12 Complications of Inflammatory Bowel Disease: Initial Medical Management and Role of Endoscopy

Nicholas R. Crews and Matthew E. Bohm

Introduction

Ulcerative colitis (UC) and Crohn's disease (CD) are the two major forms of inflammatory bowel disease (IBD). While UC is limited to inflammation of the colonic mucosal layers, CD can involve the entire gastrointestinal tract from mouth to anus with transmural involvement. In CD, the most common sites of involvement include the ileum alone (50%), ileum and colon (30%), or isolated colonic disease (20%). Perianal disease occurs in approximately 25% of patients with CD, with 45% of those patients having perianal involvement at initial presentation. The typical presentation of UC is diarrhea, bloody stools, urgency, and tenesmus. The most common CD symptoms include abdominal pain, diarrhea which is usually non-bloody, and unintentional weight loss. A severe colitis flare requiring hospitalization occurs in 18–25% of patients with UC typically after failing outpatient therapy [1, 2]. Patients with CD are typically hospitalized as a result of penetrating complications of the disease (intra-abdominal abscess, fistula, or perianal abscess), intestinal obstruction, or severe diarrhea with concomitant malnutrition. This chapter will focus on the inpatient evaluation and management of IBD complications.

Severe/Fulminant Ulcerative Colitis

Severe UC is defined by the presence of ≥6 stools daily with bleeding and abdominal pain with systemic toxicity evident by tachycardia (pulse ≥90 beats/min), fever (temperature ≥37.5 °C), anemia (hemoglobin <10.5 g/dL), and elevated inflammatory markers [3]. Severe CD colitis has similar clinical manifestations. Fulminant colitis is characterized as ≥10 bowel habits daily, continuous bleeding with or without a transfusion requirement, and severe toxicity with an increased risk (1–2%) of developing toxic megacolon [4]. Initial evaluation should include comprehensive laboratory testing including C-reactive protein (CRP), stool testing with culture and *C. difficile* PCR for toxin, and abdominal imaging. Abdominal imaging can consist of an abdominal X-ray or CT scan if indicated based on examination. Colonic dilation >6 cm or cecum dilation >9 cm is high risk for toxic megacolon and perforation. Severe IBD activity is associated with hypercoagulability which increases the risk for venous thromboembolic events (VTE) approximately threefold

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R. Lim (ed.), *Multidisciplinary Approaches to Common Surgical Problems*,
https://doi.org/10.1007/978-3-030-12823-4_12

compared to hospitalized patients without IBD [5, 6]. Thus, administration of thrombo-prophylaxis to patients hospitalized with severe IBD flares without severe gastrointestinal bleeding is recommended [7].

Endoscopic evaluation is the standard diagnostic modality which allows assessment of severity and biopsies for histopathologic examination and cytomegalovirus testing. CMV inclusions are commonly identified in colonic tissue in 16–36% of patients with IBD [8–10]. While the pathogenicity of CMV remains poorly understood, the presence of CMV with ≥5 inclusion bodies/high-power field like signifies clinically significant infection and should be treated with ganciclovir in patients with severe colitis, particularly if the patients are steroid-refractory or chronically immunosuppressed [11]. *C. difficile* infection has been associated with 7–10% of IBD flares in two retrospective studies [12, 13]. Presence of both IBD and *C. difficile* increases colectomy risk 6.6-fold compared to patients with only *C. difficile* colitis [14]. *C. difficile* colitis should be treated with oral vancomycin 125 mg four times per day whether the presentation is non-severe or severe (white blood cell count of ≥15,000 cells/mL or a serum creatinine level >1.5 mg/dL) [15]. Patients with fulminant *C. difficile* with colonic dilation or an ileus should be treated with high-dose oral vancomycin 500 mg four times per day, intravenous metronidazole 500 mg IV every 8 hours, and vancomycin enemas 500 mg in 100 ml of saline every 6 hours particularly if ileus is present [15]. Patients who fail to respond to this therapy should undergo fecal microbiota transplant.

Corticosteroids have remained the backbone of medical therapy to induce remission of active IBD since initial studies demonstrated efficacy in the 1950s–1960s [16, 17]. Intravenous methylprednisolone 40–60 mg total daily dose (or equivalent) is recommended as first-line therapy for severe colitis requiring hospitalization. Steroid refractoriness is defined by minimal improvement in active disease by clinical and/or laboratory parameters after 3–5 days. A 2007 systematic review of 23 studies noted steroid therapy failure requiring colectomy in 27% of 1991 patients with severe UC colitis [18]. Prior to colectomy, rescue medical therapy is recommended with cyclosporine or infliximab for severe UC colitis [3]. A 1994 study demonstrated cyclosporine was efficacious for severe steroid-refractory UC; further studies showed 2 mg/kg/day to be an ideal dose [19–21]. Cyclosporine induces remission in 64–90% of cases, becoming a short-term bridge therapy, while co-administered slow-acting immunomodulators (azathioprine/6-MP) become effective [22–24]. Infliximab, an antitumor necrosis factor-α (TNF-α) agent, has been shown to be efficacious for UC and CD in multiple placebo-controlled trials, including ACT 1 and 2, and specifically effective in studies enrolling patients with moderate/severe steroid-refractory UC [25–28]. Recent trials including CONSTRUCT found no significant difference in clinical efficacy of cyclosporine compared to infliximab [29–31]. While initial response rates to rescue medical therapy are favorable, durable remission rates at 1 year are 30% with subsequent colectomy rates of 30–42% at 1 year [31, 32]. Response of rescue medical therapy should be decided after 5–7 days of therapy, and surgical intervention should be pursued if medical therapy has failed [20, 21, 33].

Intestinal Obstruction in CD

Fibro-stenotic CD phenotype is reported to be present in 10% of patients at initial CD diagnosis, while fibro-stenotic disease complications occur in 20–30% of CD patients overall [34]. Obstruction is the main indication for major abdominal surgery for CD in 24–40% of patients [35]. CD strictures result from intestinal fibrosis, which can occur at any time during the disease course and involve any intestinal segment, including the upper gastrointestinal tract. Fibrostenotic disease can cause intestinal obstructive symptoms of nausea and vomiting, abdominal distension, bloating, early satiety, and small-caliber stools or even paucity of stooling.

Two types of strictures in CD are identified: de novo and anastomotic. The most common sites of de novo strictures are the terminal ileum and the ileo-colonic region. Postoperative CD recurrence at the anastomosis occurs commonly after

intestinal resection, particularly in patients with an ileo-colonic anastomosis. Strictures may be further subdivided into inflammatory, fibrotic, and mixed types. Differentiating the composition of the strictures, specifically the relative proportions of inflammation and fibrosis, aids treatment decisions. This is accomplished using clinical history, imaging, and inflammatory markers such as fecal calprotectin and C-reactive protein (CRP). Endoscopy with biopsies are unable to measure the amount of fibrosis existing in the intestinal wall, as inflammation and fibrosis in CD are transmural. Cross-sectional imaging is the best diagnostic study for evaluating patients presenting with obstructive symptoms. Three imaging techniques have high accuracy for evaluation of strictures affecting the small bowel or the colon: for CT enterography (CTE), sensitivity is 89% and specificity 99%; for magnetic resonance enterography (MRE), sensitivity is 89% and specificity 94%; and for US, sensitivity is 79% and specificity 92% [36]. CTE and MRE are most commonly employed based on the center's expertise, but kidney dysfunction can restrict the use of these contrasted studies.

A multidisciplinary approach is necessary for management which should include acute care surgeons, colorectal surgeons, gastroenterologists, radiologists, pathologists, and dietitians. Initial management includes bowel rest, intravenous fluids with electrolyte replacement, and nasogastric decompression tube if the patient is vomiting or has significant abdominal distension. Corticosteroids are used for patients with strictures that have predominantly active inflammation, whereas predominantly fibrotic strictures are best managed by endoscopic or surgical approaches. Endoscopic balloon dilation (EBD) therapy can be pursued for short (<5 cm), non-complex, non-angulated strictures that are within endoscopic reach. Numerous case series have shown the short-term efficacy of EBD to be 70–87% [37]. A 2017 systematic review including 1463 patients demonstrated a clinical efficacy of 81% with a 2.8% complication rate, although 43% of patients required surgical resection during the 24-month follow-up period [38]. The efficacy rates stratified by location (small bowel vs. colon) are comparable, though EBD may be more effective for secondary compared to primary strictures [39]. The target dilation caliber is 16–20 mm. Dilation to at least 16–18 mm has been reported to be associated with less frequent maintenance dilations [40]. Endoscopic stricturotomy with needle knife has been shown to be effective at centers with technical expertise [41]. Strictures that are long, angulated, or associated with concurrent fistula and/or abscess should be considered for strictureplasty or surgical resection. Additionally, the presence of multiple strictures has been found to be a predictor for EBD failure and requirement of surgical intervention [42]. Ultimately, surgical intervention is required in up to 66% of patients with stricturing disease [43]. Indications and contraindication for strictureplasty are presented in Table 12.1 [44]. Early complications occur in up to 13% of patients, while late complications can occur in 26% of patients. A suggested algorithm is presented in Fig. 12.1 describing which patients should

Table 12.1 Indications and contraindications for strictureplasty

Indications
1. Fibrotic strictures within diffuse involvement of the small bowel
2. Previous extensive (>100 cm) small bowel resections
3. Short bowel syndrome
4. Recurrent strictures within 12 months of previous surgery
5. Strictures at previous anastomotic sites, particularly ileorectal or ileo-colonic
6. Strictures without phlegmon or septic fistula
7. Duodenal strictures, particularly in the retroperitoneal segment
Contraindications
1. Perforation of the small bowel, with or without peritonitis
2. Preoperative malnutrition (serum albumin <2.0 g/dL)
3. Fistula or phlegmonous inflammation at intended strictureplasty site
4. Bleeding from planned strictureplasty site
5. Suspicion for carcinoma
6. Likelihood of tension on closure of strictureplasty
7. Intended strictureplasty site next to segment requiring resection

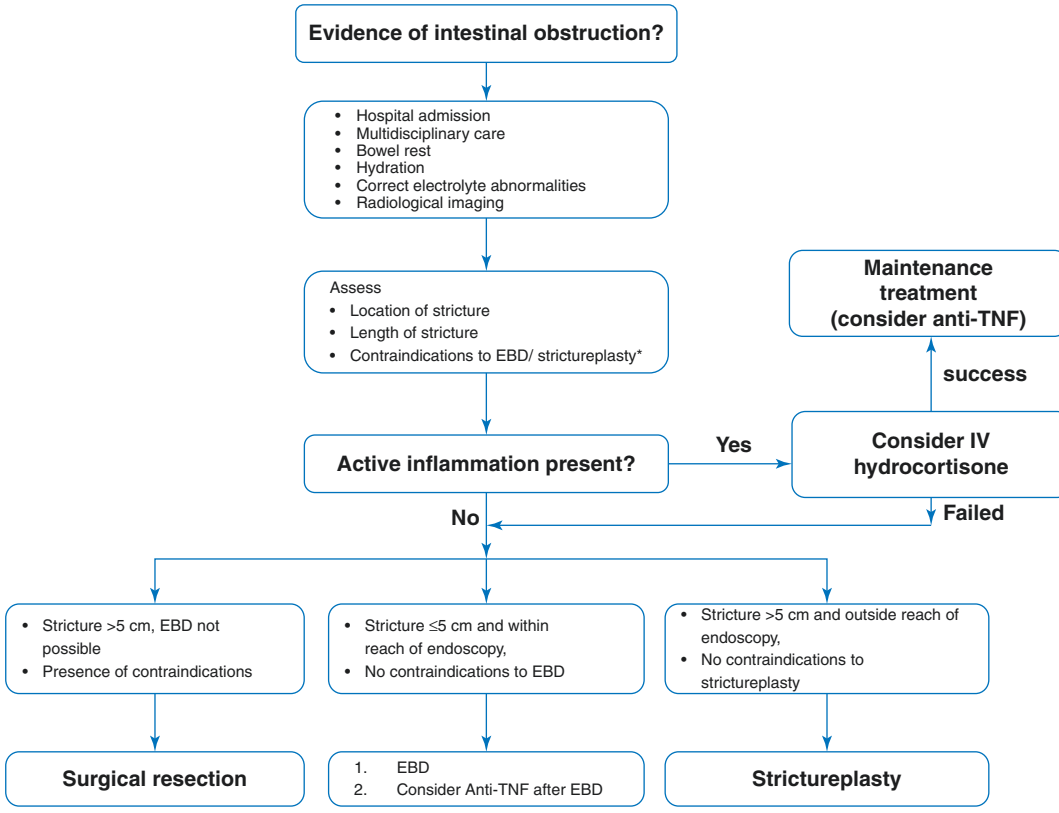

Fig. 12.1 Algorithm for management of intestinal strictures

undergo medical therapy, endoscopic therapy, or surgical therapy for CD-related strictures [44].

Penetrating Disease

Penetrating CD with fistula and/or abscess formation is common occurring at a rate of 3.8–7.5% per year [45]. Population-based studies report fistula formation in 50% of patients after 20 years of disease and intra-abdominal abscess in 25–30% of patients [46, 47]. Penetrating disease can be associated with intestinal stenosis which frequently causes increased proximal luminal pressure leading to upstream intestinal dilation followed by perforation with development of a fistula and/or abscess. Perianal disease occurs in 35–45% of patients with CD and may precede intestinal disease by years in 5–19% of cases [48–51]. Clinical manifestations of intra-abdominal abscess include fevers and/or chills, localized abdominal pain with peritoneal signs, and infrequently, a palpable mass.

CT abdomen and pelvis optimized with IV and oral contrast remains the standard diagnostic method [52, 53]. Initial management should include antibiotic therapy with adequate coverage of the typical polymicrobial bowel flora. Percutaneous drainage is now standard of care for abscess management as similar efficacy rates to surgical intervention have been demonstrated though with a less-invasive approach [54]. Abscess drainage may be guided by CT or ultrasound depending on location, depth of abscess within the abdominal cavity, and center expertise. The majority (80–90%) of abscesses are amenable to percutaneous drainage [55]. Contraindications include intestinal perforation, generalized peritonitis, or unsafe window to pass needle into the abscess [55]. Abscesses <3 cm in size can be aspirated completely without need of drain placement [47]. Figure 12.2 shows a proposed algorithm for

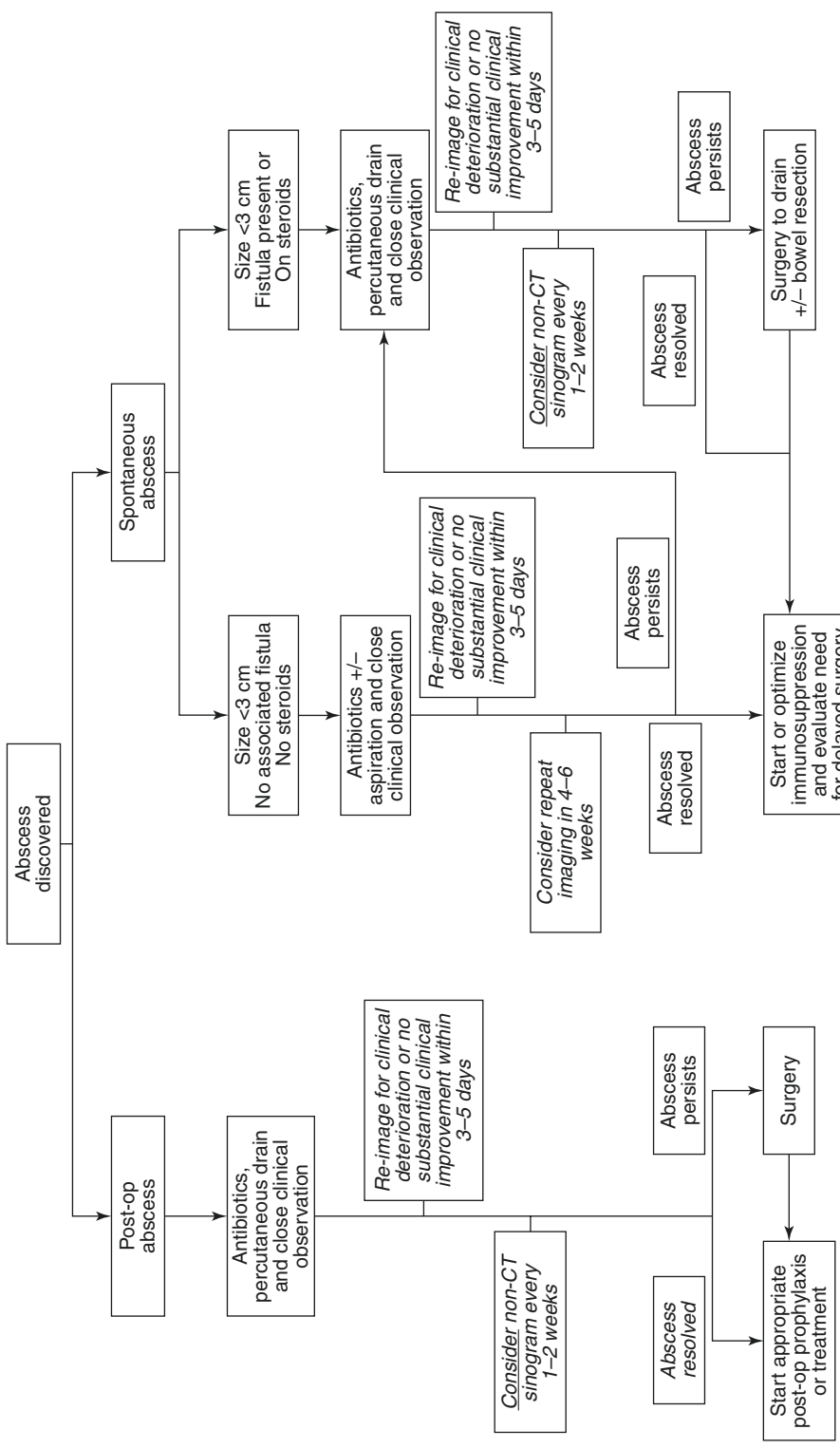

Fig. 12.2 Algorithm for management of intestinal abscess

management [47]. Drain removal can be considered when drain output decreases to 20 ml/day or less, while persistently high drainage should prompt consideration for intestinal perforation/fistula. If an abscess recurs (recurrence rates are reported to be 1–9%), repeat percutaneous drainage should be considered as it has shown to be successful in 91% of cases of recurrent abscess [54, 56]. Surgical management is indicated in cases with contraindications to percutaneous drainage, previous failed drainage attempt, and multiloculated collections or if a concurrent downstream stricture or fistula is present.

Perianal disease categorically includes fissure, fistula, abscess, and/or stenosis formation in the anorectal or perianal area. Clinical manifestations may include anal pain, painful defecation, and/or purulent discharge. Perianal fistulas are classified by their anatomic extension and location to the anal sphincter complex. Entero-cutaneous fistulas (ECFs) led to leakage of stool from a skin perforation and are classified by their output as high output (>500 mL/24 hours) and low output (<200 mL/24 hours).

MRI of the pelvis is favored for perianal disease assessment as it is superior in delineating involvement of key anal structures. MRI is as an adjunct to examination under anesthesia (EUA), which remains the standard for perianal disease evaluation and treatment. Endoscopic ultrasound (EUS) can be used as well with high sensitivity to locate perianal fistulas [57]. Antibiotics may be helpful in induction therapy and prevention of fistulous disease-associated abscess formation [58]. The most common antibiotic regimen is ciprofloxacin and metronidazole. Infliximab was demonstrated in a 1999 randomized, placebo-controlled study to be efficacious for initial fistula closure with success in 55% of patients receiving infliximab compared to 13% of patients in the placebo arm [59]. ACCENT II trial showed sustained fistula closure with maintenance infliximab therapy in 46% of patients compared to 23% in placebo group at 54 weeks follow-up [60]. Seton placement during EUA combined with infliximab has been shown to be superior to either as monotherapy in perianal disease [61]. Two randomized placebo-controlled studies showed antibiotics in combination with infliximab or adalimumab were more effective than biologic therapy alone initially (71% vs. 47% in adalimumab trial); however, the superior clinical response did not remain after antibiotics were stopped [62, 63].

High-output ECFs require initial volume resuscitation, electrolyte repletion, sepsis control if present, and then matching daily output with intake. Nutritional support is a necessity with enteral nutrition if able or TPN as fistula closure rates double in patients receiving supplemental nutrition compared to those who are not [64]. While 27–38% of IBD-related ECFs spontaneously close, 50% require definitive surgical closure and 50% recur.

Conclusion

In summary, the natural history of UC is frequently complicated by severe colitis and at times fulminant colitis or toxic megacolon. Complications of CD include severe colitis, fibro-stenotic or inflammatory intestinal obstruction, and penetrating diseases of intra-abdominal abscess, fistula, and perianal disease. Medical therapy including corticosteroids and biologic therapies has limited effectiveness, and surgical intervention is frequently indicated. Successful management of these complex IBD complications requires a carefully planned multidisciplinary approach including surgeons, gastroenterologists, radiologists, pathologists, and dieticians.

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