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Inflamematory Bowel Disease Managemnt Protocol

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Inflamematory Bowel Disease Protocol

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Ulcerative Colitis Definition And Diagnosis

Ulcerative colitis (UC) is one of the two major types of inflammatory bowel disease (IBD), along with Crohn disease. Unlike Crohn disease, which can affect any part of the gastrointestinal tract, UC characteristically involves the large bowel (colon) .It involves the rectum in about 95% of cases and may extend proximally in a symmetrical, circumferential, and uninterrupted pattern to involve parts or all of the large intestine.

The hallmark clinical symptom is bloody diarrhea often with prominent symptoms of rectal urgency and tenesmus. The clinical course is marked by exacerbations and remissions, which may occur spontaneously or in response to treatment changes or intercurrent illnesses.
In UC, subsets of T cells accumulate in lamina propria of diseased colonic segment. T cells are cytotoxic to colonic epithelium. This change is accompanied by an increase in population of B cells and plasma cells, with increased production of IgG and IgE.

The exact etiology of UC is unknown, but certain factors have been found to be associated with the disease, and some hypotheses have been presented. Etiologic factors potentially contributing to UC include genetic factors, immune system reactions, environmental factors, NSAID use, low levels of antioxidants, psychological stress factors, a smoking history, and consumption of milk products.

Epidemiology: UC is slightly more common in women than in men. Age of onset follows a bimodal pattern, with a peak at 15-25 years and a smaller one at 55-65 years, although disease can occur in people of any age.

Symptoms of UC: abdominal cramping, frequent bowel movement often with blood, weight loss, fever and tachycardia in severe disease.

Relatively minor complications: hemorrhoids, anal fissures, and perirectal abscesses.

Major complications: toxic megacolon, hepatobiliary complication as fatty liver, chronic active hepatitis, cirrhosis, sclerosing cholangitis, cholangiocarcinoma, and gallstones, arthritis, ocular complications (iritis, episcleritis, and conjunctivitis), dermatologic or mucosal complications (erythema nodosum, pyoderma gangrenosum, or aphthous stomatitis).
The risk of colonic carcinoma is much greater in patients with UC than general population.

The severity of UC flare is based on patient symptoms and extent of colitis and its assessment is important in guiding management.
The Mayo scoring system has been used to judge disease severity and to monitor patients during therapy. Scores range from zero to 12, with higher scores correlating with more severe disease.

Elements in these scales include **(1) stool frequency** (1 to 2 stools per day more than normal/ 3 to 4 stools more than normal / >= 5 stools more than normal); (**2) presence of blood in the stool** (No blood seen/Streaks of blood with stool less than half the time./Obvious blood with stool most of the time/Blood alone passes); **(3) endoscopyic findings** that defines the extent of disease (normal or inactive, mild, moderate, or severe) ; and **(4) physician's global assessment** based on physical examination , endoscopy, and laboratory data (normal, mild, moderate, severe).

Routine vaccination status should be reviewed:

- In patients on immunosuppressants, live vaccines are contraindicated, so if these are required they should be administered at the time of UC diagnosis.
- Patients on immunosuppressant drugs can and should be vaccinated routinely for influenza and pneumococcal infection, and meningococcus in the appropriate settings .
- Patients have been started on adalimumab should be screened for hepatitis B before initiating therapy**.**

Goals of treatment: induction and maintenance of remission of symptoms to provide an improved quality of life, reduction in need for long-term corticosteroids, and minimization of cancer risk.

Management Of Mild To Moderate Distal Colitis

Mild disease: limited to rectum (proctitis) with or without sigmoid involvement, often present insidiously with intermittent rectal bleeding associated with passage of mucus, and development of mild diarrhea with fewer than 4 small loose stools per day. Mild crampy pain, tenesmus, and periods of constipation are also common

Induction of remission

First presentation or inflammatory exacerbation of proctitis or proctosigmoiditis; inflammation is distal limited to below the descending colon topical corticosteroids is given :

Hydrocortisone enema 100 mg or 10% hydrocortisone foam in twice daily dosing. Symptomatic improvement is usually seen within 3 to 4 weeks and, once remission has been attained, drug can be tapered gradually to maintenance levels or discontinued altogether.

When inflammation extends proximal to reach of topical therapy (i.e., descending colon) , oral therapy is required, either solely or in combination with topical therapy.

- **5-aminosalicylic acid** (**Mesalamine**) : 500-1000 mg PO four times daily for 8 wks

In children aged ≥ 5 yrs:

- 17 to <33 kg: 36-71 mg/kg/day PO divided twice daily; not to exceed 1.2 g/day
- 33 to <54 kg: 37-61 mg/kg/day PO divided twice daily; not to exceed 2 g/day
- 54 to 90 kg: 27-44 mg/kg/day PO divided twice daily; not to exceed 2.4 g/day

Combination of oral mesalamine and topical corticosteroids is more successful than oral mesalamine alone in achieving clinical remission at 8 weeks.

Adverse effects: Common: headache, malaise, cramps and gas, watery diarrhea. Uncommon: hair loss, skin rash, colitis. Rare: pneumonitis, pericarditis, pancreatitis,interstitial nephritis.
If an UC flare coincides with a recent increase in dose or addition of an oral 5-ASA, oral 5-ASA should be discontinued
It is recommended that serum Cr and BUN should be measured before initiating treatment with mesalamine, and periodically while on treatment.

- **Oral corticosteroids** is given if patient is refractory to oral 5-ASA in combination with topical therapy in maximal doses (after 2- 4 weeks), or is systemically ill

  Prednisone or prednisolone 40–60 mg per day until significant improvement occurs , then a dose taper of 5–10 mg weekly until a daily dose of 20 mg is reached. At this point tapering proceeds at 2.5 mg per week.

  Pediatric dose: 1 mg/kg up to 40 mg once daily

- If steroid dependent, thiopurines can be given as steroid sparing agent: **Azathioprine** 1.5-2.5 mg/kg PO once daily. Thiopurines adverse events**:** BMS (leucopenia), liver abnormalities, Allergic reactions, pancreatitis, infections, lymphoma,nephrotox.

Steroid-dependent UC: if steroids cannot be tapered to less than 10 mg/day within 3 months of starting steroids without recurrent disease, or if relapse occurs within 3 months of stopping steroids.

Maintenance of remission

Maintenance therapy is not recommended in patients with a first episode that has responded promptly to treatment.

- Granulated extended release **mesalamine** capsules 1.5 g oral per day
- If mesalamine fails → give **azathioprine**1.5-2.5 mg/kg PO once daily

Maintenance therapy with corticosteroids is ineffective with added adverse effects.

Management Of Mild To Moderate Extensive Disease

Moderate (Left-side colitis) : present in descending colon up to, but not proximal to, splenic flexure. The clinical picture is characterized by frequent loose, bloody stools (4- 6 per day), mild anemia not requiring blood transfusions, abdominal pain that is not severe, and low grade fever. Adequate nutrition is usually maintained.

Induction of remission

- Should begin with **oral 5-ASA: Mesalamine** in doses up to 4.8 g per day
- **If 5-ASA failed→ oral prednisone** 40–60 mg per day until significant clinical improvement occurs and then a dose taper as mentioned before. Pediatric dose: 1 mg/kg up to 40 mg once daily
- If steroids dependent or refractory → **azathioprine**: 1.5-2.5 mg/kg PO daily

Steroid-refractory disease: patients who have active disease despite prednisolone of up to 0.75 mg/kg/day over a period of 4 weeks.

Steroid adverse effects : cushingoid features, skin striae, infections,cataract , glaucoma, psychiatric disturbances, GI mucosal injury, impaired wound healing, metabolic bone dis.

- If immunosuppressants failed→ **TNF alpha-Inhibitors are given** with tapering oral steroid over 1-2 months: **Adalimumab 'ADA'**: first dose of 160mg SQ, a second dose two weeks later of 80mg. Pediatrics: 20 mg - 40 mg every other week . Continue ADA only in patients who have demonstrated evidence of clinical remission after 8 weeks from the initial dose.

Maintenance of remission

- **Mesalamine** can reduce relapses at doses up to 4.8 g per day.
- If remission not adequately sustained → **azathioprine** 1.5-2.5 mg/kg PO once daily
- Immunomodulators refractory colitis → **Adalimumab** (40mg every other week) can be effective in maintaining improvement and remission (alone or in combination).

Management Of Severe Colitis

Extensive colitis (**Severe)** : evidence of UC proximal to splenic flexure. Bleeding per rectum, more than 6 bowel motions / day, systemic illness with hypoalbuminemia (< 30 g/L).

- Patient who presents with toxicity should be admitted to hospital for a course of **IV steroids** in a daily dose equivalent to 300 mg **hydrocortisone** (100 mg IV q8hrs) or 60 mg **methylprednisolone** (16 to 20 mg IV q8 hrs) if patient has received steroids in the previous month.
- Convert IV steroids to oral corticosteroids in 3-5 days if patient responds. Oral corticosteroids should be tapered after patient has been stable for 2 - 4 weeks. Oral corticosteroids should be tapered over 8 weeks, while adding mesalamine or AZA to maintain remission.
- Anti-TNFα agent **ADA** can be given if previous treatments failed
- If steroid resistant after 7-10 days of therapy and Failure to improve using anti-TNF agent within 3–5 days → **consider colectomy**.
- IV antibiotics (eg, **ciprofloxacin** 400 mg x 2 and **metronidazole**500 mg q 8 hrs) in severe colitis and high grade fever, leukocytosis with extreme numbers of immature neutrophils (band form count > 700/microL), and peritoneal signs or megacolon.
- **Total parenteral nutrition** → nutritional adjunct in significant nutritional depletion.
- In patients with either toxic signs (fever, leukocytosis, or worsening symptoms) or megacolon, anticholinergics , narcotic , and NSAIDs should be avoided for possibility of worsening colonic atony or dilatation, as increased colonic and small intestinal gas is a predictor of a poor outcome to medical therapy.
- **Venous thromboembolism** occurs frequently in hospitalized UC patients. Prophylaxis with heparin SQ is important.
- **Antidiarrheals** (loperamide) may be effective for symptomatic relief of persistent diarrhea despite therapy directed at colitis, but should **not** be used in acutely ill patient because of risk of precipitating toxic megacolon. Dose: 4 mg initially, then 2 mg after each loose stool until controlled, then 4-8 mg/day in divided doses.

Fulminant colitis: a subgroup of patients with severe UC who have > 10 stools per day, continuous bleeding often necessitating blood transfusion, abdominal pain, distension, and acute, severe toxic symptoms including fever up to 39.5ºC , anorexia and rapid weight loss, leading to a poor nutritional state. Such patients are at risk of progressing to toxic megacolon and bowel perforation but not always extending to cecum (pancolitis).

Patients are treated similarly as above but decisions regarding surgery or TNFα blockers should be taken within a few days of initiating IV steroid therapy. Patients who are relatively stable and respond partially or sub-optimally to IV corticosteroids within 72 hours should be considered for adalimumab induction therapy.

Colectomy: Patients with fulminant colitis who fail treatment with adalimumab (either due to a failure to respond or due to relapse) within 4-7 days, and those with toxic megacolon who do not respond to therapy within 72 hours, require colectomy.

Absolute indications for surgery: exsanguinating hemorrhage, toxic dilation (megacolon),frank perforation, and documented or strongly suspected carcinoma.

Pouchitis : inflammation of ileal pouch (an artificial rectum surgically created out of ileal gut tissue in patients who have undergone a colectomy). Antibiotics have an important role in the treatment of pouchitis.

- Ciprofloxacin 1 g daily (fewer side effects)
- Metronidazole 1 to 2 g daily for seven days if ciprofloxacin failed ,
- Combination metronidazole and ciprofloxacin have also been reported to be efficacious in the treatment of chronic refractory pouchitis
- Determining coliform sensitivities may help plan individualized therapies in patients with pouchitis that becomes refractory to treatment
- Oral budesonide (9 mg/day for eight weeks) can be effective in a series of patients with acute pouchitis refractory to antibiotics

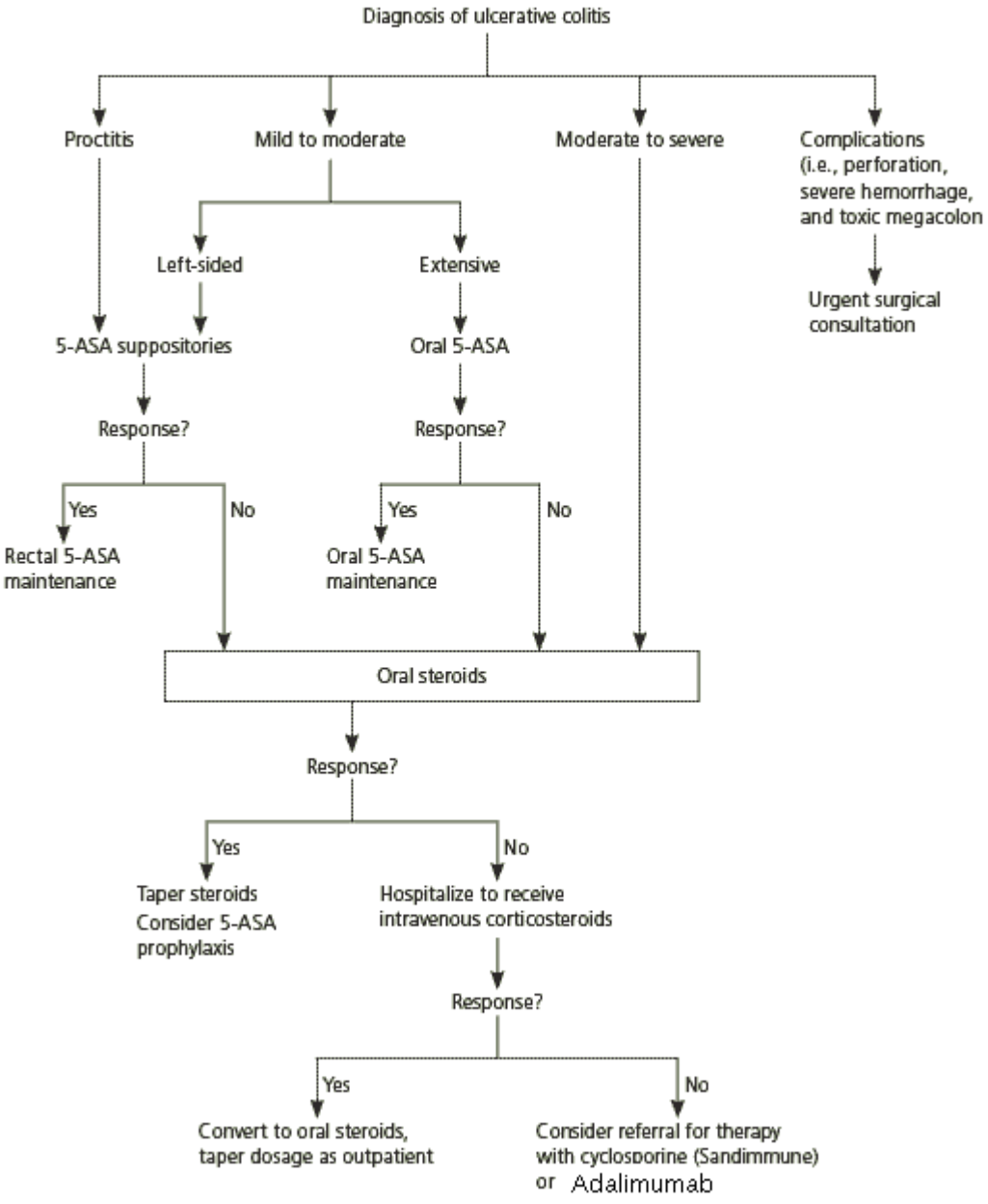
Nutritional And Dietary Considerations

- Weight loss is common in patients with more extensive forms of ulcerative colitis. Thus, patients are urged to maintain an adequate balanced diet.
- Supplemental **iron** may be necessary to prevent or treat iron deficiency anemia due to chronic blood loss. Parenteral iron may be needed for patients who cannot tolerate oral iron.

Psychotropic Agents

- Patients who are especially troubled by psychosocial stresses (can worsen disease) may benefit from minor tranquilizers (eg, diazepam).
- Addition of an antidepressant should be considered in selected patients, while lithium carbonate may be beneficial in patients with corticosteroid-induced psychoses.

Ulcerative Colitis Management Algorithm



Crohn's Disease Definition And Diagnosis

Crohn's disease (CD) encompasses a multisystem group of disorders with specific clinical and pathological features characterized by focal, asymmetric, transmural, and, occasionally, granulomatous idiopathic inflammation of the gastrointestinal (GI) tract that can affect any part of the tract from the mouth to the anus. Chronic inflammation from T-cell activation leading to tissue injury is implicated in the pathogenesis of CD.

The exact cause of CD remains unknown. Genetic, microbial, immunologic, environmental, dietary, vascular, and psychosocial factors have been implicated, as have smoking and use of oral contraceptives and nonsteroidal anti-inflammatory agents (NSAIDs).

Epidemiology: This multisystem disorder can affect any age group, but the onset (diagnosis) is most common in the second and third decades (teenagers and young adults). The rate of Crohn's disease is 1.1-1.8 times higher in women than in men.
The course of Crohn's disease is characterized by periods of remission and exacerbation.

The characteristic presentation is abdominal pain and chronic or nocturnal diarrhea, which may be complicated by intestinal fistulization or obstruction. Unpredictable flares and remissions characterize the long-term course.

Other signs and symptoms: rectal bleeding (its absence may suggest CD over UC), fever, anorexia, Nausea, vomiting, generalized fatigability. Nutritional deficiencies are common with Crohn's disease (weight loss, iron deficiency anemia, vitamin B12 deficiency, folate deficiency, hypoalbuminemia, hypokalemia, and osteomalacia).

Associated extraintestinal features: arthritis, iritis, skin lesions, and liver disease. The ileum and colon are the most frequently affected sites, commonly complicated by intestinal obstruction, inflammatory mass, or abscess

Goals of treatment: CD is a chronic inflammatory disorder that is neither medically nor surgically "curable" requiring therapeutic approaches to induce and maintain symptomatic control, improve quality of life, and minimize short- and long-term complications.

The Crohn's Disease Activity Index 'CDAI' is a commonly used grading scale to describe disease activity. The index consists of eight factors, each summed after adjustment with a weighting factor.

Individuals with Asymptomatic remission → CDAI < 150**:** may be in endoscopic remission, clinical remission, or surgical remission, patient is asymptomatic or without any symptomatic inflammatory sequelae. Individuals may have responded to medical or surgical therapy (such as ileocolonic resection) and have no residual active disease.

Individuals who require use of conventional corticosteroids to achieve clinical well-being are said to be "**steroid dependent**" and are not considered to be in remission.

The components of the CDAI and weighting factors (Multiplier) are the following:

Variable	Description	Scoring	Multiplier
Number of liquid stools	**Sum of 7 days**		**×2**
Abdominal pain	**Sum of 7 days' ratings**	**0=none 1=mild 2=moderate 3= severe**	**×5**
General well-being	**Sum of 7 days' ratings**	**0=generally well 1=slightly under par 2= poor 3= very poor 4 = terrible**	**×7**
Extraintestinal complications	**Number of complications listed**	**Arthritis/arthralgia, iritis/uveitis, erythema nodosum, pyoderma gangrenosum, aphtous stomatitis, anal fissure/fistula/abscess, fever > 37.8 °C**	**×20**
Antidiarrhoeal drugs	**Use in the previous 7 days**	**0 = no 1 = yes**	**×30**
Abdominal mass		**0 = no 2 = questionable 5 = definite**	**×10**
Haematocrit	**Expected–observed HCT**	**Men: 47 observed Women: 42 observed**	**×6**
Body weight	**Ideal/observed ratio**	**[1 − (ideal/observed)] × 100**	**×1 (not < −10)**

Management

Therapeutic recommendations depend on the disease location, disease severity, and disease-associated complications. Step-up therapy -other than top down therapy- is preferred, beginning treatment with less potent drugs that have relatively long track records and good safety profiles. We then progress to more potent treatments in patients with severe or refractory disease.

Immunization with inactivated vaccines should be brought up to date and rigorously maintained during treatment, including influenza, meningococcus, and pneumococcus. In addition to the standard pneumococcal conjugate vaccine, they should also be given the pneumococcal polysaccharide vaccine, because they are considered to be at high risk for invasive pneumococcal disease if they are treated with immunosuppressive medication.

Management of Mild–moderate disease (CDAI ≥ 150 –220)

Patients *with mild–moderate disease* are ambulatory and able to tolerate oral alimentation without manifestations of dehydration, syst. toxicity, abdominal tenderness, painful mass, intestinal obstruction, or more than 10% wt loss.

Outpatient therapy with oral medications is appropriate for most patients with mildly to moderately active CD. However, hospitalization is required for patients who present with severe symptoms or who appear toxic.

For patients with mild to moderate CD, treatment will particularly depend upon the site of disease.

Oral lesions : Aphthous ulcerations, granulomatous masses, cheilitis, and granulomatous sialadenitis. Topical medications, such as triamcinolone acetonide in Orabase, can provide local symptom relief.

Gastroduodenal Crohn's disease : Fewer than 5 % of patients with CD have gastroduodenal disease, most often in association with concurrent distal intestinal involvement (distal antrum and duodenum). Symptoms may include epigastric pain, nausea, and postprandial vomiting.

- Proton pump inhibitor, H2 receptor antagonist may provide partial or complete relief of symptoms.
- The slow release form of **mesalamine** encapsulated in ethylcellulose microgranules is partially released in proximal small bowel and theoretically may be of use in duodenal CD: 2 -2.4g daily.
- **Prednisone** is necessary and usually effective for most patients with moderate to severe gastroduodenal disease. The response to therapy is usually seen within 2 weeks, but duration of response is variable. Dose : 40 - 60 mg/day
- **Azathioprine** 2.0–3.0 mg/kg in patients who remain symptomatic despite a course of prednisone or who become steroid-dependent.

Ileitis and colitis

Patients with active ileitis typically present with diarrhea and abdominal pain; they can also have weight loss, low-grade fever, and anemia. Patients with active ileocolitis or CD limited to the colon may present with abdominal pain, bloody or nonbloody diarrhea, fever, and weight loss.

- **5-aminosalisylates** are relatively safe compared with glucocorticoids, immunomodulators, and biologic agents, particularly given the potential chemopreventative benefits of 5-ASAs in longstanding Crohn's colitis.

  SR mesalamine 2 -2.4g daily then increased up to 4.8 g/day, depending upon response.

– **Antibiotics**: luminal bacteria and perhaps fungi have an important role in the pathogenesis of IBD. We suggest antibiotics in patients who do not tolerate 5-ASAs or do not improve within 3-4 weeks of starting a 5-ASA.

  Metronidazole 10-20 mg/kg/day or 250 mg four times daily in patients not responding to 5-ASAs or combination of metronidazole and **ciprofloxacin** (500 mg twice daily) for primary or adjunctive therapy of colonic CD, but not for isolated small intestinal disease up to one month .

  Risk of peripheral neuropathy in metronidazole chronic therapy necessitates monitoring for symptoms or signs of paresthesias, also it has been documented in patients taking large doses for short periods of time for acute infections.

  Azithromycin (250 mg twice daily) for 4 weeks with continued treatment for up to 12 weeks in those who showed a response.

– **Glucocorticoids**

– **Oral glucocorticoids** → mainstay of treatment for patients who are unresponsive to above measures, or for those presenting with more severe initial symptoms (but who are not so ill that they require hospitalization and IV glucocorticoids).

  Initial dose of **prednisone** is 40 - 60 mg/day. MOST patients will respond to this dose, usually within 10 - 14 days. Generally, doses are tapered by 5–10 mg per week until 20 mg and then by 2.5–5 mg weekly from 20 mg until discontinuation of therapy. Glucocorticoids should not be used long-term due to significant side effects.

5-ASA drugs and antibiotics can be used concomitantly with prednisone. Once remission is achieved and the prednisone tapered and stopped.

- **Non-systemic glucocorticoids**: alternative to prednisone in active ileitis or right-sided crohn's colitis, in those with prior intolerance or contraindications to systemic glucocorticoids

Hydrocortisone: -Rectal suppository: one supp (25 mg) inserted rectally twice daily **or**

-Rectal enema: 60 mL (100 mg) by once a day at bedtime.

- **Azathioprine** 'AZA' 2.0–3.0 mg/kg in patients who remain symptomatic despite a course of prednisone or who become steroid-dependent.
- **Antidiarrheal medications** : should be considered in patients not responding completely to first-line therapy. We suggest loperamide because of its efficacy and relative safety: 4 mg initially, then 2 mg after each loose stool until controlled, then 4-8 mg/day in divided doses.
- **Maintenance therapy**: oral **Mesalamine** at a dose of 3 - 3.6 g/day **,** or **AZA** 2.0–3.0 mg/kg.

Management of Moderate–severe disease (CDAI 220–450)

Patients with moderate to severe CD: Patients failed to respond to treatment for mild – moderate disease, or those with more prominent symptoms of fever, significant weight loss, abdominal pain or tenderness, intermittent nausea or vomiting (without obstructive findings), or significant anemia.

- **Prednisone** 40–60 mg daily or **methyl prednisolone** (1 mg/kg) until resolution of symptoms and resumption of weight gain (generally 7–28 days). Generally, doses are tapered by 5–10 mg per week until 20 mg and then by 2.5–5 mg weekly from 20 mg until discontinuation of therapy.

  Pediatric dose: 0.5-2 mg/kg/day PO in single daily dose or divided q12hr

A baseline DEXA scan, supplementation of calcium and vitamin D, and consideration of a bisphosphonate are warranted once corticosteroid therapy is initiated.

More than 50% of patients treated acutely with corticosteroids will become “steroid dependent” or “steroid resistant”, particularly smokers, or those with colonic disease.

- **Azathioprine** → maintain steroid-induced remission or steroid sparing agents (2.0–3.0 mg/kg daily). A response will usually be seen within 3 -6 months → require concomitant steroid therapy with a gradual reduction in steroid dose after 1-2 months of treatment with azathioprine

Routine monitoring of complete blood counts, initially every 1–2 weeks, then, at least every 3 months is recommended to avoid the risk of acute or delayed bone marrow suppression .

Measuring TPMT activity prior to beginning therapy is important .

Pancreatitis, typically presenting several weeks after initiating therapy, Lymphomas also occur; a rare form of natural killer cell, hepatosplenic lymphoma has recently been associated with AZA therapy for CD either alone or in combination with IFX.

- **Parenteral Methotrexate:** alternative for patient who does not tolerate or respond to AZA , and may be preferable to AZA in patients with troublesome Crohn's disease-related arthropathy.

Induction dose: SQ or IM 15-25 mg weekly for 3-6 months (with tapering steroid if were used) Once a response achieved → switched to oral MXT with an attempt to lower dose gradually over several months to 15 mg per week (**remission dose**).

Pediatric dose: 15- 25 mg/m2/week SQ for 3-6 months. Then switching to parenteral administration

Note: Oral dosing has been reported as effective but oral absorption is highly variable. If patient relapses after a switch to oral, may consider returning to injectable.

Adverse events of MXT:

- Elevated LFT results: Minor elevations of LFT results are common
- Anemia, aplastic anemia, leukopenia, thrombocytopenia
- Interstitial pneumonitis
- GI ulceration and bleeding, ulcerative stomatitis
- Gastrointestinal problems such as NVD, stomach upset, and loose stools
- Malaise or fatigue, dizziness , alopecia
- Chills and fever, but infection should be excluded
- Decreased resistance to infection
- Photosensitivity (''radiation recall'')
- Macular punctate rash that usually occurs on the extremities and spares the trunk
- CNS problems including headache, fatigue, or impaired ability to concentrate

A baseline chest X-ray along with monitoring of CBC and liver chemistries, BUN, Cr is advocated.
Concomitant therapy with folic acid 1 mg/day may diminish adverse effects to methotrexate.
Prior to initiation of therapy with MXT, a liver biopsy is appropriate for patients with abnormal baseline liver chemistries (↑AST over 1 year or if ser albumin ↓), patients with one or more risk factors for hepatotoxicity (obesity, presence of DM, ↑baseline hepatocellular lab chemistries, a cumulative dose of MTX > 1.5 g total dose, and daily dosing of MTX), and patients who are suspected of having baseline chronic liver disease.
Reduction in MXT dose is recommended in response to ↑AST level (performed every 4–8 weeks). If moderate to severe fibrosis or cirrhosis is found, MXT should be discontinued.

Refractory Crohn's

- ☒ Repeatedly relapse after achieving remission with 1st-line agents
- ☒ Remain symptomatic despite adequate doses of glucocorticoids (steroid-resistant), 5-ASAs, and antibiotics
- ☒ Flare when glucocorticoids are decreased or stopped (steroid-dependent)

Treatment options : AZA or 6MP , MXT, biologic therapies.

- **Patients who are refractory to above treatments may require treatment with Biologic therapy: Anti-TNF monoclonal antibodies, adalimumab.**

Adalimumab→ SQ160 mg followed by 80 mg after 2 weeks .Maintenance of 40 mg every other week when response to initial induction doses. Dose escalation to 40 mg weekly may be necessary to maintain responses in some patients.

Pediatric ≥4 yrs [**≥15 kg , <30 kg**: 20 mg SC every 2 wks / **≥30 kg**: 40 mg SC every 2 wks]

Adverse events: injection site reactions, infusion reactions (acute or delayed), neutropenia, infections, HF, cutaneous reactions (including psoriasis, malignancy, induction of autoimmunity). Neurologic disturbances (confusion, ataxia, dysesthesia, paresthesia, facial nerve palsy, optic neuritis, hemiparesis, transverse myelitis, and ascending motor neuropathy).

Assessment of prior TB exposure, current purified protein derivative status, and a chest X-ray prior to anti-TNF therapy are important as anti-TNF use has been associated with reactivation of latent TB.

A significant percentage of patients treated with anti-TNF therapy develop positive anti-nuclear antibodies and a smaller proportion develop antibodies to double-stranded DNA. Patients with fibrostenotic CD without active inflammation are unlikely to benefit from anti-TNF therapy.

- In patients who failed immunomodulator and biologics *can* achieve a relative degree of remission with **low-dose prednisone**. Such patients should be maintained on lowest dose that results in decreased symptoms; alternate-day therapy can be tried for maintenance to minimize toxicity.

Management of Severe/Fulminant Disease (CDAI > 450)

Severe CD : persistent symptoms despite introduction of conventional corticosteroids or biologic agents as outpatients, or individuals presenting with high fevers, persistent vomiting, evidence of intestinal obstruction, significant peritoneal signs such as involuntary guarding or rebound tenderness, cachexia, or evidence of an abscess.

Such patients need hospitalization: bowel rest, nutritional support through elemental feeding or parenteral hyperalimentation is indicated, after 5–7 days, for patients who are unable to maintain adequate nutritional requirements or those with evidence of intestinal obstruction.

Supportive or resuscitative therapy with fluid and electrolytes is indicated for dehydrated patients. **Transfusions** are necessary in the setting of anemia and active hemorrhage.

- Once presence of an abscess has been excluded or if patient has been receiving oral corticosteroids, **parenteral corticosteroids** equivalent to 40–60 mg of prednisone daily or 60 mg **methylprednisolone** are administered in divided doses or as a continuous infusion.
  Convert IV steroids to oral corticosteroids in 3-5 days if patient responds. Oral corticosteroids should be tapered after patient has been stable for 2 - 4 weeks. Oral corticosteroids should be tapered over 8 weeks, while adding mesalamine or AZA to maintain remission. Failure to respond or worsening symptoms are indications for acute surgical intervention
- Patients who do not respond to steroids may require treatment with biologic therapy (**ADA**)
- In presence of inflammatory mass → broad-spectrum **antibiotics** should be instituted along with parenteral corticosteroids.
- Increased risk of VTE and PE in patients with IBD → **heparin** prophylaxis is recommended

<u>Management of Perianal And Fistulizing Disease</u>

- **Acute suppuration** is an indication for surgical drainage with or without placement of non-cutting setons .
- **Antibiotics**: Patients with enterovesical fistulae present with recurrent polymicrobial urinary tract infections, pneumaturia, and fecaluria.
  - Non-suppurative, chronic fistulization, or perianal fissuring is →**metronidazole** alone or combination with **ciprofloxacin**. Antibiotics are continued for 3 months in most situations.
  - Other antibiotics have also been used in perineal CD→ amoxicillin/clavulanate, TMP/SMX
- **Immunomodulators**: AZA or MXT can be given**.**
- **ADA** are effective in closure of CD fistulae (actively draining or high output enteroenteric fistulae) that had not responded to prior therapy with immunomodulators .
- **<u>Tacrolimus</u>** (0.2 mg per kg per day) is effective in patients who are refractory to AZA, <u>methotrexate</u>, and/or biologics.

Adverse effects of tacrolimus : headache, increased serum Cr, insomnia, leg cramps, paresthesias and tremors (managed with dose reduction).

Management of localized peritonitis

- Bowel rest and broad-spectrum antibiotics. A response to therapy is usually seen within 3-4 days and IV antibiotic therapy is continued for 7 to 10 days. A subsequent 2-4 week course of outpatient oral therapy with ciprofloxacin and metronidazole should be considered.
- Intestinal resection should be considered in nonresponders.

Management of Abscesses: antibiotics (and possibly steroids), percutaneous drainage, and surgery with resection of involved intestinal segments.

Management of Small bowel obstruction:

- Conservative therapy with IV hydration, nasogastric suction, and parenteral nutrition is often successful, with a response seen within 24 to 48 hours.
- Parenteral glucocorticoids should be considered in nonresponders.
- Surgery is reserved for those patients who do not respond to these noninvasive measures or who have evidence of small bowel ischemia.

High-risk predictive factors for CD recurrence

Jejunal or extensive ileal-colonic disease.
Initial presentation requiring surgery.
Age less than 30 years
Fistulizing disease
Patients undergoing a second resection.
Failure of medical management.

Maintenance therapy

AZA/6-MP and **methotrexate** have demonstrable maintenance benefits after inductive therapy with corticosteroids or anti TNF.

AZA 2.0–2.5 mg/kg has been effective at maintaining remissions for, at least, 4 years Or weekly **MXT** at a dose of 15 mg, IM Or **ADA** 40 mg SQ every other week or 40 mg SQ every week .

Indications for Surgery (Surgical resection, stricturoplasty, or drainage of abscesses)

1. Intractable hemorrhage, perforation, persisting or recurrent obstruction, abscess (not amenable to percutaneous drainage), dysplasia or cancer, or
2. Unresponsive fulminant disease
3. Refractory disease despite medical therapy or side effects of medication (steroid dependence).
4. Active luminal CD and fail to improve within 7–10 days of intensive medical management

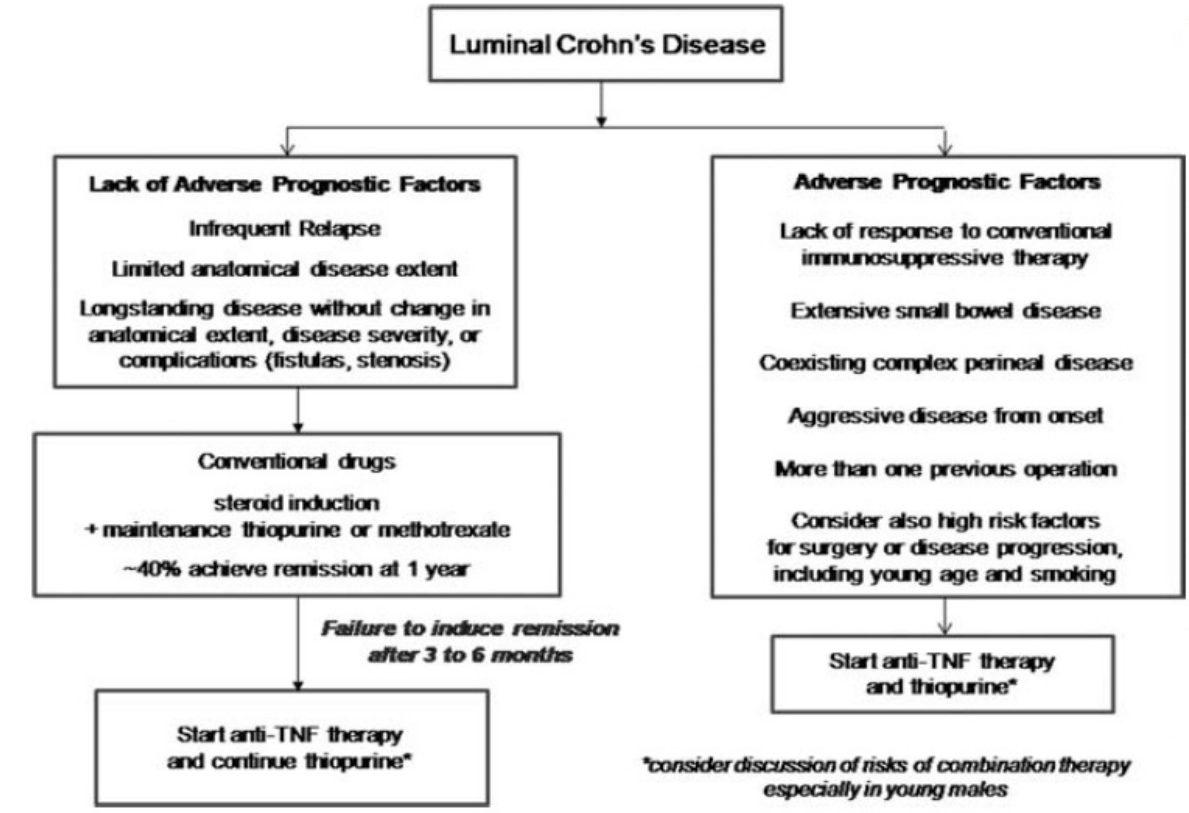
Prevention Of Postoperative and endoscopic Recurrent CD

- **Mesalamine** 3 - 4 g daily in patients prior to resection and who do not have high-risk predictive factors for recurrence, or those unwilling to consider agents with potential for more side effects.
- **High-dose metronidazole**, 20 mg/kg for 3 months
- **Long-term AZA** (2.0 to 2.5 mg/kg dly) with metronidazole (250 mg 3 times dly for first 3 months) in patients with high-risk predictive factors for recurrence
- Smoking cessation should be strongly encouraged
- Consideration should be given to endoscopic reassessment of the bowel 9 to 12 months postoperatively. Endoscopically active disease in patients maintained with antibiotics or mesalamine should prompt consideration of immunomodulator therapy, while active disease on azathioprine should prompt consideration of substituting or adding anti-TNF therapy

Monitoring Nutritional Status

- Minimize use of glucocorticoids.
- All children with IBD should have regular measurements of body weight, height, and pubertal status, body mass index at least every 4 months.
- Healthy children with CD should be screened annually for micronutrient deficiencies, or more frequently if there is active disease.
  Low levels of vitamins A, D and E, and of zinc, selenium, and folic acid have been reported. Vitamin B12 deficiency is especially common in patients who undergo ileal resection.
- Reduced bone mineral density may be associated with vitamin D deficiency, calcium malabsorption, pubertal delay, or corticosteroid therapy. Daily intake of vitamin D and calcium: vitamin D is 600 IU for all ages, and calcium is 1300 mg daily for adolescents, and 1000 mg daily for children four to eight years of age. 1200mg for adults.
- **Lactose avoidance** especially in patients with ileal disease (have an increased frequency of acquired lactase deficiency and symptomatic lactose intolerance). Patients with suggestive symptoms should undergo a trial of lactose avoidance. If the diagnosis is in doubt, a lactose breath hydrogen test can be obtained. If patient responds to lactose avoidance or if test is positive, patient should be instructed to avoid lactose containing foods. Calcium supplementation should be maintained in patients on a limited lactose intake to minimize the risk of bone loss to decrease urinary oxalate levels.

Luminal Crohn's Disease Algorithm



Management Of IBD In Pregnancy

Drug therapy for IBD is not a contraindication for pregnancy, and most pregnancies are well managed in patients with these diseases. The indications for medical and surgical treatment are similar to those in the nonpregnant patient. Doctors usually recommend that women try to conceive while their disease is in remission**.** Women with more severe disease have an increased risk of delivering prematurely and having a low birth weight infant.

- **Mesalamine** does not appear to increase complications or harm the fetus. Women can breastfeed while taking a 5-ASA compound. If 5-ASA medications are taken during breastfeeding, the American Academy of Pediatrics recommends monitoring the infant's stool consistency. There have been reports of diarrhea in breastfeeding infants of women who took rectal 5-ASA.
- **Folic acid** supplementation, 1 mg twice daily, should be given.
- **Prednisone** is only recommended for use during pregnancy when there are no alternatives and benefit outweighs risk. If a woman becomes pregnant while on steroids, doctor usually tries to minimize the dose. Women who are taking steroids during pregnancy will need to be given a "stress dose" of steroids by IV (into a vein) during labor and delivery. Steroids (eg, prednisone) are probably safe to take during breastfeeding.
- **Azathioprine** is only recommended for use during pregnancy when there are no alternatives and benefit outweighs risk. Women are often advised to avoid breastfeeding, although there are no good data about risks in a nursing infant.
- **Adalimumab** are given during pregnancy only if it is clearly needed (category B). ADA cross placenta in high levels late in pregnancy so your doctor may want to give the last dose in the middle of your third trimester. It is not clear if they are excreted into breast milk. The potential effects in infant are also unknown.
- Short courses of **metronidazole** are probably safe for use during pregnancy. However, ciprofloxacin is not recommended for pregnant or breastfeeding women.

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