Overview of the medical management of mild (low risk) Crohn disease in adults

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INTRODUCTION

Crohn disease is an inflammatory condition that can affect any portion of the gastrointestinal tract from the mouth to the perianal area. Its transmural inflammatory nature coupled with the variability of intestinal distribution (ie, which intestinal segment is affected) and systemic manifestations, gives rise to a spectrum of clinical presentations and long-term risks that have to be considered in deciding the optimal therapeutic approach.

The choice of therapy varies depending upon the anatomic location of disease, the severity of disease, and whether the treatment goal is to induce remission or maintain remission. Medical therapies that are used for Crohn disease include:

- Oral 5-aminosalicylates (eg, sulfasalazine, mesalamine)
- Glucocorticoids (eg, prednisone, budesonide)
- Immunomodulators (eg, azathioprine, 6-mercaptopurine, methotrexate)
- Biologic therapies (eg, infliximab, adalimumab, certolizumab pegol, natalizumab, vedolizumab, ustekinumab)

This topic will provide an overview of the use of 5-aminosalicylates and glucocorticoids for the treatment of patients with mild Crohn disease. Our recommendations are generally consistent with multiple societies worldwide [1-4]. The approach to patients with severe or refractory

Crohn disease, a detailed discussion of individual medications, including 5-aminosalicylates and budesonide, can be found elsewhere:

- Medical management of moderate to severe Crohn disease in adults
- Sulfasalazine and 5-aminosalicylates in the treatment of inflammatory bowel disease
- Overview of budesonide therapy for adults with inflammatory bowel disease

Detailed discussion of immunomodulators and anti-tumor necrosis factor agents can be found elsewhere:

- Overview of azathioprine and mercaptopurine use in inflammatory bowel disease
- Treatment of Crohn disease in adults: Dosing and monitoring of tumor necrosis factor-alpha inhibitors

ASSESSING DISEASE ACTIVITY, SEVERITY, AND RISK

Crohn Disease Activity Index — Clinical trials of Crohn disease often use formal grading systems to describe disease activity. Two commonly used systems are the Crohn's Disease Activity Index (CDAI) (calculator 1) and the Harvey-Bradshaw Index (HBI) (calculator 2) [5], which is a simplified derivative of the CDAI. The HBI has been shown to correlate with the CDAI [6]. A drop in the CDAI of 100 points corresponds to a 3-point drop in the HBI. A CDAI of <150 (ie, clinical remission) corresponds to an HBI of <4. These Crohn disease activity scoring systems rely on subjective symptoms, and while still utilized in clinical research trials, there is an emerging construct that defines disease burden in terms of objective findings and the presence or absence of bowel destruction. In addition, clinical trials are increasingly utilizing patient-reported outcomes to assess disease activity in Crohn disease.

In clinical practice, the following working definitions may be more useful [3]:

- Clinical remission (CDAI <150) – These patients are asymptomatic and without symptomatic inflammatory sequelae. This status is achieved either spontaneously or after medical or surgical intervention. Patients requiring glucocorticoids to remain asymptomatic are **not** considered to be in remission but are referred to as being "steroid-dependent".

- Mild Crohn disease (CDAI 150-220) – These patients are typically ambulatory and tolerating an oral diet. They have <10 percent weight loss and no symptoms of systemic disease such as fever, tachycardia, abdominal tenderness, and no signs or symptoms of obstruction.

- Moderate to severe Crohn disease (CDAI 220-450) – This group comprises patients who have failed treatment for mild to moderate disease or those patients with prominent symptoms such as fever, weight loss, abdominal pain and tenderness, intermittent nausea or vomiting, or anemia.

- Severe-fulminant disease (CDAI >450) – Patients with persistent symptoms despite glucocorticoids or biologic agents (infliximab, adalimumab, certolizumab pegol, natalizumab, vedolizumab, or ustekinumab) as outpatients, or individuals presenting with high fever, persistent vomiting, intestinal obstruction, peritoneal signs, cachexia, or evidence of an abscess.

Low- versus moderate/high-risk patients — In addition to the clinical parameters, the American Gastroenterological Association (AGA) stratifies patients into either a low or moderate/high risk category by assessing inflammatory status with the following tests [1]:

- Endoscopic evaluation for mucosal ulcerations and stricturing and disease extent
- Laboratory parameters: C-reactive protein and/or fecal calprotectin
- Presence or absence of upper gastrointestinal involvement

Patients with mild Crohn disease who are at low-risk for long term sequelae usually have no or mild symptoms as described above and lack signs of systemic inflammation (ie, normal or mild elevation in C-reactive protein and/or fecal calprotectin levels) [1] (see "Clinical manifestations, diagnosis, and prognosis of Crohn disease in adults").

Low-risk patients with mild Crohn disease have the following features [1]:

- No or mild symptoms
- Normal or minimal elevation in C-reactive protein and/or fecal calprotectin levels
- Diagnosis at age >30 years
- Limited distribution of bowel inflammation
- Superficial or no ulceration on colonoscopy
- Lack of perianal complications
- No prior intestinal resections
- Absence of penetrating or stricturing disease

Patients initially identified as low risk may be subsequently reclassified as higher risk if they develop complications or don’t respond to initial treatment. Other prognostic factors associated with a more complicated disease course include bowel damage as measured by cross sectional imaging, extra-intestinal manifestations of disease, number of flares, need for glucocorticoids, and resultant hospitalizations.

The medical treatment of patients with moderate to severe Crohn disease (ie, high risk patients) is discussed separately. (See "Medical management of moderate to severe Crohn disease in adults".)

Limitations to assessment tools — While clinicians assess a patient's disease activity at one point in time to guide their treatment recommendations, the long-term burden of disease should also be taken into account because bowel inflammation that is asymptomatic can result in future damage [7]. For example, the PROSPECT index, based on clinical, serologic, and genetic variables, is a validated tool that can be used to predict the risk of developing a Crohn disease-related complication or progression to surgery [8]. In addition, the activity and severity of inflammatory bowel disease occur on a continuum, and some patients may not clearly fit into a specific category based on the clinical features and long-term risk.

STEP-UP VERSUS TOP-DOWN THERAPY

There are two general approaches to the treatment of Crohn disease:

- **Step-up therapy** – Step-up therapy typically starts with less potent medications that are often associated with fewer side effects. More potent and potentially more toxic medications are used only if the initial therapies are ineffective.
- **Top-down therapy** – Top-down therapy starts with more potent therapies, such as biologic therapy and/or immunomodulator therapy, relatively early in the course of the disease before patients become glucocorticoid dependent, and possibly even before they receive glucocorticoids. (See "Medical management of moderate to severe Crohn disease in adults".)

When treating patients with mild Crohn disease who are low-risk, we favor step-up therapy, 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 whose disease does not respond to initial treatments or who require more than one course of glucocorticoids. Such an approach spares these low-risk patients the adverse effects of drugs that they may not need.

In contrast, high-risk patients with moderate to severe Crohn disease should be initiated on biologic or immunomodulator therapy in a top-down approach; the more potent therapies are more likely to be associated with more rapid onset of clinical remission and more favorable long-term side effect profile compared with glucocorticoids. In a trial 133 patients with newly diagnosed Crohn disease who were randomly assigned to receive combination therapy (infliximab and azathioprine) or glucocorticoids followed by azathioprine and infliximab as

needed, more patients in the combination group achieved clinical remission at 26 and at 52 weeks compared with the glucocorticoid group (60 versus 36 percent, and 62 versus 42 percent, respectively) [9]. Serious adverse events were similar in both groups (31 versus 25 percent). (See "Medical management of moderate to severe Crohn disease in adults".)

Given the heterogeneity of the disease and multiple options for combining therapies, it is unlikely that controlled trials will ever become available to guide treatment for every clinical circumstance. In addition, the cost of therapy, patient compliance, individual susceptibility to drug toxicity, and patient preferences are equally relevant factors for making patient-specific decisions.

INDUCTION OF REMISSION

Outpatient therapy with oral medications is appropriate for patients with mild Crohn disease, and choice of treatment will in part depend upon the distribution of disease.

Treatment goals — The treatment goal for patients with Crohn disease is to achieve remission (endoscopic, histologic, and clinical remission) by demonstrating complete mucosal healing.

Ileum and/or proximal colon involvement — The ileum is the region of the small bowel most often involved in Crohn disease. Patients with mildly active ileitis and/or colitis typically present with diarrhea and abdominal pain. (See "Clinical manifestations, diagnosis, and prognosis of Crohn disease in adults".)

Budesonide — We and several society guidelines recommend enteric-coated budesonide as the first line treatment for inducing remission in low-risk patients with mildly active Crohn disease of the ileum and proximal colon [1-4]. Controlled ileal release budesonide is a corticosteroid with a high first-pass hepatic metabolism. (See "Overview of budesonide therapy for adults with inflammatory bowel disease".)

Budesonide is started at 9 mg per day for at least four weeks, but not more than eight weeks. Budesonide is then tapered by 3 mg increments every two to four weeks for a total of eight to 12 weeks of therapy. We do not recommend using budesonide for longer than 12 weeks per course (table 1). Once remission is achieved in patients with mild Crohn disease with primary involvement of the distal ileum and right colon and budesonide is tapered or stopped, maintenance therapy can be initiated [3]. (See 'Maintenance of remission' below.)

In patients who cannot successfully taper budesonide by three to six months, treatment escalation with either a thiopurine or biologic is indicated, similar to treatment of moderate to

severe Crohn disease. This is discussed separately (algorithm 1) (see "Medical management of moderate to severe Crohn disease in adults").

Systemic side effects are less common with budesonide compared with conventional glucocorticoids such as prednisone. (See "Overview of budesonide therapy for adults with inflammatory bowel disease".)

Budesonide is effective for inducing remission in patients with ileal and ileocecal Crohn disease [10-14]. In a meta-analysis of two trials including 458 patients with active Crohn ileitis and/or right colon involvement, patients receiving budesonide 9 mg per day were more likely to achieve remission compared with those given placebo (RR of failure to achieve remission 0.73, 95% CI 0.63-0.84) [10]. In a meta-analysis of three trials that included 379 patients with Crohn disease, clinical remission rates at eight weeks were higher in patients treated with budesonide 9 mg daily as compared with placebo (47 versus 22 percent; RR 1.9, 95% CI 1.37-2.73) [15].

It is unclear if budesonide is more effective at inducing remission than mesalamine [15,16]. In one trial that included 182 patients with active Crohn disease who were assigned to treatment with budesonide 9 mg or mesalamine, remission rates were higher in patients treated with budesonide as compared with mesalamine (68 versus 42 percent, RR 1.63, 95% CI 1.23-2.16). However, another trial found no significant difference in remission rates at eight weeks [17].

Alternative agents

Prednisone — Oral glucocorticoids (ie, prednisone and prednisolone) are alternatives as initial therapy for patients with mild Crohn disease involving the ileum and/or proximal colon. Prednisone can be given to low-risk patients who do not respond to budesonide; however, patients who initially respond to oral glucocorticoids but cannot tolerate gradual tapering of prednisone are no longer regarded as low-risk and should be reassigned to the moderate/high risk category. (See "Medical management of moderate to severe Crohn disease in adults".)

The initial dose of prednisone is 40 mg per day for one week, and many patients will respond to this dose. At that point, a gradual tapering by 5 to 10 mg per week should be started with the goal of discontinuing the prednisone over one to two months. Glucocorticoids should not be used long-term due to significant side effects. (See "Major adverse effects of systemic glucocorticoids".)

In a systematic review of two trials, patients with Crohn disease who were treated with glucocorticoids were more likely to achieve remission compared with those receiving placebo (RR 2.0, 95% CI 1.5-2.6) [18-20]. Glucocorticoid treatment was associated with higher rate of adverse events compared with placebo (RR 4.9, 95% CI 2.0-12.1).

5-aminosalicylates — The use of 5-aminosalicylates (5-ASA) for Crohn disease is controversial, and we limit its use to patients with mild Crohn disease with limited ileocolonic involvement who prefer to avoid glucocorticoids. For such patients, a slow release, oral 5-ASA agent is suitable, such as mesalamine (eg, Pentasa) (table 2). (See "Sulfasalazine and 5-aminosalicylates in the treatment of inflammatory bowel disease", section on '5-ASA formulations'.)

By contrast, sulfasalazine (the prodrug of 5-aminosalicylate) is less useful for ileitis because colonic bacteria must cleave the drug to release the active 5-ASA moiety, so it is reserved for cases of colitis. (See 'Diffuse colitis or left colonic involvement' below.)

Studies evaluating the efficacy of 5-ASA in Crohn disease have had mixed results; some suggest that higher doses of mesalamine (ie, defined as either ≥1.5 g or ≥2.4 g per day) may be more effective compared with lower doses of mesalamine.

- In a meta-analysis of 22 trials of adult patients with mild to moderate Crohn disease, patients receiving high dose mesalamine (ie, a dose above 2.4 g per day) were more likely to achieve remission compared with those receiving placebo (OR 2.3; 95% credible interval 1.6-3.3) [21]. Sulfasalazine did not result in significantly higher rates of remission compared with placebo. This paper was critiqued to have a data extraction error and that if the data were extracted appropriately, mesalamine would lack effectiveness in inducing remission in Crohn disease patients [22].

- In a meta-analysis of six trials of patients with active Crohn disease, 5-ASAs (taken as a group) were superior to placebo for the induction of remission. Failure to achieve remission was seen in 68 percent of patients treated with 5-ASAs compared with 75 percent of patients treated with placebo (RR 0.89; 95% CI 0.80-0.99) [23]. There was no significant benefit in remission rates when only trials using mesalamine were examined. However, higher doses of mesalamine (≥1.5 g per day) were associated with achieving a combined endpoint of remission or symptom improvement (RR 0.96; 95% CI 0.48-0.98).

- In a meta-analysis of 19 randomized trials of patients with mild to moderate Crohn disease, neither low-dose mesalamine (1 to 2 g per day) nor high-dose mesalamine (3 to 4.5 g per day) was superior to placebo for induction of remission [24].

Some data suggest that 5-ASA are inferior to budesonide for inducing remission. (See 'Budesonide' above.)

Side effects of these medications include nausea, headache, fever, rash, pancreatitis, and pneumonitis (table 3) and are more common with sulfasalazine. (See "Sulfasalazine and 5-

aminosalicylates in the treatment of inflammatory bowel disease", section on 'Side effects'.)

Diffuse colitis or left colonic involvement — For patients with mild, diffuse Crohn colitis or left-sided colonic disease, we suggest initial therapy with oral prednisone 40 mg per day for one week. At that point, a gradual tapering by 5 to 10 mg per week should be started with the goal of discontinuing the prednisone over one to two months [1]. (See 'Prednisone' above.)

Sulfasalazine (3 to 6 g per day over a course of 16 weeks) may be an alternative option for initial treatment of patients with mild colonic (left-sided) Crohn disease [19,25,26]. In a meta-analysis of 19 randomized trials of patients with mild to moderate Crohn disease, sulfasalazine was more likely to induce remission compared with placebo (RR 1.38; 95% CI 1.02-1.87), with the benefit being confined primarily to patients with isolated colitis [24]. Sulfasalazine was inferior to glucocorticoids for inducing remission (RR 0.66, 95% CI 0.53-0.81), and it may be poorly tolerated because of side effects including fever, leukopenia, and rarely, agranulocytosis [27]. (See "Sulfasalazine and 5-aminosalicylates in the treatment of inflammatory bowel disease", section on 'Sulfasalazine'.)

Asymptomatic patients diagnosed incidentally — For asymptomatic patients who undergo a routine, screening colonoscopy and are incidentally found to have very small, shallow aphthous ulcers, a repeat ileocolonoscopy is performed in six to 12 months in addition to clinical monitoring. (See 'Patients who did not require induction therapy' below.)

Other sites of disease

Oral lesions — Aphthous ulcerations, the most common oral lesions, occur in 20 to 30 percent of adult patients with Crohn disease [28]. Aphthous ulcerations may represent mild disease that corresponds with bowel inflammation or a more severe manifestation of Crohn disease. The lip and buccal mucosa are the most commonly affected oral areas by Crohn disease. A wide variety of additional lesions have been described, including buccal swelling, granulomatous masses, cheilitis, and granulomatous sialadenitis. These abnormalities can be severe and may dominate the clinical picture by causing discomfort that impairs oral intake. Oral lesions usually coexist with intestinal disease and respond to treatment directed at the intestinal disease. Topical medications, such as triamcinolone acetonide, can provide local symptom relief. (See "Recurrent aphthous stomatitis".)

Gastroduodenal disease — A small subset of patients with Crohn disease have inflammation affecting the upper gastrointestinal tract, and the distal antrum of the stomach and duodenum are most commonly affected. The management of patients with gastroduodenal Crohn disease is discussed separately. (See "Medical management of moderate to severe Crohn disease in adults", section on 'Gastroduodenal disease'.)

Perianal disease — Patients with perianal abscess and fistula and their associated symptoms (eg, pain, fever, fistula drainage) are assigned to a moderate- to high-risk category and the management of such patients is discussed in detail elsewhere. (See "Perianal Crohn disease".)

MAINTENANCE OF REMISSION

Patients who required induction therapy — After clinical remission has been achieved in a patient with mild Crohn disease, the goal of management is to prevent clinical and endoscopic relapse.

For low-risk patients with mild Crohn disease who achieved remission with a glucocorticoid (eg, budesonide or prednisone), we recommend tapering and then discontinuing the glucocorticoid, followed by clinical observation and ileocolonoscopy in six to 12 months. (See 'Budesonide' above and 'Prednisone' above.)

Conventional glucocorticoids (ie, prednisone) should not be used to maintain remission given their side effect profile [3,29,30]. (See "Major adverse effects of systemic glucocorticoids".)

For low-risk patients with mild Crohn colitis who achieved remission with a 5-ASA agent (or sulfasalazine), we continue the same agent for long-term maintenance therapy and perform an ileocolonoscopy in 6 to 12 months (although some societies advise against 5-ASA) [2]. In a meta-analysis of 11 trials including over 1700 patients with quiescent Crohn disease, relapse rates were not significantly lower in patients receiving mesalamine compared with placebo (53 versus 57 percent) [23]. In a meta-analysis of four trials of 415 patients with quiescent Crohn disease, relapse rates were similar in patients receiving sulfasalazine compared with those receiving placebo.

For patients with Crohn colitis, some data suggest that long-term use of 5-ASA agents may decrease the risk of colon cancer. (See "Surveillance and management of dysplasia in patients with inflammatory bowel disease", section on 'Chemoprevention'.)

Alternative approaches to preventing relapse of Crohn disease include the following:

- Budesonide – When using budesonide, our goal is to induce remission over a 12-week period and then to stop this medication. However, in some patients who have difficulty tapering budesonide, we continue budesonide at a dose of 6 mg daily for no longer than three to six months. In patients who require glucocorticoids to maintain remission, we also initiate a thiopurine. (See "Medical management of moderate to severe Crohn disease in adults", section on 'Alternative approaches'.)

Although budesonide (6 mg daily) is approved by the US Food and Drug Administration for the maintenance of remission in mild to moderate Crohn disease involving the ileum and/or ascending colon for up to three months, there are limited data to support its use in the maintenance of remission beyond six months [10,30]. A meta-analysis of 12 studies that included 1273 patients concluded that budesonide was not more effective than placebo for maintaining remission [31]. Although modest benefits were noted in lowering disease activity scores and prolonging time to relapse of disease, these benefits were offset by higher treatment-related adverse effects (mainly adrenal suppression).

- **Immunomodulator** – Start an immunomodulator such as azathioprine, 6-mercaptopurine, or methotrexate [3]. Typically, these agents are reserved for patients with moderate to severe disease and patients with mild Crohn disease who become glucocorticoid-dependent. (See 'Step-up versus top-down therapy' above and "Medical management of moderate to severe Crohn disease in adults", section on 'Alternative approaches'.)

Patients who did not require induction therapy — In low-risk, asymptomatic patients with mild Crohn disease who did not begin any specific therapy (eg, patients who were diagnosed incidentally at colonoscopy), we suggest clinical observation with a follow-up ileocolonoscopy in six to 12 months. An alternative approach for asymptomatic, low-risk patients with mild endoscopic disease is maintenance therapy with an oral 5-aminosalicylate (5-ASA) agent, especially if the erosions are primarily affecting the colon, although there are little data to support either approach. (See '5-aminosalicylates' above.)

Monitoring during remission — In addition to assessing patients clinically and with ileocolonoscopy in six to 12 months after achieving clinical remission, noninvasive markers of inflammation can be useful. We obtain noninvasive markers of inflammation including C-reactive protein (CRP) and fecal calprotectin at the time of colonoscopy and correlate these tests with the degree of mucosal healing. In some patients with Crohn disease, CRP does not correlate with endoscopic findings, and we do not rely solely on noninvasive markers for monitoring patients in remission.

MANAGING RELAPSE

In patients who have clinical recurrence after achieving remission following glucocorticoid therapy, we begin a second course of a glucocorticoid. Initiation of a thiopurine and/or biologic therapy is also recommended. (See "Clinical manifestations, diagnosis, and prognosis of Crohn disease in adults".)

Patients who are initially low-risk but who relapse following withdrawal of glucocorticoid therapy are given another course of glucocorticoids and are also started on a thiopurine (ie, azathioprine or 6-mercaptopurine). If they fail to respond to the second course of glucocorticoids, they are regarded as high-risk, and the approach to such patients is discussed separately. (See "Medical management of moderate to severe Crohn disease in adults".)

OTHER THERAPIES

Antidiarrheal medications — Symptomatic treatment with antidiarrheal drugs is an option for patients not responding completely to first-line therapy who have mild Crohn disease without complications such as strictures. Patients with moderate or severe Crohn disease or those at risk for bowel obstruction should not receive antidiarrheal agents.

We suggest loperamide as needed in small doses (ie, 2 to 4 mg after an episode of loose stool) for management of diarrhea in this setting because of its efficacy and relative safety in low doses [32]. Cholestyramine or other bile sequestrants are other options for patients with non-stricturing ileal disease who have chronic watery diarrhea. It is also indicated for patients with previous ileal resections who have bile salt diarrhea. The initial dose is 4 g per day, which is increased as needed to a maximum dose of 16 g per day, taken in four divided doses. For patients who do not tolerate cholestyramine because of dyspepsia, colestipol or colesevelam, which are similar binding resins, are often suitable alternatives. (See "Low-density lipoprotein cholesterol lowering with drugs other than statins and PCSK9 inhibitors", section on 'Bile acid sequestrants'.)

Probiotics — Probiotics are viable microorganisms with beneficial physiologic and therapeutic activities. The available data do not support clinical effectiveness of probiotic therapy for either induction or maintenance of remission in patients with Crohn disease [33]. Whether certain patient subgroups might benefit remains to be determined. (See "Probiotics for gastrointestinal diseases", section on 'Crohn disease'.)

Antibiotics — We generally do not use antibiotics for patients with mild Crohn disease. The data pertaining to the use of antibiotics for treatment of active luminal Crohn disease has been somewhat inconsistent [34]. A 2011 meta-analysis of 10 randomized controlled trials found that antibiotics had a modest benefit over placebo for the induction of remission of active Crohn disease (RR of active disease not in remission 0.85, 95% CI 0.73-0.99) as well as maintenance of remission (RR of relapse 0.62, 95% CI 0.43-0.96) [35]. Conclusions were limited by moderate heterogeneity of results and diverse number of antibiotics studied. An independent meta-

analysis reported a modest benefit of antibiotics for improved clinical symptoms in patients with active Crohn disease (OR 1.35, 95% CI 1.16-1.58) [36].

It is unclear if the efficacy of antimicrobial therapy is due to treatment of an undetected pathogen, bacterial overgrowth, or an unsuspected microperforation. The most frequently utilized antibiotics include metronidazole or ciprofloxacin, which also carry potential side effects.

Dietary interventions — Patients with Crohn disease, particularly those with ileal disease, have an increased frequency of acquired lactase deficiency and symptomatic lactose intolerance [37,38].

If lactose intolerance is suspected, we suggest an empiric trial of lactose avoidance. If the diagnosis is in doubt, a lactose breath hydrogen test can be obtained. If the patient responds to lactose avoidance or if the breath test is positive, the patient should be instructed to avoid lactose containing foods (table 4). Calcium supplementation should be given to patients with limited lactose intake to minimize the risk of bone loss. (See "Lactose intolerance and malabsorption: Clinical manifestations, diagnosis, and management".)

Other dietary interventions, including multivitamin and nutritional supplements, and elimination diets in patients with Crohn disease, aim to improve nutrition and eliminate food triggers. This topic is discussed in detail elsewhere. (See "Nutrition and dietary management for adults with inflammatory bowel disease".)

HEALTH MAINTENANCE

It is important to address routine health maintenance, including screening and prevention of other diseases as well as monitoring for side effects of therapy in patients with inflammatory bowel disease [39-41]. These issues are discussed in detail separately. (See "Medical management of low-risk adult patients with mild to moderate ulcerative colitis", section on 'Health maintenance'.)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Crohn disease in adults".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Crohn disease in adults (The Basics)")
- Beyond the Basics topics (see "Patient education: Crohn disease (Beyond the Basics)" and "Patient education: Sulfasalazine and the 5-aminosalicylates (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- **General principles** – Low-risk patients are patients with mild Crohn disease who are identified as low-risk based on prognostic factors that suggest a nonaggressive form of disease: superficial ulcers on colonoscopy, limited anatomic involvement, age (if >30 years), lack of perianal complications, no prior intestinal resections, and absence of penetrating or stricturing disease. These patients usually have no to mild symptoms and lack signs of systemic inflammation (ie, normal or minimal elevation in C-reactive protein and/or fecal calprotectin levels). (See 'Low- versus moderate/high-risk patients' above.)

  There are two general approaches to the outpatient treatment of Crohn disease: step-up therapy and top-down therapy. Step-up therapy starts with medications that are less potent and associated with fewer side effects. If those therapies are ineffective, more potent (and potentially more toxic) medications are used. Top-down therapy starts with more potent therapies, such as biologic therapy or immunomodulator therapy, relatively early in the course of the disease.

In general, we favor step-up therapy for low-risk patients with mild Crohn disease, but top-down therapy for patients with moderate to severe Crohn disease. (See 'Step-up versus top-down therapy' above.)

- **Induction therapy**

  - Patients with ileal and/or right colon disease – For induction of remission in low-risk patients with mild Crohn disease affecting the ileum and/or right colon, we suggest starting controlled ileal release budesonide 9 mg by mouth daily (**Grade 2B**). (See 'Ileum and/or proximal colon involvement' above.)

  - Patients with diffuse or left-sided colitis – For low-risk patients with diffuse Crohn colitis or left-sided colonic disease, we suggest initial therapy with oral glucocorticoids (ie, prednisone) (**Grade 2B**). Sulfasalazine is an alternative option in patients with left-sided colonic Crohn disease. (See 'Diffuse colitis or left colonic involvement' above.)

- **Maintenance therapy** – For low-risk patients with mild Crohn disease who achieved remission with a glucocorticoid (eg, budesonide or prednisone), we taper and then discontinue the glucocorticoid, followed by clinical observation and ileocolonoscopy in 6 to 12 months. Conventional glucocorticoids (ie, prednisone) should not be used to maintain remission given their side effect profile. (See 'Maintenance of remission' above.)

  For patients who have achieved clinical remission with budesonide but who are unable to stop glucocorticoids after six months, we suggest maintenance therapy with an immunomodulator or biologic agent (**Grade 2C**). (See 'Managing relapse' above.).

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Topic 4069 Version 41.0

GRAPHICS

Oral budesonide formulations used in treatment of inflammatory bowel disease

Brand names	Type	Description	pH release	Delivery	Uses
▪ Entocort EC (Canada, US) ▪ Entocort CR, Entocir (EU, UK) ▪ Ortikos (US) NOTE: Generic equivalents may be available	Controlled ileal release (CIR) formulation, pH- and time-dependent	▪ Entocort EC, Entocort CR, Entocir: • 3 mg gelatin capsule filled with enteric-coated granules ▪ Ortikos: • 6 mg gelatin capsule filled with pellets • 9 mg gelatin capsule filled with pellets	≥5.5	Terminal ileum and/or ascending colon	Mild to moderately active Crohn o ileum and/or ascending colon
▪ Budenofalk (EU, UK) NOTE: Not available in US or Canada	pH-dependent release	▪ 3 mg gelatin capsule filled with enteric-coated granules ▪ 9 mg sachet filled with enteric-coated granules	>6.4	Terminal ileum and/or ascending colon	Mild to moderately active Crohn o ileum and/or ascending colon

▪ Uceris (US) ▪ Cortiment (Canada, EU, UK)	Multi-matrix (MMX) structure with gastric acid-resistant coating	▪ 9 mg delayed- and extended-release tablet	≥7.0	Controlled delivery to ascending, transverse, and descending colon	Mild to moderately active ulcerative colitis

Orally administered budesonide has high presystemic clearance and topical antiinflammatory activity.

EU: European Union; UK: United Kingdom; US: United States.

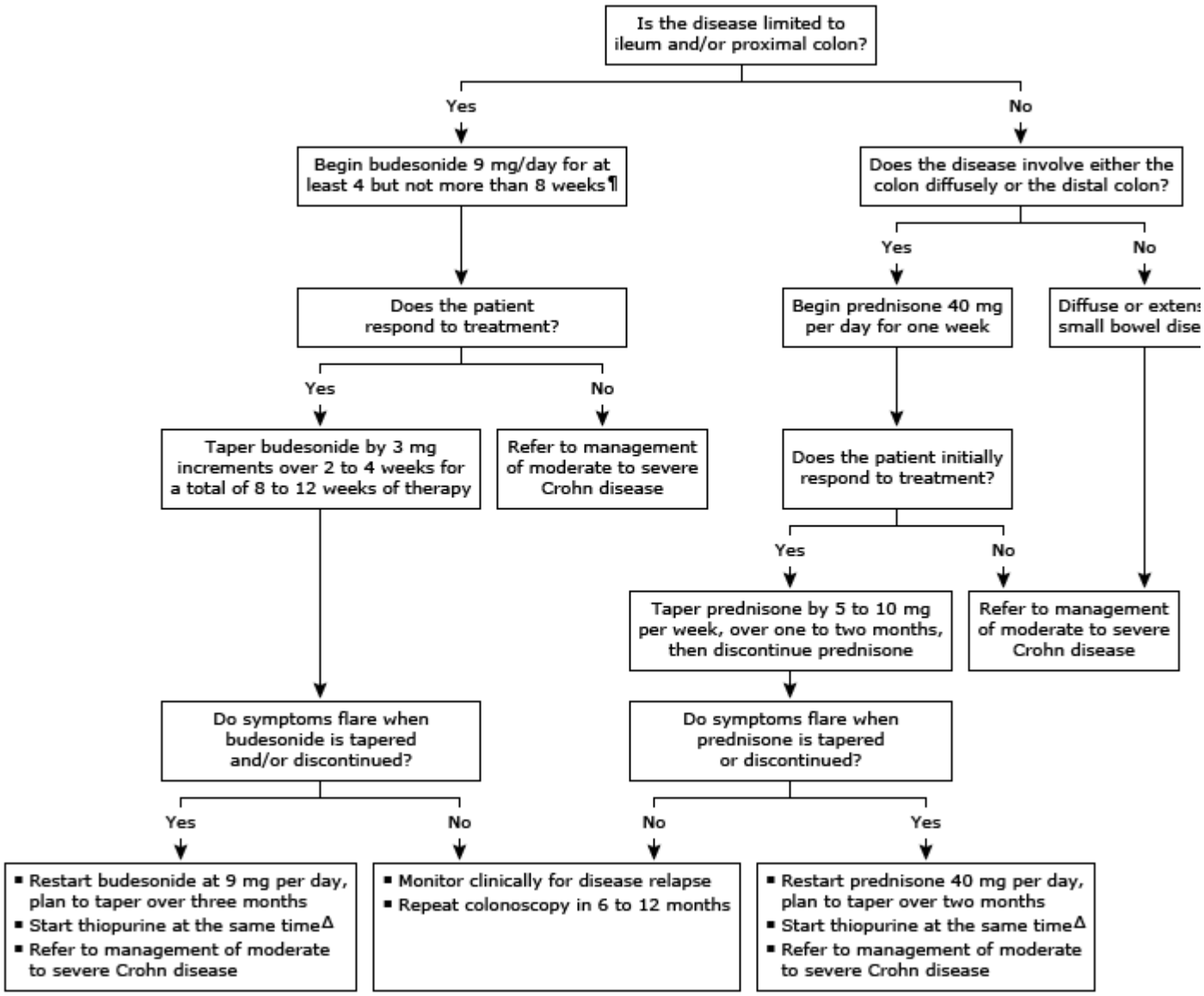
Adapted from: Iborra M, Alvarez-Sotomayor D, Nos P. Long-term safety and efficacy of budesonide in the treatment of ulcerative colitis. Clin Exp Gastroenterol 2014;7:39.

Additional data from:

1. *US FDA approved drug product information, available at https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm (Accessed on September 13, 2017).*

Graphic 116034 Version 2.0

Management of low-risk adult patients with mild, symptomatic Crohn disease*



Refer to UpToDate topics for additional details on the medical management of Crohn disease.

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* Low-risk patients with mild Crohn disease have the following features:

- No or mild symptoms
- Normal or mild elevation in C-reactive protein and/or fecal calprotectin levels
- Diagnosis at age >30 years
- Limited distribution of bowel inflammation
- Superficial or no ulceration on colonoscopy
- Lack of perianal complications
- No prior intestinal resections
- Absence of penetrating or stricturing disease.

¶ Budesonde is first line treatment for inducing remission in low-risk patients with mild ileocolonic Crohn disease.

Δ Refer to relevant UpToDate topic review.

Graphic 116345 Version 2.0

Sulfasalazine and 5-aminosalicylic acid (5-ASA) formulations

Medication	Trade name (US or as noted)	Strength of commonly available oral preparations (mg)
Oral 5-aminosalycylic acid (5-ASA) derivatives		
Sulfasalazine		
Non enteric-coated tablet (scored)	Azulfidine, Sulfazine, Salazopyrin*	500
Suspension	Salazopyrin*	250 per 5 mL*
Enteric-coated tablet (not scored)	Azulfidine EC, Sulfazine EC, Salazopyrin EN-tabs*	500
Mesalamine[¶]		
Delayed release enteric-coated tablet	Asacol[Δ ◇], Asacol HD[◇]	400[Δ], 800
Capsule containing delayed release tablet	Delzicol	400
Delayed and extended release tablet, multimatrix	Lialda, Mezavant*	1200
Capsule containing delayed release enteric-coated granules	Apriso	375
Controlled release capsule	Pentasa[§]	250, 500, 1000*
Enteric-coated delayed release granules (packet, sachet)	Salofalk*, Pentasa Sachet*	500, 1000, 1500, 2000 sachet*
Olsalazine capsule	Dipentum	250, 500*
Balsalazide		
Capsule	Colazal, Colazide*	750
Tablet	Giazo[¥]	1100

US: United States.

* Not available in US. Trade names shown are for products commonly available elsewhere (eg, Canada, United Kingdom, and Europe).

¶ Mesalamine is US generic name. Mesalazine is an international generic name.

Δ Asacol 400 mg tablets are no longer marketed in US. Asacol 400 mg delayed-release tablets and generic versions are available widely elsewhere.

§ According to US prescribing information, Pentasa capsules can be swallowed whole or opened and contents sprinkled over spoonful of applesauce or yogurt and swallowed immediately; capsule contents should not be crushed or chewed.

¥ US approval is limited to treatment of ulcerative colitis in male patients; failed to demonstrate efficacy in female patients.

Data courtesy of authors with additional data from: Ordás I, Eckmann L, Talamini M, et al. Ulcerative colitis. Lancet 2012; 380:1606.

Graphic 86818 Version 14.0

Side effects of sulfasalazine and aminosalicylates

	Common (>10%)	Uncommon (1 to 10%)	Rare (<1%)
Sulfasalazine	Nausea/headache Rash Male infertility Headache	Abdominal pain Hemolytic anemia Leukopenia Thrombocytopenia	Hepatitis Pneumonitis Neutropenia Pancreatitis Agranulocytosis Otalgia Severe cutaneous adverse reaction
Aminosalicylates	Watery diarrhea Abdominal pain Headache Nausea	Pancreatitis Colitis exacerbation Fever/rash Rash	Pneumonitis Pericarditis Nephritis Thrombocytopenia Photosensitivity Nephrolithiasis* Severe cutaneous adverse reaction

* Nephrolithiasis has been reported with mesalamine use; it is unknown whether other aminosalicylate formulations (eg, balsalazide, olsalazine) pose a similar risk.

Graphic 64059 Version 4.0

Lactose content of dairy products

Product	Lactose content (grams)
Milk (1 cup)	
Whole, 2%, 1%, skim	9 to 14
Buttermilk	9 to 12
Evaporated milk	24 to 28
Sweetened condensed milk	31 to 50
Lactaid milk (lactose-reduced)	3
Goat's milk	11 to 12
Acidophilus, skim	11
Yogurt, low fat (1 cup)	4 to 17
Cheese (1 ounce)	
Cottage cheese (1/2 cup)	0.7 to 4
Cheddar (sharp)	0.4 to 0.6
Mozzarella (part skim, low moisture)	0.08 to 0.9
American (pasteurized, processed)	0.5 to 4
Ricotta (1/2 cup)	0.3 to 6
Cream cheese	0.1 to 0.8
Butter (1 pat)	0.04 to 0.5
Cream (1 tablespoon)	
Light, whipping, sour	0.4 to 0.6
Ice cream (1/2 cup)	2 to 6
Ice milk (1/2 cup)	5
Sherbet (1/2 cup)	0.6 to 2

Adapted from: Scrimshaw NS, Murray EB. The acceptability of milk and milk products in populations with a high prevalence of lactose intolerance. Am J Clin Nutr 1988; 48:1079. Copyright © 1988 American Society for Clinical Nutrition.

Graphic 54826 Version 4.0

Contributor Disclosures

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