharges of patients with CD and 43,645 discharges of patients with UC; the risk of VTE was 1.5- to 1.8-fold higher among patients with vs without IBD (*P*<.001). In patients with IBD, VTE risk was higher among patients with UC or fistulizing CD.[101]

The Joint Commission National Quality Core measures specifications include the appropriate use in patients undergoing general surgery of pharmacological VTE prophylaxis, including unfractionated heparin, low-molecular-weight heparin (LMWH), factor Xa inhibitor (fondaparinux), and any pharmacological choice combined with a physical measure (stockings or intermittent pneumatic compression devices). Nonpharmacological prophylaxis is used in patients with a high risk of bleeding.[102]

No studies have specifically evaluated the potential benefit of VTE prophylaxis in hospitalized or ambulatory patients with IBD. Studies to date do not support an increased bleeding risk with moderate doses of anticoagulant medications in patients with active IBD.[103]

During the perioperative period, we recommend that patients with IBD receive prophylaxis based on American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition).[104] However, a recent study by Scarpa et al[105] demonstrated that standard prophylactic LMWH may be insufficient for VTE prophylaxis in patients with IBD. In a series of patients undergoing major colorectal surgery from 1999 until 2006, they demonstrated an elevated risk of postoperative DVT in patients with UC colitis (OR, 7.4; 95% CI, 1.4-44.4; *P*=.017) despite prophylactic anticoagulation with 4000 IU/d of LMWH. The rate of DVT in patients with UC was higher than in patients with colorectal cancer (*P*=.009).

For patients undergoing open surgery, we recommend prophylaxis with 5000 U of subcutaneous heparin 3 times daily, 40 mg of subcutaneous enoxaparin once daily, or 2.5 to 5.0 mg of subcutaneous fondaparinux daily.

CONCLUSION

Perioperative physicians play a critical role in controlling and standardizing the management of surgical patients receiving immunomodulator or immunosuppressant therapy. However, sound research in this field has been limited, especially in the subgroup of patients with IBD.

Over the years, the management of patients receiving glucocorticoids perioperatively has become fairly standardized. Guidelines for the management of patients receiving methotrexate have been based largely on findings from orthopedic studies. Although the evidence on which these recommendations are based is admittedly less than robust, we recommend a conservative approach in patients older than 65 years and in patients with renal impairment.

Azathioprine and 6-mercaptopurine use should be carefully monitored in patients at risk for toxicity. Cyclosporine use poses a substantial risk of postoperative opportunistic infections. Patients receiving cyclosporine therapy tend to be much sicker and prone to an increased rate of opportunistic infections.

With the exciting advent of biologic agents have come new challenges. The experience in the perioperative use of most of these agents is certainly not sufficient to make any accurate predictions regarding their efficacy and safety; however, the current level of evidence, although limited, has been reassuring for the use of infliximab in the perioperative period.

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