Inflammatory Bowel Disease Guidelines
Introduction
Inflammatory bowel disease (IBD) is a chronic inflammatory disease affecting the gastrointestinal (GI) system. It is comprised of two major disorders: ulcerative colitis (UC) and Crohn disease (CD). Ulcerative colitis and Crohn disease have distinct pathologic and clinical characteristics and their pathogenesis remains poorly understood.

Both disorders are associated with acute and chronic inflammation of the GI tract. Differences exist between UC and CD with regard to regions of the GI affected, the distribution and depth of intestinal inflammation.

Patients with IBD may also develop inflammation involving organs other than the GI tract, known as extraintestinal manifestations.

Epidemiology and etiology
The age of initial presentation is bimodal, with patients typically diagnosed between the ages of 20 to 40 or 60 to 80 years.

Men and women are approximately equally affected by IBD (male are more likely to experience UC compared with females, younger age who are more likely to have CD.

Whites are affected more often than blacks.

Patients with first relative who have IBD are 10 to 40 times at higher risk to develop IBD compared with the normal population.

Etiology
The exact cause of IBD is not fully understood. Genetic predisposition, dysregulation of the inflammatory response within the GI tract, and environmental or antigenic causes are possible factors.

Positive family history is a strong predictor of IBD; people are 10-40 times higher the risk to develop IBD if first relative degree has the disease.

Alteration in the inflammatory response regulated by intestinal epithelial cells may contribute to development of IBD.

Bacterial translocation (or its products) across the mucosal layer of the CI system may trigger many of the immunologic cells resulting in excess
production of proinflammatory cytokines and persistent inflammation within the GI tract.

Medications such as: nonsteroidal anti-inflammatory drugs (NSAIDs)

Use of oral contraceptives: a strong causal relationship has not been proven.

Smoking has protective effects in UC, leading to reduction in UC flares, opposite is true in CD because smoking increases and may worsen the symptoms.

Some products may increase the risk of IBD; cow milk hypersensitivity in infancy (linked to UC), refined sugar (linked to CD)

High omega 3, lower omega 6 intake has been associated with lower risk of developing CD.

**Pathophysiology**

**Ulcereative colitis**
The inflammatory response in UC is related to the production of pro-inflammatory cytokines such as interleukin (IL)-1, IL-6, and tumor necrosis factor-alpha (TNF-α).

Environmental factors (immune response against unknown antigen)

Smoking and appendectomies are protective factors.

The inflammatory process in UC is limited to the colon and rectum.

UC can be divided based on the location into:
1- Proctitis: involves only the rectum (most of the patients)
2- Proctosigmoiditis: involves both the rectum and the sigmoid colon
3- Pancolitis (extensive disease): inflammation involving the entire colon
4- Left- sided (distal): from the rectum to the splenic flexure (30-40 % of the patients)

5- Backwash ileitis: when UC involves the terminal ileum.
Figure 1: classification of UC

The pattern of inflammation in UC is continuous and confluent throughout the affected areas of the GI tract.

The inflammation is superficial and does not typically extend below the submucosal layer of the GI tract.

Formation of crypt abscesses within the mucosal layers of the GI tract is a characteristic of UC and may help to distinguish it from CD.

Severe inflammation may also result in areas of hypertrophied GI mucosa (manifested as pseudopolyps).

Severe inflammation eventually will lead to ulcerations and bleeding.
Crohn Disease
Proinflammatory cytokines release is the major contributor in CD.

CD may affect any part of the GI tract from the mouth to the anus.

The small intestine is most commonly involved. The terminal ileum and cecum are almost always affected.

The pattern of inflammation in CD is discontinuous

Areas of inflammation are intermixed with areas of normal GI mucosa, resulting in characteristic “skip lesions.”

Superficial ulcers may also develop in the GI mucosa. These ulcers may coalesce together resulting in fissure formation “cobblestone” pattern

The inflammation may be transmural, penetrating to the muscularis or serosal layers of the GI tract

Complications such as strictures, fistulae, abscesses, and perforation are common in CD.

Rectal inflammation is less common in CD than UC, including: hemorrhoids, fissures, anal ulcers, abscesses and fistula.
Figure 3: cobblestone formation in CD

Figure 4: depth of disease penetration in UC and CD
Clinical presentation and laboratory findings

Differentiation between UC and CD is based on signs and symptoms endoscopic findings (the extent, pattern, and depth of inflammation).

Clinical presentation:
Patients with UC or CD may present with similar symptoms.
Table 1: comparison between CD and UC

<table>
<thead>
<tr>
<th></th>
<th>CD</th>
<th>UC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Site of origin</strong></td>
<td>Terminal ileum</td>
<td>Rectum</td>
</tr>
<tr>
<td><strong>Pattern</strong></td>
<td>Skip lesions/irregular</td>
<td>Contiguous</td>
</tr>
<tr>
<td><strong>Thickness of inflammation</strong></td>
<td>Transmural</td>
<td>Submucosa/mucosa</td>
</tr>
<tr>
<td><strong>Symptoms</strong></td>
<td>Crampy abdominal pain</td>
<td>Bloody diarrhea</td>
</tr>
<tr>
<td><strong>complications</strong></td>
<td>Fistula/abscess and obstruction</td>
<td>Hemorrhage, toxic megacolon</td>
</tr>
<tr>
<td><strong>Risk of colon cancer</strong></td>
<td>Slight increase</td>
<td>Marked increase</td>
</tr>
<tr>
<td><strong>surgery</strong></td>
<td>For complications as stricture</td>
<td>Curative</td>
</tr>
</tbody>
</table>

**Extraintestinal Manifestations and Complications of IBD**

Painful joint complications associated with IBD include sacroiliitis and ankylosing spondylitis.

Ocular involvement with uveitis, or iritis (manifested as blurred vision, eye pain, and photophobia).

Skin findings: pyoderma gangrenosum and erythema nodosum
Nephrolithiasis may also develop at a higher rate in patients with IBD. Oxalate stones are more common in CD, and uric acid-containing stones are more common in UC.

Increase the incidence of gallstone formation in patients with CD and development of sclerosing cholangitis or cholangiocarcinoma in patients with UC.

Patients with UC are at increased risk for developing colorectal cancer.

Ongoing inflammation due to active IBD may induce a hypercoagulable state, resulting in deep vein thrombosis and pulmonary embolism.

Chronic anemia due to bleeding and malabsorption.

High rates of osteopenia, osteoporosis, and fractures

Nutritional deficiencies are more common in CD than in UC; including folate, vitamin B12, zinc and fat soluble vitamins.

Toxic megacolon: a serious complication of UC defined as dilation of the transverse colon greater than 6 cm. The patients present with fever, tachycardia and abdominal distention. Surgical intervention is usually required.

**Diagnosis**
The diagnosis is based on the symptoms, severity, frequency of diarrhea, systemic complications and the colonoscopic findings

Stool cultures to rule out infectious causes of diarrhea are recommended.

Endoscopy: useful for determining the disease distribution, pattern and depth of inflammation, and to obtain mucosal biopsy specimens.

Computed tomography, abdominal x-ray, abdominal ultrasound, or intestinal barium studies: evidence of complications such as obstruction, abscess.

For UC, a score called Mayo score used to assess the severity of the disease; ranges from 0-12 with higher values indicate more severe disease.
For CD: Crohn's Disease Activity Index (CDAI) is a score ranges from less than 150 to more than 450 used to stage CD, with higher values means more severe.

**Classification:**
UC is classified as mild, moderate, severe, or fulminant.

![Montreal classification of severity of ulcerative colitis](image)

Table 2: classification of UC

Fulminant UC: more than 10 stool per day with continuous bleeding, signs of systemic toxicity, abdominal distention or tenderness, colonic dilation, or a requirement for blood transfusion.

For CD:
Patients with mild to moderate CD:
Ambulatory and have no evidence of dehydration; systemic toxicity; loss of body weight; or abdominal tenderness, mass, or obstruction.
Moderate to severe disease:
Fail to respond to treatment for mild to moderate disease or systemic manifestations.

Severe to fulminant:
The presence of persistent symptoms or evidence of systemic toxicity despite outpatient corticosteroid treatment, or the presence of intestinal obstruction, or abscess.

**Treatment**

**Non pharmacologic therapy:**

- No specific dietary restrictions are recommended for patients with IBD.

- Avoidance of high-residue foods in patients with strictures may help prevent obstruction.

- Avoidance of excess dietary fat may be preferred.

- In patients with long standing IBD, nutritional supplements including the use of some vitamin and minerals such as: vitamin B12, folic acid, fat-soluble vitamins (vitamin D), iron, and calcium.

- Most malabsorption cases occur in patients with CD. Some cases may be severe enough requiring enteral or parenteral nutrition.

- Surgical intervention is an option in patients with complications such as fistulae or abscesses, or in patients with medically refractory disease.

- The effectiveness of transdermal nicotine patches for the treatment of mild to moderate ulcerative colitis has suggested. However, studies have not shown any effects on objective measures of disease.

- UC is curable with a total colectomy; patients with UC may choose to do a colectomy to reduce the chance of developing colorectal cancer.

- CD may recur following surgical resection.

**Pharmacologic Therapy**
Several pharmacologic classes are available for acute treatment and maintenance therapy of IBD.

The selection of an initial agent for active IBD should be designed to deliver maximum efficacy while minimizing toxicity.

*Symptomatic Interventions*

Patients with active IBD often have severe abdominal pain and diarrhea.

Antidiarrheal medications that reduce GI motility such as loperamide, diphenoxylate/atropine and hyoscyamine should be avoided in patients with severe active IBD due to the risk of acute colonic dilation (toxic megacolon).

They may be considered in mild active IBD till the effect of the IBD medications start.

NSAIDs should be avoided for pain management

Opioid analgesics should be used with caution because they reduce GI motility.

**Aminosalicylates:**

- The aminosalicylates are the most commonly used drugs for inducing and maintaining remission in patients with mild to moderate IBD.

- They are designed to deliver 5-aminosalicylate (5-ASA, mesalamine) to areas of inflammation within the GI tract. They have anti-inflammatory effects.

- Linking mesalamine to a carrier or changing the formulation to allow drug release according to intestinal pH ensures local drug delivery.

- Suppositories and enemas are designed to deliver mesalamine directly to the distal colon and rectum.

- Sulfasalazine (the prototype of meselamine), designed to prevent early absorption in the small intestine.
Common dose-related adverse effects of sulfasalazine include: headache, dyspepsia, nausea, vomiting, and fatigue.

Idiosyncratic effects: bone marrow suppression, reduction in sperm counts in males, hepatitis, and pulmonitis.

Hypersensitivity reactions may occur in patients allergic to sulfonamide-containing medications.

Nonsulfapyridine-based aminosalicylates are better tolerated than sulfasalazine.

They have the same type of adverse effects. However, they occur much less frequently.

Olsalazine is associated with a higher incidence of secretory diarrhea than other aminosalicylates.

These agents can be used in patients with sulfonamide allergy.

To reduce sulfasalazine GI symptoms: the patient better to take this medication with food and in divided doses.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Trade Names</th>
<th>Formulation</th>
<th>Strengths</th>
<th>Daily Dosage Range (g)</th>
<th>Site of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfasalazine</td>
<td>Azulidine</td>
<td>Immediate-release or enteric-coated tablets</td>
<td>500 mg</td>
<td>2-6</td>
<td>Colon</td>
</tr>
<tr>
<td></td>
<td>Azulidine En-tabs</td>
<td>Tablets</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Sulfazine</td>
<td>Suspension</td>
<td>250 mg/5mL</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Sulfazine EC</td>
<td></td>
<td></td>
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<tr>
<td>Mesalamine</td>
<td>Rowasa</td>
<td>Enema</td>
<td>4g/40 mL</td>
<td>4</td>
<td>Distal left colon and rectum</td>
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<tr>
<td></td>
<td>Asacol</td>
<td>Delayed-release resin tablet</td>
<td>400 mg</td>
<td>1.5-4.8</td>
<td>Distal ileum and colon</td>
</tr>
<tr>
<td></td>
<td>Asacol HD</td>
<td></td>
<td>800 mg</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Canasa</td>
<td>Rectal suppository</td>
<td>1000 mg</td>
<td></td>
<td>Rectum</td>
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<tr>
<td></td>
<td>Pentasa</td>
<td>Microgranule controlled-release capsule</td>
<td>250 mg</td>
<td>2-4</td>
<td>Small bowel</td>
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<tr>
<td></td>
<td>Lialda</td>
<td>MMX formulated pH-dependent polymer film coated tablet</td>
<td>500 mg</td>
<td>2-4</td>
<td>Colon</td>
</tr>
<tr>
<td></td>
<td>Olsalazine</td>
<td></td>
<td></td>
<td></td>
<td>Terminal ileum and colon</td>
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<td></td>
<td>Dipentum</td>
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<td></td>
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<tr>
<td></td>
<td>Colazal</td>
<td>Delayed-release capsule</td>
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<td>Colon</td>
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<tr>
<td></td>
<td>Glazio</td>
<td>Tablet</td>
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<td>Colon</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>250 mg</td>
<td>1-3</td>
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<td></td>
<td></td>
<td></td>
<td>1.1 g</td>
<td>2.2-6.6</td>
<td>Colon</td>
</tr>
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</table>

Table 3: Aminosalicylates for IBD treatment

Corticosteroids

Used in active IBD to suppress inflammation rapidly.

May be administered systemically or locally to the site of action.
- Use should be restricted to short-term management of active disease.


- Budesonide is a high-potency glucocorticoid used in IBD that has low systemic bioavailability when administered orally.

- Oral formulations may release in either the terminal ileum or colon.

- Compared to traditional corticosteroids, budesonide may reduce long-term adverse effects and can be used for induction therapy.

<table>
<thead>
<tr>
<th>Corticosteroids for Treatment of IBD</th>
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</thead>
<tbody>
<tr>
<td>Drug</td>
</tr>
<tr>
<td>Prednisone</td>
</tr>
<tr>
<td>Prednisolone</td>
</tr>
<tr>
<td>Budesonide</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Methylprednisolone</td>
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<tr>
<td></td>
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<tr>
<td></td>
</tr>
<tr>
<td>Cortenema</td>
</tr>
<tr>
<td>Cortifoam</td>
</tr>
<tr>
<td>Anusol-HC</td>
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<tr>
<td>Proctocort</td>
</tr>
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</table>

Table 4: corticosteroid doses in IBD

**Immunosuppressants**

- Agents targeting the immune response or cytokines involved in IBD are potential treatment options.

- Azathioprine and its active metabolite 6-mercaptopurine (6-MP) are used to suppression the inflammation in IBD

- These agents generally have slow onset (3-12) months and thus, should not be used for induction.
They are used in maintaining the remission to reduce the need for long term use of corticosteroids.

Adverse effects include: hypersensitivity reactions causes pancreatitis, fever, rash, hepatitis, and leukopenia.

Patients should be tested for activity of thiopurine methyltransferase (TPMT), the major enzyme responsible for metabolism of azathioprine prior to use. Deficiency or reduced activity of TPMT may result in toxicity from azathioprine and 6-MP and may require dose reductions.

Methotrexate (MTX) is a folate antagonist used for maintaining remission of CD. It may be administered orally, subcutaneously or IV. It has a steroid-sparing effect in steroid dependent patients. Adverse effects associated with long term use of MTX include: hepatotoxicity, pulmonary fibrosis, and bone marrow suppression. It is started IM 25 mg weekly then maintenance 15 mg weekly.

Cyclosporine: used in patients with fulminant or refractory symptoms in patients with active disease. Significant toxicities associated with cyclosporine are nephrotoxicity, risk of infection, seizures, hypertension, and liver function test abnormalities.

Biologic Agents
- Reduction in tumor necrosis factor (TNF-α) activity is associated with improvement in the inflammation in IBD.
- Infliximab, adalimumab, certolizumab, natalizumab are biologic agents that are used in moderate to severe cases of IBD.
- Disadvantages of anti-TNF biologic therapy include: the need for parenteral administration, high cost, and the potential for serious adverse effects.
- Adalimumab and certolizumab are administered subcutaneously, whereas infliximab requires intravenous (IV) infusion.
- Infliximab side effects include: infusion-related reactions such as fever, chest pain, hypotension, and dyspnea.
- Infliximab efficacy may be reduced over time, requiring change the patient to other anti-TNF such as adalimumab.
All TNF-α inhibitors have been associated with reactivation of serious infections such as tuberculosis and hepatitis B.

They should not be used in patients with existing infections.

Patients should be screened for latent tuberculosis and viral hepatitis prior to initiating therapy.

These agents should be avoided in patients with advanced or decompensated heart failure since they have the potential to induce heart failure exacerbation.

Anti-TNF-α agents also carry a risk of developing lymphoma.

The risk appears to be highest in younger male patients and those using concomitant azathioprine or 6-MP.

Natalizumab and vedolizumab are humanized monoclonal antibodies that antagonize integrin heterodimers.

Natalizumab is associated with development of progressive multifocal leukoencephalopathy (PML).

Use of natalizumab and vedolizumab is restricted to patients with who have failed all other therapies, including anti TNF-α agents.
Other Agents

- Antibiotics (such as metronidazole and ciprofloxacin) have been used in IBD, their use in IBD should be restricted for patients with infection (pouchitis), ileal resection or perianal fistula.

- Ciprofloxacin has shown some efficacy in refractory active CD and may be used in combination with metronidazole.

- Long-term metronidazole use leads to peripheral neuropathy.
The use of probiotics may prevent the relapse in mild to moderate UC. Inconsistent results for CD.

When treating patients who are low risk, step up in the treatment is generally recommended (by using less potent and less toxic medications). In contrast, patients with moderate to high risk patients require starting with more potent medications to achieve rapid remission (step-down therapy)

**Treatment of UC**

**Mild to Moderate Active UC**

- Topical mesalamine is superior to both topical corticosteroids and oral aminosalicylates in active mild to moderate UC, they provide quicker response time than oral preparations and typically require less frequent dosing.

- Patients with mild to moderate disease confined to the distal 5 to 8 cm of rectum: meselamine suppositories twice daily are the first line therapy.

- Mildly to moderately active disease (greater than 8 cm of distal; proctosigmoiditis):
  - 5-ASA enemas given twice daily in addition to (optional) 5-ASA suppositories twice daily

- Oral and topical mesalamine preparations may be used together for maximal effect. Oral mesalamine may also be used for patients who are unwilling or unable to use topical preparations.

- Topical corticosteroids are usually reserved for patients who do not respond to topical mesalamine.

- Oral budesonide may be used as either an alternative or add-on to aminosalicylates in patients with active UC.

- For patients with disease extending proximal to the splenic flexure, oral sulfasalazine or any of the oral mesalamine products are considered first-line therapy.
Doses should provide 4 to 6 g of sulfasalazine or 2.4 g of mesalamine or equivalent.

Induction of remission may require 4 to 8 weeks of therapy at appropriate treatment doses, then tapering and dose reduction should be considered.

Patients who cannot tolerate topical 5-ASA medications should be treated with steroid preparations (suppositories, enema) for the induction of remission, the choice of the topical steroid preparation depends on the extent of the disease.

Patients who do not have an adequate response to topical therapy should be treated with the combination of oral 5-ASA and topical 5-ASA enemas or suppositories.

In mild cases, oral 5-ASA products should be started at lower doses. Patients with moderate disease, previous steroid use, and frequent relapse are more likely to benefit from higher doses.

Oral mesalazine acts in two to four weeks. Patients who fail to respond to combination therapy with oral 5-ASA and topical 5-ASA/steroids require treatment with oral glucocorticoids.

**Maintenance therapy:**

- Maintenance therapy is not recommended in patients with a first episode of mild ulcerative proctitis that has responded promptly to treatment.

- Patients with ulcerative proctitis who have more than one relapse a year and in all patients with proctosigmoiditis require long term treatment.

- Discontinuation of medication in these patients should only be considered if they have been in remission for two years.

- For patients on topical therapy for induction of remission, a maintenance regimen of one 5-ASA suppository in proctitis and 5-ASA enema every night in proctosigmoiditis is recommended.

- Patients with frequent relapses need higher doses of maintenance therapy.

**Left-sided colitis (extensive colitis) and pancolitis:**
Initial approach: Combination of oral plus rectal 5-ASA leads to a higher rate and a reduced time to remission compared with either therapy alone.

Oral 5-ASA medications can be started at the lowest dose. In patients who remain symptomatic despite the combination therapy, the dose of oral 5-ASA medications should be increased to the maximum tolerated dose.

In patients with severe symptoms and those who fail to respond, oral corticosteroids (budesonide) are the next option.

Prednisone is used when budesonide failed to achieve remission; it is usually effective within 10 to 14 days, after which the dose can be tapered.

**Moderate to Severe Active UC**

- Oral corticosteroids may be used for short-term treatment of patients who are unresponsive to sulfasalazine or mesalamine.
- Prednisone doses of 40 to 60 mg/day (or equivalent) are recommended.
- Infliximab, adalimumab and certolizumab are effective for patients with moderate to severe disease who are unresponsive to oral therapies.
- Azathioprine or 6-MP (for maintaining the remission) is used for patients unresponsive to corticosteroids or those who become steroid dependent and may be combined with infliximab for increased effectiveness.

**Severe or Fulminant UC**

- Patients with severe UC symptoms require hospitalization.
- If the patient is unresponsive to mesalamine and oral corticosteroids, a course of IV corticosteroids should be initiated (hydrocortisone 300 mg/day IV given in three divided doses or methylprednisolone 60 mg IV once daily for 7 to 10 days) are recommended.
- Infliximab and adalimumab are also options for severe UC.
- Cyclosporine 2 to 4 mg/kg/day given as a continuous IV infusion is reserved for patients unresponsive to 7 to 10 days of IV corticosteroid therapy.

**Maintenance of Remission in UC**

- 50% of patients receiving oral therapies and up to 70% of untreated patients relapse within 1 year after remission.

- Maintenance of remission of UC may be achieved with oral or topical aminosalicylates:
  - In patients with proctitis, mesalamine suppositories may prevent relapse in up to 90% of patients.
  - Oral mesalamine at lower doses (e.g., 1.2–1.6 g/day) may be combined with topical therapies to maintain remission.
  - Oral sulfasalazine or mesalamine is effective in maintaining remission in patients with more extensive disease.

- Glucocorticoids should be tapered over eight weeks after the patient has been stable for two to four weeks.

- If glucocorticoids cannot be tapered to less than 10 mg daily or if relapse occurs within three months of stopping them, patients are considered “steroid-dependent”.

- Immunosuppressants such as azathioprine, 6-MP, infliximab and adalimumab can be used to maintain UC remission in unresponsive patients or those who develop corticosteroid dependency.

- Patients without a response to glucocorticoids (doses of oral prednisone 40 to 60 mg/day or equivalent) within 30 days or 7 to 10 days for intravenous therapy are considered “steroid-refractory”. Medical therapy with cyclosporine as a "bridge" to therapy with longer acting medications (AZA or 6-MP) or a biologic agent should be considered.

- Combining azathioprine and infliximab may be more effective initially, and patients may be able to be transitioned to azathioprine monotherapy.
Colectomy is an option for patients with progressive disease who cannot be maintained on drug therapy alone.

Algorithm 1: management of UC
Algorithm 2: Steroid refractory UC

**Steroid-refractory ulcerative colitis**

Lack of a meaningful clinical response to glucocorticoids up to doses of prednisone 40 to 60 mg/day (or equivalent) within 30 days for oral therapy or 7 to 10 days for IV therapy

1. **Already on IV steroids?**
   - No
     - Initiate IV methylprednisolone (40 to 60 mg/day) or equivalent
     - Responding within 3 days: well by 7 days?
       - Yes
         - Switch to oral prednisone 40 to 60
       - No
         - Refer to Algorithm 1: Steroid-dependent ulcerative colitis (Entry point "A")
   - Yes
     - Previous/current 6-MP/AZA failure/allergy?
       - Yes
         - Infliximab
       - No
         - Cyclosporine

2. **Relapse**
   - Wean steroids: maintain infliximab
   - Check serum biologic levels: check for neutralizing antibodies
     - Low biologic level: no antibodies
       - Dose escalate biologic
     - Low biologic level: antibodies present
       - Switch to a biologic in the same class
     - Adequate biologic level: no antibodies
       - Switch to a different class of biologic

Algorithm 3: Steroid dependent UC
Treatment of CD
Mild to Moderate Active CD

Induction of remission of mild to moderate active CD may be accomplished with oral budesonide or possibly aminosalicylates.

Some studies suggest superiority of budesonide over meselamine, while other studies found no difference.

Budesonide orally for up to 8-12 weeks may be used for mild to moderate active CD in patients with involvement of the terminal ileum or ascending colon.

For those non-responding to budesonide in mild CD involving the ileum, prednisone oral (40 mg daily for one week with tapering over one to two months) is recommended.

Meselamine is more useful for ileitis than the prodrug sulfasalazine (since colonic bacteria must cleave the drug to release the active 5-ASA moiety, so it is reserved for cases of colitis)

Higher doses of meselamine (>1.5 gm or 2.4 gm/day) are more effective than lower doses to achieve remission.

Metronidazole or ciprofloxacin can be used in patients who do not respond to budesonide or oral aminosalicylates, these agents should generally not be considered first-line therapy, their role in the management of IBD (particularly CD) is uncertain.

Diffuse colitis or left colonic involvement

- Mild, diffuse Crohn colitis or left-sided colonic disease can be initially treated with oral prednisone 40 per day for one week, and then tapered (over 2-3 months); combination with other agents (including biologic or thiopurine agents) can be considered for maintenance.

- Because the formulation releases budesonide in the terminal ileum, it is not effective in reaching sites distal to the ascending colon.

- 5-ASA products have minimal efficacy but generally may be used in patients with ileocolonic involvement. Induction of remission may require up to 16 weeks of treatment at full doses of meselamine
Sulfasalazine is an alternative initial option for mild colonic (left-sided) CD.

**Moderate to Severe Active CD**

- Patients with moderate to severe active CD may be treated with oral corticosteroids (eg, prednisone 40–60 mg daily).

- Infliximab is an alternative to corticosteroid therapy for patients with moderate to severe CD including patients with fistulizing or perianal disease.

- Anti-TNF monotherapy may be indicated as induction therapy:
  - Patients over the age of 60 years, young male patients who prefer to avoid immunomodulators, Patients at increased risk for infections or malignancy

- Short course of corticosteroids (8 weeks) can be used as a bridge for a maintenance agent such as thiopurine or a biologic agent.

- For patients with perianal fistulae antibiotics (metronidazole or ciprofloxacin), AZA, infliximab, adalimumab, and certolizumab are appropriate options.

**Severe to Fulminant Active CD**

- Patients with severe to fulminant CD require hospitalization and should be evaluated for possible surgery.

- IV doses of corticosteroids equivalent to prednisone 40 to 60 mg are recommended as initial therapy to rapidly suppress severe inflammation, cyclosporine therapy may be second line after IV hydrocortisone.

**Maintenance of Remission in CD**

- Up to 80% of patients with CD experience relapse within 2 years; therefore, many patients require indefinite maintenance therapy.

- Maintenance of remission of CD may be achieved with immunosuppressants (azathioprine, 6-MP, or methotrexate), biologic agents, and less frequently oral or topical 5-ASA derivatives.
In contrast to their use in UC, sulfasalazine and the newer aminosalicylates are marginally effective in preventing CD relapse. However, they are still used as first line maintenance therapy due to their favorable side effect profile.

For patients who have achieved remission with combination therapy, continuing long-term treatment with a biologic agent and also continue thiopurine for one to two years is recommended.

Prior to withdrawing thiopurine therapy, ileocolonoscopy should be performed to confirm mucosal healing and histologic remission.
Algorithm 4: Mild CD management

Managing relapse

- For patients who relapse after achieving remission on glucocorticoids, a second course of glucocorticoids (with possible alternatives: thiopurine/biologic agents) to be initiated.

- Patients are considered high risk if they fail to improve on a second course of corticosteroids.

Acutely ill patients:
Partial small bowel obstruction, peritonitis, or a disease flare that is not responding to outpatient treatment are conditions requiring hospitalization of CD patients.

Management may include intravenous fluid and electrolyte replacement, intravenous broad spectrum antibiotics, nutritional assessment, and possible surgery. Some patients require treatment with intravenous glucocorticoids or biologic therapy.

**Abscess**

Patients with CD may be presented with abscess; these patients require treatment with antibiotics and surgical drainage of this abscess.

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**Algorithm 5: management of CD**

**Treatment of IBD in Special Populations**

**Elderly Patients**
15% of patients with IBD develop symptoms after age 65.

IBD presents similarly in older patients and younger individuals.

The onset of IBD at an advanced age does not appear to increase the risk of developing colorectal cancer.

Treatment of elderly with IBD is similar to that for younger patients.

Special consideration should be given. Corticosteroids may worsen diabetes, hypertension, heart failure, or osteoporosis.

The TNF-α inhibitors should be used cautiously in patients with heart failure, they should be avoided in class III and IV heart failure.

Monotherapy with anti-TNF are generally preferred over combination therapy.

**Children and Adolescents**

CD occurs twice as frequently as UC in children.

The risk of growth failure secondary to inadequate nutritional intake and corticosteroid therapy is a major concern in children with IBD.

Guidelines for management of acute severe UC in children favor methylprednisolone over other corticosteroids as first-line therapy.

The aminosalicylates, azathioprine, 6-MP, and infliximab are all can be used in pediatrics with IBD.

Infliximab and adalimumab are approved in patients 6 years and older.

Certolizumab, natalizumab, and vedolizumab are only FDA approved for use in adults with IBD, limited data for their use in children.

**Pregnant Women**

Inducing and maintaining remission of IBD prior to conception is the optimal approach in women planning to become pregnant.
Active IBD may result in prematurity and low birth weight newborns.

Patients do not need to discontinue drug therapy for IBD once they become pregnant.

The aminosalicylates are safe in pregnancy.

Sulfasalazine is associated with folate malabsorption. Pregnant patients treated with sulfasalazine should be supplemented with folic acid 1 mg orally twice daily.

Corticosteroids may be used for treatment of active disease but not for maintenance of remission.

Both azathioprine and 6-MP have been used in pregnant patients and appear to carry minimal risk despite carrying an FDA pregnancy category D.

Infliximab, adalimumab, golimumab, and certolizumab are all FDA category B. Little is known about excretion of these drugs in breast milk, so benefit versus risk should be considered.

Methotrexate is an abortifacient, it is contraindicated during pregnancy (category X).

Metronidazole carries a theoretical risk of mutagenicity in humans, but short courses are safe during pregnancy.

Ciprofloxacin should be avoided in pregnant women.
Table 6: dosing considerations of IBD therapies in special populations

Preventive care in IBD:

Immunization: Patients with IBD are at increased risk for infections. Live vaccines (MMR, varicella) are contraindicated in patients on immunosuppressants, within the last 3 months or planning to start immunosuppressive therapy within the next six weeks.

The herpes zoster virus vaccine (HSV) should be given to all non-immunosuppressed IBD patients over the age of 50 (and for patients on low doses of immunosuppressants).

The HSV vaccine is contraindicated in patients on biologic therapy.

Cancer screening

Colorectal cancer: Patients with IBD are at increased risk for colorectal cancer (CRC), colonoscopy should be done based on the extent and duration of their disease.

Osteoporosis screening
At the time of diagnosis and periodically in some patients include: postmenopausal, corticosteroid treatment, history of corticosteroids use more than three months, history of low-trauma fractures, or age over 60 years

**OUTCOME EVALUATION**

- Reduction in the number of daily stools, abdominal pain, fever, and heart rate are important factors to be assessed in patients with active IBD.

- Patients on 5-ASA, a baseline kidney function and periodically thereafter should be done.

- Patients using more than 5 mg daily of prednisone for more than 2 months or for steroid dependent patients should be evaluated for the need of calcium and vitamin D supplements.

- Baseline complete blood count (CBC), liver function tests, and TPMT activity should be considered when treating patients with azathioprine or 6-MP.

- These tests, except TPMT, should be monitored closely (every 2–4 weeks) at the start of therapy and then approximately every 3 months during maintenance therapy.

- Prior to initiating methotrexate therapy CBC, serum creatinine, liver function tests, chest x-ray, and pregnancy test (if female) should be done.

- Prior to initiating the biologic agents, a tuberculin skin test should be done to rule out latent tuberculosis,

- In patients with fistulae, monitor at every biologic agent dosing interval for evidence of fistula closure and overall reduction in the number of fistulae.
References


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