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Gastrointestinal Disorders: Inflammatory Bowel Disease

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The idiopathic inflammatory bowel diseases (IBD) consist of Crohn's disease (CD) and ulcerative colitis (UC). CD may involve any part of the gastrointestinal tract while UC is restricted, with a variable extent of involvement, to the colon. UC of the distal colon is termed ulcerative proctosigmoiditis.

Investigations

Refer all patients to specialist care for confirmation of diagnosis, initial management and exacerbations.

- History:
 - diarrhea, abdominal pain, rectal bleeding and weight loss are the most frequent symptoms
 - presence of nocturnal diarrhea usually indicates "organic" pathology in distinction to functional disorders such as irritable bowel syndrome
 - extraintestinal manifestations, e.g., aphthous ulcers, arthritis, erythema nodosum, iritis, perianal disease, fever
 - family history of IBD
 - previous endoscopic/radiologic test results
 - previous medical (e.g., drugs, dose, duration) or surgical treatment (e.g., type and number of surgeries)
- Physical examination: weight, nutritional assessment, abdominal tenderness, presence of abdominal mass, perianal disease (fistulae, abscess)
 - growth failure in children (chart height and weight, growth curve Tanner stage)
 - extraintestinal manifestations (e.g., peripheral arthritis, sacroiliitis, ankylosing spondylitis, osteoporosis, erythema nodosum, pyoderma gangrenosum, oral aphthous ulcers, stomatitis, uveitis, scleritis, episcleritis, primary sclerosing cholangitis, nephrolithiasis and thromboembolic events)
- Laboratory tests:
 - hemoglobin, electrolytes, renal function, liver function tests and liver enzymes
 - measures of inflammation (white blood cell and platelet count, erythrocyte sedimentation rate, C-reactive protein, albumin)
 - stool testing to exclude other diagnoses or concomitant infections (*Clostridium difficile*, culture, ova and parasites)
- Further investigations to establish a precise diagnosis:
 - endoscopy (gastroscopy, ileocolonoscopy, capsule endoscopy, balloon assisted enteroscopy)
 - imaging studies (CT/MR enterography, small bowel follow through)
 - biopsy/histopathology (presence of small bowel involvement; granulomata are characteristic of CD)
 - 10% of cases with colonic disease cannot be classified and are termed *colitis not yet determined*
- A definitive diagnosis is important since:
 - colectomy cures UC; CD recurs after surgery
 - the conditions respond differently to drug therapy (especially to aminosalicylates)
 - precise anatomic localization is necessary for selecting drug therapy and planning surgery

Goals of Therapy

- Relieve symptoms and improve patients' quality of life
- Improve nutritional status and growth (children/adolescents)
- Prevent disease recurrence
- Prevent development of colon cancer, which is associated with UC and colonic CD
- Identify and treat extraintestinal manifestations (e.g., arthritis, arthralgia, iritis, uveitis)

Therapeutic Choices

Therapy is determined by the site and extent of disease, and by the severity of symptoms. Patients with mild to moderate disease activity are managed as outpatients, whereas those with severe symptoms may require hospitalization. Therapy is sequential in first inducing and then maintaining remission.

Pharmacologic Choices

Pharmacologic management of IBD includes the use of aminosalicylates, corticosteroids, immunosuppressives, antidiarrheals, antibiotics and, to a limited degree, opioid analgesics ([Table 1](#)). In selecting therapy consider, in addition to efficacy, the route of

administration (oral, iv, rectal) and potential adverse events.

Aminosalicylates

Preparations containing **5-aminosalicylic acid** (5-ASA) are formulated to release the drug at specific sites in the gastrointestinal tract, since efficacy is dependent on luminal concentration. **Salofalk**, **Mesasal** and **Pentasa** release 5-ASA in the small bowel, allowing 5-ASA to be available in the small bowel and the colon. **Sulfasalazine**, **olsalazine**, **Asacol** and **Mezavant** release 5-ASA primarily in the colon.

All 5-ASA compounds are effective for the treatment of UC. However, sulfasalazine has only modest efficacy in active CD (approximately 40% efficacy for induction of remission versus 30% with placebo) and is generally used in patients with mild disease.¹ Pentasa and Asacol have been evaluated in active CD with equivocal results, and their widespread use for both induction and maintenance of remission is under increasing scrutiny. Although these compounds are often used interchangeably in clinical practice, evidence favours use of sulfasalazine for mildly active colonic CD.¹ Sulfasalazine has the least-favourable adverse effect profile, which includes nausea, headache, rash, hemolytic anemia and hepatotoxicity. However, many of these effects are minor and dose-related. The majority of these events (>90%) are related to the sulfapyridine moiety which is not present in 5-ASA preparations. Reversible oligospermia has been reported with sulfasalazine, but has not been associated with 5-ASA.

Corticosteroids

Patients with a moderately severe exacerbation of CD or UC are treated initially with oral **prednisone** 40–60 mg/day.² In those with more severe disease, hospitalization and treatment with iv corticosteroids (e.g., **hydrocortisone**, **methylprednisolone**) may be necessary. Patients who respond to iv therapy are switched to oral prednisone once stabilized. Taper the prednisone dose as improvement occurs (total duration of therapy is 12–16 weeks for CD; 8–12 weeks for UC).² ³

Avoid long-term use of glucocorticoids and reserve for patients unresponsive to other drugs. Inform patients of the possible side effects and obtain informed consent. Osteoporosis is a concern with long-term therapy. Supplemental calcium and vitamin D, smoking cessation, exercise and, in select individuals, treatment with bisphosphonates are useful interventions. Use of corticosteroids is also associated with avascular necrosis of the femoral head.

Budesonide is rapidly inactivated in the liver, resulting in lower systemic bioavailability and a reduced effect on the hypothalamic-pituitary-adrenal axis. It is available as an oral controlled-release capsule for induction of remission of terminal ileal/right-sided colonic CD⁴ ⁵ and as an enema for treatment of UC. In clinical trials, response rates for oral budesonide are marginally lower than those for prednisone in patients with active CD (50–60% versus 70%). An important advantage of budesonide over prednisone is that the manifestations of Cushing's syndrome occur less frequently.⁶ Budesonide enemas are as effective as other steroid enemas and have a lower incidence of side effects, but are more costly.⁷

Immunosuppressive Agents

Azathioprine, **6-mercaptopurine (6-MP)** or **methotrexate** is used in patients with refractory CD to control symptoms or to reduce the dose of prednisone.⁸ ⁹ ¹⁰ ¹¹ All immunosuppressive drugs have important side effects (e.g., bone marrow suppression, cytopenias and infections). Hypersensitivity pneumonitis and hepatotoxicity are the most important adverse effects of methotrexate. Coadministration of folic acid (1 mg daily) is recommended with methotrexate. Pancreatitis occurs in approximately 3% of patients treated with azathioprine or 6-MP.¹² Although the development of nonmelanoma skin cancer is an uncommon complication of treatment with purine antimetabolites, ongoing and past exposure to these medications significantly increases the risk in all patients with IBD.¹³ ¹⁴ Recommend yearly skin checks and UV protection in patients treated with azathioprine or 6-MP.¹³ No strong evidence exists to support a similar relationship with methotrexate.

Biologic Response Modifiers

Antibodies directed towards tumor necrosis factor-alpha (TNF- α) are effective in patients with IBD. The chimeric (murine/human) antibody, **infliximab**, is effective for induction of remission¹⁵ ¹⁶ and closure of fistulae¹⁷ in patients with active CD refractory to other treatments, and in patients with active UC who do not respond to conventional therapy.¹⁸ Infliximab is given intravenously and can provoke minor (headache, flushing, lightheadedness) or major (manifestations of anaphylaxis) infusion reactions. **Adalimumab** is a recombinant human anti-TNF- α antibody that is administered subcutaneously. Adalimumab closes fistulae¹⁹ and induces/maintains disease remission in patients with moderate to severe CD unresponsive to corticosteroids and/or immunosuppressants.²⁰ ²¹

Adalimumab is also effective in patients refractory or intolerant of infliximab.²² **Certolizumab pegol**, the newest of the biologic agents, is a humanized monoclonal antibody Fab' fragment that is bound to polyethylene glycol. Certolizumab pegol has been shown to be effective in achieving a sustained response rate,²³ and improving quality of life²⁴ in patients with moderate to severe CD. It is also effective in patient's refractory or intolerant to infliximab.²⁵ Certolizumab pegol is not currently approved for use in IBD in Canada.

Formation of anti-nuclear antibodies, a rare lupus-like syndrome, lymphoma, non-melanoma skin cancer, cervical dysplasia and worsening of heart failure are important concerns associated with anti-TNF- α therapies. Bacterial pneumonia and sepsis in the pelvis are the most common serious infections associated with anti-TNF- α use. Immunizations against influenza, *S. pneumoniae* and hepatitis B are indicated with anti-TNF- α therapy. Opportunistic infections and tuberculosis have occurred during treatment. Screen for tuberculosis prior to treatment by obtaining a history of exposure, chest x-ray and by performing tuberculin skin testing. Manage patients who are infected with tuberculosis in collaboration with an infectious disease specialist.

Antibiotics

Short courses (2–4 weeks) of **metronidazole** and/or **ciprofloxacin** are useful as a treatment for patients with CD and perianal fistulae.²⁶ Metronidazole has a potent disulfiram-like activity if alcohol is ingested. Neuropathy may also occur with its long-term use.

Antidiarrheals

Use antidiarrheals with caution and avoid in severe disease because of the risk of toxic megacolon. **Diphenoxylate with atropine** is a combination of an opiate and an anticholinergic drug which can cause CNS side effects. **Loperamide** acts on both cholinergic and opiate receptors, but has a lower incidence of adverse effects than diphenoxylate.

Opiate Analgesics

Opiates decrease gastrointestinal motility. Chronic use may lead to narcotic bowel syndrome, increase risk for habituation and, in some individuals, worsen symptoms.

Codeine is useful for pain control and decreasing the number of bowel movements (although approximately 10% of patients may not respond to the drug because of a genetic polymorphism; see the section on analgesics in [Musculoskeletal Disorders: Rheumatoid Arthritis](#)). Avoid use of morphine or meperidine; if necessary to use, restrict to short-term treatment in select patients.

Crohn's Disease

Therapeutic Choices

[Nonpharmacologic Choices](#)

[Pharmacologic Choices](#)

[Therapeutic Tips](#)

Therapeutic Choices

Nonpharmacologic Choices

- Encourage smoking cessation (limited evidence suggests smoking worsens CD).²⁷
- Advise patients not to arbitrarily limit food groups. The goal is to ensure an adequate caloric intake. Nutritional supplements or parenteral nutrition may be necessary in select patients who are malnourished.
- Surgery may be necessary to treat strictures, abscesses, fistulae or for patients refractory to medical management. Recurrence after surgery is almost universal, so conservative surgical management with resection of a minimum amount of bowel is favoured.
- Psychological and social support is important, especially for adolescents.

Pharmacologic Choices

See the previous general discussion of pharmacologic choices in inflammatory bowel diseases. [Figure 1](#) - Management of Crohn's Disease outlines the pharmacologic management of CD and [Table 1](#) lists the drugs used in the treatment of IBD.

- **Corticosteroids** are most effective for the *induction of remission* (70% response rate). **Prednisone** (40–60 mg/day for 12–16 weeks) is the most commonly used drug.²
- Chronic low-dose corticosteroid therapy is ineffective for the *maintenance of remission*.²⁸ However, some patients with chronically active disease may require continuous low-dose prednisone (10–15 mg/day) to suppress their symptoms.
- **The antimetabolites azathioprine and 6-mercaptopurine are ineffective for induction of remission in active Crohn's disease but are effective in maintaining remission [SORT A].^{29,30} In patients intolerant to azathioprine, a trial of 6-mercaptopurine may be safely attempted before abandoning this class of medications.³¹** Useful Info?
- **Sulfasalazine** (6–8 g/day) is only marginally effective for the induction of remission (approximately 40% response rate versus 30% with placebo in patients with mild disease).²

- Oral **5-ASA** is ineffective for treatment of active disease.³² The value of 5-ASA as a maintenance therapy for CD is controversial (in contrast to its status in UC). Available data are conflicting.³³
- **Infliximab**¹⁵ and **adalimumab**²⁰,³⁴ are effective for patients who are refractory to antimetabolite therapy and those with moderate to severe disease with fistulae (infliximab has the best evidence for inducing fistula closure).¹⁷,¹⁹ Combining infliximab with **azathioprine** is more effective than infliximab monotherapy³⁵ suggesting that initial dual therapy may be preferable for high-risk patients. Whether these findings can be extrapolated to the other biologic agents is unclear.

Therapeutic Tips

- A rare hypersensitivity reaction to **5-ASA** preparations can worsen symptoms.
- 5-ASA does not have a corticosteroid-sparing effect.
- Bile salt-induced diarrhea may occur in patients who have had resection of their terminal ileum. This usually responds to **cholestyramine** or **antidiarrheals**. Vitamin B₁₂ deficiency may occur in this setting.
- Infusion reactions from **infliximab** may require treatment with epinephrine, antihistamines and corticosteroids.
- Avoid NSAIDs because they may exacerbate symptoms of IBD.

Ulcerative Colitis

Therapeutic Choices

[Nonpharmacologic Choices](#)

[Pharmacologic Choices](#)

Therapeutic Choices

Nonpharmacologic Choices

- Advise patients not to arbitrarily limit food groups. Watch for dehydration and electrolyte abnormalities especially during disease flares.
- Surgery (colectomy) may be used to treat patients who are refractory to medical therapy or who have pre-cancerous or cancerous changes in the colon.
- Start colon cancer surveillance with colonoscopy within 8 years of diagnosis of pancolitis and 15 years of diagnosis of left-sided colitis. Consider an early start in those with history of severe inflammation, primary sclerosing cholangitis and if date of disease onset is uncertain.³⁶
- Although colectomy "cures" UC, pouchitis, a chronic inflammatory condition which occurs after ileal-anal reservoir construction, can be troublesome.²⁶ Symptoms of pouchitis include tenesmus, diarrhea and bleeding.

Pharmacologic Choices

See the previous general discussion of pharmacologic choices in inflammatory bowel diseases. [Table 1](#) lists the drugs used in the treatment of IBD and [Figure 2](#) - Management of Ulcerative Pancolitis outlines the management of UC.

Sulfasalazine and **5-ASA** are effective for maintaining remission of quiescent ulcerative colitis and for inducing remission in patients with mild to moderate disease and should be used in these situations [[Evidence: SORT A](#)].³⁷,³⁸ Sulfasalazine may be less tolerated than 5-ASA products when used for inducing remission [[Evidence: SORT A](#)].³⁸ Sulfasalazine may be marginally superior to 5-ASA for maintaining remission but not for inducing remission [[Evidence: SORT A](#)].³⁷,³⁸ **MMX mesalamine** (Mezavant) is a newer 5-ASA compound that uses Multi Matrix System (MMX) technology to delay and extend delivery of 5-ASA throughout the colon allowing for once-daily dosing and possibly better compliance rates. Once-daily dosing of **Asacol** (1.6–2.4 g/day) may be as effective as twice daily dosing for maintenance of remission in patients with UC.³⁹ Combination oral/topical 5-ASA therapy is more effective than oral therapy alone for mild to moderate active UC.⁴⁰ Continuous use of **corticosteroids**, **immunosuppressive agents** or **infliximab** is reserved for patients with refractory disease who decline surgery. Use the lowest possible dose of prednisone to control disease activity.

The efficacy of the **purine antimetabolites** (azathioprine and 6-MP) in UC is less well established than in CD. The efficacy of **methotrexate** in the treatment of UC is not known.⁴¹ Intravenous **cyclosporine** may be effective in up to 80% of patients with severe UC refractory to corticosteroids, but is associated with a 1% one-year mortality rate.⁴² Offer it only to patients who refuse surgery and inform them of the potential for toxicity. Recent studies have confirmed the efficacy of **infliximab** for the treatment of refractory UC.¹⁸,⁴³

Therapeutic Tips

- Use extreme caution when prescribing narcotics and anticholinergic drugs for patients with active UC due to the risk of toxic megacolon. Use these drugs only when all other alternatives have failed.
- Weak evidence suggests that folate supplementation and high compliance with aminosalicylate maintenance therapy may reduce the risk of colon cancer.⁴⁴, ⁴⁵
- Patients with severe colitis often will not tolerate tube feeds due to diarrhea.
- Avoid NSAIDs because they may exacerbate symptoms or precipitate relapse.
- Be aware that *C. difficile* may cause severe exacerbations of IBD, including megacolon. Independent risk factors include antibiotic exposure, colonic involvement and immunosuppressive drug therapy.

Ulcerative Proctosigmoiditis

Therapeutic Choices

[Pharmacologic Choices](#)

Therapeutic Choices

Pharmacologic Choices

Given the limited extent of the inflammation (rectum/sigmoid colon), the focus is on topical therapy ([Table 1](#), [Figure 3](#) - Management of Ulcerative Proctosigmoiditis).⁴⁰ **5-ASA** preparations (suppositories, enemas) administered at bedtime are the initial treatment of choice. Alternatively, **topical corticosteroids** can be used. If a response is not achieved with one of these strategies, switching to the other is advised. Suppositories are effective only for proctosigmoiditis, whereas enemas can be used to treat disease in the descending colon and rectum from the splenic flexure distally.

If remission is not induced within 2–4 weeks, oral 5-ASA can be added. Limited data suggest that there is an additive benefit of combined oral and topical 5-ASA induction therapy.⁴⁶ Rectal 5-ASA monotherapy may be effective for maintenance of remission of mild to moderate distal disease.⁴⁶ Switch patients unresponsive to these measures to **prednisone** or (rarely) iv corticosteroids. Discontinue all medications if patients are brought into remission easily after a first episode (within 4–8 weeks). Follow-up is essential; place patients on chronic maintenance therapy with 5-ASA if symptoms recur. Most patients prefer oral maintenance therapy, although in practice many will require prolonged topical 5-ASA therapy.

Patients brought into remission with difficulty should continue on long-term oral or topical 5-ASA preparations or corticosteroid enemas, without an attempt to discontinue therapy.

Patients rarely require chronic treatment with low-dose prednisone or **purine antimetabolites**. Colectomy may be necessary in some patients despite the limited extent of the disease. **Infliximab** has not been specifically evaluated in this group of patients, although it may be considered before surgery is recommended.

Therapeutic Tips

- Topical therapy is preferred.
- In patients who are difficult to manage, perform a repeat sigmoidoscopy to ensure that the inflammation is still confined to the lower bowel and has not developed into more extensive colitis.

Choices during Pregnancy and Breastfeeding

Inflammatory bowel disease (IBD) in pregnant women increases the risk of preterm birth, low birth weight and miscarriages.⁴⁷ However, the evidence is not as strong for an increased risk of congenital abnormalities.⁴⁷ Pregnant IBD patients in remission at the time of conception are likely to remain in remission during pregnancy but up to 1/3 may relapse during the pregnancy.⁴⁸ Advise women with IBD who are planning a pregnancy to try conceiving at a time when the disease is in remission. Most IBD medications (except methotrexate) should not be discontinued at conception or while breastfeeding since their cessation might lead to disease flare; the risk of the untreated disease (preterm birth, miscarriage) is often greater than the risk of most available medications.⁴⁷

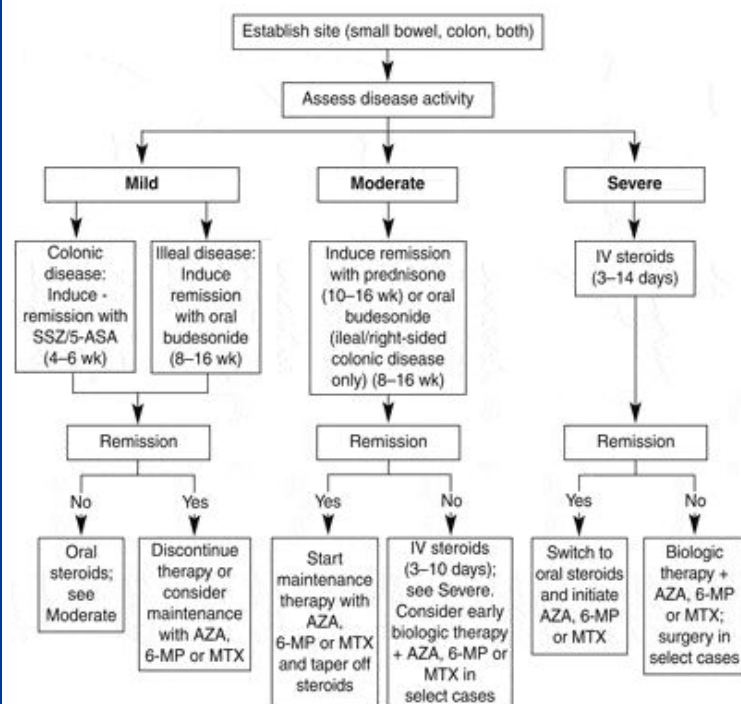
Methotrexate is contraindicated in pregnancy and breastfeeding owing to its teratogenic and cytotoxic effects.⁴⁹ Recommend effective contraception if patient is receiving methotrexate. Discontinue the drug 3–6 months prior to attempted conception.

Azathioprine and **6-mercaptopurine** use during pregnancy is considered low risk despite the conflicting safety data.⁴⁷ Azathioprine and 6-mercaptopurine are generally considered compatible with breastfeeding but it is considered safest to separate breastfeeding by

a few hours from dosing.⁵⁰ **Cyclosporine** is not usually used for treatment of IBD but is considered to have an overall low risk during pregnancy. Do not use cyclosporine during breastfeeding; anti-TNF agents are safer in this situation. **Corticosteroids** are considered safe and may be continued in pregnancy if indicated. However, use them with caution in the first trimester since they have been associated with increased risk (albeit low) of oral clefts in the newborn.⁵¹ Corticosteroids may be used at any stage of pregnancy (including 1st trimester) if benefits outweigh potential risks (e.g., during disease flares). **Prednisone** and **prednisolone** are considered compatible with breastfeeding.⁴⁷ **Aminosalicylates** are considered low risk for use in pregnancy or while breastfeeding.⁵² Due to potential anti-folate effects, women taking **sulfasalazine** may be safely switched to 5-ASA or are generally advised to supplement with 2 mg daily of folic acid starting before conception and continuing throughout their pregnancy.⁴⁷ **Metronidazole** has a low teratogenic risk when used during pregnancy but do not use while patient is breastfeeding because it transfers to breast milk.⁴⁷ Avoid prolonged metronidazole use in pregnant patients. The **fluoroquinolones** can be regarded as safe during pregnancy when used for short periods.⁴⁷ Fluoroquinolones are probably safe to use while breastfeeding if necessary. **Infliximab**, **adalimumab** and **certolizumab pegol** are considered low risk in pregnancy⁵³ during at least the first 2 trimesters.⁵⁴ Carefully time infusions of infliximab and adalimumab in the 3rd trimester since they are actively transported across the placenta. Certolizumab pegol is not transferred across the placenta and from this point of view may be a better choice than infliximab or adalimumab for use in pregnancy particularly in the 3rd trimester.⁵⁵ Infliximab and certolizumab pegol are compatible with breastfeeding, whereas adequate safety data for adalimumab is not available.

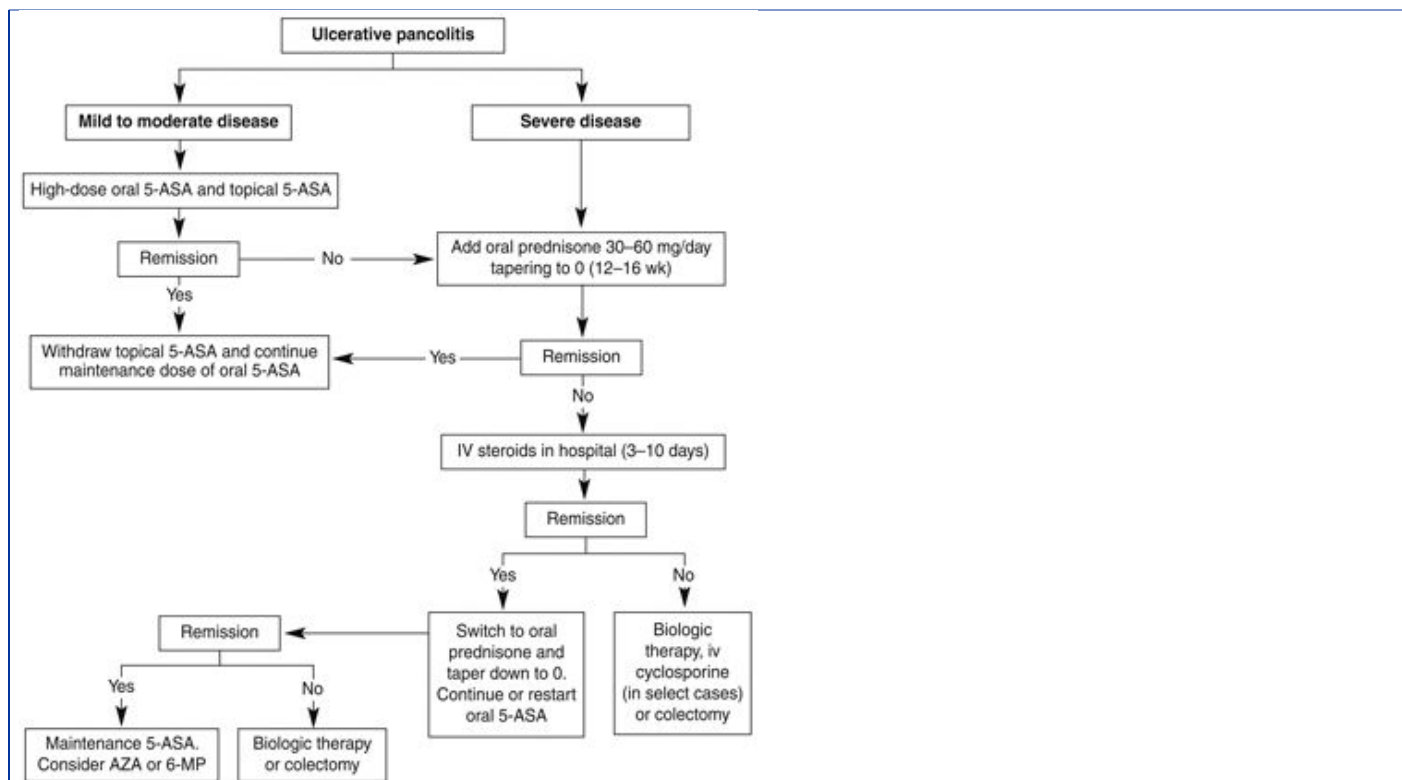
A discussion of general principles on the use of medications in these special populations can be found in [Drug Use During Pregnancy](#) and [Drug Use During Breastfeeding](#). Other specialized reference sources are also provided in these appendices.

Figure 1 - Management of Crohn's Disease



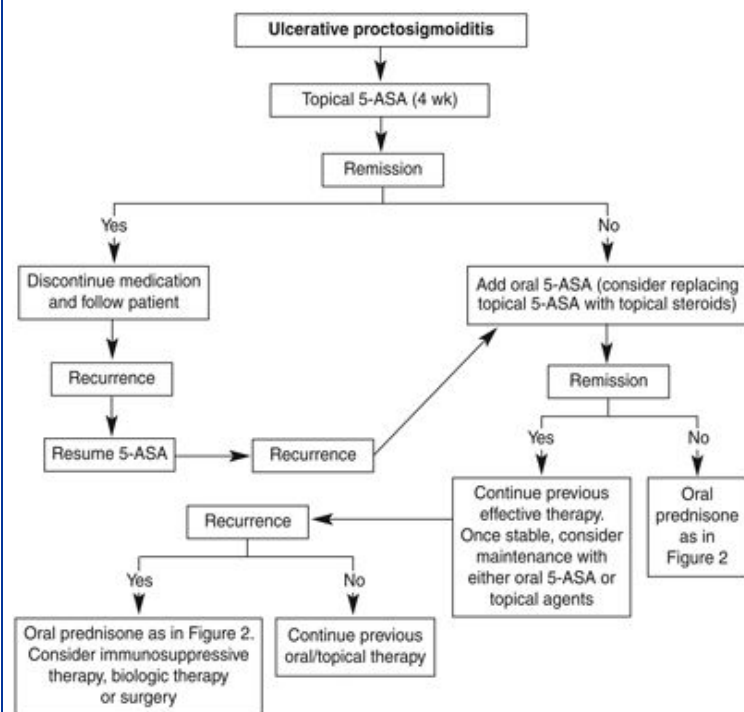
Abbreviations: 5-ASA=5-aminosalicylic acid; 6-MP=6-mercaptopurine; AZA=azathioprine; MTX=methotrexate; SSZ=sulfasalazine

Figure 2 - Management of Ulcerative Pancolitis



Abbreviations: 5-ASA=5-aminosalicylic acid; 6-MP=6-mercaptopurine; AZA=azathioprine

Figure 3 - Management of Ulcerative Proctosigmoiditis



Abbreviations: 5-ASA=5-aminosalicylic acid

Table 1: Drugs Used for the Treatment of Inflammatory Bowel Disease

Class	Drug	Dose	Adverse Effects	Drug Interactions	Comments	Cost ^a
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Class	Drug	Dose	Adverse Effects	Drug Interactions	Comments	Cost ^a
Aminosalicylates	<i>5-aminosalicylic acid (5-ASA)</i> , oral 5-ASA, Asacol , Asacol 800 , Mesasal , Pentasa , Salofalk Tablets , generics	5-ASA – Active disease: up to 4.8 g/day divided Maintenance: 0.8–3.2 g/day divided Asacol – Active disease: up to 4.8 g/day divided. Maintenance: 1.6 g/day divided Mesasal – Active disease: 1.5–3 g/day divided Maintenance: 1.5 g/day divided Mezavant – Active disease: 2.4–4.8 g once daily Maintenance: 2.4 g once daily Pentasa – Active disease: 2–4 g/day divided Maintenance: 1.5–3 g/day divided Salofalk – Active disease: 3–4 g/day divided Maintenance: 1.5–3 g/day divided	Abdominal pain, cramps, diarrhea, headache, nausea, rash including urticaria, vomiting. Rare hypersensitivity reactions, including pneumonitis, hepatitis and worsening of colitis.	↑ risk of myelosuppression when coadministered with azathioprine or 6-mercaptopurine. ↑ risk of renal failure when coadministered with other nephrotoxic agents such as NSAIDs and azathioprine.	All aminosalicylates are equally effective in UC. The value of 5-ASA as maintenance therapy in CD is controversial. Abrupt discontinuation of 5-ASA is not recommended, and may result in relapse. Best evidence for Asacol 2.4 g/day and Pentasa 3 g/day.	\$
Aminosalicylates	<i>5-aminosalicylic acid, rectal</i> Pentasa , Salofalk Enema , Salofalk Suppositories	Active disease: Enema: 4 g QHS Suppositories: 1 g QHS Maintenance: Enema: 2 g QHS or 4 g every 2nd or 3rd night Suppositories: 1 g every 2nd or 3rd night based on patient's	Local reactions (e.g., pruritus, rectal discomfort and urgency), fever, flu-like symptoms, worsening of hemorrhoids, abdominal pain, cramps or discomfort.		Enemas and suppositories effective in ulcerative proctitis.	\$

Class	Drug	Dose	Adverse Effects	Drug Interactions	Comments	Cost ^a
		response				
Aminosalicylates	<i>olsalazine</i> Dipentum	Active disease: 500 mg QID po Maintenance: 500 mg BID po	Secretory diarrhea; may be minimized by increasing dose gradually.			\$
Aminosalicylates	<i>sulfasalazine</i> Salazopyrin , generics	Active disease: 1000–2000 mg 3–4 times daily po Maintenance: 1000 mg 2–3 times daily po	Dose-related adverse effects: nausea, vomiting, diarrhea, anorexia, headache. Hypersensitivity reaction (rash, fever), hemolytic anemia (particularly in patients with G6PD deficiency), oligospermia (reversible). Maintain adequate fluid intake to prevent crystalluria and stone formation.	Reduced absorption of folic acid and digoxin.	All aminosalicylates are equally effective in UC.	\$
Biologic Response Modifiers	<i>adalimumab</i> Humira	CD: Active disease: 160 mg sc at wk 0 (given as 4 injections in a single day or as 2 injections/day x 2 days), then 80 mg sc at wk 2 (given as 2 injections) Maintenance: 40 mg sc every other wk beginning at wk 4	Nausea, injection site reactions (e.g., erythema, itching, pain, swelling), tuberculosis, opportunistic infections, upper respiratory tract infections, abdominal pain, reactivation of hepatitis B infection, formation of antinuclear antibodies, reversible lupus-like syndrome, worsening heart failure, lymphoma, CNS demyelinating disorders.	Patients should not receive live vaccines during treatment.	Evaluate patients for risk of tuberculosis, hepatitis B, hepatitis C and varicella (if no history of disease) before starting therapy.	\$725 /dose
Biologic Response Modifiers	<i>certolizumab pegol</i> Cimzia	Not an approved indication in Canada CD: Active disease: 400 mg sc at wk 0, 2 and 4 Maintenance: 400 mg sc every 4 wk	Patients should not receive live vaccines during treatment.	Patients should not receive live vaccines during treatment.	Evaluate patients for risk of tuberculosis, hepatitis B, hepatitis C and varicella (if no history of disease) before starting therapy.	\$700 /dose
Biologic Response Modifiers	<i>infliximab</i> Remicade	CD (luminal or fistulizing) or UC: Active disease: 5 mg/kg iv at 0, 2	Nausea, injection site reactions (e.g., erythema, itching, pain, swelling), tuberculosis,	Patients should not receive live vaccines during treatment.	Evaluate patients for risk of tuberculosis, hepatitis B, hepatitis C and	~\$3300 /dose

Class	Drug	Dose	Adverse Effects	Drug Interactions	Comments	Cost ^a
		and 6 wk; consider ↑ dose up to 10 mg/kg if no response. Maintenance: 5 mg/kg iv every 8 wk.	opportunistic infections, upper respiratory tract infections, abdominal pain, reactivation of hepatitis B infection, formation of antinuclear antibodies, reversible lupus-like syndrome, worsening heart failure, lymphoma, CNS demyelinating disorders.		varicella (if no history of disease) before starting therapy.	
Corticosteroids, systemic	<i>budesonide, oral</i> Entocort Capsules	Acute exacerbation: 9 mg QAM po before food Maintenance (maximum of 3 mo): 6 mg QAM po before food	Dyspepsia, muscle cramps, palpitations, blurred vision, rash, urticaria, suppression of the hypothalamic pituitary adrenal axis, hypokalemia, osteoporosis.	CYP3A4 inhibitors: budesonide is metabolized via CYP3A4. Inhibitors of CYP3A4 (e.g., clarithromycin, erythromycin, grapefruit juice, itraconazole, ketoconazole) ↑ plasma levels of budesonide. Antidiabetic agents: glucocorticoids may ↑ blood glucose. NSAIDs: may ↑ the risk of GI ulceration. Thiazide and loop diuretics also deplete potassium.	Controlled- release capsule for treating CD in the ileum and/or ascending colon. Benefits are mostly due to its topical action since it is rapidly and almost completely degraded by hepatic 1st pass metabolism. Exhibits somewhat fewer adverse effects than conventional corticosteroids. Can be used up to 3 months for maintenance therapy.	\$
Corticosteroids, systemic	<i>hydrocortisone</i> sodium succinate Solu-Cortef , generics	Acute exacerbation: 300–400 mg/day iv	Acne, glucose intolerance, weight gain, hypertension, hypokalemia, osteoporosis, aseptic necrosis of femoral head, suppression of the hypothalamic pituitary adrenal axis, impaired wound. Caution in hyperthyroidism, osteoporosis, peptic ulcer, cirrhosis.	Clearance may decrease with estrogens; may increase digitalis toxicity secondary to hypokalemia.	Avoid immunization during corticosteroid use. No role in maintenance therapy.	\$\$
Corticosteroids, systemic	<i>methylprednisolone</i> sodium succinate Solu-Medrol , generics	Acute exacerbation: 40–60 mg/day iv	Acne, glucose intolerance, weight gain, hypertension, hypokalemia, osteoporosis, aseptic necrosis of femoral head, suppression of the hypothalamic pituitary adrenal axis, impaired wound. Caution in	Clearance may decrease with estrogens; may increase digitalis toxicity secondary to hypokalemia.	No advantage over hydrocortisone. No role in maintenance therapy.	\$

Class	Drug	Dose	Adverse Effects	Drug Interactions	Comments	Cost ^a
			hyperthyroidism, osteoporosis, peptic ulcer, cirrhosis.			
Corticosteroids, systemic	prednisone generics	Acute exacerbation: 30–60 mg QAM po	Acne, glucose intolerance, weight gain, hypertension, hypokalemia, osteoporosis, aseptic necrosis of femoral head, suppression of the hypothalamic pituitary adrenal axis, impaired wound. Caution in hyperthyroidism, osteoporosis, peptic ulcer, cirrhosis.	Clearance may decrease with estrogens; may increase digitalis toxicity secondary to hypokalemia. Phenobarbital, phenytoin, and rifampin may ↑ metabolism which may necessitate increased maintenance dose. ↑ risk of hypokalemia with coadministration of diuretics.	Useful in moderately severe and severe UC and CD. No role in maintenance therapy.	\$
Corticosteroids, topical	betamethasone, enema Betnesol	Acute exacerbation: 5 mg (100 mL) QHS pr	Topical therapy, in general, has less severe adverse effects than systemic therapy.		Enemas effective in ulcerative proctitis. Useful in UC; role in CD not well established. As much as 75% of administered topical dose may be absorbed if the lower colon is severely inflamed.	\$\$
Corticosteroids, topical	budesonide, enema Entocort Enema	Acute exacerbation: 2 mg (100 mL) QHS pr	Topical therapy, in general, has less severe adverse effects than systemic therapy.		Enemas effective in ulcerative proctitis. Useful in UC; role in CD not well established. As much as 75% of administered topical dose may be absorbed if the lower colon is severely inflamed.	\$\$
Corticosteroids, topical	hydrocortisone, enema Cortenema , Cortifoam, Hycort	Acute exacerbation: 80–100 mg QHS as enema	Topical therapy, in general, has less severe adverse effects than systemic therapy.		Enemas effective in ulcerative proctitis. Useful in UC; role in CD not well established. As much as 75% of administered topical dose may be	\$\$

Class	Drug	Dose	Adverse Effects	Drug Interactions	Comments	Cost ^a
					absorbed if the lower colon is severely inflamed.	
Immunomodulators	<i>6-mercaptopurine</i> Purinethol	100 mg daily po	Nausea, stomatitis, GI discomfort, arthralgias, diarrhea, anorexia, increased risk of opportunistic infection, blood dyscrasias, and rarely pancreatitis, hepatotoxicity.	Oral anticoagulants: mercaptopurine may inhibit hypoprothrombinemic response to warfarin and possibly other anticoagulants. Allopurinol may ↑ azathioprine toxicity; dosage adjustment may be necessary (1/4 of regular dose); similar interaction with mercaptopurine. ACE inhibitors may ↑ the likelihood of neutropenia when combined with azathioprine or mercaptopurine.	Low risk in pregnancy and breastfeeding. Metabolism of azathioprine and mercaptopurine is influenced by a genetic polymorphism.	\$\$
Immunomodulators	<i>azathioprine</i> Imuran , generics	1–2.5 mg/kg daily po	Nausea, stomatitis, GI discomfort, arthralgias, diarrhea, anorexia, increased risk of opportunistic infection, blood dyscrasias, and rarely pancreatitis, hepatotoxicity.	Oral anticoagulants: mercaptopurine may inhibit hypoprothrombinemic response to warfarin and possibly other anticoagulants. Allopurinol may ↑ azathioprine toxicity; dosage adjustment may be necessary (1/4 of regular dose); similar interaction with mercaptopurine. ACE inhibitors may ↑ the likelihood of neutropenia when combined with azathioprine or mercaptopurine. Concurrent use with ACE inhibitors may induce severe leukopenia; may increase levels of methotrexate metabolites.	Low risk in pregnancy and breastfeeding. Metabolism of azathioprine and mercaptopurine is influenced by a genetic polymorphism. Reduce dose in oliguric patients.	\$
Immunomodulators	<i>cyclosporine</i> Sandimmune	2–5 mg/kg daily iv	Renal toxicity (monitor renal function), hypertension, hypertrichosis, cytopenia, gum hyperplasia, electrolyte imbalances, nausea, diarrhea, seizures, opportunistic	Metabolized by CYP450: many possible drug interactions (e.g., erythromycin, ketoconazole, rifampin, St. John's wort).	May help avoid colectomy in select patients with severe disease not responding to other therapies. Do not use in pregnancy.	\$\$\$\$

Class	Drug	Dose	Adverse Effects	Drug Interactions	Comments	Cost ^a
			infection.			
Immunomodulators	<i>methotrexate</i>  Methotrexate Injection USP , Metoject, other generics	25 mg im weekly	Nausea, flu-like aches, headache, oral ulcers, bone marrow and liver toxicity, pneumonitis, immunosuppression, lymphoma.	Alcohol restriction may minimize hepatotoxicity. NSAIDs may ↑ methotrexate serum concentrations (probably not significant with low once-weekly methotrexate doses). Some penicillins may ↓ methotrexate clearance.	Potentially hepatotoxic. Oral methotrexate has not been evaluated in controlled trials. Do not use in pregnancy.	\$\$

^a. Cost of 1-day supply for 70 kg person unless otherwise specified; includes drug cost only.



Dosage adjustment may be required in renal impairment; see [Appendices: Dosage Adjustment in Renal Impairment](#).

Abbreviations: CD=Crohn's disease; G6PD=glucose-6 phosphate dehydrogenase; UC=ulcerative colitis

Legend: \$ <\$5 \$\$ \$5-10 \$\$\$ \$10-20 \$\$\$\$ \$20-30

Suggested Readings

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