

## REVIEW ARTICLE

# Intra-abdominal abscesses in CD – When to treat with biologics?

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**Abstract**

Management of intra-abdominal abscesses complicating Crohn's disease (CD) is challenging. After initial drainage and antibiotherapy treatment, surgery with delayed intestinal resection is often recommended but new data suggests efficacy of biotherapies in this context. This review aims to summarize new data regarding efficacy and safety of anti-TNF in the management of intra-abdominal abscesses complicating CD. We performed a review of the literature on medical management of intra-abdominal abscesses complicating CD. After effective drainage of abscess, treatment with anti-TNF can allow resolving of abscess. In some patients and at a specific timing, the use of biotherapies could avoid delayed surgery and long-term abscess recurrence.

**KEYWORDS**

abscess, anti-TNF, Crohn's disease, surgery

**INTRODUCTION**

Crohn's disease (CD) is a chronic inflammatory disease evolving by acute episodes separated by periods of remission. It is characterized by transmural inflammation of the intestinal wall, which can lead to complications such as bowel obstruction, perforation or intra-abdominal abscess. These complications correspond to different phenotypes of the disease, stricturing and fistulizing respectively. Natural history of CD leads to appearance of intra-abdominal or pelvic abscess in approximately 10%–30% of patients, thus classifying the disease as 'fistulizing'.<sup>1</sup> Intra-abdominal abscesses should be considered as serious complications of CD as they reflect disease's activity. Their management is challenging: immunosuppressive drugs are needed to control disease activity but expose the patient to infectious complications and potential worsening of the septic state. The first steps of the therapeutic strategy have been standardized in ECCO guidelines: systemic antibiotic therapy to

control sepsis, followed by radiologic drainage of the abscess if technically feasible.<sup>2</sup> However, global further management remains unclear. Intra-abdominal abscess reflect an advanced-stage disease, theoretically considered as unresponsive to medical treatment. Surgery has indeed been traditionally the gold standard for these types of complications, consisting of delayed resection of the perforated intestinal segment. It is only recently that medical treatment has been incorporated into ECCO guidelines, stating that 'medical management without surgery may be considered following successful image-guided drainage of an intra-abdominal abscess'.<sup>2</sup> Anti-TNF have proven their efficacy in induction and maintenance of remission in inflammatory and fistulizing disease, improving quality of life and decreasing hospitalization rates.<sup>3</sup> Some data also suggest that anti-TNF therapy is associated with a decrease in surgery need.<sup>4</sup> In clinical practice, these beneficial aspects are balanced out by potential infectious adverse events, all the more in patients with intra-abdominal abscess risking evolution towards

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systemic sepsis.<sup>5</sup> In consequence, data concerning management of intra-abdominal abscesses with biologics is scarce.

The aim of this review is to clarify, based on recent data of the literature, indications and timing of biologics treatment in the management of intra-abdominal abscesses complicating the course of CD.

## EPIDEMIOLOGY

Intra-abdominal abscesses in CD are complications of a fistulizing disease. Fistula tract result from transmural inflammation of the mucosal wall. They can develop between the bowel and any adjacent organ including other areas of the bowel. Intra-abdominal abscesses form when the sinus tract is not complete between the two parts of the bowel.<sup>6</sup> Terminal ileum is the most frequent location of fistulizing CD. The overall cumulative risk of fistula development has been estimated around 33% at 10 years and 50% after 20 years.<sup>7</sup>

## INITIAL MANAGEMENT

Initial management of intra-abdominal abscess has been clarified by recent ECCO guidelines.<sup>2</sup> The latter stress out the importance of combining systemic antibiotic therapy and drainage of intra-abdominal abscess when possible.

**Antibiotherapy:** Initial management of intra-abdominal abscess includes efficient antibiotherapy. It should be targeted against Gram negative bacteria and anaerobes.<sup>8</sup> When drainage is feasible, antibiotherapy can be adapted to sensitivity of bacteria after analysis of drained pus. Classically, fluoroquinolones or third-generation cephalosporin combined with metronidazole are efficient.<sup>9</sup> Duration of treatment is not clearly established but a 3–4 week regimen is typically performed in clinical practice, until evaluation of abscess evolution by MRI.<sup>10</sup>

**Drainage:** Progress in interventional radiology in the past decade has led to recommend radiologic drainage as a treatment option.<sup>2</sup> Ananthakrishnan et. al analyzed data related to the 3296 hospitalizations for CD intra-abdominal abscesses that occurred in 2007, when percutaneous drainage was becoming increasingly frequent. They found that 29% of patients underwent percutaneous drainage and 32% were treated surgically (laparotomy +/- bowel resection). In comparison, in 2004, proportion of patients treated with percutaneous drainage was approximately 10% while those undergoing surgery was around 44%, confirming the growing proportion of radiologic drainage indication.<sup>9</sup> A recent meta-analysis confirmed that percutaneous drainage could avoid surgery in up to 30% of patients presenting with intra-abdominal abscess complicating CD.<sup>11</sup> Therefore, ECCO consensus recommends percutaneous image-guided drainage as the first therapeutic step.<sup>2</sup> When feasible (mostly well-defined unilocular abscess), percutaneous radiologic drainage has reported successful drainage rates of 74%–100%.<sup>12</sup> In clinical practice, the chosen approach depends on the availability of the interventional radiologists, the characteristics of the abscess and

the severity of septic state of the patient. Indeed, even if no study has specifically studied association of abscess size and percutaneous drainage's success rate, only relatively collected abscesses measuring more than 3 cm are usually considered for radiological drainage.<sup>10</sup>

**Nutritional management:** Nutritional status optimization is crucial in the initial management of intra-abdominal abscess complicating CD, both to prepare a possible surgical resection and to maximize success rate of medical treatment. Indeed, malnutrition is an independent risk factor for all postoperative complications following abdominal surgery. Furthermore, in the context of intra-abdominal sepsis, bowel rest is in itself an important therapeutic tool. There is no randomized trial in the literature comparing parenteral to enteral nutrition in this context, and most studies report the use of parenteral nutrition to prepare for surgery in CD. However, following American Society for Parenteral and Enteral Nutrition guidelines and as enteral nutrition avoids central venous catheter-associated complications, enteral nutrition is often the first step in clinical practice.<sup>13</sup> Enteral nutrition can consist in administration of Modulen IBD, containing whole protein and Transforming Growth factor-Beta 2 (TGF- b2), a cytokine with anti-inflammatory properties, which has shown to facilitated CD remission in children.<sup>14</sup> Switch to parental nutrition will occur in case of patient's intolerance of insufficient coverage of nutritional needs. There is no data regarding the recommended duration of artificial nutrition in this situation but it is usually maintained for at least 3 weeks before abscess reevaluation.

After optimal initial management of CD intra-abdominal abscesses including systemic antibiotic therapy, nutritional status optimization and abscess drainage, question of surgical indication for management of fistulizing bowel segment or medical treatment remains.

## SURGICAL TREATMENT

Surgery has traditionally been considered the best way to manage complications of CD, including fistulization and abscesses.<sup>15</sup> Recent ECCO guidelines still mention considering 'a low threshold for surgery in the event that medical management is not successful'.<sup>2</sup> ECCO-ESCP consensus from 2018 also stresses out the importance of surgical treatment at an early stage, mentioning that 'in patients with significant symptoms owing to fistulas between diseased bowel loops and adjacent organs, there is a higher risk of non-response to medical treatment'.<sup>16</sup> Surgery can also be recommended at the acute stage, for patients presenting with systemic signs of sepsis despite 48 h of antibiotic therapy and percutaneous drainage.<sup>8</sup> Moreover, even for patients without criteria for urgent surgical management, some data suggest the efficacy of initial surgical management, contrasting with ECCO recommendations: Nguyen et. al' meta-analysis compared outcomes of initial medical (antibiotics alone or antibiotics and percutaneous drainage) to surgical (laparotomy with or without bowel resection) strategies in the management of intra-abdominal abscesses in patients with CD. Pooled analysis of 9

retrospective studies including 603 patients showed abscess resolution in 180 of 318 patients (56.6%) in the medical group versus 229 of 284 (80.7%) patients in the surgical group. Abscess resolution was three times more likely to be achieved when an initial surgical strategy was used at time of diagnosis than when medical strategy was chosen [OR 3.44, 95% confidence interval (CI): 1.80–6.58,  $p < 0.01$ ].

In the case of successful percutaneous drainage but persistence of abscess at MRI after combination of parenteral antibiotherapy and nutritional support, surgery must be considered.<sup>2</sup> Waked et. al studied retrospectively outcomes of 43 patients with spontaneous intra-abdominal abscesses complicating CD undergoing conservative medical treatment. The majority (71.4%) of patients required bowel resection to achieve complete abscess resolution. The risk factors for the failure of conservative treatment were the use of corticosteroids and the non-use of anti-TNF agents after abscess diagnosis.<sup>17</sup> However, clear criteria leading to surgical indication are still not known. History of medical treatment refractory disease, presence of a symptomatic stenosis and/or enterocutaneous fistula are arguments in favor of surgical management.<sup>2</sup>

## MEDICAL TREATMENT

After initial management of CD intra-abdominal abscess comprising of antibiotic therapy, nutritional status optimization and percutaneous drainage, there is growing data suggesting that medical treatment alone seems to be a legitimate option<sup>18</sup> (Table 1). Some studies have reported encouraging results of anti-TNF therapy in this context, avoiding any surgical procedure. In 2012, Cullen et. al studied retrospectively 13 patients with CD complicated by a phlegmon (associated with an abscess in 12/13) over a period of 6 years. All were treated with antibiotics. Out of the 12 patients with repeat imaging before initiation of anti-TNF, one underwent drainage for a 7.5 cm abscess, 4 had persistent <2 cm abscesses and 7 showed radiological resolution of abscess. Only 2 patients required surgery more than a year after initiating anti-TNF treatment (one patient for loss of response to adalimumab, the other for a symptomatic ileal stricture). Out of the 11 patients treated

exclusively by anti-TNF therapy, 10 were considered asymptomatic at time of publication. One important result was that anti-TNF therapy was not associated with the occurrence of infectious complications, suggesting a reassuring safety profile in this situation.<sup>19</sup> The same year, Nguyen et. al evaluated risks factors for abscess recurrence in 95 patients with CD complicated with abdominal abscess (>1 cm) from 1999 to 2006. They compared medical/nonsurgical methods (percutaneous aspiration or drain placement) which were used in for 55 patients with surgical intervention (laparotomy ± bowel resection) for 40 patients. In total, there were 25 cases of abscess recurrence after initial management of abscess (17 in the medical group and 8 in the surgical group). Regarding medical treatment which followed initial management of abscess: 13 patients received no treatment, 23 patients received anti-TNF monotherapy, 44 patients received monotherapy with an immunosuppressive agent and 15 patients received combination therapy (immunosuppressive agent and anti-TNF). They concluded that treatment after abscess resolution with an anti-TNF agent compared with no therapy was protective against abscess recurrence (HR, 0.08; 95% CI, 0.02–0.36;  $p < 0.001$ ). This study, baring its limitations such as the choice of initial management which was as the discretion of the physician, showed the feasibility of treating abscess complicating CD without surgery. Safety of anti-TNF treatment immediately following per cutaneous drainage was also reported, as of the 82 patients who received either an immunosuppressive agent and/or anti-TNF therapy, 12 patients started therapy on the same day as abscess drainage, with no infectious complication reported.<sup>20</sup> More recently, we performed a multicenter, prospective study including CD patients receiving adalimumab after medically resolved intra-abdominal abscess. The primary endpoint was adalimumab success at W24 defined as the absence of: steroids use after the 12th week, intestinal resection, abscess recurrence, and clinical relapse. Secondary post-hoc endpoint was long-term success defined as survival without abscess relapse nor intestinal resection at W104.<sup>21</sup> One hundred and ninety patients with a diagnosis of spontaneous intra-abdominal or pelvic CD abscess according to radiologic criteria confirmed by US, CT-scan or magnetic resonance enterography (MRE) were enrolled. All patients initially underwent treatment with systemic antibiotics and

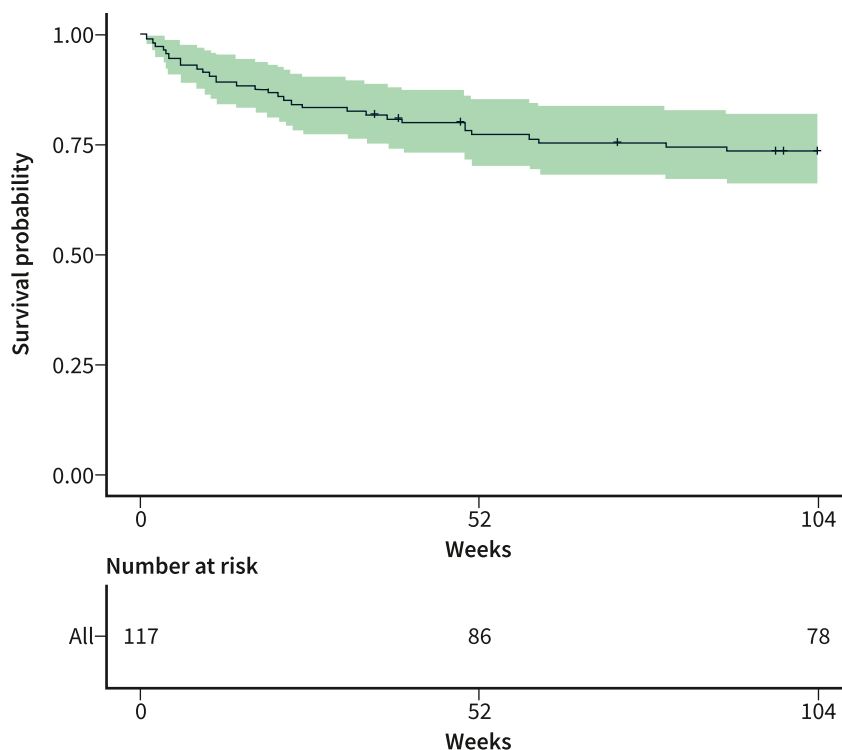
**TABLE 1** Summary of main studies assessing medical management of intra-abdominal abscess complicating Crohn's disease (CD)

| Author, publication year           | Study type    | Nb of patients | Percutaneous drainage | Surgical drainage | Anti-TNF (nb of patients; time from drainage, d) | Infectious complications | Need of surgery post drainage | Follow up |
|------------------------------------|---------------|----------------|-----------------------|-------------------|--|--------------------------|-------------------------------|-----------|
| Cullen G et al., 2012              | Retrospective | 12             | 1                     | 0                 | 12; 14   | 0                        | 2                             | 27.6 mo   |
| Ibanez-Samaniego L et al., 2015    | Retrospective | 12             | 7                     | 0                 | 12; unk  | 0                        | unk                           | 37.8 mo   |
| Nguyen D et al., 2012              | Retrospective | 95             | 55                    | 40                | 38; 9  | 0                        | 0                             | unk       |
| Waked B et al., 2020               | Retrospective | 40             | 39                    | 0                 | 25; 15   | 0                        | 30                            | 72 mo     |
| Bouhnik Y et al., article in press | Prospective   | 117            | 8                     | 3                 | 111 21   | 17                       | 27                            | 26 mo     |

radiologic-guided percutaneous drainage of the abscess whenever indicated and feasible, depending on the size of the abscess and its accessibility. When percutaneous drainage was not possible, antibiotics were pursued alone as in case of a small abscess (<30 mm diameter). Notably, the abscess was not drained for 106 patients. This was due to the small size of the abscess in 59 (67%) patients and the difficulty to access the abscess site in 29 (33%) subjects. Treatment with adalimumab was started in the 117 patients which showed complete disappearance of the abscess after initial management (minimal duration of systemic antibiotics of 2 weeks in case of drainage and 3 weeks when the drainage was not feasible). The first dose of adalimumab had to be administered less than 21 days after the MRE control for abscess disappearance. At week 24, 74% (CI<sub>95%</sub>: 65.5–82.0) patients achieved success with adalimumab therapy. Thirty patients were considered with treatment failure: 15 had recurrence of intra-abdominal abscess and 15 required intestinal resection, which was performed for abscess recurrence in 8 of them. At W104, the survival probability without abscess recurrence or surgery was 71.6% (62.1–79.8, *n* = 109), whereas 27 patients underwent surgical resection, of which 13 were caused by abscess recurrence (Figure 1). Safety analysis was done on 118 patients. In total, 290 adverse events were reported, including 73 (25%) as 'serious' and involving 45 (15.5%) patients exposed to the treatment. Those adverse events were classified as 'gastrointestinal disorders' in 21 patients and as 'infections and infestations' in 17 patients exposed to treatment.<sup>18</sup> Overall, the latter results strongly plead for the feasibility and safety of a medical strategy for CD-

associated intra-abdominal abscess, after percutaneous drainage when feasible, considering surgery only after failure of anti-TNF. Amiot's et al. clinical guidelines have suggested an algorithm to help decision making based on the MICA study, insisting on abscess image reevaluation by MRI after 3–4 weeks of systemic antibiotic therapy.<sup>10</sup> Choice of biotherapy depends on previous exposure to anti-TNF: for a patient with an abscess occurring without anti-TNF treatment, initiation of anti-TNF is recommended. Regarding the choice of anti-TNF, there is no argument in the literature to favor adalimumab or infliximab in this specific context. On the other hand, for patients having already been exposed to anti-TNF therapy, two options should be considered: a second line biotherapy or surgery. Decision involves multiples factors such as mechanism of resistance to anti-TNF therapy (which biotherapy dosages can help identify), length of intestinal damage, luminal dilatation above the stricture >45 mm, evidence of symptomatic ileal stricture.<sup>22,23</sup> When the option of a second line biotherapy is eventually preferred, there is no evidence in the literature strictly favoring ustekinumab over vedolizumab in the context. However, two recent retrospective studies comparing ustekinumab to vedolizumab in anti-TNF-refractory CD concluded on the superiority of ustekinumab to achieve long term clinical remission.<sup>24,25</sup> Factors associated with success of ustekinumab were ileal disease and penetrating phenotype, suggesting the possible interest of ustekinumab in the context of CD-intra-abdominal abscess.<sup>24,25</sup>

Treatment with biologics can also be indicated after delayed surgery for persistent intra-abdominal abscess as discussed earlier. In



**FIGURE 1** Survival probability without abscess recurrence or resection surgery post adalimumab treatment.

this case, initiation of biologics depends on previous treatment as well as risk of post-surgery CD recurrence including factors such as smoking, previous bowel resection and perianal fistulae.<sup>26</sup>

In regards of new treatments such as anti-JAK and selective sphingosine-1-phosphate receptor modulator, there is no report in the literature of their use in the management of intra-abdominal abscess complicated CD. As they are new molecules with growingly reported infectious adverse effects, time and experience will tell if they become a legitimate therapeutic option for management of CD intra-abdominal abscesses.

## CONCLUSION

Management of intra-abdominal abscesses complicating CD is challenging. Traditionally considered as a clear surgical indication, progress in interventional radiology techniques and efficacy of anti-TNF therapy have led to reconsider the best suited strategy for those patients. Recent studies have shown success of a 'no surgery' management, starting by both antibiotic therapy and radiologic drainage if needed, followed by initiation of anti-TNF without the need of surgical resection after up to 5 years follow-up. One of the remaining issue is to determine which patients are 'good candidates' for medical treatment alone. Futures studies will probably have to consider factors such as past course of CD, history of resection, abscess radiologic features, history of medical treatment failure in order to predict probability of success of medical treatment in the management of intra-abdominal abscesses complicating CD.

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## CONFLICTS OF INTEREST

Manon Haas declares fees from Abbvie, Biogen, Celltrion, Fresenius Kabi, Janssen, Mylan, Sandoz, Takeda and Tillots. Xavier Treton declares fees from Abbvie, Amgen, Celltrion, Lilly, MSD, Pfizer, Sandoz, Takeda, Thabor Therapeutics. Carmen Stefanescu declares fees from Abbvie, Amgen, Janssen, MSD, Pfizer, Takeda, and Tillots. Yoram Bouhnik declares fees from Abbvie, Amgen, Biogaran, Biogen, Boehringer Ingelheim, Celltrion, Ferring, Fresenius Kabi, Galapagos, Gilead, Hospira, Janssen, Lilly, Mayoli Spindler, Merck, MSD, Norgine, Pfizer, Roche, Sandoz, Sanofi, Shire, Takeda, UCB.

## DATA AVAILABILITY STATEMENT

Data and study materials will not be shared.

## ETHICS STATEMENTS

I ensure that all the authors mentioned in the manuscript have agreed for authorship, read and approved the manuscript, and given consent for submission and subsequent publication of the manuscript. The manuscript in part or in full has not been submitted or published anywhere. In other words, the authors should ensure that the manuscript is not a duplicate publication.

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