What Are the Complications of Home IBD Medications?

90

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Pearls and Pitfalls

- Side effects of glucocorticoids are generally dose-dependent, and even low doses are associated with adverse effects when they are used long term.
- Fluoroquinolones may cause QT prolongation and predispose to life-threatening cardiac dysrhythmias. Ciprofloxacin prolongs the QT interval less than other fluoroquinolones.
- While side effects occur with both sulfasalazine and mesalamine, they are more common with sulfasalazine. 20–25% of patients will discontinue sulfasalazine use due to significant side effects.
- Anti-TNF medications should be used with extreme caution in patients with preexisting demyelinating disease or heart failure.

Inflammatory bowel disease (IBD) medications are vital for both managing acute exacerbations and decreasing long-term morbidity. They have wide-ranging and significant side effects that clinicians must consider both when initiating these medications and when evaluating patients who are already on them. Many of these side effects are class specific (Table 90.1).

Table 90.1 Adverse reactions of common IBD medications

Drug class	Significant adverse reactions
Steroids[a]	Immune deficiency Endocrine abnormalities, including hyperglycemia and adrenal suppression Osteopenia
Antibiotics[b]	Peripheral neuropathy QT prolongation *Clostridium difficile*
Aminosalicylates	Idiosyncratic reactions Paradoxical worsening Gastrointestinal effects Central nervous system effects Hematologic effects
Immunomodulatory agents	Hepatotoxicity Nephrotoxicity Neurotoxicity Malignancy Infection Bone marrow suppression Gastrointestinal effects
Anti-TNF biologics	Infection Anaphylactoid reactions Anaphylactic reactions Serum sickness-like reaction Pulmonary fibrosis Hepatotoxicity Cutaneous reactions

aSee Table 90.2 for a more complete list of steroid side effects
bSee Table 90.3 for a more complete list of antibiotic side effects

Glucocorticoids

Systemic steroids play an important role in the management of IBD and are generally used when patients have severe symptoms or have not responded to other treatments. Side effects are generally dose-dependent, and even low doses are associated with adverse effects when they are used long term [1]. Glucocorticoids produce a broad range of side effects in various organ systems, many of which are shown in Table 90.2.

Side effects decrease when topical glucocorticoids (rectal foams and enemas) are substituted for systemic steroids. Patients with distal bowel symptoms are candidates for these topical glucocorticoids.

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Table 90.2 Glucocorticoid side effects

Systemic glucocorticoid side effects	
Organ system	Side effects
Skin	Skin thinning, purpura, skin cancer
Eye	Cataracts, glaucoma
Cardiovascular	Ischemic heart disease, heart failure
Gastrointestinal	Gastritis, ulcers, gastrointestinal bleeding
Musculoskeletal	Osteopenia, muscle weakness
Central nervous system/ psychiatric	Mood disorders, psychosis, memory decline
Endocrine	Hyperglycemia, adrenal suppression
Immune system	Immune deficiency, leukocytosis, neutrophilia
Genitourinary	Fluid retention, decreased fertility

Table 90.3 Side effects of commonly used antibiotics in IBD patients

Antibiotic	Side effects
Ciprofloxacin	Gastrointestinal effects CNS effects Tendinopathy QT prolongation
Metronidazole	Gastrointestinal effects Peripheral neuropathy
Rifaximin	Peripheral neuropathy Ascites
Clarithromycin	Gastrointestinal effects

Antibiotics

Patients with IBD are frequently treated with antibiotics, most commonly ciprofloxacin, metronidazole, rifaximin, and clarithromycin. Table 90.3 summarizes the side effects of these medications.

Ciprofloxacin and other fluoroquinolone antibiotics most commonly produce mild gastrointestinal (GI) side effects, including anorexia, nausea, and abdominal discomfort. Central nervous system (CNS) side effects also occur, including headache, dizziness, and peripheral neuropathy [2]. Ciprofloxacin predisposes to tendon rupture. Fetal cartilage defects may occur if given during pregnancy [3]. Fluoroquinolones may cause QT prolongation and predispose to life-threatening cardiac dysrhythmias. Ciprofloxacin prolongs the QT interval less than other fluoroquinolones [4].

Metronidazole produces many GI side effects, including anorexia, nausea, altered taste, and disulfiram-like reactions. Metronidazole has also been associated with a 4.3-fold increased risk of permanent peripheral neuropathy [5].

Rifaximin is a broad-spectrum antibiotic which most commonly causes peripheral neuropathy, dizziness, nausea, fatigue, and ascites.

Clarithromycin's most common side effects are gastrointestinal.

Importantly, antibiotics increase the risk of *Clostridium difficile* infection because they disrupt the normal intestinal flora and allow this bacterium to proliferate and increase toxin production. Many antibiotics predispose to *C. difficile*, including ciprofloxacin and metronidazole [6].

Aminosalicylates

Aminosalicylates (5-ASAs), including sulfasalazine and mesalamine, are well tolerated in the majority of patients. Mesalamine is an unconjugated aminosalicylate. Sulfasalazine includes a sulfapyridine group, which accounts for many of its side effects. While side effects occur with both drugs, they are more common with sulfasalazine. In fact, 20–25% of patients will discontinue sulfasalazine use due to significant side effects [7].

Idiosyncratic reactions are an important class of reactions to aminosalicylates, and they occur due to either hypersensitivity or immune-related reactions. They include skin rash, hepatitis, pancreatitis, pneumonitis, interstitial nephritis, agranulocytosis, and aplastic anemia. When these occur, the drug must be stopped, and other aminosalicylates should be avoided. While agranulocytosis is a rare and life-threatening side effect, most leukopenias with these medications are mild, are transient, and occur during the first 3 months of treatment [8].

A small number of patients on oral 5-ASAs will have paradoxical worsening of their abdominal pain, bleeding, and/or diarrhea. These patients should be considered allergic, and the medication should be stopped [9].

Dose-related effects of sulfasalazine include gastrointestinal, central nervous system, and mild hematologic toxicities. The most common symptoms include nausea, headache, fever, and rash.

Immunomodulatory Agents

Immunomodulatory agents commonly used to treat inflammatory bowel disease include azathioprine, 6-mercaptopurine, methotrexate, and tacrolimus.

6-Mercaptopurine is a metabolite of azathioprine, and both are classified at thiopurines. These two drugs produce side effects in 9–15% of patients, usually during the first month. The most common side effects are nausea, vomiting, and anorexia. Dose-dependent adverse reactions include bone marrow suppression in 1–2% and liver dysfunction in 0.3%. Other dose-independent reactions include pancreatitis, allergic reactions, nausea, and pneumonitis [10]. Importantly, patients taking thiopurines are at increased risk of cancers: mostly lymphomas but also lymphoproliferative disorders and non-melanoma skin cancers [11].

The most common side effects of methotrexate include nausea and vomiting. Hepatotoxicity may occur and is related to both the dose and duration of treatment [12].

Tacrolimus and cyclosporine may occasionally be used in refractory inflammatory bowel disease. Their side effects are similar and include nephrotoxicity, hypertension, neurotoxicity, infections, and malignancies. Nephrotoxicity manifests as either an acute reversible creatinine increase or a chronic progressive disease [13]. Hypertension is caused by renal vasoconstriction and sodium retention, and it usually responds to dose reduction [14]. A variety of reversible neurologic side effects have been described, including tremor, headache, seizure, mutism, and pain syndromes [15]. Patients taking cyclosporine and tacrolimus are at increased risk of bacterial, viral, and fungal infections [16]. Both drugs are also associated with an increased risk of developing squamous cell skin cancers and lymphoproliferative disorders [17].

Biologic Therapies

Biologic therapies are generally reserved for severe inflammatory bowel disease.

The most commonly used subclass of medications within the biologics are the antitumor necrosis factor (TNF) antibodies, including infliximab, adalimumab, and certolizumab pegol.

Patients on anti-TNF therapy are thought to be at increased risk for infection, particularly pneumonia, herpes zoster, tuberculosis, and opportunistic pathogens; however, this risk appears to be greatly affected by additional medications and comorbidities [18].

Both acute (within 24 h) and delayed (1–14 days) infusion reactions may occur. Acute reactions are mostly anaphylactoid, but some are anaphylactic, and the treatment of both is the same. Delayed reactions are less common and include fever, rash, myalgias, and fatigue. These delayed reactions resemble serum sickness [19].

While mild neutropenia is not uncommon, pancytopenia and aplastic anemia are rare [20].

TNF inhibitors carry a small but serious risk of pulmonary fibrosis and hepatotoxicity.

Multiple cutaneous reactions occur with TNF inhibitors, including autoimmune dermatologic conditions and cutaneous malignancies [21].

Demyelinating diseases and heart failure have been suggested to occur with anti-TNF medications, but the data remains inconclusive. However, these drugs should be used with extreme caution in patients with preexisting demyelinating disease or heart failure [22, 23].

Suggested Resources

- Overview of inflammatory bowel disease. Merck manual: professional version. http://www.merckmanuals.com/professional/gastrointestinal-disorders/inflammatory-bowel-disease-ibd/overview-of-inflammatory-bowel-disease.
- Management of inflammatory bowel disease flares in the emergency department. EB medicine. Nov 2017. https://www.ebmedicine.net/topics.php?paction=showTopic&topic_id=559.
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