Chapter 2
Management of Inflammatory Bowel Disease

Gregory Gaspard, Samir Hussaini, Dileep Mandali, and Ethan Lieberamn

Introduction

Inflammatory bowel disease (IBD) describes chronic, relapsing inflammatory disorders of the gastrointestinal (GI) tract, likely due to an abnormal immune response to enteric flora. The two most common types are Crohn's disease (CD) and ulcerative colitis (UC), each with its own distinct characteristics. CD may affect the entire GI tract, from mouth to anus, but classically affects the ileum or the distal part of the small intestine, whereas UC classically affects the rectum and extends in a continuous fashion, proximally through the colon; it spares the small intestine and everything above.

Treatment and management of IBD are aimed at bringing the disease into a state of remission and sustaining that state for as long as possible. IBD typically presents in an inpatient setting during an acute flare or due to a complication of the disease process. A flare is described as the reappearance of symptoms due to active disease-related inflammation, and the most common symptoms at presentation include:

- Increased frequency and urgency of bowel movements (BMs)
- Bloody BMs
- Abdominal pain
- Nausea, vomiting, and diarrhea
- Reduced appetite

G. Gaspard (✉)
Ochsner Health, New Orleans, LA, USA
e-mail: Gregory.gaspard@ochsner.org

S. Hussaini · E. Lieberamn
Ochsner Health, New Orleans, LA, USA

University of Queensland- Ochsner Clinical School of Medicine, New Orleans, LA, USA

D. Mandali
The University of Queensland-Ochsner Clinical School, New Orleans, LA, USA

K. Conrad (ed.), *Clinical Approaches to Hospital Medicine*,
https://doi.org/10.1007/978-3-030-95164-1_2

Several factors can cause a flare or worsen existing symptoms. These include:

- Inefficacy of IBD medications due to medication resistance, inadequate dosing, antidrug antibodies, and/or nonadherence to treatment
- Infection
- Stress
- Dietary factors
- Smoking
- Antibiotics
- Nonsteroid anti-inflammatory drugs (NSAIDs)

An exacerbation of symptoms warrants an evaluation of the cause of ongoing issues. The nature and process of evaluation for both CD and UC are discussed later in the chapter.

Factors Causing IBD Flares

A large percentage of Americans use NSAIDs to relieve headaches, fever, musculoskeletal issues, and other common body discomforts. People with IBD are cautioned against the use of NSAIDs due to its induced GI toxicity through several mechanisms: increased mucosal permeability, intracellular adenosine triphosphate (ATP) depletion, and formation of drug-enterocyte adducts [1]. However, the most discussed mechanism of NSAID-induced GI toxicity is the effect on prostaglandin synthesis. Prostaglandins are pivotal in maintaining the microcirculation and modulation of the gastroenteric immune system. Experimental models have shown that inhibition of COX1, COX2, and their prostaglandins (E2, F2A, and D2) resulted in the development of intestinal ulcers, exacerbation of dextran sulfate sodium-induced colitis, and frequent flares of IBD [1].

Smoking is implicated in both the development of CD and in subsequent flares. Those who regularly smoke tend to have increased severity of disease, reduced response to medical treatment, and an increased risk of disease complications. The pathogenesis of CD through smoking is thought to be due to generation of reactive oxygen species and their effects on the immune system by intensifying vasodilation in chronically inflamed GI microvasculature [2]. Paradoxically, smoking is considered a protective factor for UC. This is potentially due to nicotine and/or its byproduct, cotinine, having an immunomodulatory effect that leads to decreased production of pro-inflammatory cytokines through the activation of nicotinic receptors α7 in macrophages and dendritic cells. However, this benefit was only observed in mild to moderate UC, whereas smoking has shown to increase the activity of disease in severe UC [2].

Recent studies show that chronic stress, depression, and even adverse life events may increase the likelihood of IBD flares. The damaging effects of stress on the gut involve a comprehensive integrated interaction among the neuronal, endocrine, and

immune systems. Stress contributes to the development of IBD via dysbiosis, alterations in intestinal permeability and mobility, and release of inflammatory factors by activating the brain-gut axis, hypothalamic pituitary-adrenal axis (HPA axis), autonomic nervous system (ANS), and enteric nervous system (ENS) [3]. In the HPA axis, the main culprit is corticotropin-releasing factor, which increases inflammation by activating mast cell degranulation and increasing tumor necrosis factor-alpha (TNF-α) and protease production, thereby damaging the intestinal barrier. Stress also activates the sympathetic part of the ANS, leading to increased production of catecholamines and inhibition of the vagus nerve, which is responsible for intestinal inflammation attenuation by activating cholinergic enteric neurons that have inhibitory effects on macrophages in the muscularis externa [3, 4]. Catecholamines induce increased intestinal inflammation through increased activation of inflammatory nuclear factor kB. Stress also induces dysbiosis by abundance reduction in *Lactobacillus*, leading to opportunistic infections, notably *Shigella flexneri* and *Campylobacteri jejuni*. This also alters the functionality of proteins constituting the gut flora; specifically, this inhibits nucleotide-binding oligomerization domain-like receptors (NOD-like receptors) and pyrin domain containing (NLRP)-6 inflammasome, leading to inflammation of the intestine [3]. Increased intestinal permeability through inflammation further causes immune dysregulation by allowing microbiota to cross the gut-epithelial barrier and activating the innate immune system.

Dietary causes of IBD flares have several plausible mechanisms including alterations in gut microbiome, dietary antigen presentation, and mucosal immune system and epithelial barrier function. Two theories attempt to highlight the etiology of diet-induced IBD. The "cold chain hypothesis" suggests that prolonged refrigeration of food promotes growth of psychotropic pathogens such as *Yersinia* and *Listeria*, which have been identified in patients with CD [5]. The "hygiene hypothesis," on the other hand, suggests that reduced exposure to various enteric organisms in early childhood due to hygienic practices results in an ineffective and aberrant immune response, triggering IBD later in life. A high fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAP) diet has been associated with increased gastrointestinal symptoms since these substances are poorly absorbed, draw water, and ferment in intestines causing abdominal bloating and distension, crampy pain, flatulence, and diarrhea [5].

Crohn's Disease

Presentation of Crohn's Disease Flares

CD can affect the entire GI tract. It generally involves full-thickness or transmural inflammation with deep fissuring ulcers. Granulomatous lymphoid aggregates can be seen. Based on the location of active disease, patients may also present with

symptoms of enteritis related to small bowel inflammation, colitis related to large bowel inflammation, bowel obstruction due to fibrotic or inflammatory structuring disease, and complications such as fistulas and abscesses [6].

"Enteritis" is defined as inflammation of the small intestine, whereas "colitis" is defined as inflammation of the colon. In CD, enteritis is more common with approximately 80% of patients presenting with small bowel involvement. One-third of patients with CD have isolated ileitis. About 50% of patients present with involvement of both the ileum and colon (ileocolitis). About 20% of patients have disease limited to the colon, with half of them sparing the rectum. About a third have perianal disease [7].

The cardinal symptoms of CD include abdominal pain, diarrhea (typically nonbloody), weight loss, and fatigue. A patient may present specifically with right lower quadrant (RLQ) pain due to involvement of ileum; however, CD can often lead to localized pain in other areas of the abdomen due to formation of fibrotic strictures leading to small bowel obstruction or less commonly colonic obstruction [7]. Intermittent diarrhea can result from excessive fluid secretion and lack of fluid absorption by inflamed bowel, bile salt malabsorption due to ileitis, and enteroenteric or enterocolic fistulas leading to bypass of segments of bowel. Additionally, patients with predominant colitis may have grossly bloody bowel movements [7].

The transmural nature of inflammation in CD can create sinus tracts, which are responsible for fistula and abscess formation. Fistulas are connections between two epithelial-lined organs, and in CD, they may connect one segment of bowel to another (enteroenteric), bowel to bladder (enterovesical), bowel to vagina (enterovaginal), and/or bowel to skin (enterocutaneous). Each type of fistula presents with a specific presentation as seen in Table 2.1.

Some sinus tracts may simply cause abscess formation, e.g., a sinus tract extending to the retroperitoneum causing a psoas abscess and presenting with fever and localized abdominal pain and tenderness. Some may even present with phlegmon, an acute suppurative inflammation that occurs subcutaneously and can spread within the connective tissue as it is unbound and lacks a capsule.

Table 2.1 Fistulas in inflammatory bowel disease

Fistula type	Presentation
Enteroenteric	Palpable mass, diarrhea, or asymptomatic
Enterovesical	Pneumaturia (passage of gas in urine); recurrent UTIs with multiple organisms
Enterovaginal	Passage of fecal matter or gas through the vagina
Enterocutaneous	Drainage of fecal matter through the surface of skin or subcutaneous abscess

Severity of Crohn's Disease

Crohn's Disease Activity Index (CDAI) is the gold standard for defining CD clinical activity and assessing clinical response and remission. CDAI takes into consideration signs, symptoms, and history during a 7-day period; its criteria include number of liquid stools, abdominal pain, general well-being, extraintestinal/physical complaints (i.e., arthritis/arthralgia, mucocutaneous lesions such as erythema nodosum and aphthous ulcers, uveitis/iritis, anal disease such as fistulas and fissures, and fever over 37.8 C), antidiarrheal drugs, abdominal mass, hematocrit, and body weight [9]. A CDAI score <150 indicates remission of CD, while a score >450 indicates severe CD. CDAI was developed to assess disease activity at any given point, but since CD is a chronic, progressive disorder, evaluating long-term disease severity is also important. This requires exploring three main domains relevant to evaluating disease severity: (1) disease impact on the patient, (2) disease burden, and (3) disease course. Clinical symptoms, quality of life, and disability are some of the factors considered to assess CD's impact on the patient [8]. To assess disease burden, a combination of lab testing, imaging, and endoscopic evaluation is typically required.

Disease Impact on the Patient

Harvey-Bradshaw Index (HBI) is a modified CDAI assessment that only requires 1 day of patient diary entries rather than 7 day and omits hematocrit level, antidiarrheal medication use, and body weight. Both allowed for the development of disease activity thresholds but correlate poorly with mucosal inflammation [9]. As a result, the van Hees Index was derived to combine clinical and laboratory data contributing most to the activity index, and Perianal Disease Activity Index is derived to more adequately quantify symptoms specific to perianal fistulizing disease. The Manitoba IBD index and Inflammatory Bowel Disease Questionnaire were commonly used to assess the impact of CD on a patient's quality of life, and in recent years, the Crohn's Disease Patient-Reported Outcomes Signs and Symptoms (CD-PRO/SS) was developed to best assess CD's impact on a patient's quality of life and to assess primary outcome measures in pivotal clinical trials per recommendation by the US Food and Drug Administration and the International Society for Pharmacoeconomics and Outcomes Research [8, 10].

Disease Burden

The degree of mucosal inflammation, location, and complications are important measures of disease severity. Biomarkers (i.e., CRP, fecal calprotectin, fecal lactoferrin) can be used to assess disease activity, but they are nonspecific and should not be used exclusively. CRP levels can be normal in up to one-third of CD patients with active disease [8].

Endoscopy, usually ileocolonoscopy, continues to be the gold standard to assess disease activity. Crohn's Disease Endoscopic Index of Severity and the Simple Endoscopic Score for Crohn's Disease have been developed to assess severity. CT and MRI are also useful in assessing disease activity, complications, and distribution and are important tools to aid in the assessment of patients with Crohn's disease. Additionally, ultrasound can differentiate active from inactive disease with a specificity of 85% and sensitivity of 71%, respectively, when assessed against endoscopy or surgery [11] and can be a useful assessment tool in locations where expertise in this technique is available.

Disease Course

Disabling CD can be defined as having one of the following: steroid dependence, need for more than two steroid courses, disabling chronic symptoms for a cumulative time of 12+ months, and need for immunosuppressive therapy or surgery. Severe disease can be defined as having one or more of the following: any colonic resection, complex perianal disease, two or more small bowel resections, or permanent stoma reconstruction. "Aggressive" CD can be defined as penetrating disease, complications or flares of the disease requiring hospitalization, EIMs involving two or more systems, disease refractory to currently available treatments, and need for surgery. "Complicated" disease can be defined as presence of bowel damage, presence of EIMs, and/or the need for surgery [9].

Evaluation of Crohn's Disease

There are no laboratory tests that definitively rule out or rule in CD, but serum and stool testing can assist with reaching a diagnosis. An initial evaluation of a patient presenting with symptoms thought to be related to CD should start with stool studies, including tests for parasitic and bacterial pathogens such as *C. difficile*, to rule out other causes of diarrhea and gastrointestinal symptoms. Patients with severe and longer duration of CD may have thrombocytosis and anemia from chronic inflammation, iron deficiency, and cobalamin (vitamin B12) deficiency, and these findings can be evident on serum studies [12]. Inflammatory markers such as C-reactive protein (CRP) and/or erythrocyte sedimentation rate (ESR) may be elevated, but normal levels do not rule out CD. Fecal calprotectin or fecal lactoferrin may be used to evaluate the degree of gastrointestinal tract inflammation [9].

CD is diagnosed using a combination of clinical features, endoscopic findings, and radiologic findings. In cases of colonic or ileal involvement, endoscopic findings classically indicate skip lesions next to areas of normal-appearing mucosa and with varying degrees of transmural inflammation [9]. In some cases, such as isolated jejunal involvement, affected area(s) may not be easily visualized. As a result, capsule endoscopy may be performed to visualize and assess the small bowel mucosa

[13]. It is a highly sensitive test for finding abnormal mucosa, but it has low specificity for a diagnosis of CD and has the risk of the capsule being impacted or retained in structuring CD; this risk is around 13% in known CD cases [14]. To reduce the risk, patency capsule, specifically designed to disintegrate in 2–3 days, is placed, and small bowel imaging is obtained 24 hours after placement to determine if it has passed through the small bowel. If it is successful in passing through, then regular capsule endoscopy is performed without significant risk of capsule retention [13].

Both magnetic resonance enterography (MRE) and computed tomography enterography (CTE) also allow for visualization of the bowel wall, mucosa, and extraluminal complications. CTE allows for accurate assessment of disease activity and is economical compared to MRE, but it has high radiation exposure and requires iodinated contrast. MRE, on the other hand, is expensive, but it lacks radiation and is an accurate tool for assessment of disease distribution and assessment with its ability to often capture perianal fistulation [15].

Management for Crohn's Disease

When a patient is hospitalized with an increase in or new-onset gastrointestinal symptoms concerning for either a Crohn's disease flare or a possible new diagnosis of Crohn's disease, it is imperative to not immediately assume that the symptoms are solely related to disease-related inflammation and not another cause. Initial evaluation should include an evaluation of labs and stool studies as noted above to assess for signs of inflammation and disease severity. Arguably, the most important step in the evaluation is to assess for infection. Stool testing for *C. difficile* is important for all patients presenting with diarrheal symptoms, especially those with IBD or suspected IBD. Stool testing for other infections should be done in the appropriate clinical situation (i.e., acute diarrhea, especially with fevers). If the patient is immunosuppressed, consider additional testing including serum testing for cytomegalovirus (CMV) and Epstein-Barr virus (EBV). In febrile patients, a chest x-ray, urinalysis with microscopic analysis, and blood cultures should also be obtained.

In addition to the evaluation noted above, cross-sectional imaging – usually with a contrast enhanced CT or MRE – is usually helpful if there is any concern for possible structural complications such as bowel obstruction from stricturing disease or penetrating disease with a possible abscess or phlegmon as well as to evaluate for other possible causes of the patient's symptoms. If a perianal abscess or fistula is suspected, MRI of the pelvis can be a helpful adjunct to a careful physical examination.

Endoscopic evaluation is often needed to complete the evaluation of a patient with gastrointestinal symptoms suspected to be related to Crohn's disease. For any patient with an unclear diagnosis or with suspected new-onset Crohn's disease, endoscopic evaluation is an absolutely necessary part of making the diagnosis. In a patient with known Crohn's disease with a known disease distribution presenting with typical symptoms and having undergone a recent ileocolonoscopy for disease

evaluation, this may not be needed, but if there is any question about disease activity or possible CMV colitis or enteritis, colonoscopy with biopsy should be performed. If imaging suggests disease activity in a location that might not be able to be assessed through routine colonoscopy, then other endoscopic techniques such as upper endoscopy or enteroscopy (routine or balloon assisted) can be considered.

Once the underlying cause of the patient's issues is identified, then treatment can be initiated. Appropriate treatment of luminal inflammatory CD depends on the severity of disease, location and extent of inflammation, and the disease phenotype. Severity of disease is classified into mild, moderate, and severe disease. The medical management for mild to moderate disease differs from the medical management of moderate to severe disease. The medical management of inflammatory CD typically involves induction and maintenance therapy. The goal of induction therapy is to acutely control the inflammation and achieve symptomatic remission in a period of less than 3 months. The goal of maintenance therapy is to gain long-term control of the inflammation for the period following 3 months, preventing symptoms (diarrhea and abdominal pain) and consequences (fistulas and strictures). Maintenance therapy is typically done in an outpatient setting by a gastroenterologist. Induction therapy used for acute exacerbations of inflammatory CD can involve corticosteroids, biologics, and antibiotics in addition to diet modification.

For patients with mild to moderate disease that is limited to the proximal colon or ileum, treatment with 9 mg of enteric-release budesonide daily for 4 weeks is an effective induction therapy. If the patient responds to the treatment, tapering budesonide by 3 mg every 2–4 weeks for 8–12 weeks can begin [16]. If the disease involves the distal colon or is diffusely spread throughout the colon, it is recommended to begin an induction of 40 mg of prednisone daily for 1 week. A taper of 5–10 mg per week over the next 1–2 months can begin if the patient responds to initial treatment. The use of 5-aminosalicylates is not recommended in the treatment of inflammatory CD in patients hospitalized with active Crohn's disease [17, 18].

Management of patients with moderate to severe inflammatory CD is more complicated as there are several factors that need to be considered in determining the best treatment. A gastroenterologist should be consulted as treatment is often individualized. Similar to the management of mild to moderate inflammatory CD, steroids can be used in hospitalized patients with acute flares. Typically, intravenous methylprednisolone is used to mitigate exacerbations. In addition, induction for moderate to severe inflammatory CD may involve the use of TNF inhibitors such as infliximab. Infliximab, a monoclonal antibody against TNF-alpha, can be used as an induction treatment and has been shown to be effective at obtaining remission quickly in patients with severe disease [19]. Prior to treatment, the patient should undergo testing for hepatitis B (HBsAg, HBsAb, HBcAb) and tuberculosis as reactivation of latent disease has been reported with infliximab. Infliximab is given intravenously in dosages of 5 mg/kg at zero, two, and six weeks for induction therapy [20]. There is evidence to demonstrate that combination therapy (infliximab plus immunomodulator) is more effective than monotherapy, but immunomodulators are not indicated for induction of remission, so this treatment strategy is more suited for maintenance therapy than for induction therapy [21].

Current therapies for moderate to severe CD include methotrexate, TNF inhibitors, thiopurines, IL 12/23 inhibitors, and integrin inhibitors. Difficulties in tolerating these medications and increased rates of treatment failure in the case of TNF inhibitors due to the development of antidrug antibodies, for instance, have prompted increased interest in novel CD therapies [22]. Such novel therapies include small molecule therapies, like Janus kinase (JAK) inhibitors that have advantages over biologics like TNF inhibitors such as less variability in pharmacokinetics, convenient oral route of administrations, and minimal risk of immunogenicity. Despite a greater risk of drug-drug interactions compared to biologics, the unique benefits of small molecule therapies make them a promising alternative to the management of CD [22]. Currently, JAK inhibitors are not FDA approved for induction or maintenance of CD.

Management of Intra-abdominal Abscesses (IAA) Due to Crohn's Disease

Intra-abdominal abscesses secondary to CD are treated using antibiotics or a combination of antibiotics and drainage. Antibiotics used to target intra-abdominal abscesses should cover enteric pathogens, such as gram-negative aerobic and facultative bacteria, gram-positive streptococci, and obligate anaerobic bacilli. Rueken et al. compiled a microbiological spectrum of those with IAA from perforating Crohn's disease, finding E. coli as the most frequent isolated pathogen (45 patients), then Streptococcus spp (28 patients), then Enterococci (27 patients), then Candida (12 patients), and finally anerobic bacteria (11 patients) [23]. Appropriate antibiotic monotherapy would include any of the following: cefoxitin, ertapenem, moxifloxacin, or tigecycline [24]. Combination therapy with metronidazole plus either cefazolin, cefuroxime, ceftriaxone, cefotaxime, levofloxacin, or ciprofloxacin can also be used [24]. There has been no clear indication on whether parenteral or oral antibiotics are superior in resolution of abscess [24]. Some IAA have resolved with antibiotic use only. Two previous studies found that 37% of patients treated with antibiotics alone had IAA recurrence with these reoccurrences occurring within 12–47.5 months of follow-up [25, 26]. More recently, Graham et al. found 31% of patients treated with solely antibiotics had recurrence of IAA; however, their follow-up period was only 6 months [27]. There are no clear indications for what patient qualifies for treatment of IAA solely with antibiotics, but it has been suggested that abscesses larger than 3 cm in size are not likely to resolve with antibiotic therapy alone [24].

Percutaneous vs. Surgical Drainage

If antibiotics do not resolve an intra-abdominal abscess, or if recurrent intra-abdominal abscesses develop, abscesses should be drained percutaneously or surgically. Gutierrez et al. conducted a retrospective cohort study comparing percutaneous and surgical abscess drainage, which showed no significant time difference for time

to resolution of abscess. It did however show about one-third of percutaneous drainage patients underwent surgical drainage for abscess within 1 year [28]. Clancy et al. conducted a recent meta-analysis searching for comparisons between percutaneous and surgical drainage for spontaneous Crohn's disease-related intra-abdominal abscesses and found that 29.3% of surgical drainage can be avoided by percutaneous drainage [29] although an increased likelihood of abscess reformation with percutaneous drainage (OR of 6.54, 95% CI: 1.78–24.0, $p = 0.005$) was also noted [29].

Management of Structural Issues Secondary to Crohn's Disease (CD)

Over time, chronic inflammation in CD can lead to fibrostenotic disease that can ultimately result in mechanical bowel obstruction. According to the European Crohn's and Colitis Organisation (ECCO) guidelines, stricturing CD is defined as persistent, localized narrowing whereby functional effects may be evident by prestenotic dilation with accompanying obstructive symptoms [30]. Strictures can be inflammatory, fibrotic, or mixed, and they appear in roughly 50% of patients with CD after 20 years of disease [31]. Up to 80% of patients with ileal or ileocecal disease require surgery within 10 years from onset of diagnosis for stricturing disease [32, 33]. Traditionally, the use of steroid therapy and procedures like bowel resections were utilized to treat stricturing CD. In the case of resection, they carried with them the high risk of malabsorptive disorders and short bowel syndrome.

Many factors contribute to the consideration of using medical therapy vs. surgical therapy for stricturing CD. Patients with the following characteristics have demonstrated better outcomes from medical therapy initially rather than surgical treatment: previous resection or short bowel syndrome, current smoker, naiveté toward anti-TNF drugs, severe nutritional deficiency, and acute history of obstructive symptoms. Mechanical features like multifocal strictures, long strictures (>40 cm), limited dilatation of upstream tract (<35 mm), and absence of complex fistulizing disease also support the use of medical therapy initially. Conversely, patients without these characteristics or morphologic features should be considered for surgical intervention [31].

Procedures involving conservative endoscopic approaches and surgical strictureplasty have been utilized more recently and were developed as bowel-sparing techniques providing excellent short-term and moderate long-term efficacy. Endoscopic balloon dilatation can be performed during regular colonoscopies. This technique is best reserved for short (<2–3 cm), noncomplicated strictures (minimal inflammation, no fistula, single stenosis). The procedural success rate of endoscopic balloon dilatation is 71–100%, whereby success is defined as the ability to pass a scope through the stricture. Symptomatic recurrence can occur, requiring repeat dilatation or surgery in 30–41% of patients after 15–36 months [34, 35]. Risks of bowel

perforation during endoscopic balloon dilatation are low at 1.1% compared to a risk of postoperative complications at 8.8%. Bowel-sparing surgical options like strictureplasty are a viable option when medical therapies and endoscopic balloon dilatations fail or are unable to be performed due to multiple small bowel strictures. Strictureplasty works to maintain absorptive function of the bowel by increasing its luminal diameter rather than resecting large portions. Strictureplasty has been proven to be a safe and effective alternative to bowel resection. The overall short-term complication rate ranged from 5% to 20% with no mortalities and a long-term recurrence rate of 25–70% [36]. It is important for hospitalists to get gastroenterologists and general surgeons onboard early in the decision-making process to optimize care in patients with complicated CD.

Ulcerative Colitis

Ulcerative Colitis Flares

Ulcerative colitis is characterized by recurrent inflammation limited to the mucosal and submucosal layers of the colon. It begins in the rectum and extends proximally toward the cecum in a continuous fashion with the extent of distribution varying [6]. On imaging, plain films showing a loss of haustra ("lead pipe" sign) is classic for UC. Otherwise, cross sectional imaging may show inflammatory changes of the colon. On colonoscopy, continuous inflammation in a circumferential pattern generally starting in the rectum can be seen, and the classic findings include ulcerations, friability, granularity, erythema, and the loss of a normal vascular pattern. Histological findings of distortion of crypt architecture with crypt shortening, basal plasmacytosis, Paneth cell metaplasia, and mucin depletion are suggestive of UC [37].

Patients with UC typically present with frequent diarrhea that may be bloody and in small volumes. They may also have colicky abdominal pain (often in the left lower quadrant), urgency, tenesmus, and fecal incontinence due to rectal inflammation [37]. Severity can range from mild (four or less bowel movements per day with or without blood) to severe (10+ bowel movements daily with severe cramps and bleeding). Patients may also have fatigue, weight loss, fever, and symptoms of anemia secondary to iron deficiency from blood loss or chronic inflammation. Progression of these symptoms can be gradual, occurring over several weeks [38].

Up to 15% of patients can present with acute severe UC [37]. Massive hemorrhage can be present in up to 3% of these patients during the course of their disease and may warrant urgent colectomy [37]. Urgency and tenesmus are typically seen in proctitis, whereas bloody diarrhea and abdominal pain are more prominent in pancolitis. Physical examination may reveal signs of abdominal tenderness, signs of anemia, blood on digital rectal exam, and tympany on percussion of the abdomen which may indicate colonic dilatation and requires prompt imaging [37]. Patients with fulminant colitis (10+ stools per day with bleeding, abdominal pain/distension,

and toxic presentation such as fever and anorexia) are at risk for toxic megacolon (colonic diameter of equal/greater than 6 cm or cecal diameter greater than 9 cm and the presence of systemic toxic symptoms). Toxic megacolon commonly leads to perforation that has a high mortality rate.

Severity of Ulcerative Colitis

When describing the severity of ulcerative colitis, the Truelove and Witt's criteria has been the most prevalently used. The Truelove and Witt's criteria published in 1955 differentiates between mild and severe disease [39]. Mild colitis according to this criterion will have fewer than four bowel movements a day, normal vitals, a hemoglobin of greater than 11 g/dL, and an ESR less than 22 mm/hr. Severe disease according to this criterion will have six or more bowel movements a day, with fever, tachycardia, anemia, or elevated ESR. These criteria do not take account endoscopic information [39]. The most commonly used criteria that take account of endoscopic information are the Mayo score and Ulcerative Colitis Endoscopic Index of Severity. These three criteria have been incorporated by the American College of Gastroenterology to make their own disease activity index that combines clinical and endoscopic data [39].

Evaluation of Ulcerative Colitis

While laboratory tests are not used to diagnose UC, they are useful to describe the severity of disease, evaluate nutritional status of the patient, and evaluate for any infectious etiology of the patient's symptoms. Complete blood count (CBC), comprehensive metabolic panel (CMP), ESR, C-reactive protein, and albumin are helpful to assess for disease severity. A fecal calprotectin can also be helpful to assess for bowel inflammation. Evaluation of prealbumin, vitamin D, vitamin B12, and iron studies (iron, total iron binding capacity, and ferritin) is helpful to evaluate the patient's nutritional status as well as evaluating patients with anemia. It is very important to evaluate for possible infections. Stool cultures for Salmonella, Shigella, Campylobacter, and Yersinia, stool testing for Escherichia coli O157:H7, giardia stool antigen, C. difficile toxin, and stool microscopy for ova and parasites are helpful in the appropriate clinical setting. In febrile patients, an evaluation for other sources of fever should be completed with urinalysis and urine culture, blood cultures, and a chest radiograph. In patients who are immunosuppressed or in patients with fevers, testing for cytomegalovirus infection and Epstein-Barr virus infection should be done.

Imaging with computed tomography of the abdomen or an abdominal x-ray can be helpful to evaluate for bowel obstruction, colonic dilatation, or perforation. CT

scans or MRIs can be used to identify intra-abdominal abscesses or pelvic abscesses, fistulizing disease, or stricturing disease although these are much less common in UC than in CD due to the nature of the disease [40].

Once hospitalized, the care of all patients with severe ulcerative colitis should involve a gastroenterologist, and in most cases, colonoscopy to assess disease severity and to get allow for biopsy looking for CMV or EBV infection will be helpful. If not done within the past 6 months or if risk factors exist, evaluation for hepatitis B and tuberculosis should be performed at the time of admission in the event that TNF inhibitors are needed as to avoid delaying care.

Management of Ulcerative Colitis

Systemic Glucocorticoids

As outlined in Fig. 2.1, systemic glucocorticoids are first-line treatment for inpatient management of acute severe ulcerative colitis (ASUC). According to the American Gastroenterological Association (AGA) guidelines, treatments with 60 mg of IV methylprednisolone (IVMP) or 300 mg IV of hydrocortisone (IVHC) daily is recommended [41]. Doses can be divided. ASUC patients usually respond within 3–5 days of initiation of IV steroids. Systemic glucocorticoids treatment exceeding 7 days for ASUC without clinical improvement is not recommended as the potential for significant improvement past the 7-day mark is minimal. Additionally, longer treatment with glucocorticoids increases the risk for adverse effects such as infection, venous thromboembolism, fractures, poor wound healing, mood changes, irritability, psychosis, weight gain, and increased appetite [42]. While the AGA does not specify whether to use methylprednisolone or

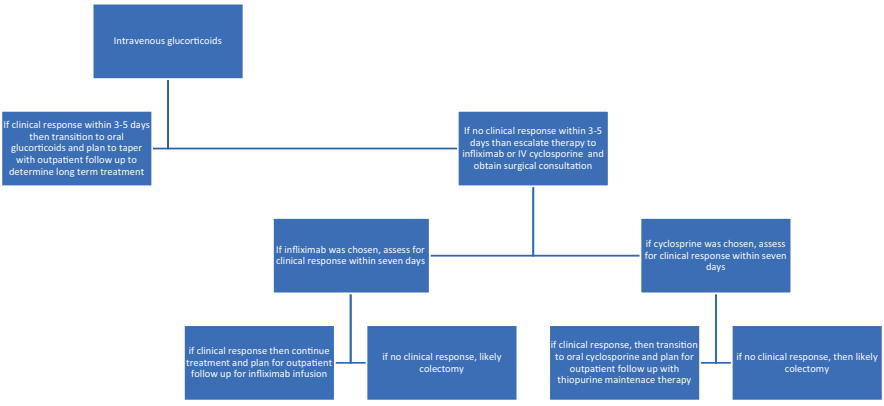

Fig. 2.1 Algorithm for inpatient management of moderate to severe ulcerative colitis flares

hydrocortisone, some research suggests that IVMP use in ASUC may lead to increased need to step up treatment to cyclosporine or biologics compared to IVHC [43]. IVHC has however been seen to have higher rates of hypokalemia and need for potassium supplement compared to IVMP.

Cyclosporine

One of the two established therapies for corticosteroid-resistant ASUC is intravenous cyclosporine, a calcineurin inhibitor. The recommended dose of cyclosporine is 2–4 mg/kg/day given as an intermittent intravenous dose with a serum level goal between 250 and 400 ng/mL [41]. A randomized double-blind study between 2 mg/kg and 4 mg/kg of cyclosporine showed no difference in clinical efficacy for ASUC [44]. Response to cyclosporine in ASUC patients is reported to occur at a median of 4–5 days [43]. Contraindications to cyclosporine include hypocholesteremia, due to its increased risk of precipitating seizures, and decreased renal function as cyclosporine is cleared renally [45].

Infliximab

The other established therapy for corticosteroid resistant is infliximab, an antitumor necrosis factor (TNF) monoclonal antibody [41]. Infliximab is the first agent mentioned that can be used in both acute management and being used as a maintenance treatment. Administration of infliximab is 5 mg/kg at weeks 0, 2, and 6 followed by maintenance dosing of 5 mg/kg every 8 weeks [41]. Expected timing to clinical response for ASUC should be noted by 7 days [43]. Infliximab is contraindicated in those with congestive heart failure, demyelinating diseases, any active infections, latent TB, and hepatitis B [46]. It is also contraindicated in patients with prior antibodies to infliximab or with prior infusion reactions to infliximab.

Infliximab vs. Cyclosporine

Currently, the AGA makes no direct recommendation on preference of treatment between infliximab and cyclosporine [41]. The most recent trial of 135 patients comparing these two drugs found no statistically significant difference in quality of life and 12-month colectomy rate around 40% [47]. Cost-utility analysis demonstrated a significantly higher cost of infliximab due to acquisition costs, but cyclosporine treatment is estimated to have longer hospital stay by a factor of 1.527 times longer (95% CI 1.278–1.817, $p < 0.001$) [47]. This study was done in the United Kingdom under the National Health Service health-care system, so cost analysis may differ when applied to the United States health-care system.

Novel Treatments for ASUC

There are two promising novel treatments for ASUC, vedolizumab and tofacitinib. Vedolizumab is a monoclonal antibody that is an integrin antagonist targeting T lymphocytes. For corticosteroid refractory ASUC, once a calcineurin inhibitor has been used for rescue therapy, the patient can then be bridged to vedolizumab. Ollech et al. conducted a retrospective observational study showing a 7% colectomy rate at 3 months for patients treated with vedolizumab after rescue therapy with cyclosporine [48]. A year later, 33% of this patient cohort had a colectomy and 45% had a colectomy after 2 years [48, 49].

Tofacitinib is a small-molecule Janus kinase inhibitor that has demonstrated efficacy in the inpatient management of corticosteroid-resistant ASUC. Berinstein et al. conducted a retrospective observational study evaluating colectomy rates in patients treated with tofacitinib compared to intravenous corticosteroids [50]. They found that tofacitinib was protective against colectomy at the 90 day mark compared to intravenous corticosteroids with a hazard ratio 0.28, 95% confidence interval of 0,10–0.81, and $p = 0.018$ [12]. It was also noted that 10 mg three times daily dosing of tofacitinib was significantly protective, while 10 mg twice daily was not [50]. This is an exciting prospect as this drug has a rapid-onset action, rapid clearance, and lower costs compared to infliximab [50].

References

1. Klein A, Eliakim R. Non steroidal anti-inflammatory drugs and inflammatory bowel disease. Pharmaceuticals (Basel). 2010;3(4):1084–92. https://doi.org/10.3390/ph3041084.
2. Berkowitz L, Schultz BM, Salazar GA, Pardo-Roa C, Sebastián VP, Álvarez-Lobos MM, Bueno SM. Impact of cigarette smoking on the gastrointestinal tract inflammation: opposing effects in Crohn's disease and ulcerative colitis. Front Immunol. 2018;9(74). https://doi.org/10.3389/fimmu.2018.00074.
3. Sun Y, Li L, Xie R, Wang B, Jiang K, Cao H. Stress triggers flare of inflammatory bowel disease in children and adults. Front Pediatr. 2019;7:432. https://doi.org/10.3389/fped.2019.00432.
4. Stakenborg N, Boeckxstaens GE. Bioelectronics in the brain–gut axis: focus on inflammatory bowel disease (IBD). Int Immunol. 2021;33(6):337–48. https://doi.org/10.1093/intimm/dxab014.
5. Limdi JK. Dietary practices and inflammatory bowel disease. Indian J Gastroenterol. 2018;37(4):284–92. https://doi.org/10.1007/s12664-018-0890-5.
6. Lee JM, Lee KM. Endoscopic diagnosis and differentiation of inflammatory bowel disease. Clin Endosc. 2016;49(4):370–5. https://doi.org/10.5946/ce.2016.090.
7. Peppercorn MA, Kane SV. Clinical manifestations, diagnosis, and prognosis of Crohn disease in adults. UpToDate. 2021. https://www.uptodate.com/contents/clinical-manifestations-diagnosis-and-prognosis-of-crohn-disease-in-adults. Accessed 18 June 2021.
8. Peyrin-Biroulet L, Panes J, Sandborn WJ, Vermeire S, Danese S, Feagan BG, Colombel JF, Hanauer SB, Rycroft B. Defining disease severity in inflammatory bowel diseases: current and future directions. Clin Gastroenterol Hepatol. 2016;14(3):348–354 e317. https://doi.org/10.1016/j.cgh.2015.06.001.

9. Best WR. Predicting the Crohn's disease activity index from the Harvey-Bradshaw index. Inflamm Bowel Dis. 2006;12(4):304–10. https://doi.org/10.1097/01.MIB.0000215091.77492.2a.
10. Dulai PS, Jairath V, Khanna R, Ma C, McCarrier KP, Martin ML, Parker CE, Morris J, Feagan BG, Sandborn WJ. Development of the symptoms and impacts questionnaire for Crohn's disease and ulcerative colitis. Aliment Pharmacol Ther. 2020;51(11):1047–66. https://doi.org/10.1111/apt.15726.
11. Panes J, Bouzas R, Chaparro M, Garcia-Sanchez V, Gisbert JP, Martinez de Guerenu B, Mendoza JL, Paredes JM, Quiroga S, Ripolles T, Rimola J. Systematic review: the use of ultrasonography, computed tomography and magnetic resonance imaging for the diagnosis, assessment of activity and abdominal complications of Crohn's disease. Aliment Pharmacol Ther. 2011;34(2):125–45. https://doi.org/10.1111/j.1365-2036.2011.04710.x.
12. Vermeire S, Van Assche G, Rutgeerts P. Laboratory markers in IBD: useful, magic, or unnecessary toys? Gut. 2006;55(3):426–31. https://doi.org/10.1136/gut.2005.069476.
13. Feuerstein JD, Cheifetz AS. Crohn disease: epidemiology, diagnosis, and management. Mayo Clin Proc. 2017;92(7):1088–103. https://doi.org/10.1016/j.mayocp.2017.04.010.
14. Cheifetz AS, Kornbluth AA, Legnani P, Schmelkin I, Brown A, Lichtiger S, Lewis BS. The risk of retention of the capsule endoscope in patients with known or suspected Crohn's disease. Am J Gastroenterol. 2006;101(10):2218–22. https://doi.org/10.1111/j.1572-0241.2006.00761.x.
15. Dambha F, Tanner J, Carroll N. Diagnostic imaging in Crohn's disease: what is the new gold standard? Best Pract Res Clin Gastroenterol. 2014;28(3):421–36. https://doi.org/10.1016/j.bpg.2014.04.010.
16. Coward S, Kuenzig ME, Hazlewood G, Clement F, McBrien K, Holmes R, Panaccione R, Ghosh S, Seow CH, Rezaie A, Kaplan GG. Comparative effectiveness of mesalamine, sulfasalazine, corticosteroids, and budesonide for the induction of remission in Crohn's disease: a Bayesian network meta-analysis. Inflamm Bowel Dis. 2017;23(3):461–72. https://doi.org/10.1097/MIB.0000000000001023.
17. Ford AC, Kane SV, Khan KJ, Achkar JP, Talley NJ, Marshall JK, Moayyedi P. Efficacy of 5-aminosalicylates in Crohn's disease: systematic review and meta-analysis. Am J Gastroenterol. 2011;106(4):617–29. https://doi.org/10.1038/ajg.2011.71.
18. Hanauer SB, Stromberg U. Oral Pentasa in the treatment of active Crohn's disease: a meta-analysis of double-blind, placebo-controlled trials. Clin Gastroenterol Hepatol. 2004;2(5):379–88. https://doi.org/10.1016/s1542-3565(04)00122-3.
19. Kawalec P, Mikrut A, Wisniewska N, Pilc A. Tumor necrosis factor-alpha antibodies (infliximab, adalimumab and certolizumab) in Crohn's disease: systematic review and meta-analysis. Arch Med Sci. 2013;9(5):765–79. https://doi.org/10.5114/aoms.2013.38670.
20. Hanauer SB, Feagan BG, Lichtenstein GR, Mayer LF, Schreiber S, Colombel JF, Rachmilewitz D, Wolf DC, Olson A, Bao W, Rutgeerts P, Group AIS. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. Lancet. 2002;359(9317):1541–9. https://doi.org/10.1016/S0140-6736(02)08512-4.
21. Colombel JF, Sandborn WJ, Reinisch W, Mantzaris GJ, Kornbluth A, Rachmilewitz D, Lichtiger S, D'Haens G, Diamond RH, Broussard DL, Tang KL, van der Woude CJ, Rutgeerts P, Group SS. Infliximab, azathioprine, or combination therapy for Crohn's disease. N Engl J Med. 2010;362(15):1383–95. https://doi.org/10.1056/NEJMoa0904492.
22. Boland BS, Vermeire S. Janus kinase antagonists and other novel small molecules for the treatment of Crohn's disease. Gastroenterol Clin N Am. 2017;46(3):627–44. https://doi.org/10.1016/j.gtc.2017.05.015.
23. Reuken PA, Kruis W, Maaser C, Teich N, Büning J, Preiß JC, Schmelz R, Bruns T, Fichtner-Feigl S, Stallmach A, Group TGIS. Microbial spectrum of intra-abdominal abscesses in perforating Crohn's disease: results from a prospective German registry. J Crohn's Colitis. 2018;12(6):695–701. https://doi.org/10.1093/ecco-jcc/jjy017.
24. Feagins LA, Holubar SD, Kane SV, Spechler SJ. Current strategies in the management of intra-abdominal abscesses in Crohn's disease. Clin Gastroenterol Hepatol. 2011;9(10):842–50. https://doi.org/10.1016/j.cgh.2011.04.023.

25. Lee H, Kim YH, Kim JH, Chang DK, Son HJ, Rhee PL, Kim JJ, Paik SW, Rhee JC. Nonsurgical treatment of abdominal or pelvic abscess in consecutive patients with Crohn's disease. Dig Liver Dis. 2006;38(9):659–64. https://doi.org/10.1016/j.dld.2005.12.001.
26. Garcia JC, Persky SE, Bonis PAL, Topazian M. Abscesses in Crohn's disease: outcome of medical versus surgical treatment. J Clin Gastroenterol. 2001;32(5):409–12.
27. Graham E, Rao K, Cinti S. Medical versus interventional treatment of intra-abdominal abscess in patients with Crohn disease. Infect Dis Res Treat. 2017;10:1179916117701736. https://doi.org/10.1177/1179916117701736.
28. Gutierrez A, Lee H, Sands BE. Outcome of surgical versus percutaneous drainage of abdominal and pelvic abscesses in Crohn's disease. Am J Gastroenterol. 2006;101(10):2283–9. https://doi.org/10.1111/j.1572-0241.2006.00757.x.
29. Clancy C, Boland T, Deasy J, McNamara D, Burke JP. A meta-analysis of percutaneous drainage versus surgery as the initial treatment of Crohn's disease-related intra-abdominal abscess. J Crohns Colitis. 2016;10(2):202–8. https://doi.org/10.1093/ecco-jcc/jjv198.
30. Gionchetti P, Dignass A, Danese S, Magro Dias FJ, Rogler G, Lakatos PL, Adamina M, Ardizzone S, Buskens CJ, Sebastian S, Laureti S, Sampietro GM, Vucelic B, van der Woude CJ, Barreiro-de Acosta M, Maaser C, Portela F, Vavricka SR, Gomollón F. 3rd European evidence-based consensus on the diagnosis and management of Crohn's disease 2016: part 2: surgical management and special situations. J Crohns Colitis. 2017;11(2):135–49. https://doi.org/10.1093/ecco-jcc/jjw169.
31. Rieder F. Managing intestinal fibrosis in patients with inflammatory bowel disease. Gastroenterol Hepatol. 2018;14(2):120–2.
32. Thienpont C, Van Assche G. Endoscopic and medical management of fibrostenotic Crohn's disease. Dig Dis. 2014;32 Suppl 1:35–8. https://doi.org/10.1159/000367824.
33. Molodecky NA, Soon IS, Rabi DM, Ghali WA, Ferris M, Chernoff G, Benchimol EI, Panaccione R, Ghosh S, Barkema HW, Kaplan GG. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. Gastroenterology. 2012;142(1):46–54.e42; quiz e30. https://doi.org/10.1053/j.gastro.2011.10.001.
34. Hassan C, Zullo A, De Francesco V, Ierardi E, Giustini M, Pitidis A, Taggi F, Winn S, Morini S. Systematic review: endoscopic dilatation in Crohn's disease. Aliment Pharmacol Ther. 2007;26(11–12):1457–64. https://doi.org/10.1111/j.1365-2036.2007.03532.x.
35. Bettenworth D, Gustavsson A, Atreja A, Lopez R, Tysk C, van Assche G, Rieder F. A pooled analysis of efficacy, safety, and long-term outcome of endoscopic balloon dilation therapy for patients with stricturing Crohn's disease. Inflamm Bowel Dis. 2017;23(1):133–42. https://doi.org/10.1097/mib.0000000000000988.
36. Campbell L, Ambe R, Weaver J, Marcus SM, Cagir B. Comparison of conventional and non-conventional strictureplasties in Crohn's disease: a systematic review and meta-analysis. Dis Colon Rectum. 2012;55(6):714–26. https://doi.org/10.1097/DCR.0b013e31824f875a.
37. Ungaro R, Mehandru S, Allen PB, Peyrin-Biroulet L, Colombel JF. Ulcerative colitis. Lancet. 2017;389(10080):1756–70. https://doi.org/10.1016/S0140-6736(16)32126-2.
38. Silverberg MS, Satsangi J, Ahmad T, Arnott ID, Bernstein CN, Brant SR, Caprilli R, Colombel JF, Gasche C, Geboes K, Jewell DP, Karban A, Loftus EV Jr, Pena AS, Riddell RH, Sachar DB, Schreiber S, Steinhart AH, Targan SR, Vermeire S, Warren BF. Toward an integrated clinical, molecular and serological classification of inflammatory bowel disease: report of a Working Party of the 2005 Montreal World Congress of Gastroenterology. Can J Gastroenterol. 2005;19 Suppl A:5A–36A. https://doi.org/10.1155/2005/269076.
39. Rubin DT, Ananthakrishnan AN, Siegel CA, Sauer BG, Long MD. ACG clinical guideline: ulcerative colitis in adults. Off J Am Coll Gastroenterol | ACG. 2019;114(3):384–413. https://doi.org/10.14309/ajg.0000000000000152.
40. Feuerstein J. Hospital management of acute severe ulcerative colitis. Gastroenterol Hepatol (N Y). 2021;17(3):128–31.
41. Feuerstein JD, Isaacs KL, Schneider Y, Siddique SM, Falck-Ytter Y, Singh S, Chachu K, Day L, Lebwohl B, Muniraj T, Patel A, Peery AF, Shah R, Sultan S, Singh H, Singh S, Spechler S, Su G, Thrift AP, Weiss JM, Weizman AV, Feuerstein J, Singh S, Isaacs K, Schneider Y, Falck-

Ytter Y, Siddique SM, Allegretti J, Terdiman J, Singh S, Siddique SM. AGA clinical practice guidelines on the management of moderate to severe ulcerative colitis. Gastroenterology. 2020;158(5):1450–61. https://doi.org/10.1053/j.gastro.2020.01.006.

42. Waljee AK, Rogers MAM, Lin P, Singal AG, Stein JD, Marks RM, Ayanian JZ, Nallamothu BK. Short term use of oral corticosteroids and related harms among adults in the United States: population based cohort study. BMJ. 2017;357:j1415. https://doi.org/10.1136/bmj.j1415.
43. Vasudevan A, Gibson PR, van Langenberg DR. Time to clinical response and remission for therapeutics in inflammatory bowel diseases: what should the clinician expect, what should patients be told? World J Gastroenterol. 2017;23(35):6385–402. https://doi.org/10.3748/wjg.v23.i35.6385.
44. Van Assche G, D'haens G, Noman M, Vermeire S, Hiele M, Asnong K, Arts J, D'hoore A, Penninckx F, Rutgeerts P. Randomized, double-blind comparison of 4 mg/kg versus 2 mg/kg intravenous cyclosporine in severe ulcerative colitis. Gastroenterology. 2003;125(4):1025–31. https://doi.org/10.1016/S0016-5085(03)01214-9.
45. Rubin DT, Traboulsi C, Rai V. A practical clinical approach to the management of high-risk ulcerative colitis. Gastroenterol Hepatol (N Y). 2021;17(2):59–66.
46. Rosiou K, Selinger CP. Acute severe ulcerative colitis: management advice for internal medicine and emergency physicians. Intern Emerg Med. 2021. https://doi.org/10.1007/s11739-021-02704-0.
47. Williams JG, Alam MF, Alrubaiy L, Arnott I, Clement C, Cohen D, Gordon JN, Hawthorne AB, Hilton M, Hutchings HA, Jawhari AU, Longo M, Mansfield J, Morgan JM, Rapport F, Seagrove AC, Sebastian S, Shaw I, Travis SPL, Watkins A. Infliximab versus ciclosporin for steroid-resistant acute severe ulcerative colitis (CONSTRUCT): a mixed methods, open-label, pragmatic randomised trial. Lancet Gastroenterol Hepatol. 2016;1(1):15–24. https://doi.org/10.1016/S2468-1253(16)30003-6.
48. Ollech JE, Dwadasi S, Rai V, Peleg N, Normatov I, Israel A, Sossenheimer PH, Christensen B, Pekow J, Dalal SR, Sakuraba A, Cohen RD, Rubin DT. Efficacy and safety of induction therapy with calcineurin inhibitors followed by vedolizumab maintenance in 71 patients with severe steroid-refractory ulcerative colitis. Aliment Pharmacol Ther. 2020;51(6):637–43. https://doi.org/10.1111/apt.15616.
49. Narula N, Marshall JK, Colombel J-F, Leontiadis GI, Williams JG, Muqtadir Z, Reinisch W. Systematic review and meta-analysis: infliximab or cyclosporine as rescue therapy in patients with severe ulcerative colitis refractory to steroids. Am J Gastroenterol. 2016;111(4):477–91. https://doi.org/10.1038/ajg.2016.7.
50. Berinstein JA, Sheehan JL, Dias M, Berinstein EM, Steiner CA, Johnson LA, Regal RE, Allen JI, Cushing KC, Stidham RW, Bishu S, Kinnucan JAR, Cohen-Mekelburg SA, Waljee AK, Higgins PDR. Tofacitinib for biologic-experienced hospitalized patients with acute severe ulcerative colitis: a retrospective case-control study. Clin Gastroenterol Hepatol. https://doi.org/10.1016/j.cgh.2021.05.038.