The Management of Intestinal Penetrating Crohn's Disease

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Crohn's disease (CD) leads to the development of complications through progressive uncontrolled inflammation and the transmural involvement of the bowel wall. Most of the available literature on penetrating CD focuses on the perianal phenotype. The management of nonperianal penetrating complications poses its own set of challenges and can result in significant morbidity and an increased risk of mortality. Few controlled trials have been published evaluating this subgroup of patients for clinicians to use for guidance. Utilizing the available evidence, we review the epidemiology, presentation, and modalities used to diagnosis and assess intestinal fistulas, phlegmons, and abscesses. The literature regarding the medical, endoscopic, and surgical management options are reviewed providing physicians with a therapeutic framework to comprehensively treat these nonperianal penetrating complications. Through a multidisciplinary evidence-based approach to the complex sequela of CD outcomes can be improved and patient's quality of life enhanced.

Keywords: Crohn's disease, fistula, phlegmon, abscess

Crohn's disease (CD) is a progressive inflammatory disease affecting any portion of the gastrointestinal tract in a segmental pattern and involving the entire thickness of the bowel wall.[1] Progressive uncontrolled inflammation can lead to the development of complications such as strictures, fistulas, and abscesses, which are present in approximately 20%–30% of patients at the time of diagnosis.[2,3] The transmural involvement of the bowel wall can result in the development of sinus tracts that once penetrating the serosa can result in fistulas, or abnormal connections between 2 epithelialized surfaces. The manifestations of fistulas depend upon their sites of origin and termination. Sinus tracts that do not terminate on another epithelialized surface may present as a sealed off perforation that develops into an ill-defined inflammatory mass known as a phlegmon or, if infected, into an abscess.[4] Penetrating CD can be anatomically divided into 2 groups, fistulas originating from within the abdomen and those that involve the perianal region and perineum, with 35%-40% of patients with CD having some type of fistula present.[5–7] This review will focus on the management of non-perianal penetrating Crohn's disease (NPPCD) and its complications (Fig. 1).

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EPIDEMIOLOGY, CLASSIFICATION, AND PRESENTATION

The incidence and prevalence of NPPCD vary with referral-based studies demonstrating a higher incidence than population-based studies.[8] Whereas referral-based studies have calculated a lifetime risk of developing a fistula ranging from 20%–40%, this figure may not reflect the actual prevalence in the population.[9–11] Two inception cohorts, respectively evaluating 169 adults and 913 children, found that 35% of adults developed 1 fistula over a 25 year period, with 45% being not perianal; whereas only 2.6% of children developed fistulas, of which 83% had an internal penetrating phenotype.[6,12] This translates into approximately 16% of adults and 2.2% of children having NPPCD. There is a strong association between perianal and non-perianal fistulizing disease; 1 population-based cohort found up to 14% of patients with isolated perianal disease, approximately 10% with only luminal fistulas, whereas almost 8% had both phenotypes.[13] This association is stronger in Crohn's colitis than in cases limited to the small bowel.[14] Complications of fistulas or sinus tracts such as phlegmons and abscesses are reported in up to 10%–28% of patients with CD and are present in 3.4% and 4.2% of patients with CD undergoing cross-sectional imaging, respectively.[15–17] They are common causes of hospitalization representing 2.7% of all CD-related admissions.[18]

Non-perianal fistulas are classified based upon their anatomic involvement as either internal or external and based on the organ or structure where they originate and terminate (Fig. 2). External fistulas terminate on the skin. Their site of termination can be influenced by previous surgeries, either following the surgical plane and emerging at the site of the surgical scar or in virgin abdomens following embryonic pathways like the ligamentum teres out of the umbilicus.[19] Enterocutaneous fistulas (ECF) can be further classified based on output, which can have both clinical and prognostic

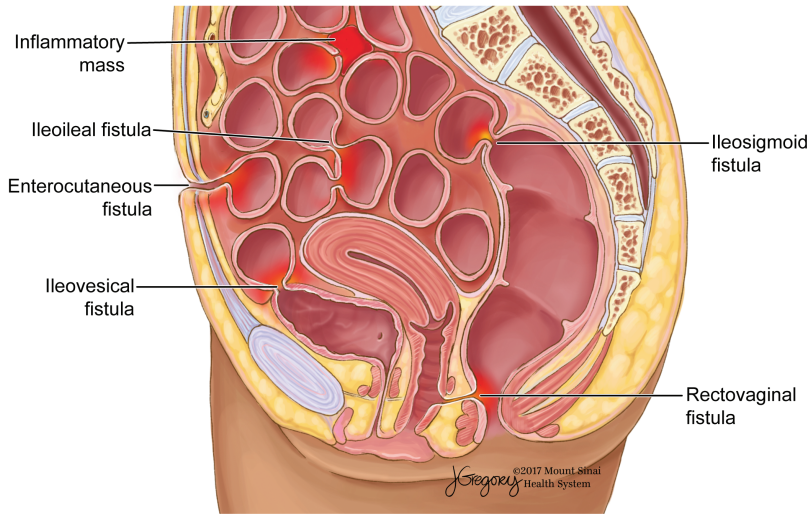

FIGURE 1. Intestinal penetrating complications of CD.

significance, as having <200 ml, 200–500 ml, or >500 ml of output per day.[20] Non-perianal fistulas are most commonly enterocolic (29%), enteroenteric (18%–24%), or specifically enterosigmoid (17%–26%). Other organs including the duodenum, urinary bladder, skin, vagina, or stomach may be involved with varying frequency (Table 1).[6,15,21–25]

The clinical presentation of NPPCD varies depending upon the organs involved and whether or not phlegmons or abscesses are present. The most common locations for enterocolic and enteroenteric fistulas are, respectively, ileosigmoid, often with the sigmoid spared from intrinsic disease, and ileoileal. Most of these fistulas are asymptomatic; however, if long segments of bowel are bypassed, diarrhea, malabsorption, or weight loss can occur.[26–28] Cologastric fistulas commonly originate in the distal transverse colon and involve the greater curvature of the stomach. They may be asymptomatic or can result in malnutrition, nausea, feculent vomiting or halitosis, weight loss, borborygmi, and diarrhea. Cases of dehydration and steatorrhea have been reported and physical examination may reveal a mass.[29,30] Likewise, coloduodenal fistulas arise from the proximal transverse colon and involve the third portion of the duodenum. Fistulas involving the duodenum and stomach usually originate from another point of origin and terminate at these sites.[23,31]

An ECF presents with leakage of intestinal contents onto the skin surface with associated inflammatory skin changes and in the setting of high output can present with dehydration, malabsorption, or electrolyte abnormalities.[32] Approximately three-quarters of these are postoperative fistulas and more than half originate from the small intestine.[33]

Enterovesical fistulas arise from the ileum in up to 80% of cases. They can present with pneumaturia in 68%–77% of cases, a symptom often requiring solicitation to identify, dysuria (64%), fecaluria (28%–51%), increased urinary frequency (45%), urinary tract infections (32%–45%), and abdominal pain (33%). Additionally, up to 9% of patients will report urine per rectum.[34,35] They most often occur in men, are unilateral, and right sided.[34,36] Women are likely protected by the barrier created by the uterus and vagina.[35]

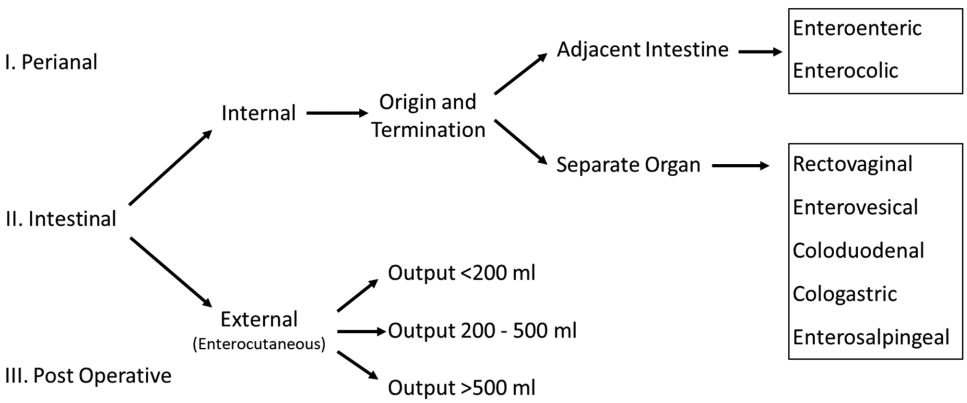

FIGURE 2. Schematic for the classification of intestinal fistula.

TABLE 1: Relative Frequency of Reported Non-Perianal Fistulas by Location[6,15,21–25]

Anatomic Location	Frequency (%)[a]
Enterocolonic Fistula	29
Enterosigmoid Fistula	17–26
Enteroenteric Fistula	18–24
Enterocutaneous Fistula	6–16
Rectovaginal Fistula	4–9
Enterovesical Fistula	2–8
Coloduodenal Fistula	5
Colosigmoid Fistula	2
Enterosalpingeal Fistula	2
Cologastric Fistula	<1

[a]Adds up to greater than 100% due to the possibility of multiple fistula types present in a subject

The rectum and vagina are anatomically opposed to each other with low rectovaginal fistulas adjoining the distal third of the rectum to the lower half of the vagina, and high rectovaginal fistulas located between the middle third of the rectum and the upper half of the vagina. These often present with the passage of stool or gas through the vagina, purulent or foul-smelling discharge, or painful intercourse.[37] Phlegmon or abscess, which can develop with or without an associated fistula, are commonly adjacent to a diseased bowel segment in the right abdomen that is most likely near a site of prior resection.[38] They can result in abdominal pain, fever, or a palpable mass in one third of patients. Abscesses involving the psoas muscle can present with a limp and pain in the flank, hip, thigh, or knee.[39]

ASSESSMENT OF INTESTINAL PENETRATING COMPLICATIONS OF CD

Imaging is the primary modality of assessment of NPPCD with endoscopy and surgery providing adjuvant data (Table 2). Abdominal ultrasound, using various techniques, can accurately assess the distribution and length of bowel involvement in CD. A fistula appears as a hypoechoic tract with or without internal debris. Six studies comprising over 500 patients evaluated the diagnostic value of ultrasound; 4 of them used surgical specimens as their reference standard. The sensitivity and specificity of ultrasound were 70.1% (95% CI, 59.7–80.6%) and 95.6% (95% CI, 92.5%-98.8%), respectively.[40–46] Additionally, ultrasonography is used to evaluate intraabdominal abscesses that appear as roundish anechoic lesions with irregular walls.[42] Abscesses will often have peripheral flow on color doppler, whereas phlegmons will lack internal color doppler signals, although in clinical practice these features can be difficult to differentiate.[47,48] Ultrasound's diagnostic value in detecting intraabdominal collections has been evaluated in 6 studies, yielding a sensitivity and specificity of 85.6% (95% CI, 83.3%–88%) and 94.5% (95% CI, 87.9%–100%), respectively.[40–46]

TABLE 2: Effectiveness of Imaging Modalities for Assessing CD Complications

Imaging Modality	Fistula		Inflammatory Mass	
	Sensitivity	Specificity	Sensitivity	Specificity
US	70.1%	95.6%	85.6%	94.5%
CTE	81.0%	95.3%	84.2%	92.8%
MRE	69.9%	94.5%	90.5%	98.4%

Computed tomography enterography (CTE) and magnetic resonance enterography (MRE) are the preferred imaging modalities for the assessment of complications of internal penetrating disease. These procedures offer high sensitivity and specificity, ease of access, and the ability to provide three-dimensional characterization of the complication. This latter feature allows precise localization within the abdomen and accurately identifies the involved structures. A recent meta-analysis evaluating 6 studies, comprising 290 patients, calculated the pooled sensitivity of MRE and CTE for extraenteric complications such as fistulas and abscesses. For MRE, the sensitivities for fistula and abscess detection were 69.9% (95% CI: 53.7–83.1) and 90.5% (95% CI: 69.6–98.8), respectively; whereas the corresponding specificities were 94.5% (95% CI: 89.8–97.4) and 98.4% (95% CI: 93.5–99.9) (Fig. 3A, B). Comparatively, CTE had a sensitivity of 81.0% (95% CI: 65.9–91.4) and 84.2% (95% CI: 60.4–96.6) and specificity of 95.3% (95% CI: 90.8–98.0) and 92.8% (95% CI: 85.7–97.0), for detecting these respective complications (Fig. 3C, 3D).[49] Both MRE and CTE appear equally efficacious at detecting fistulas (14.2% vs 17.1%; Incremental Yield -3%, $P = 0.42$) and abscesses (16.7% vs 14%; Incremental Yield 4%, $P = 0.56$).[49–54]

Additional imaging modalities beyond standard MRE and CTE can be employed if further characterization of a fistula is needed or if its presence is suspected but not visualized via these modalities. Whereas fistulograms have been largely replaced by CTE and MRE, they can provide additional characterization of ECF if needed.[55] They are performed by injecting contrast agents into the cutaneous opening to demonstrate its main axis. Further investigation can be done using an angiographic catheter and guidewire under fluoroscopy to delineate the fistula course and any pockets or cavities.[56] For rectovaginal fistulas that are suspected but not visualized on CTE or MRE, proctography with barium enemas or vaginography with instillation of contrast in the vagina aided by an occluding vaginal balloon can be performed, with vaginography demonstrating superior sensitivity for fistula detection.[57] Enterovesical or colovesical fistulas are best evaluated on CTE or MRE with a diagnostic accuracy close to 100%.[58,59] Whereas cystography and barium enemas have a low yield, cystoscopy can be performed to establish the diagnosis and identify the site in up to 60% of cases.[34,60,61]

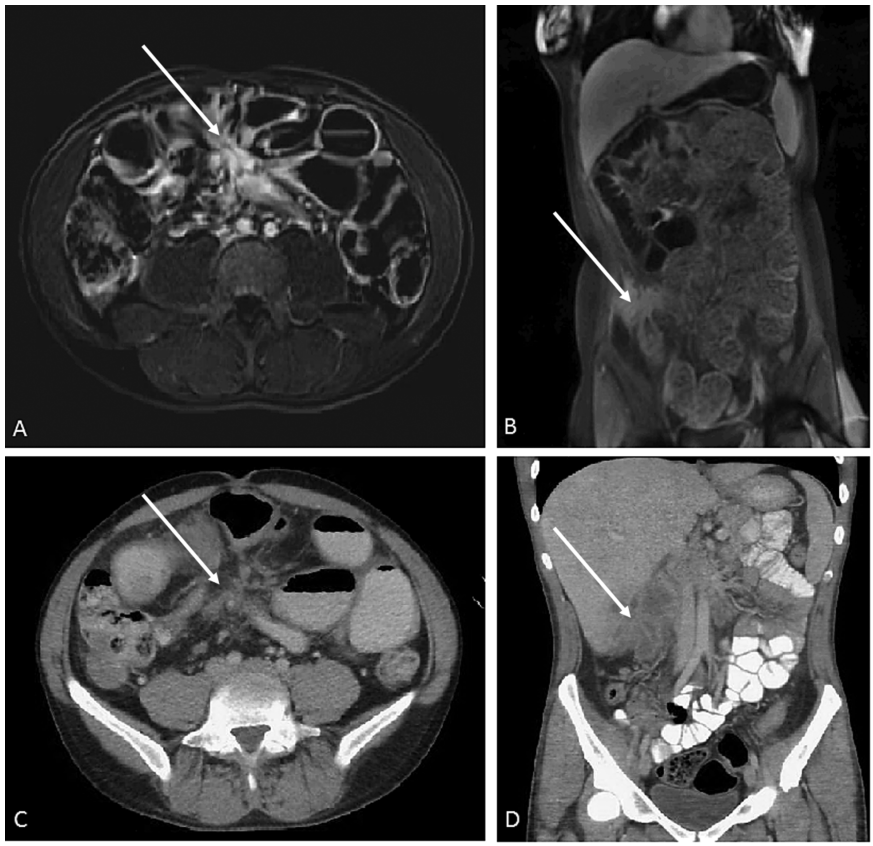

FIGURE 3. Cross-sectional imaging of enteroenteric fistulas and inflammatory masses in patients with CD. A, Enteroenteric fistulas visualized on MRE B, Inflammatory mass (phlegmon) adjacent to the terminal ileum seen on MRE. C, Enteroenteric fistulas visualized on CTE. D, Inflammatory mass (abscess) below the liver seen via CTE.

For small pinpoint fistulas, not visible with standard imaging studies, use of a dye can assist in recognizing the presence of a tract. To identify rectovaginal fistulas, methylene blue dye or indigo carmine can be mixed with lubricating gel and massaged into the anterior rectal wall; or, alternatively, a saline enema containing methylene blue dye can be instilled into the rectum. Leaking of blue dye from the vagina confirms the presence of a tract. Similarly, a dye can be ingested or added to enteric feeding or instilled into the bladder allowing for determination of a fistula tract if drainage is evident from another location.

GENERAL MEDICAL MANAGEMENT PRINCIPLES

The appropriate treatment plan for intestinal fistulas depends on their likelihood of responding to conservative or medical management. A study by Campos et al evaluated prognostic factors for spontaneous closure with general and nutritional care. Spontaneous closure was 5-fold lower if there was a nonsurgical cause of the fistula, 3-fold greater for ECFs with low output, and significantly lower if infectious complications were present, whereas the organ of origin was not a significant predictor.[62] In other studies, tracts less than 2 cm, high fistula output, fistula chronicity, distal obstruction, poor nutritional status, and the presence of comorbidities have been associated with a lower chance of spontaneous closure, especially with cutaneous points of termination.[63–65] However, the rates of truly "spontaneous" (placebo-treated) fistula closure remain low, ranging from 6%–13%, although these figures include both perianal and non-perianal fistulas.[66–68]

Upper gastrointestinal fistulas—such as cologastric, coloduodenal, colojenjunal, or ileojejunal—are often high output. The same problem may characterize ECFs. Initial conservative management for these high-output fistulas includes intravenous hydration and correction of electrolyte abnormalities.[55] Somatostatin, or its analogues such as octreotide, also can be used to decrease output.[69,70] These hormonal treatments have been studied mostly in ECFs, with a recent meta-analysis demonstrating that they may lead to decreased duration of fistula drainage and shorter hospitalization.[71] For additional reduction of diarrhea or drainage from high-output fistulas, loperamide, diphenoxylate/atropine, or tincture of opium can provide symptomatic relief. Furthermore, proton pump inhibitors also may reduce output from ECFs.[72]

Malnutrition from high-output ECFs or internal fistulas that bypass large segments of bowel can develop both from loss of ingested nutrients and from inflammation or infection

resulting in increased energy demands. Correction of malnutrition is needed as it can impair wound healing and increase postoperative infections or complications.[73–75] Both total parenteral nutrition (TPN) and exclusive enteral nutrition are used for nutritional support and have been found to be equally effective in inducing remission in CD without pharmacologic support.[76] They should be used primarily to improve the nutritional status of a patient, although they also may act as an adjuvant therapy to treat non-perianal fistulizing disease through decreased fistula output.[77]

Enteral nutrition should be favored over TPN as it is safer and demonstrates trophic effects on the intestinal mucosa, however, with high output proximal ECFs the latter may be warranted. It may also reduce inflammation by altering the gut microbiota, promoting epithelial healing, affecting the differentiation of stem cells, and promoting a global anti-inflammatory effect.[78–80] A recent prospective observational study demonstrated significant rates of fistula healing with 12 weeks of exclusive enteral nutrition, with 75% of patients with ECFs noting complete closure.[81] The benefits of TPN in fistula closure likely stem from its reduction of gastrointestinal secretions by up to 50% and its promotion of protein synthesis. Unlike enteral nutrition, however , it is associated with increased bacterial translocation due to small intestine mucosal atrophy and it can be complicated by line-associated infections.[77,82–85] Despite these risks, TPN has been associated with spontaneous closure of non-perianal fistula, with some studies demonstrating up to a 70% closure rate of ECFs.[86,87]

PREBIOLOGIC MEDICAL MANAGEMENT OF INTESTINAL FISTULAS

In selected patients, medical therapy can be used to treat fistulizing disease or improve its severity before a surgical intervention (Table 3). However, most of the published literature focuses on the treatment of perianal CD, with few studies and no randomized controlled studies dedicated to the intestinal phenotype.[88] Antibiotics are well documented to improve or induce closure of perianal fistulizing disease, but there are no controlled studies of their efficacy in healing non-perianal fistulizing disease.[89,90] A study from the Mayo Clinic demonstrated control of symptoms and prevention of surgery in 1 of 5 patients with enterovesical fistulas. However, with increasing antibiotic resistance and rising rates of *Clostridium difficile* infections, their use in non-perianal CD should be limited as an adjuvant agent to control or reduce infectious complications, such as cystitis from enterovesical fistulas.[35,89]

Azathioprine and mercaptopurine (MP) have demonstrated efficacy in treating fistulizing disease, although most studies include both perianal and non-perianal fistulas in their analysis. A meta-analysis including 5 randomized placebo-controlled trials that characterized response as decreased fistula drainage or complete healing found that 54% of patients in the treatment group responded compared to 21% in the placebo group, with an odds ratio of 4.44 favoring healing.[91,92] In an uncontrolled study by Korelitz and Present, 39% of fistulas were noted to close completely, whereas 26% showed signs of improvement. The authors noted that abdominal wall and enteroenteric fistula responded best, with a mean time to response of 3.1 months.[93] In one series of 8 patients with enterovesical fistulas, treatment with MP resulted in symptomatic tolerance of the fistulas. Another cohort of 59 patients with internal fistulas identified 16 fistulas involving the bladder. Azathioprine resulted in the elimination of pneumaturia in 3 of the affected patients.[28,89]

Similarly, rectovaginal and cologastric fistulas have been noted to improve with thiopurine use. Six patients with rectovaginal fistulas were treated with thiopurines; half noted improvement in drainage and induration.[92,94] One of the 6 cologastric fistulas reported at The Mount Sinai Hospital in a series spanning 3 decades completely responded to MP, with another intermittently improved.[23] There are limited data about methotrexate in non-perianal fistula treatment. In 1 case series of 7 patients with abdominal wall, bladder, rectovaginal fistulas, or rectovaginal with perianal fistulas, 2 patients were noted to have a complete response, 2 a partial response, and 3 no response to therapy.[95]

Calcineurin inhibitors such as tacrolimus and cyclosporine may be effective in the treatment of non-perianal fistulas, although the data are from uncontrolled studies, and in light

TABLE 3: Medical Therapies for the Treatment of Non-Perianal Fistulas in CD

Medication	Therapeutic Effect and Treatment Recommendation
Antibiotics[35,89]	Limited efficacy data regarding treatment effect. Recommended for control of infectious complications.
Azathioprine[23,28,89,91–94,108] Mercaptopurine	The limited data available in isolated non-perianal fistulizing disease demonstrates efficacy. Favored as an adjuvant therapy to anti-TNF agents.
Cyclosporine[68,96–100] Tacrolimus	The limited data available in isolated non-perianal fistulizing disease demonstrates efficacy. Side effects limit long- term use and tolerability. Not recommended as a first- line agent.
Infliximab[105,106,111–116] Adalimumab Certolizumab	The limited data available in isolated non-perianal fistulizing disease demonstrates efficacy. Randomized controlled trials and uncontrolled studies of infliximab that include ECFs, rectovaginal, and enterovesical fistulas demonstrate treatment effect supporting the use of infliximab as a first- line agent. There is less evidence supporting the use of adalimumab and certolizumab.

of associated adverse events should be reserved for refractory patients. A randomized placebo-controlled trial evaluating the efficacy of tacrolimus in the treatment of fistulizing CD demonstrated that 43% of patients with fistulas treated with tacrolimus improved compared to 8% of placebo-treated patients ($P = 0.004$). However, the majority of these patients had perianal fistulas. The 3 patients with abdominal fistulas treated with placebo and the 1 patient with both an abdominal and perianal fistula treated with tacrolimus failed to improve.[68] In an uncontrolled study including 6 patients with steroid refractory CD and fistulas, 2 non-perianal fistulas completely healed with tacrolimus.[96] In another study, 3 patients with ECFs and 3 with rectovaginal fistulas refractory to infliximab were treated with tacrolimus; 2 of the ECFS and 1 of the rectovaginal fistulas completely healed.[97]

Uncontrolled series have additionally demonstrated the efficacy of cyclosporine in intestinal fistulizing CD. One study of 5 patients with a total of 12 fistulas (5 enterovaginal, 3 perianal, 3 enterocutaneous, and 1 enterovesical) were treated with intravenous cyclosporine with complete resolution documented in 10 of the fistulas after a mean of 7.9 days, though 2 enterovaginal and 1 ECF subsequently reoccurred.[98] Similar closure rates were reported in 2 other small case series. One study evaluated 16 patients of whom 4 had ECFs and 2 had rectovaginal fistulas, whereas the other included 9 patients of whom 2 had enterocutaneous and 2 had enterovaginal fistulas. Whereas the remainder of the patients had perianal fistulas, the overall response rates in these 2 studies were 88% and 78%.[99,100]

MANAGEMENT OF INTESTINAL FISTULAS WITH ANTI-TNF ALPHA AGENTS

Biologic therapy, specifically anti-tumor necrosis factor (anti-TNF) alpha agents such as infliximab, are the most effective at treating fistulizing disease. Studies of non-perianal fistulas treated with infliximab are limited and demonstrate wide variability in efficacy, with internal and external fistula responses in some studies ranging from 14%–25% and 50%, respectively.[101–104] Randomized controlled studies evaluating the use of infliximab primarily include perianal fistulas, limiting their applicability to this review. In a landmark randomized, double-blind, placebo-controlled trial, Present and colleagues showed infliximab to be efficacious in the treatment of 94 adults with abdominal or perianal fistulas, although only 10% had an abdominal location. The resolution of draining fistulas occurred in 46% and 13% of patients in the treatment and placebo groups, respectively ($P = 0.001$), yet it is difficult to generalize these findings to non-perianal fistulas as the effect on the subgroup with abdominal fistulas was not provided.[66]

Similarly, infliximab was shown to be efficacious as a maintenance agent in 282 patients with perianal, enterocutaneous, or rectovaginal fistulas with associated ECFs. At week 54, 19% in the placebo group and 36% in the infliximab maintenance group had no draining fistulas ($P = 0.009$).[105] Whereas most of the patients in this study had perianal fistulizing disease, post-hoc analysis was conducted to determine infliximab's efficacy in the subgroup of 25 women with 27 draining rectovaginal fistulas. After induction, 44.8% of rectovaginal fistulas were closed by week 14 with the duration of closure longer in the infliximab maintenance group compared to the placebo group (median, 46 weeks vs 33 weeks, respectively).[106] Furthermore, the addition of a thiopurine or methotrexate to infliximab may provide additional benefit in treating fistulas, although this suggestion is based on small uncontrolled studies.[107,108]

There are limited data for the efficacy of other anti-TNF agents in the treatment of non-perianal fistulizing disease, since most studies describe a mixture of fistula types.[109,110] Adalimumab's impact on fistulas was assessed in 3 placebo-controlled trials that included few non-perianal fistulas. The CLASSIC I trial included 32 patients with either perianal or ECFs and found no difference in the rates of fistula improvement and remission between the treatment and placebo groups at week 4, a very short observation period.[111] The CHARM trial evaluated adalimumab's efficacy as a maintenance agent and found that 33% and 13% of perianal or ECFs were closed at week 56 of therapy ($P = 0.16$ vs placebo); moreover, those achieving closure by week 26 continued to have closure through week 56.[112] Furthermore, 90% of these patients maintained fistula healing for an additional year of open-label treatment.[113]

Data on certolizumab are very limited, with most patients (55/58) in the PRECiSE 2 study having perianal fistulas. Whereas certolizumab maintenance therapy did not result in a significant increase in the percent of patients with at least 50% fistula closure at week 26, 36% of patients in the certolizumab group and 17% of patients in the placebo group had 100% fistula closure ($P = 0.038$).[114] The limited sample size of non-perianal fistulizing disease in anti-TNF randomized control trials does not allow confident extrapolation of the efficacy of these agents to the intestinal fistulizing phenotype.

The GETAID group performed a retrospective study looking at anti-TNF therapy in the treatment of 48 patients with ECFs. Approximately 78% of patients had received infliximab, 10% had received adalimumab, and the remainder had received infliximab followed by adalimumab; the cohort was followed for a median of 3 years. One third of patients had complex fistulas whereas 23% had high output fistulas requiring ostomy bags. Complete ECF closure was achieved in 33% of patients, with multivariable analysis finding closure associated with the absence of multiple tracts or stenosis.[115] A metaanalysis of 9 studies evaluating anti-TNF therapy alone or in combination with other agents to treat rectovaginal fistulas described complete response in 41% of fistulas, partial response in 21.8%, and no response in 17.2%. The same study also evaluated 5 publications exploring enterovesical fistula treatment with anti-TNF agents noting complete response in 57.1% of fistulas, partial response in 35.7%, and no response in 7.1%.[116]

MEDICAL MANAGEMENT OF PHLEGMONS

Noninfected, ill-defined inflammatory masses or phlegmons are frequently managed with traditional therapy consisting of either treatment with antibiotics and resection or drainage of any collections.[4] However, since these complications represent an inflammatory process, the use of immunosuppressive medications to treat these abdominal masses has been explored. In an uncontrolled, retrospective study by Felder et al, the use of steroids was not found to be contraindicated when the steroids were combined with antibiotics, which the majority of patients in this study received. In this series of 24 patients with CD with abscess or phlegmon, 15 of the patients who received steroids experienced complete resolution. Although 14 of the patients required surgery, it was performed electively and at least 8 patients never required resection during the 40-month follow-up.[117]

Another study of 13 patients evaluated the efficacy of anti-TNF therapy in CD complicated by a phlegmon. On imaging, 12 of the patients were found to have an abscess in addition to the phlegmon and 4 also had enteroenteric or enterocolic fistulas. All 13 patients were started on antibiotics before anti-TNF therapy and 11 of them continued the antibiotics after TNF initiation. There was a median follow-up of 2.3 years with no patients developing new infections or abscess exacerbations and all achieving clinical remission. Eleven patients never required surgery and in the 2 that did, the operation was unrelated to the phlegmon or abscess. Although small, these studies highlight the safety of utilizing immunosuppressive medications in the setting of phlegmons, as long as concomitant antibiotics are used.[4]

MEDICAL MANAGEMENT OF ABSCESSES

The management of intraabdominal or pelvic abscesses usually involves a combination of medical therapy with either percutaneous or surgical drainage. Medical therapy with antibiotics against enteric flora should be initiated and continued after drainage, with the duration dictated by the completeness of the drainage and the subsequent clinical response.[17] Factors associated with failure of antibiotics are an abscess that has been previously drained, one that is >3 cm, the concomitant use of immunosuppression, associated upper GI disease, and associated fistula.[17,118,119] Additionally, active ileal disease has been identified in 1 study as a risk for abscess reoccurrence.[120] Although all these factors militate against the success of medical therapy, the fact remains that up to two thirds of abscesses resolve with antibiotics in the appropriate setting.[119,121] In patients where primary medical therapy is chosen, close clinical follow-up to assure improvement is recommended with a low threshold for repeat imaging. Depending on the risk factors for failure of antibiotics, repeat imaging in 4–6 weeks can be considered (Fig. 4).[122]

Once an abscess is controlled by antibiotics or drainage, the initiation or optimization of immunosuppressive therapy needs to be considered. There are few studies evaluating the safety of initiating immunosuppressive therapy in the presence of an abscess, although once the infection is controlled, this treatment should be safe. In addition to the previously mentioned study by Felder et al, a study by Sahai and colleagues reported the safety of using steroids in 27 patients with abscesses who were also treated with antibiotics and percutaneous drainage.[123] Whereas these studies are not evidence proposing initiating steroids in the setting of an abscess, they highlight that they can be safely used. The success of posttreatment medical therapy with biologics or immunomodulators in preventing reoccurrences is not clearly established, as variable results have been reported.[119,120,124] Bermejo and colleagues followed 77 patients who started thiopurines, 12 who started biologics, and 39 who continued their current therapy after abscess resolution.[119] No correlation was found between reoccurrence and medical treatment. In contrast, Nguyen et al showed that initiation of anti-TNF agents after abscess resolution reduced the chance of reoccurrence compared with no therapy (HR, 0.08; 95% CI 0.02–0.36; $P < 0.001$).[120] Nonetheless, the presence of a perforating complication such as an abscess demands aggressive, surgical, radiologic, and/or medical interventions, to control the underlying disease and reduce future complications.

ENDOSCOPIC MANAGEMENT OF NON-PERIANAL FISTULAS

The treatment of penetrating CD has expanded to include a growing trove of endoscopic management options, and although the data are still limited for newer advanced endoscopic technologies, their success as primary nonsurgical and definitive modalities is promising. Before endoscopy the patient should be optimized for the procedure with correction of fluid and electrolyte derangements and control of any infections with antibiotics. There are currently 3 main endoscopic techniques for fistula closure, including endoscopic clipping [(eg, over-the-scope (OTS) and through-the-scope clips (TTS)], endoscopic suturing, and filling agents (eg, sealants and plugs). The goal is to close the feeding or upstream orifice of the fistula, whereas keeping the downstream orifice of the fistula open to prevent creation of a closed space. Through diversion of the fecal stream, the tract should heal over time so long as the inflammatory burden of disease is also quiescent. Although endoscopic closure of fistula in patients without IBD is extensively described in the literature, the successes cannot be extrapolated to CD since these tend to be longer, more complex fistula with fibrotic tissue that, in general, make closure less successful.

Data are markedly limited for the success rates of TTS and OTS clips in closure of NPPCD, with no published case series identified on literature review as of July 2017. Inflammatory margins, chronicity and epithelialization of the fistula tract, fibrosis at the orifice, and larger defects (>20 mm) are reasons for failure of the OTS clip in CD-related fistula.[125–127] Argon

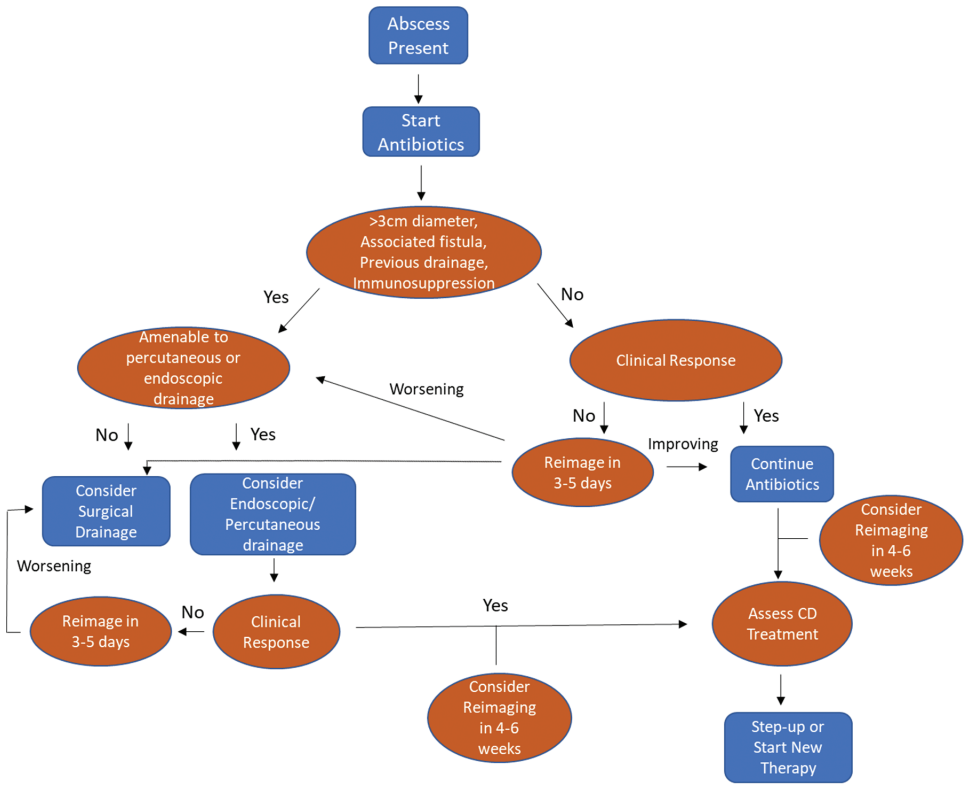

FIGURE 4. Algorithm for the evaluation and management of intraabdominal abscesses in patients with CD.

plasma coagulation or other cauterization to debride the edges of the fistula orifice and promote granulation tissue may facilitate closure, but there are no data supporting this technique in CD fistula closure specifically.[128] Closure of acute anastomotic leaks related to CD surgery, on the other hand, have had higher anecdotal success.[125] Whereas ECFs in CD are generally appropriate indications, OTS clips should be used cautiously for the closure of rectovaginal, rectovesical, or pouch-vaginal/vesicular fistula because of the thin apposing wall. OTS clips are safe with little risk of complication related to placement of the device itself; however, more data are needed before they can be routinely recommended for the management of CD-related fistula.[129–132]

Data are variable regarding the use of filling agents, such as fibrin sealant, bioprosthetic plugs, and even topical application of stromal and stem cells, for the treatment of perianal CD. There are currently no data reporting the use of these agents in NPPCD and their use is not advocated for this indication.

In 1 large multicenter study evaluating endoscopic suturing, 40 patients with gastrointestinal fistula were included with no details provided with respect to IBD history or fistula chronicity, with over 37% having a prior endoscopic attempt at closure. Long-term clinical success was achieved in 80% of patients in this study, but this was defined as success only past 30 days.[133] One case series was identified that included 3 patients with IBD-related fistula in a cohort of 56 patients (5.4%), but there were no additional details provided for these patients, such as type of IBD, location of fistula, and the success of endoscopic suturing in these 3 patients. Notably, the overall success rate in this case series was 22.4% at 12 months, with the majority being gastrogastric fistulas related to bariatric surgery.[134] Similar to OTS clips, the role of endoscopic suturing for CD-related fistula such as rectovaginal fistulas is unclear with respect to safety and efficacy.

Endoscopic fistulotomy has been described in a small series and is typically only feasible in the distal bowel such as a coloanal anastomosis or pouch, and when the fistula is short, shallow, and a single tract. Because of these restraints, fistulotomy has been more appropriate for perianal disease where its use is limited.[125,135] It should be reserved for centers with wide experience to limit risk of complications.

Self-expandable metal stents (SEMSs) for the enteral tract includes esophageal, gastroduodenal, and colonic stents. For benign indications, SEMSs have been successfully used for strictures, anastomotic leaks, and uncomplicated perforations with limited data for fistula management.[136–138] There are no published data for SEMS efficacy and safety in the IBD population and further studies are needed to define their role.

ENDOSCOPIC ABSCESS DRAINAGE

Abscesses larger than 3cm or having other characteristics associated with the failure of medical therapy should be

considered for drainage either percutaneously by interventional radiology (IR) or surgically, with the percutaneous approach regarded as first-line therapy if feasible. Factors to consider when choosing a modality includes patient stability, location of the abscess and accessibility (eg, overlying organs or abscess between loops of bowel precluding a safe IR drainage tract), size, number, and complexity of the abscess including multiloculariity, surrounding anatomy including fistula, and overall CD history including prior surgeries and therapies (Fig. 4).[139] Given the morbidity and mortality with surgery, which often involves a 2-stage procedure and temporary diverting ostomy, nonsurgical drainage is first-line if feasible for non-perianal disease-related abscesses, or for patients who are not surgical candidates.

Whereas endoscopic drainage via an endoscopic ultrasound (EUS)-guided transluminal approach is commonly performed for non-IBD-related intrabdominal and pelvic abscesses, it has not routinely been used for CD-related abscesses owing to the high efficacy and safety of IR-guided drainage.[139,140] Whereas endoscopic drainage is likely safe based on data from the non-IBD population, there is a theoretical concern for internal fistula formation.[141] There is 1 case series of 8 patients who underwent EUS-guided drainage of pelvic abscesses that could not be accessed via IR-guided percutaneous drainage. One patient in the series had a CD related abscess that was unilocular, perirectal, and approximately 37mm x 45 mm in size and was drained with a single 7 French pigtail stent. Although it is unclear how long it remained in place, there were no reported complications and the abscess resolved.[142] Anecdotal reports of endoscopic drainage of intraabdominal abscesses in IBD patients via placement of either 7 or 10 French pigtail stents have been reported, but no details provided.[125]

Short-term success rates for percutaneous drainage—which varies in definition, but typically is defined as avoidance of surgery within the next 1–2 months—range from 50%–95% in the literature.[123,143–146] However, 31%–50% may require surgery within 3–12 months due to abscess recurrence. If clinical improvement and abscesss resolution does not occur within 5 days, then repeat imaging should be pursued to determine if repositioning of the drain is needed or an alternative intervention is needed. Continued drainage of over 20 ml/day should raise concern for fistula formation as the etiology of drainage failure; appropriate imaging should be pursued, and surgery may be necessary for definitive management.[39] Multiple or multiloculated abscesses, abscesses associated with fistula, or related to progression of CD, as opposed to postoperative complications, are associated with lower drainage success rates.[123,143,144,147,148] Currently, there are insufficient data to recommend endoscopic drainage of CD-related abscesses and radiology- guided percutaneous drainage should continue to remain first-line therapy. If the abscess is not accessible percutaneously, but is readily accessible endoscopically, then endoscopic drainage may be discussed as a nonsurgical intervention.

GENERAL SURGICAL CONSIDERATIONS

Penetrating disease is a common indication for surgery, including patients with free perforation, intrabdominal, and/or retroperitoneal abscesses unsuccessfully managed with antibiotics and nonsurgical drainage, internal fistulas with ongoing symptoms or sepsis not responding to medical, and/or endoscopic management. Generally, if disease is quiescent and patients are asymptomatic despite evidence of internal fistula, surgery is not indicated.

If surgery is indicated, patients should be referred to medical centers with expertise and the ability to provide a multidisciplinary approach involving adequate nutritional and medical management of CD; referral to specialized centers has been associated with improved outcomes and mortality.[55,149,150] Before proceeding to surgery, fluid and electrolyte imbalances should be corrected, infection controlled, and overall nutritional status and operative candidacy assessed. The risk versus benefit of intervention must be very carefully considered in malnourished patients and those with underlying comorbidities. Additionally, adequate imaging should be obtained to rule out distal obstruction, assess the complexity of the fistulous connections, identify any anatomic barriers, and stage the CD. The CD-associated fistula pose special surgical challenges given their chronicity and complexity, the health of the remaining GI tract, the patient's nutritional status, and the use of immunosuppressive medications that may hinder postoperative healing.

SURGICAL MANAGEMENT OF NON-PERIANAL FISTULAS

Historically, symptomatic CD fistula were managed with bowel rest and TPN, proximal intestinal diversion, or resection. Indications for surgery include ongoing diarrhea, malabsorption, recurrent infections such as chronic UTI with enterovesicular fistula not responding to an adequate trial of medical therapy and/or endoscopic management, sepsis related to fistula, and a lack of response to medical management. Complete resection of the fistulous tract is required and the diseased bowel to decrease recurrence.[151] Enteroenteric fistula requiring a surgical intervention characteristically have only 1 orifice in an area of diseased bowel, whereas the other orifice is typically within a normal bowel segment. In such a scenario, the fistula is transected and only the active diseased segment is resected whereas the healthy segment can simply be closed and preserved.[15,152] If disease is extensive and there is a risk of short bowel syndrome, or if patients already have short bowel syndrome, then wedge resection or oversewing the fistula in the unhealthy segment are alternative options, albeit suboptimal compared to complete resection given the risk of recurrence and complications.[55,151] Ureteral stent placement is advocated if colon mobilization is anticipated during the procedure. Fecal diversion is common to optimize postoperative healing and maximize the potential efficacy of medical and nutritional management.

ECFs pose additional challenges. Morbidity and mortality from ECFs is high, and ranges from 5%–29% overall, with surgical mortality cited as 3%–3.5% in 1 series.[63,153] These figures underscore the need for a collaborative approach among gastroenterologists, surgeons, wound care nurses, and nutritionists; this approach has achieved closure rates as high as 80% in some series.[151] Unfortunately, despite this high frequency of closure, mortality rates in 1 series still approached 7% due to ECF-related complications.[63] Surgical intervention should be avoided until intraabdominal sepsis is resolved, nutritional status is optimized, maximal medical therapy has been initiated, and local wound care has been accomplished.

For postoperative ECFs, which represent the majority of ECFs, their development in relation to the prior surgery is key.[154,155] Those occurring in the early postoperative setting represent an anastomotic leak or iatrogenic bowel injury; most of these ECFs will close with a diverting ostomy, nutritional management, and antibiotics.[64,154,155] If they persist, then fistula and bowel resection should be considered. Efforts to treat these early leaks with CD-related therapies are futile and not standard of care. ECFs that form later postoperatively are often anastomotic in origin and require resection of the fistula and affected bowel.[156–158] Primary ECFs by definition develop from active disease. Maximal medical treatment should first be attempted for fistula closure; unfortunately, in the majority of ECFs, surgery is typically required to achieve permanent closure.[159]

It is advised to resect the entire diseased bowel segment if possible, but in cases of short bowel syndrome or risk of short bowel syndrome, wedge resection or oversewing of the defect may be indicated. Closure of the abdominal defect introduces a separate set of challenges since prosthetic material or mesh are relatively contraindicated on account of the increased risk of infection and fistula recurrence.[152] Human-derived dermal grafts appear promising in patients with CD, as they resist intestinal adhesion and will not become chronically infected. Peristomal ECFs may be managed conservatively, but if surgery is indicated, the stoma must often be revised or resited with any affected bowel resected. Wound vacuum closure devices have been used in non-CD related open wound closure, but their role in ECF management in CD is not defined.[151,160]

For rectovaginal fistula, transrectal and transvaginal advancement flaps are most often used, with no difference between the 2 techniques in closure rates (up to 69%).[161] Inflammation should be controlled since active proctitis significantly reduces the likelihood of successful closure. Another option is to resect the affected bowel and fistula and close the defect.[162] Enterovesical fistula are managed similarly with bowel resection, fistula resection, and closure of the bladder defect in either single or multistage operations. Successful 1 stage operations have been reported in up to 92% of enterovesical fistula surgeries.[163] Generally, bladder drainage is recommended for 7 days postoperatively.

SURGICAL MANAGEMENT OF INTRAABDOMINAL AND PELVIC ABSCESSES

Historically, surgery was the treatment of choice for intrabdominal abscesses. However, as noted above, over the past few decades, percutaneous drainage under CT or ultrasound guidance and antibiotic coverage has replaced surgery as the first-line modality for CD-related non-perianal abscesses (Fig. 4). The standard surgical approach used to involve an exploratory laparotomy with abscess drainage and concomitant resection of affected bowel. Unfortunately, this procedure is often technically difficult because of inflammation, infection, and structural considerations such as fistulas; resection may also result in extensive loss of bowel. Although resection can theoretically be done as 1 stage with primary reanastomosis, this opportunity is not often available because surgery is often performed urgently with a high risk of postoperative complications such as anastomotic leak, wound infection, and fistulization. Concomitant malnutrition and active disease and/or sepsis also increase the risk of complications. In such instances, a diverting temporary ostomy often is indicated and allows medical and nutritional optimization before subsequent elective reestablishment of continuity.

Percutaneous drainage is therefore particularly appealing as a bridge to elective surgical intervention allowing for stabilization and optimization with improved outcomes. There are no randomized controlled trials of primary surgical intervention versus primary percutaneous intervention with or without subsequent surgical intervention in abscesses that are percutaneously accessible. Nonetheless, retrospective data have shown that primary percutaneous drainage is associated with significantly fewer complications (eg, 20% vs 69%, $P = 0.04$ in 1 study), higher likelihood of successful primary anastomosis, and shorter length of stay.[17,164–167]

There is no consensus as to whether surgical intervention is needed after successful abscess drainage and the published literature is mixed. In up to 20% of cases, multiple percutaneous procedures may be needed for successful drainage.[165] After successful percutaneous drainage, 15%–85% of patients may avoid surgery. If there are fistula associated with the prior abscess site, concomitant stenosis, or refractory disease activity, then that patient is unlikely to avoid surgical intervention.[168]

SURGICAL MANAGEMENT OF FREE PERFORATION

Free perforation of the small or large bowel in penetrating CD is a rare event with 1 large series reporting a rate of approximately 3%.[169–171] Resection of the perforated segment is preferred with the length of the resection depending on the state of the efferent and afferent limbs of adjoining bowel, which may have active CD or be impaired by sequelae of prior surgeries such as fibrosis and adhesions. If ischemic injury occurred, the viability of a larger segment of bowel may be compromised.

Primary suture closure of the perforation without bowel resection is generally not recommended due to a higher failure rate and risk of complication.[169,172] In uncomplicated perforations without severe soilage and with limited bowel wall edema or inflammation, primary anastomosis is typically feasible and preferred. Otherwise, a diverting small bowel ostomy or end ostomy is recommended if there are factors present that would compromise the integrity of an anastomosis and increase the risk of leak or other complications. Patient-related factors include severe malnutrition, intrabdominal contamination due to perforation, associated abscess, hemodynamic instability, and severe active disease. Procedural factors include technical difficulty in creating an anastomosis, particularly if the bowel wall is edematous or friable.[173]

CONCLUSIONS

NPPCD complications represent a complex clinical challenge in the care of patients with CD often requiring medical, endoscopic, radiologic guided. or surgical interventions. They are associated with significant morbidity and increased risks of mortality necessitating a comprehensive multidisciplinary approach. The primary limitation in our therapeutic care of these complications is that there are few published controlled studies evaluating their management, with most of the literature on fistulizing disease and its sequela focused on the perianal phenotype. In light of this limitation, the coordinated care of patients with fistulas, phlegmons, and abscesses should be taken in concert among a gastroenterologist expert in their management, an experienced colorectal surgeon, an interventional radiologist, and an infectious disease physician when needed. In symptomatic patients, there should be a low threshold for referral to a tertiary center where the close coordination and expertise of these specialties is present. With a comprehensive treatment strategy successful management can be achieved in most individuals with improved outcomes and an enhanced quality of life.

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