Medical management of moderate to severe Crohn disease in adults

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Literature review current through: **Feb 2024.**
This topic last updated: **Mar 11, 2024.**

INTRODUCTION

Crohn disease is an inflammatory condition of unknown etiology that can affect any portion of the gastrointestinal tract from the mouth to the perianal area. Its transmural nature coupled with the variability of intestinal distribution (ie, which intestinal segment is affected) and systemic, extraintestinal manifestations, gives rise to a spectrum of clinical presentations and risk for long-term sequelae. (See "Clinical manifestations, diagnosis, and prognosis of Crohn disease in adults".)

The primary focus of this topic is the medical management of high-risk patients with moderate to severe Crohn disease in the outpatient setting. This topic also provides an overview of the approach to the acutely ill patient with Crohn disease. Our recommendations are generally consistent with the American Gastroenterological Association and American College of Gastroenterology guidelines on medical therapy for induction and remission in inflammatory Crohn disease. (See 'Society guideline links' below.)

As a guiding principle, each treatment regimen must be individualized to meet the needs of the patient. The risks and benefits of each medical therapy must be discussed with the patient and a shared decision-making process is recommended.

The management of low-risk patients with mild Crohn disease, the management of patients who have had surgical resection, and surveillance for dysplasia in patients with inflammatory

bowel disease are discussed separately:

- (See "Overview of the medical management of mild (low risk) Crohn disease in adults".)
- (See "Management of Crohn disease after surgical resection".)
- (See "Surveillance and management of dysplasia in patients with inflammatory bowel disease".)

DEFINING DISEASE ACTIVITY AND SEVERITY

Clinical trials of Crohn disease often use formal grading systems that rely on subjective symptoms to describe disease severity. Two commonly used systems are the Crohn Disease Activity Index (calculator 1) and the Harvey-Bradshaw Index (calculator 2). Details of these grading systems and the stratification of patients with Crohn disease into either a low or moderate/high risk category by assessing inflammatory status are discussed separately. (See "Overview of the medical management of mild (low risk) Crohn disease in adults", section on 'Assessing disease activity, severity, and risk'.)

High-risk patients with moderate to severe Crohn disease may have the following features [1,2]:

- Diagnosis at a younger age (<30 years)
- History of active or recent tobacco use
- Elevated C-reactive protein and/or fecal calprotectin levels
- Deep ulcers on colonoscopy
- Long segments of small and/or large bowel involvement
- Perianal disease
- Extra-intestinal manifestations
- History of bowel resections

High-risk patients also include patients who have not responded to glucocorticoids (ie, refractory) or who relapse after achieving clinical remission following induction therapy with glucocorticoids. (See "Overview of the medical management of mild (low risk) Crohn disease in adults", section on 'induction of remission'.)

THE ACUTELY ILL PATIENT WITH CROHN DISEASE

Inpatient hospitalization is required for patients with Crohn disease who are acutely ill due to a complication such as partial small bowel obstruction, peritonitis, or a disease flare that is not responding to outpatient therapy. Management may include intravenous fluid and electrolyte

replacement, intravenous broad spectrum antibiotics, nutritional assessment, and consultation with a gastrointestinal surgeon. Some patients may also require treatment with intravenous glucocorticoids or biologic therapy.

The initial evaluation and management of the acutely ill patient is guided by several factors, including the clinical presentation, severity of illness, history of prior inpatient hospitalizations for complications of Crohn disease (eg, recurrent partial small bowel obstruction), and assessment from gastroenterology and gastrointestinal surgery specialists.

The clinical features of complications or flares due to Crohn disease (eg, abdominal pain, diarrhea and inadequate oral intake) are broadly overlapping and the need for imaging depends, in part, upon the clinical presentation and prior history. For example, a young patient with Crohn disease and a history of partial small bowel obstruction who previously responded to medical management and now presents with mildly obstructive symptoms may respond to medical management without requiring advanced imaging. For other patients, an abdominal and pelvic computed tomography scan at the time of hospital admission may help to distinguish among the diagnostic possibilities.

Partial small bowel obstruction — Partial small bowel obstruction is common in longstanding Crohn disease. The symptoms most commonly associated with acute small bowel obstruction are nausea, vomiting, cramping, abdominal pain, and inability to pass flatus or stool. Small bowel obstruction may result from a stricture causing mechanical obstruction, a stenotic area with superimposed inflammation and spasm, a stenotic area in which undigested food has impacted, an enterolith or, in patients who have had prior surgery, intestinal adhesions. (See "Etiologies, clinical manifestations, and diagnosis of mechanical small bowel obstruction in adults", section on 'Clinical presentations'.)

Affected patients most commonly present with partial obstruction and, except in those who have an adhesion, the mechanism is non-strangulating. Medical management with intravenous hydration, nasogastric suction, and parenteral nutrition is often successful, with a response seen within 24 to 48 hours [3]. For patients who do not have proximal small bowel dilation and who have no evidence of long strictures (>10 cm) (on cross sectional imaging), we suggest initial medical management with parenteral glucocorticoids. Surgery is reserved for those patients who do not respond to medical management or who have evidence of small bowel ischemia. (See "Surgical management of Crohn disease".)

Localized peritonitis — Patients with small bowel Crohn disease may present with fever, chills, and right lower quadrant pain associated with leukocytosis. Patients with such presentation have often suffered a microperforation with localized peritonitis that is contained by the

surrounding mesentery and bowel loops. Appendicitis is also a potential source of peritonitis, and an abdominal and pelvic computed tomography scan at the time of hospital admission may help to distinguish among the diagnostic possibilities. (See "Acute appendicitis in adults: Diagnostic evaluation", section on 'Computed tomography'.)

The management of localized peritonitis includes bowel rest and empiric antibiotic therapy (table 1). (See "Antimicrobial approach to intra-abdominal infections in adults", section on 'Empiric antimicrobial therapy'.)

Although medical management is the initial approach, consultation with a gastrointestinal or colorectal surgeon is suggested. A response to intravenous antibiotic therapy is usually seen within three to four days. Most patients will then be transitioned to oral antibiotics, but some patients may require up to two weeks of intravenous antibiotic therapy. A subsequent two- to four-week course of outpatient oral therapy with a fluoroquinolone and metronidazole, or equivalent broad spectrum antibiotics, is suggested. Intestinal resection should be considered in nonresponders. (See "Surgical management of Crohn disease", section on 'Perforation'.)

There is some controversy as to the role of glucocorticoids in this setting. For patients already on glucocorticoids, a small increase in the dose may be required. However, for those not previously on glucocorticoids, we suggest withholding glucocorticoids to avoid masking any further clinical deterioration. There are, however, few data to support this concern for increased complications in patients who receive glucocorticoids; one case-control study did find an increased risk of developing an intraabdominal or pelvic abscess in patients with penetrating Crohn disease who received glucocorticoids (OR 9.0; 95% CI 2.4-34.0) [4].

Abscess — An intra-abdominal abscess may present acutely with fever, abdominal pain and tenderness; however, a walled-off inflammatory mass without infection may present with milder abdominal discomfort and a palpable mass on physical examination. (See "Clinical manifestations, diagnosis, and prognosis of Crohn disease in adults", section on 'Features of transmural inflammation'.)

Patients with an intra-abdominal abscess resulting from Crohn disease should receive antibiotic treatment and either percutaneous or surgical drainage of the abscess, followed by surgical resection of the involved bowel segment. Details regarding abscess drainage and bowel resection in patients with Crohn disease are discussed separately. (See "Surgical management of Crohn disease", section on 'Abscess'.)

Risk of venous thromboembolism — Patients with inflammatory bowel disease (IBD) are at increased risk of venous thromboembolism and pulmonary embolism [5,6]. We recommend prophylaxis with low molecular weight heparin for venous thromboembolism in all hospitalized

patients with IBD [7]. (See "Prevention of venous thromboembolic disease in acutely ill hospitalized medical adults", section on 'Our approach'.)

In a cohort of over 2700 patients with at least one hospitalization related to IBD, patients receiving thromboprophylaxis had a lower risk of post-hospitalization venous thromboembolism compared with those who did not receive prophylaxis (HR 0.46, 95% CI, 0.22-0.97) [8].

INDUCTION THERAPY

Our approach to induction of remission in high-risk patients with moderate to severe Crohn disease is generally consistent with guidelines from the American Gastroenterology Association and American College of Gastroenterology [9,10]. These patients may have newly diagnosed moderate to severe Crohn disease, or were initially mild and progressed to more severe disease. (See 'Defining disease activity and severity' above.)

The goal of therapy is to induce and then to maintain remission. Once remission is achieved, an ileocolonoscopy is performed in 6 to 12 months.

Selecting induction therapy — Selecting induction therapy for patients with moderate to severe Crohn disease takes into account several factors including patient preferences, patient characteristics (eg, age), disease characteristics (eg, fistulizing or penetrating disease), and response to prior therapy for Crohn disease.

Because multiple factors inform the decision to begin a specific induction regimen, the choice is individualized and decision-making is shared with the patient. This selection process results in treatment variability among patients. For the patient with moderate to severe Crohn disease, first-line options for induction therapy include a biologic agent with or without an immunomodulator [9]. For example, for patients who are naïve to biologics, anti-TNF agents (eg, infliximab) are typically given as combination therapy (anti-TNF agent plus immunomodulator) to prevent immunogenicity, whereas anti-IL 12/23 or anti-integrin therapies are generally given as monotherapy. In addition, combination therapy is first-line therapy for patients with fistulizing disease (perianal or intestinal [eg, enterocutaneous fistula]). (See 'Combination therapy' below.)

Combination therapy — For most patients with fistulizing moderate to severe Crohn disease (eg, perianal or intestinal fistula), we use combination therapy consisting of tumor necrosis factor-alpha (TNF) inhibitor (eg, infliximab) and an immunomodulator (eg, azathioprine [AZA], 6-mercaptopurine [6-MP], or methotrexate) [11,12]. (See 'Choice of anti-TNF agent' below.)

We modify our approach for older patients (age >60 years) and young male patients, and this is discussed below. (See 'Special populations' below.)

Azathioprine (AZA) or 6-mercaptopurine (6-MP) can be initiated gradually, with a suggested starting dose of 50 mg per day for either drug, or at a higher dose if thiopurine methyltransferase (TPMT) genotype is normal. We also suggest TPMT genotype testing prior to beginning therapy with AZA or 6-MP [13]. Patients receiving AZA or 6-MP require regular monitoring for toxicity, and this is discussed separately. (See "Thiopurines: Pretreatment testing and approach to therapeutic drug monitoring for adults with inflammatory bowel disease".)

The dose of azathioprine can be gradually increased to a maximum of 2.5 mg/kg per day (6-MP can be increased to a maximum of 1.5 mg/kg per day). Details regarding thiopurine dose escalation, pharmacology, and adverse effects are discussed separately. (See "Overview of azathioprine and mercaptopurine use in inflammatory bowel disease".)

Combination therapy is used for the following reasons:

- To 'attack' Crohn disease through two different mechanisms of action and the synergistic effect of the combination of drugs
- To reduce immunogenicity against biologic therapy which is highest when the biologic agent is first started
- To improve the pharmacokinetics of biologic therapy

Choice of anti-TNF agent — Three anti-tumor necrosis factor (anti-TNF) therapies are approved for treatment of Crohn disease in adults in the United States [14,15]: infliximab, adalimumab, and certolizumab pegol (not approved in Europe). Infliximab and adalimumab are preferred for induction of remission, while all three anti-TNF agents are used to maintain remission. (See "Treatment of Crohn disease in adults: Dosing and monitoring of tumor necrosis factor-alpha inhibitors".)

- Infliximab – Infliximab (Remicade) is a chimeric IgG 1 monoclonal antibody against tumor necrosis factor-alpha comprised of 75 percent human and 25 percent murine sequences, which has a high specificity for and affinity to tumor necrosis factor (TNF)-alpha. In a pooled analysis of three placebo-controlled trials of 390 patients with moderate to severe Crohn disease, patients receiving infliximab were less likely to fail induction of remission at a minimum of 12 weeks (RR 0.68, 95% CI 0.52-0.90) [15-18].

- Adalimumab – Adalimumab (Humira) is a recombinant human IgG1 monoclonal antibody directed against tumor necrosis factor-alpha and is administered by subcutaneous injection. In a meta-analysis of three trials including over 700 patients with moderate to

severe Crohn disease, patients receiving adalimumab were less likely to fail induction of remission at weeks four and 12 compared with patients receiving placebo (RR 0.85, 95% CI 0.79-0.91) [15,19-22].

- Certolizumab pegol – We reserve the use of certolizumab as a second- or third-line anti-TNF agent in patients with Crohn disease who responded to infliximab or adalimumab and then lose response or become intolerant. Certolizumab pegol (Cimzia) is a humanized monoclonal antibody Fab fragment linked to polyethylene glycol that neutralizes TNF. The polyethylene glycol increases its plasma half-life and reduces the requirement for frequent dosing, possibly reducing immunogenicity as well.

  Certolizumab pegol was effective in inducing remission in patients with moderately to severely active Crohn disease. In a meta-analysis of four trials including 1485 patients with moderate to severe Crohn disease, patients given certolizumab pegol were more likely to achieve clinical remission after eight weeks of therapy compared with placebo (27 versus 20 percent, RR 1.36, 95% CI 1.11-1.66) [23].

While there are no randomized controlled trials that have directly compared anti-TNF agents in patients with Crohn disease, indirect evidence suggests that there are no significant differences in the efficacy between infliximab and adalimumab but that certolizumab may be less effective in inducing remission than the other two agents [24-26]. (See 'Anti-TNF agent monotherapy' below.)

Adalimumab and certolizumab are given subcutaneously, whereas infliximab is given intravenously every eight weeks. Adalimumab maintenance dose is given every two weeks while certolizumab is given every four weeks. Adverse events related to anti-TNF agents are discussed separately. (See "Treatment of Crohn disease in adults: Dosing and monitoring of tumor necrosis factor-alpha inhibitors", section on 'Adverse events' and "Overview of dosing and monitoring of biologic agents and small molecules for treating ulcerative colitis in adults", section on 'Adverse events'.)

Efficacy of combination therapy — The combination of an anti-TNF agent and a thiopurine is more effective for induction of remission when compared to anti-TNF (infliximab) monotherapy or thiopurine monotherapy [16]. (See 'Less effective therapies' below and 'Anti-TNF agent monotherapy' below.)

In a trial of 508 patients with moderate-to-severe Crohn disease who had not previously received immunosuppressive or biologic agents, patients received treatment with infliximab, azathioprine, or combination therapy for 30 weeks. At 26 weeks, patients who were treated with infliximab plus azathioprine were more likely to have a glucocorticoid-free clinical remission

compared with those receiving infliximab or azathioprine monotherapy (57 versus 44 [OR 1.7, 95% CI 1.1-2.6] and 30 percent [OR 3.1, 95% CI 2.0-4.9], respectively) [16]. Serious infections were not more common in patients receiving combination versus monotherapy.

Alternatives to combination therapy — Although our preferred approach for induction when using anti-TNF agents, namely infliximab, is combination with an immunomodulator, there is considerable variation in clinical practice among IBD specialists. Practice ranges from avoiding combination therapy altogether, to continuing combination therapy indefinitely, and here we discuss alternatives to combination therapy. In addition, some patients have a contraindication to thiopurines such as a prior adverse reaction or abnormal TPMT enzyme. (See "Thiopurines: Pretreatment testing and approach to therapeutic drug monitoring for adults with inflammatory bowel disease".)

Anti-TNF agent monotherapy — While anti-TNF agents in combination with an immunomodulator is preferred for induction therapy, some high-risk patients with moderate to severe Crohn disease are good candidates for anti-TNF monotherapy. We suggest anti-TNF monotherapy as induction therapy for patients over the age of 60 years, young male patients who prefer to avoid thiopurines, those without a history of Epstein Barr virus infection, or those at increased risk for infectious complications or malignancy. In addition, some patients may prefer to start monotherapy after discussion of the treatment options. (See 'Special populations' below.)

In a pooled analysis of ten trials including over 2700 patients with Crohn disease, patients who were treated with any of three different anti-TNF agents (ie, infliximab, adalimumab, or certolizumab pegol) were less likely to fail to achieve remission compared with placebo (RR 0.87, 95% 0.80-0.94) [27]. (See 'Choice of anti-TNF agent' above.)

Anti-interleukin antibody therapy

- Ustekinumab – Ustekinumab (Stelara) is an anti-IL 12/23 antibody that was approved by the US Food and Drug Administration (FDA) for adults with moderate to severe Crohn disease. Ustekinumab is used for treating patients who are naïve to biologics or who have not responded to other biologic therapy (eg, anti-TNF-agents) [28-30]:
  - For patients with no prior exposure to biologics, we use ustekinumab as monotherapy.
  - For patients who have not responded to at least one biologic agent and/or who formed antidrug antibodies, we may use ustekinumab plus an immunomodulator (eg, thiopurine). However, due to low immunogenicity rates of ustekinumab, we typically use it as monotherapy for such patients. (See "Treatment of Crohn disease in adults:

Dosing and monitoring of tumor necrosis factor-alpha inhibitors", section on 'Therapeutic drug monitoring'.)

Induction therapy with ustekinumab is given intravenously with weight-based dosing. Maintenance dosing is 90 mg subcutaneously every eight weeks. Common adverse events include infection and nasopharyngitis.

For patients without clinical response after 12 weeks (ie, those with persistent symptoms [abdominal pain, diarrhea] and no improvement in CRP and fecal calprotectin), we increase the frequency of maintenance dosing to every four weeks for the next 8 to 12 weeks. For patients without clinical response after escalating the dose, we typically switch to an alternative agent.

Data from randomized trials suggested that ustekinumab was effective for treating moderate to severe Crohn disease. In two induction trials (UNITI-1 and UNITI-2), over 1300 patients with Crohn disease and nonresponse to anti-TNF therapy were assigned to intravenous ustekinumab (either 130 mg or 6 mg/kilogram) or placebo for eight weeks [31]. In both trials, patients treated with ustekinumab had higher clinical response rates at week 6 compared with placebo (UNITI-1, 34, 34, and 22 percent, respectively; UNITI-2, 52, 56 and 29 percent, respectively). During the maintenance phase, 397 patients who responded to induction therapy with ustekinumab were assigned to receive subcutaneous ustekinumab (90 mg either every 8 or every 12 weeks) or placebo. During the maintenance phase, patients treated with ustekinumab every eight weeks or every 12 weeks had higher rates of remission at week 44, compared with placebo (53, 49, and 36 percent, respectively).

Data from randomized trials suggest that rates of clinical remission are similar for ustekinumab and anti-TNF therapy [32]. In a trial including 386 patients with moderate to severe Crohn disease and no prior exposure to biologic therapy, rates of clinical remission were not significantly different for patients given ustekinumab compared with adalimumab at 52 weeks (65 versus 61 percent) [32]. In addition, rates of serious infections were similar in both groups (2 versus 3 percent).

Ustekinumab is a human IgG_{1k} monoclonal antibody that blocks the biologic activity of IL-12 and IL-23 by inhibiting receptors for these cytokines on T cells, natural killer cells, and antigen-presenting cells [33].

- Risankizumab – Risankizumab (Skyrizi) is a humanized monoclonal antibody directed against the p19 subunit of IL-23 [34]. Risankizumab was approved by the FDA for treating

moderate to severe Crohn disease [35]. Other indications for risankizumab include psoriasis and psoriatic arthritis, and these conditions are discussed separately.

The induction dose of risankizumab for Crohn disease is 600 mg intravenously at zero, four, and eight weeks. For maintenance dosing, we use 360 mg administered by subcutaneous injection at week 12 and every eight weeks thereafter [36]. Reported adverse reactions include upper respiratory infection, headache, arthralgia, and drug-induced liver injury. Pretreatment evaluation includes liver enzymes and bilirubin in addition to other laboratory studies performed before initiating biologic therapy (ie, hepatitis B surface antigen [HBsAg], interferon-gamma release assay), and such testing is discussed in more detail separately. (See "Treatment of Crohn disease in adults: Dosing and monitoring of tumor necrosis factor-alpha inhibitors", section on 'Pretreatment screening' and "Tuberculosis infection (latent tuberculosis) in adults: Approach to diagnosis (screening)".)

During treatment, we obtain liver enzymes and bilirubin eight weeks after initiating risankizumab and every three to six months thereafter. If liver enzymes or bilirubin increase by >3 times the upper limit of normal, we hold the next dose (if due) and recheck liver enzymes and bilirubin in one to two weeks.

Data from randomized trials suggested that risankizumab was effective for treating moderate to severe Crohn disease [37-39]. In two induction trials including 931 biologic therapy-experienced patients (ADVANCE trial) and 618 biologic and/or conventional therapy-experienced patients (MOTIVATE trial) with moderate to severe Crohn disease, risankizumab, 600 mg or 1200 mg, or placebo was administered intravenously at weeks 0, 4, and 8 [37]. Risankizumab resulted in higher rates of clinical remission as measured by Crohn Disease Activity Index (CDAI) score compared with placebo after 12 weeks (ADVANCE trial: 45 and 42 percent, respectively, versus 25 percent; MOTIVATE trial: 42 and 40 percent, respectively, versus 20 percent). In the induction trials, rates of overall adverse events were not numerically higher in the treatment groups. In the maintenance trial including 712 patients, risankizumab, 180 mg or 360 mg, or placebo was administered every eight weeks [39]. Risankizumab resulted in higher rates of sustained remission (as measured by CDAI score) after 52 weeks (55 and 52 percent, respectively, versus 41 percent). Adverse event rates with maintenance therapy were similar among the groups. We anticipate using risankizumab as an alternative to other first-line biologic therapies. (See "Overview of the medical management of mild (low risk) Crohn disease in adults", section on 'Crohn Disease Activity Index'.)

Anti-integrin antibody therapy

- Vedolizumab – Vedolizumab (Entyvio) is a humanized anti-alpha-4-beta-7 integrin monoclonal antibody. The induction dose of vedolizumab is 300 mg intravenously at zero, two, and six weeks and for maintenance, every eight weeks thereafter. Adverse reactions include headache, arthralgias and nasopharyngitis.

  Vedolizumab is often used as first-line therapy for patients over the age of 60 years or for those who have a history of malignancy or infectious complications [40,41]. Vedolizumab can be used with or without an immunomodulator for patients with active moderate to severe Crohn disease [9]. For first-line biologic therapy, we use vedolizumab as monotherapy, but if used as a second- or third-line agent and/or the patient has a history of antidrug antibodies to monoclonal agents, we may use vedolizumab in combination with an immunomodulator. However, due to the low immunogenicity rates of vedolizumab, we more frequently use it as a monotherapy agent.

  Data from clinical trials suggested that vedolizumab was effective for treating Crohn disease [42,43]. In a meta-analysis of four induction trials including 1126 patients with Crohn disease, vedolizumab resulted in higher rates of clinical remission at 6 to 10 weeks compared with placebo (19.8 versus 11.6 percent, RR 1.61, 95% CI 1.2-2.17) [43]. In a meta-analysis of three maintenance trials including 894 patients with Crohn disease, vedolizumab resulted in higher rates of sustained clinical remission after 52 to 60 weeks compared with placebo (42.5 versus 27.1 percent, RR 1.52, 95% CI 1.24-1.87). In addition, the rates of overall adverse events were not significantly different between the treatment and placebo groups.

- Natalizumab – Natalizumab (Tysabri) is a humanized monoclonal antibody directed against alpha-4 integrin. It acts by blocking leukocyte migration to sites of inflammation. While effective in the induction of remission in CD, its use is limited because of its association with serious adverse events, including progressive multifocal leukoencephalopathy (PML).

  Natalizumab is rarely used for Crohn disease because of the risk of PML in patients with positive anti-JC virus (JCV) status. While society guidelines have suggested against using natalizumab given that other biologics are available, they also state that natalizumab may be an option for patients with Crohn disease who are anti-JCV antibody negative and who agree to ongoing monitoring, if the benefit of the drug outweighs the risks [10].

  Natalizumab should not be used in patients who may have impaired immunity, are taking immunosuppressants, or are taking TNF inhibitors [44,45]. We suggest stopping glucocorticoids within a few months of initiation of natalizumab. A two-month washout is reasonable for azathioprine/6 mercaptopurine, methotrexate, anti-TNF agents, and

mycophenolate [44]. Leukocyte and neutrophil counts should be within or close to the normal range prior to starting therapy.

Natalizumab was shown to be superior to placebo for induction of remission in a meta-analysis that included five trials including patients with luminal Crohn disease [27]. Patients treated with natalizumab were less likely to fail to achieve remission compared with those given placebo (RR 0.88, 95% CI 0.83-0.94).

In the maintenance phase of the Efficacy of Natalizumab as Active Crohn's Therapy (ENACT-2) trial, 339 patients with Crohn disease who had responded to natalizumab following induction were then reassigned to receive 300 mg of natalizumab or placebo every four weeks through week 56 [46]. Patients receiving natalizumab had higher rates of sustained response (61 versus 28 percent) and remission (44 versus 26 percent) through week 36, as well as higher discontinuation rates of glucocorticoids.

Janus kinase (JAK) inhibitor therapy — Upadacitinib (Rinvoq) is an oral JAK inhibitor that was approved in the United States for treating adults with moderate to severe Crohn disease who have not responded to or have not tolerated anti-TNF therapy [47-49]. Other indications for upadacitinib include ulcerative colitis, rheumatoid arthritis, axial spondyloarthritis, atopic dermatitis, and psoriatic arthritis [48]. (See "Overview of the Janus kinase inhibitors for rheumatologic and other inflammatory disorders".)

The onset of action of JAK inhibitors varies. Some patients have a rapid response (ie, within a few days to two weeks), while for other patients, response may take up to 12 weeks [49-51].

Pretreatment evaluation includes assessing the patient's risk of thromboembolism, vaccination status, liver enzymes, and lipid profile in addition to other laboratory studies (ie, hepatitis B surface antigen [HBsAg], interferon-gamma release assay). Pretreatment testing is discussed in more detail separately. (See "Management of moderate to severe ulcerative colitis in adults", section on 'Small molecules' and "Overview of dosing and monitoring of biologic agents and small molecules for treating ulcerative colitis in adults", section on 'Janus kinase (JAK) inhibitors'.)

The induction dose of upadacitinib for Crohn disease is 45 mg, once daily, for 12 weeks [48]. We assess response by evaluating patient symptoms (abdominal pain, diarrhea) and biomarkers (CRP and fecal calprotectin). For patients with clinical improvement, we continue upadacitinib for maintenance. The maintenance doses include 15 mg or 30 mg once daily. For patients with prior exposure to anti-TNF therapy, the maintenance dose is 30 mg once daily. For patients with no prior anti-TNF therapy, we use the lowest upadacitinib dose that maintains clinical remission.

Data from randomized trials suggested that upadacitinib was effective for treating patients with moderate to severe Crohn disease [48-50]. In two induction trials including 526 patients (U-EXCEL trial) and 495 patients (U-EXCEED trial) with moderate to severe Crohn disease, upadacitinib (45 mg once daily) resulted in higher rates of clinical remission (as measured by CDAI score) compared with placebo after 12 weeks (U-EXCEL trial: 49.5 versus 29.1 percent and U-EXCEED trial: 38.9 versus 21.1 percent) [49]. In the maintenance trial including 502 patients, upadacitinib (15 or 30 mg daily) resulted in higher rates of sustained remission compared with placebo after 52 weeks (37.3 and 47.6 percent, respectively, versus 15.1 percent). Herpes zoster infections were numerically more common with upadacitinib, 30 or 45 mg daily, compared with placebo. We anticipate using upadacitinib for patients who have not responded to anti-TNF therapy, while we await further studies on efficacy and safety.

Glucocorticoids — Glucocorticoids are commonly used for primary initial medical treatment for patients with moderate to severe Crohn disease who require more immediate symptom relief [52], and they are regarded as short-term induction therapies because of their association with many long-term side effects [52]. A limited course (eg, eight weeks) of glucocorticoid therapy should serve as a "bridge" to a long-term maintenance treatment (usually with a thiopurine or a biologic agent). Glucocorticoids should not be used long-term because of the side effect profile and also because they are not used for maintaining disease remission. (See "Major adverse effects of systemic glucocorticoids".)

- Prednisone – In patients with active mucosal inflammation, prednisone is initiated at a dose of 40 mg orally daily with a 10 mg or 5 mg taper on a weekly basis for a total duration of four to eight weeks of therapy. For many patients, prednisone results in rapid improvement. (See "Overview of the medical management of mild (low risk) Crohn disease in adults", section on 'Prednisone'.)

- Budesonide – Enteric-coated budesonide, designed for release in the ileum and cecum, is an alternative to oral prednisone. Budesonide is usually reserved for low-risk patients with Crohn disease and this is discussed separately. (See "Overview of the medical management of mild (low risk) Crohn disease in adults", section on 'Budesonide'.)

We prefer to administer glucocorticoids intravenously for patients who are hospitalized for an exacerbation of IBD. We use methylprednisolone 60 mg intravenously daily, if there are no contraindications such as a bowel-related infection (eg, *Clostridioides* [formerly *Clostridium*] *difficile* or cytomegalovirus). Glucocorticoids may be administered as a single daily dose, or in divided doses (eg, two or three times per day), or as a continuous infusion. There are no data showing that dosing schedule impacts outcome, and continuous dosing has largely been

abandoned due to inconvenience. If the patient responds to treatment and can tolerate oral intake, we transition therapy to oral prednisone 40 mg daily.

Less effective therapies — Although thiopurines are used as maintenance therapy, thiopurine monotherapy is not recommended for induction of remission of Crohn disease [53,54]. The slow onset of action of azathioprine (AZA) and 6-mercaptopurine (6-MP) results in a delayed clinical response.

In a meta-analysis of 13 trials including over 1200 patients, there was no significant difference in clinical remission rates, clinical improvement, or steroid-sparing effect in patients treated with AZA and 6-mercaptopurine (6-MP) as compared with placebo [54]. (See 'Thiopurines' below.)

Nonresponders to medical therapy — Patients with moderate to severe Crohn disease who do not respond to induction therapies (eg, combination therapy or anti-TNF agent monotherapy, anti-integrin antibody, or anti-IL 12/23 antibody) and who have persistent symptoms and inflammation that is refractory to medical therapy (ie, intractable disease) may require further intervention (eg, bowel rest with parenteral nutrition, surgical resection), and this is discussed separately. (See "Surgical management of Crohn disease".)

MAINTENANCE THERAPY

Our approach for maintaining remission in patients with moderate to severe Crohn disease reflects society guidelines [9,10]. Once clinical remission is achieved, an ileocolonoscopy is performed in 6 to 12 months.

Remission achieved with anti-TNF-based regimen — For patients who achieve clinical, endoscopic, and histologic remission following induction with combination therapy (ie, anti-TNF agent plus an immunomodulator) or with anti-TNF monotherapy, we continue long-term anti-TNF therapy. (See 'Combination therapy' above.)

For patients who achieved remission with combination therapy, the optimal duration of immunomodulator use is uncertain. Thus, the decision to discontinue the immunomodulator is individualized and informed by severity of disease, patient's prior response to other agents, and risk factors for adverse events related to immunomodulators. As an example, we generally prefer continuing long-term combination therapy (ie, >24 months) for patients with severe disease (eg, perianal fistula) or history of nonresponse to at least one biologic agent.

However, some patients may be at higher risk of adverse effects from long-term combination therapy (eg, younger males, patients over the age of 60 years, patients with history of recurrent nonmelanoma skin cancer). (See 'Adverse events' below.)

For such patients, we typically discontinue the thiopurine after 12 to 24 months from initiation of combination therapy. Prior to withdrawing immunomodulator therapy, we perform endoscopic evaluation to confirm mucosal healing. We also obtain anti-TNF drug trough levels prior to and several months after immunomodulator withdrawal to confirm that the anti-TNF drug level is optimized. Additionally, a fecal calprotectin level that normalizes with combination therapy and parallels mucosal healing may be a useful biomarker to measure after withdrawing the immunomodulator.

The efficacy of anti-TNF monotherapy for maintaining remission is established, but evidence supporting additional benefits from long-term combination therapy is more limited [16,27,55-59]:

- **Anti-TNF monotherapy** – In a meta-analysis of five trials including 1390 patients with moderate to severe Crohn disease with 26 to 60 weeks of follow-up, patients treated with anti-TNF agents were less likely to relapse compared with those without maintenance therapy (RR 0.71, 95% CI 0.65-0.76) [27]. For the anti-TNF agents, infliximab and certolizumab pegol, the effect estimates were similar (RR 0.72 and 0.73, respectively). For adalimumab, there was a nonsignificant trend towards lower risk of relapse (RR 0.54, CI 0.27-1.07). Infliximab has also been associated with improved quality of life and reduction in the risk of hospitalization and surgery [55].

- **Combination therapy** – In a meta-analysis of five trials including 404 patients with IBD who had glucocorticoid-free clinical remission for >6 months on combination therapy (ie, anti-TNF agent plus immunomodulator), there were no significant differences in relapse rates after one to two years for patients treated with combination therapy compared with anti-TNF agent alone (15 versus 17 percent) [59].

For patients who have achieved remission with combination therapy, we do not stop the anti-TNF agent unless the patient develops drug intolerance or adverse side effects. Data have suggested that disease relapse rates were higher following discontinuation of anti-TNF therapy [59-61]. In a meta-analysis of five trials including 404 patients with IBD who had glucocorticoid-free clinical remission for >6 months on combination therapy (anti-TNF therapy plus an immunomodulator), disease relapse rates at one to two years were higher following withdrawal of the anti-TNF agent compared with continuing combination therapy (32 versus 11 percent, RR

2.35, 95% CI 1.38-4.01) [59]. However, relapse rates did not increase following immunomodulator withdrawal.

We do not routinely switch patients in remission from infliximab to adalimumab for reasons of convenience, as doing so may worsen outcomes [62].

Patients who lose response to anti-TNF therapy — For patients who are no longer responding to anti-TNF therapy, options include optimizing the dose, switching to an alternative anti-TNF agent, or switching to a different class of agents (table 2 and algorithm 1). The preferred approach depends on the underlying cause of loss of clinical response (see 'Induction therapy' above):

- **Patients with low drug levels and positive anti-drug antibodies** – Immunogenicity failures are characterized by low or absent drug trough levels in the presence of anti-drug antibodies. These patients can be switched to an alternative anti-TNF agent, especially in the presence of high anti-drug antibody titers.

- **Patients with low drug levels and negative anti-drug antibodies** – Pharmacokinetic failures are characterized by low or absent drug trough levels in the absence of anti-drug antibodies. These patients require dose optimization by either dose escalation or shortening the dosing interval.

- **Patients with a normal drug level and negative anti-drug antibodies** – Pharmacodynamic failures are characterized by adequate drug levels with absent anti-drug antibodies. These patients are managed by switching outside the anti-TNF class to another agent (eg, anti-integrin antibody).

Therapeutic drug monitoring is discussed in greater detail separately. (See "Treatment of Crohn disease in adults: Dosing and monitoring of tumor necrosis factor-alpha inhibitors", section on 'Therapeutic drug monitoring'.)

Experience with adalimumab for patients who have lost response or had an adverse reaction to infliximab is greater than with certolizumab, although data suggest that certolizumab is also effective in such patients [19,63-66].

Remission achieved with anti-interleukin therapy — For patients who achieved remission with an anti-interleukin agent (eg, ustekinumab), the biologic agent is typically continued long-term to maintain remission. Efficacy data for anti-interleukin maintenance therapy is discussed above. (See 'Anti-interleukin antibody therapy' above.)

For patients who develop a disease flare despite ustekinumab maintenance therapy every eight weeks, we may decrease the dosing interval to every four weeks without checking drug levels.

Remission achieved with anti-integrin therapy — For patients who achieved remission with anti-integrin therapy (vedolizumab), the biologic agent is typically continued long-term to maintain remission. Efficacy data for vedolizumab maintenance therapy is discussed above. (See 'Anti-integrin antibody therapy' above.)

Remission achieved with a JAK inhibitor — For patients who achieved remission with a JAK inhibitor (eg, upadacitinib), the small molecule is typically continued long-term to maintain remission. Efficacy data for JAK inhibitor maintenance therapy is discussed above. (See 'Janus kinase (JAK) inhibitor therapy' above.)

Alternative approaches

Thiopurines — For patients who have achieved clinical remission with glucocorticoids or for patients who are no longer responding to biologic agents, maintenance therapy with thiopurine monotherapy is an alternative. (See 'Adverse events' below and "Tumor necrosis factor-alpha inhibitors: An overview of adverse effects".)

Azathioprine (AZA) or 6-mercaptopurine (6-MP) can be initiated at a dose of 50 mg per day (for either drug) or at the full (ie, goal dose) if thiopurine methyltransferase (TPMT) genotype is normal. (See "Overview of azathioprine and mercaptopurine use in inflammatory bowel disease", section on 'Dosing and monitoring'.)

We suggest TPMT genotype testing prior to beginning therapy with AZA or 6-MP [13]. Patients receiving AZA or 6-MP require regular monitoring for toxicity, and this is discussed separately. (See "Thiopurines: Pretreatment testing and approach to therapeutic drug monitoring for adults with inflammatory bowel disease".)

The dose of 6-MP can be increased to a maximum of 2 mg/kg per day (although more commonly 1.5 mg/kg is given as the maximum dose), and the dose of azathioprine can be increased to 2.5 mg/kg per day, provided that laboratory monitoring does not suggest bone marrow suppression.

Because it may take three to six months for thiopurines to provide a full, long-term maintenance effect, patients often require concomitant glucocorticoid therapy with a gradual reduction in the glucocorticoid dose starting after one to two months of thiopurine treatment.

AZA is effective for reducing the risk of Crohn disease recurrence. In a meta-analysis of six trials including 489 patients with quiescent Crohn disease, patients on azathioprine (1.0 to 2.5

mg/kg/day) had higher rates maintaining remission over a six to 18 month period compared to patients receiving placebo (73 versus 62 percent; OR 1.2, 95% CI 1.1-1.3) [67].

In addition to bone marrow suppression, these agents have also been associated with malignancy, particularly non-melanoma skin cancers and lymphomas. (See "Overview of azathioprine and mercaptopurine use in inflammatory bowel disease", section on 'Adverse effects'.)

Methotrexate — Methotrexate is an alternative for maintenance therapy for the patient who does not tolerate thiopurines and may be preferable to azathioprine or 6-MP in patients with Crohn disease-related arthropathy. (See "Treatment of arthritis associated with inflammatory bowel disease".)

Methotrexate is initiated intramuscularly or subcutaneously at a dose ranging from 12.5 mg once weekly (when used in combination with a biologic agent) or 15 mg once weekly (when used as monotherapy) to 25 mg once weekly [9]. A clinical response is expected within three months. For patients on glucocorticoid therapy, the glucocorticoid should be continued during this period with a gradual tapering of the dose. Once a response to methotrexate is achieved, the dose of once weekly methotrexate is given by any of the following routes: oral, subcutaneous, or intramuscular.

For patients who do not respond to a lower initial methotrexate dose (ie, 12.5 to 15 mg once weekly), the dose may be increased gradually (eg, by 5 mg every month) up to a maximum dose of 25 mg once weekly [68].

In a systematic review of two trials including 128 patients with quiescent Crohn disease, patients receiving methotrexate had lower rates of disease relapse compared with those receiving placebo (47 versus 65 percent; RR 0.74, 95% CI 0.5-1.0) [69].

For patients taking methotrexate, folic acid at a dose of 1 mg per day is given since folic acid supplementation may reduce nausea, vomiting, and abdominal distress associated with the drug. Further discussion regarding side effects and toxicity related to methotrexate, including hepatotoxicity, is found elsewhere. (See "Major adverse effects of low-dose methotrexate" and "Hepatotoxicity associated with chronic low-dose methotrexate for nonmalignant disease".)

ADVERSE EVENTS

A number of adverse events have been associated with biologic agents, immunomodulators, and small molecules. In addition to the drug monographs, adverse effects are summarized

separately along with pretreatment evaluation and monitoring:

- (See "Treatment of Crohn disease in adults: Dosing and monitoring of tumor necrosis factor-alpha inhibitors".)
- (See "Overview of azathioprine and mercaptopurine use in inflammatory bowel disease", section on 'Adverse effects'.)
- (See "Overview of dosing and monitoring of biologic agents and small molecules for treating ulcerative colitis in adults".)
- (See "Major adverse effects of low-dose methotrexate".)
- (See "Hepatotoxicity associated with chronic low-dose methotrexate for nonmalignant disease".)

In our practice, we screen all patients for latent tuberculosis before starting anti-TNF therapy. We limit annual testing for tuberculosis to patients on anti-TNF therapy who live in endemic areas. For those with new exposure to tuberculosis, a tuberculin skin test or interferon-gamma release assay is performed at that time and then annually.

- (See "Tuberculosis infection (latent tuberculosis) in adults: Approach to diagnosis (screening)".)
- (See "Use of interferon-gamma release assays for diagnosis of tuberculosis infection (tuberculosis screening) in adults".)

Hepatosplenic T-cell lymphoma — Long-term thiopurine use (more than two years) appears to be associated with hepatosplenic T-cell lymphomas (HSTCL), particularly in young males. In a systematic review that identified 36 patients with HSTCL and inflammatory bowel disease (IBD), all patients had received a thiopurine (16 as monotherapy and 20 in combination with infliximab) [70]. The duration of thiopurine use was known in 30 patients, and in all but one case it had been used for at least two years prior to the diagnosis of HSTCL (mean 5.5 years, range 1 to 13.5 years). Of the 31 patients whose sex was known, 29 (94 percent) were male. In addition, of the 30 patients whose age was known, 27 (90 percent) were under the age of 35 years.

It appears that the risk of HSTCL for all patients with IBD who receive thiopurines is exceedingly rare, at 1:45,000 patients. This is estimated as follows: among the approximately 3.6 million patients with IBD in the United States and Europe, there have been 36 cases of HSTCL; if 44.5 percent of this group (1.6 million people) had been exposed to thiopurines, then the absolute risk is 1:44,444 [71]. However, based upon the available data, the risk in men under the age of 35 who are exposed to thiopurines is significantly higher, on the order of 1:7500, and in those receiving both thiopurines and anti-TNF agents the risk is approximately 1:3500 [70].

BIOSIMILARS

Biosimilars are biologic products that are highly similar to a reference product. Biosimilars of anti-TNF agents and other biologics (eg, ustekinumab) have been marketed and are in use [72,73]. (See "Overview of biologic agents in the rheumatic diseases", section on 'Biosimilars for biologic agents'.)

Commercially available biosimilars that have received regulatory designation as a biosimilar are described in the drug information monographs for the reference product. A list of biologic products and biosimilars approved by the US Food and Drug Administration (FDA) is available through the FDA Center for Drug Evaluation and Research [74]. We support the use of biosimilars for initial therapy or for switching from a reference product to a biosimilar.

Evidence for efficacy of biosimilars in patients with IBD is established. Infliximab-dyyb (also termed CT-P13) is an example of a biosimilar to the reference product, and this biosimilar has shown equivalent clinical efficacy in patients with Crohn disease [75-77]. In a trial of 220 patients with Crohn disease and no prior biologic use, the clinical response rate at six weeks for patients given a biosimilar (CT-P13) was not significantly different compared with patients given infliximab (69 versus 74 percent) [77]. Additionally, in a database study of over 5000 infliximab-naïve patients with Crohn disease, treatment with CT-P13 resulted in similar outcomes (composite endpoint of death, surgery, hospitalization, or use of another biologic agent [eg, adalimumab]) compared with the reference product [75].

NUTRITION AND HEALTH MAINTENANCE

The use of nutrition and dietary therapy, including total parenteral nutrition, in patients with inflammatory bowel disease is discussed separately. (See "Nutrition and dietary management for adults with inflammatory bowel disease".)

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 (IBD) [78-80]. Patients with longstanding IBD affecting the colon also require endoscopic surveillance for dysplasia. 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' and "Surveillance and management of dysplasia in patients with inflammatory bowel disease".)

OTHER DISEASE MANIFESTATIONS

Fistulizing disease — The transmural inflammatory nature of Crohn disease can lead to the formation of sinus tracts or fistula, and enteric fistulas most often connect the intestine to the bladder (enterovesical), skin (enterocutaneous), bowel (enteroenteric), or vagina (enterovaginal) (image 1). Clinical manifestations of fistula complicating Crohn disease are variable and may include a palpable mass or recurrent urinary tract infections, for example. (See "Clinical manifestations, diagnosis, and prognosis of Crohn disease in adults", section on 'Features of transmural inflammation'.)

For most patients with fistulizing disease, multidisciplinary care from both gastroenterology and colorectal surgery is important, and we recommend consultation with a surgeon with expertise in inflammatory bowel disease for an examination under anesthesia and seton placement for drainage. In centers where surgical expertise in inflammatory bowel disease is not available, evaluation of the pelvis with magnetic resonance imaging can be helpful to define the perianal process. The management of perianal fistula is discussed separately. (See "Perianal Crohn disease", section on 'Perianal fistula'.)

For most patients with fistulizing disease, we suggest combination therapy (ie, anti-TNF agent combined with an immunomodulator such azathioprine) for at least 12 to 24 months before stopping the immunomodulator. (See 'Combination therapy' above.)

For patients with fistulizing disease but no infection, there is no indication for antibiotic therapy.

Patients with enterovesical fistula present with recurrent polymicrobial urinary tract infections, pneumaturia, and fecaluria. Antibiotics will treat the urinary tract infection, but therapy with an anti-TNF agent can be given to promote closure of the fistula. Some patients with this complication will require surgery. (See "Surgical management of Crohn disease", section on 'Fistula'.)

Gastroduodenal disease — For patients with mild gastroduodenal Crohn disease, treatment using a proton pump inhibitor may suffice while in more severe disease, systemic glucocorticoids or a biologic agent is recommended per society guidelines [81]. A trial of histamine-2 receptor antagonist or sucralfate may also be effective for mild symptoms. Patients with gastroduodenal Crohn disease should avoid nonsteroidal anti-inflammatory medications [82].

The slow release form of mesalamine encapsulated in ethylcellulose microgranules (ie, Pentasa) is partially released in the proximal small bowel and theoretically may be of use in duodenal

Crohn disease. However, there are no clinical trials to confirm its efficacy, and its use in this setting is off-label.

Prednisone is the first-line of therapy for most patients with moderate to severe gastroduodenal disease, and dosing is similar to the regimen given to patients with more distal disease [82]. The response to therapy is usually seen within two weeks, but the duration of response is variable. We suggest azathioprine or 6-mercaptopurine in patients who become glucocorticoid-dependent. In patients with severe or refractory disease, we recommend initiation of a biologic agent with or without an immunomodulator. (See "Overview of the medical management of mild (low risk) Crohn disease in adults", section on 'Prednisone'.)

POSTOPERATIVE RECURRENCE

Postoperative recurrence of Crohn disease is discussed separately. (See "Management of Crohn disease after surgical resection".)

SPECIAL POPULATIONS

In general, we modify our approach to therapy for selected patients (eg, older patients, young male patients), in addition to involving the patient in shared decision-making.

Older patients — For older patients (age >60 years), we prefer anti-TNF monotherapy, anti-IL 12/23 monotherapy, or anti-integrin monotherapy as induction therapy due to the potentially higher risk for infection and malignancy with combination therapy. For selected older patients (eg, those with severe disease in the absence of comorbidities), we use combination therapy for induction but then discontinue the immunomodulator after 12 to 24 months of therapy. In these patients, we may use methotrexate as the preferred immunomodulator (rather than a thiopurine) due to the lower risk for immunosuppression and lymphoma [83]. Prior to withdrawing the immunomodulator, we perform an ileocolonoscopy to confirm mucosal healing and histologic remission, and in patients receiving anti-TNF therapy, we obtain anti-TNF drug trough levels to confirm that the anti-TNF drug level is optimized.

Data have suggested that biologic agents have demonstrated comparable efficacy and safety in older patients with IBD. In an observational study including 234 older patients with IBD, clinical remission rates at 12 months were not significantly different for patients on anti-TNF therapy compared with vedolizumab (58 versus 54 percent) [84]. In addition, there were no significant differences in rates of infection for anti-TNF therapy compared with vedolizumab (20 versus 17

percent). Limited indirect data on use of ustekinumab in older patients with psoriasis have suggested that the risk of serious infection was low [85].

Young male patients — For young male patients who may be at increased risk from long-term thiopurine use, we prefer to use methotrexate rather than a thiopurine for patients starting combination therapy. However, if use of a thiopurine in combination with the biologic agent is necessary, we aim to discontinue the thiopurine in 12 to 24 months. (See 'Hepatosplenic T-cell lymphoma' above.)

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

- **Defining disease activity and severity** – Defining disease activity and severity includes the assessment of the inflammatory burden, disease course, and patient symptoms as part of the patient-centered management approach. High-risk patients are often young, have deep ulcers on colonoscopy, have perianal disease, and have extensive disease. They may have extra-intestinal manifestations, a history of intestinal resection, and tend to have objective markers of disease based on laboratory testing (C-reactive protein and/or fecal calprotectin) and cross sectional imaging. (See "Overview of the medical management of mild (low risk) Crohn disease in adults", section on 'Assessing disease activity, severity, and risk' and 'Defining disease activity and severity' above.)

- **Patients who are acutely ill** – Patients with Crohn disease who are acutely ill due to a complication such as partial small bowel obstruction, peritonitis, or a disease flare that is not responding to outpatient therapy will require inpatient hospitalization. Management may include intravenous fluid and electrolyte replacement, intravenous broad spectrum antibiotics, nutritional assessment, and consultation with a gastrointestinal surgeon. (See 'The acutely ill patient with Crohn disease' above.)

- **Induction therapy** – For patients with moderate to severe Crohn disease who have fistulizing disease, we suggest using combination therapy with an anti-TNF agent plus an immunomodulator (eg, azathioprine) compared with anti-TNF monotherapy (**Grade 2B**). This approach is referred to as combination therapy, and the goal is to induce remission. (See 'Combination therapy' above.)

  For patients with moderate to severe Crohn disease and fistulizing complications in whom combination therapy (anti-TNF agent and immunomodulator) is not an option, anti-TNF monotherapy is an effective alternative. (See 'Anti-TNF agent monotherapy' above and 'Special populations' above.)

  For biologic naïve patients with moderate to severe Crohn disease without fistulizing complications, options for induction therapy include:

  - Anti-interleukin antibody monotherapy,
  - Vedolizumab monotherapy,
  - Anti-TNF therapy with or without an immunomodulator

  For patients who require second-line therapy (ie, nonresponders to initial biologic therapy and/or for patients who formed anti-drug antibodies to biologic agents), an anti-

interleukin antibody (eg, ustekinumab) or vedolizumab may be used alone or in combination with an immunomodulator. (See 'Alternatives to combination therapy' above.)

- **Maintenance therapy** – For most patients who achieve clinical, endoscopic, and histologic remission with combination therapy, we recommend continued maintenance with the biologic agent (**Grade 1B**). While the biologic agent is continued indefinitely, we plan to discontinue the thiopurine in one to two years. Prior to de-escalating the medications, we perform an ileocolonoscopy to confirm mucosal healing, and in patients on anti-TNF agents we obtain anti-TNF drug trough levels to confirm that the anti-TNF drug level is optimized. (See 'Maintenance therapy' above.)

  For patients who have achieved clinical remission with glucocorticoids or for patients who are not candidates for long-term therapy with an anti-TNF agent, thiopurine maintenance therapy is an alternative. (See 'Alternative approaches' above.)

ACKNOWLEDGMENT

The UpToDate editorial staff acknowledge Richard J Farrell, MD, and Mark A Peppercorn, MD, who contributed to earlier versions of this topic review.

The UpToDate editorial staff also acknowledges Paul Rutgeerts, MD (deceased), who contributed as a section editor for UpToDate in Gastroenterology.

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Topic 16224 Version 55.0

GRAPHICS

Empiric antibiotic regimens for high-risk community-acquired intra-abdominal infections in adults

	Dose
Single-agent regimen	
Imipenem-cilastatin	500 mg IV every 6 hours
Meropenem	1 g IV every 8 hours
Doripenem	500 mg IV every 8 hours
Piperacillin-tazobactam	4.5 g IV every 6 hours
Combination regimen with metronidazole	
ONE of the following:	
Cefepime	2 g IV every 8 hours
OR	
Ceftazidime	2 g IV every 8 hours
PLUS:	
Metronidazole	500 mg IV or orally every 8 hours

High-risk community-acquired intra-abdominal infections are those that are severe or in patients at high risk for adverse outcomes or antimicrobial resistance. These include patients with recent travel to areas of the world with high rates of antibiotics-resistant organisms, known colonization with such organisms, advanced age, immunocompromising conditions, or other major medical comorbidities. Refer to the UpToDate topic on the antimicrobial treatment of intra-abdominal infections for further discussion of these risk factors.

For empiric therapy of high-risk community-acquired intra-abdominal infections, we cover streptococci, Enterobacteriaceae resistant to third-generation cephalosporins, *Pseudomonas aeruginosa*, and anaerobes. Empiric antifungal therapy is usually not warranted but is reasonable for critically ill patients with an upper gastrointestinal source.

Local rates of resistance should inform antibiotic selection (ie, agents for which there is >10% resistance among Enterobacteriaceae should be avoided). If the patient is at risk for infection with an extended-spectrum beta-lactamase (ESBL)-producing organism (eg, known colonization or prior infection with an ESBL-producing organism), a carbapenem should be chosen. When beta-lactams or carbapenems are chosen for patients who are critically ill or are at high risk of infection with drug-resistant pathogens, we favor a prolonged infusion dosing strategy. Refer to other UpToDate content on prolonged infusions of beta-lactam antibiotics.

The combination of vancomycin, aztreonam, and metronidazole is an alternative for those who cannot use other beta-lactams or carbapenems (eg, because of severe reactions).

The antibiotic doses listed are for adult patients with normal renal function. The duration of antibiotic therapy depends on the specific infection and whether the presumptive source of infection has been controlled; refer to other UpToDate content for details.

IV: intravenous.

Graphic 106949 Version 12.0

Interventions based on therapeutic drug monitoring in patients with inflammatory bowel disease and loss of response to anti-TNF agents

Anti-drug antibody (ADAb)	Drug trough concentration*	
	Inadequate (subtherapeutic)	**Adequate (therapeutic)**
Undetectable	Non immune-mediated pharmacokinetic failure: ▪ Escalate dose of index drug¶	Mechanistic failure: ▪ Switch to drug out of classΔ
Detectable	Immune-mediated pharmacokinetic failure: ▪ If low level ADAb: escalate dose of index drug¶ ▪ If high level ADAb: switch to drug in class◇	Mechanistic failure: ▪ Switch to drug out of class

Refer to UpToDate for additional discussion on therapeutic drug monitoring.

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* Target drug trough concentration: infliximab ≥5 mcg/mL; adalimumab ≥7.5 mcg/mL; certolizumab pegol ≥20 mcg/mL.

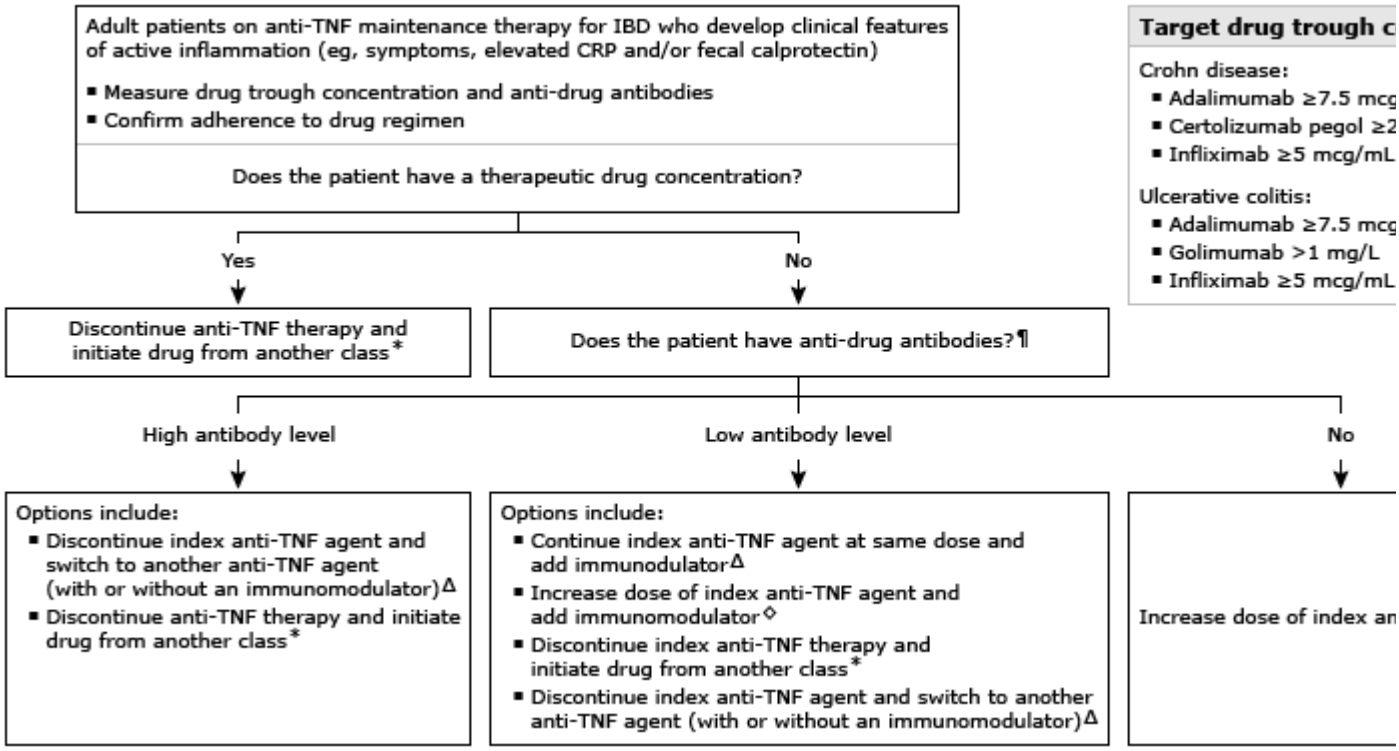
¶ Dose can be escalated by either shortening dosing interval or increasing drug dose.

Δ An alternative is to escalate anti-TNF dose, especially for patients in clinical remission but with endoscopic disease activity.

◇ In addition to switching to a drug in class, some patients may also benefit from adding an immunomodulator.

Graphic 117391 Version 2.0

Approach to patients with inflammatory bowel disease and loss of response to anti-TNF therapy



This figure summarizes the general approach to drug monitoring for adults who had initially responded to anti-TNF therapy for IBD but who develop loss of response. Anti-TNF agents for maintaining remission in IBD include adalimumab, certolizumab pegol, golimumab, and infliximab. Adalimumab and infliximab are used for treating either Crohn disease or ulcerative colitis, whereas certolizumab pegol is used for treating Crohn disease and golimumab is used for treating ulcerative colitis. Drug monitoring can help inform whether escalating the dose or switching to a different drug is preferred. This algorithm is intended for use in conjunction with other UpToDate content. Refer to the UpToDate topic on dosing and monitoring of anti-TNF agents for additional details.

CRP: C-reactive protein; IBD: inflammatory bowel disease; JAK: Janus kinase; TNF: tumor necrosis factor.

* Examples of other drug classes for IBD include anti-12/23 antibody therapy, anti-integrin therapy, and JAK inhibitor therapy.

¶ Reporting of anti-drug antibodies varies among laboratories and has not been standardized. In general, low antibody levels occur with detectable drug levels, whereas high antibody levels usually occur when drug levels are undetectable.

Δ Immunomodulators that are typically used in combination with anti-TNF agents include azathioprine, 6-mercaptopurine, or methotrexate.

◇ Options for escalating anti-TNF therapy include shortening dosing interval or increasing drug dose.

Graphic 143130 Version 1.0

Entero-enteric fistula in Crohn disease

Coronal reformat computed tomography (CT) scan with both intravenous and oral contrast demonstrates an entero-enteric fistula between the ileum and cecum in this patient with Crohn disease.

Courtesy of J Pierre Sasson, MD.

Graphic 58575 Version 3.0

Contributor Disclosures

Jana Al Hashash, MD, MSc, FACG, AGAF Consultant/Advisory Boards: Bristol Myers Squibb [Ulcerative colitis]. All of the relevant financial relationships listed have been mitigated. **Miguel Regueiro, MD, AGAF, FACG, FACP** Consultant/Advisory Boards: AbbVie [Crohn disease]; Allergan [Inflammatory bowel disease]; Amgen [Inflammatory bowel disease]; Bristol Myers Squibb [Inflammatory bowel disease]; Celgene [Crohn disease]; Celgene [Inflammatory bowel disease]; Eli Lilly [Inflammatory bowel disease]; Genentech [Inflammatory bowel disease]; Gilead [Inflammatory bowel disease]; Janssen [Crohn disease]; Miraca [Crohn disease]; Pfizer [Inflammatory bowel disease]; Prometheus [Inflammatory bowel disease]; Salix [Inflammatory bowel disease]; Seres [Inflammatory bowel disease]; Takeda [Crohn disease]; TARGET Pharma Solutions [Inflammatory bowel disease]; UCB [Crohn disease]. All of the relevant financial relationships listed have been mitigated. **Sunanda V Kane, MD, MSPH** Grant/Research/Clinical Trial Support: Bristol Myers Squibb [IBD]. Consultant/Advisory Boards: Boehringer Ingelheim [IBD]; Bristol Myers Squibb [IBD]; Fresenius Kabi [IBD]; InveniAI [IBD]; Janssen [IBD]; Lilly [IBD]; Takeda [IBD]; Techlab [IBD]. Other Financial Interest: PredicaMed [Scientific Board]. All of the relevant financial relationships listed have been mitigated. **Kristen M Robson, MD, MBA, FACG** No relevant financial relationship(s) with ineligible companies to disclose.

Contributor disclosures are reviewed for conflicts of interest by the editorial group. When found, these are addressed by vetting through a multi-level review process, and through requirements for references to be provided to support the content. Appropriately referenced content is required of all authors and must conform to UpToDate standards of evidence.

Conflict of interest policy