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Therapeutic strategies in Crohn's disease in an emergency surgical setting.

Acute complications in Crohn's disease

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Abstract

Crohn's disease remains a chronic, incurable disorder that present unique challenges to the surgeon. Multiple factors must be considered to allow development of an appropriate treatment plan. Medical therapy often precedes or complements the surgical management. The indications for operative management of Crohn's disease include acute and chronic disease complications and failed medical therapy. Elective surgery comes into play when patients are refractory to medical treatment if they have an obstructive phenotype. Toxic colitis, acute obstruction, perforation, acute abscess, or massive hemorrhage represent indications for emergency surgery. These patients are generally in critical conditions and present with intra-abdominal sepsis and a pre-operative status of immunosuppression and malnutrition which expose them to a higher risk of complications and mortality. A multidisciplinary team including surgeons, gastroenterologists, radiologists, nutritional support services, and enterostomal therapists are required for optimal patient care and decision making. Management of each emergency should be individualized based on patient age, disease type and duration, and patient goals of care. Moreover, the recurrent nature of disease mandates that we continue searching for innovative medical therapies and operative techniques that reduce the need to repeat surgical operations. In this review, we aimed to discuss the acute complications of CD and their treatment.

Key Words: Crohn's disease; Intestinal obstruction; Free perforation; Intra-abdominal sepsis; Perineal sepsis; Acute bleeding.

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Core Tip: Crohn's disease remains a chronic and incurable disorder. Multiple factors must be considered to allow the development of an appropriate treatment. The

indications for operative management of Crohn's disease include acute and chronic disease complications and failed medical therapy. Progression into a complicated phenotype can be characterized by the formation of stenosis or abscesses/fistulas. Elective surgery comes into play when patients are refractory to medical treatment if they have an obstructive phenotype. Indications for emergency surgery include intestinal obstruction, abdominal and perineal sepsis, toxic colitis, or massive hemorrhage.

INTRODUCTION

¹⁸ Crohn's disease (CD) is a chronic and unremitting inflammatory disease that can involve all the gastrointestinal tract. It was first described by Crohn, Ginzburg and Oppenheimer in a case series presented at the American Medical Association annual meeting in 1932, at which time they noted a transmural inflammatory condition of the terminal ileum^[1].

The incidence of CD has increased in recent years^[2, 3]; Ng *et al*^[4] described that the higher prevalence was in Europe (322 per 100,000 in Germany) and North America (319 per 100,000 in Canada). In the last thirty years, it has been described a major increase also in Asia, Africa, and South America^[5, 6].

There is no agreement between the various authors on the gender predominance^[7]; some case studies propose a female predominance in Western population and a male predominance in Eastern countries, in others there are no differences^[8]. The age of presentation shows a bimodal trend with a first peak between 15-30 years (men manifest the disease earlier than women) and a second peak between 60 and 70 years (mostly women)^[9].

CD has a multifactorial etiology^[10-12]. It has been described in literature that patients who had an appendectomy for perforating appendix have a major risk to develop CD, while appendectomy for other causes is linked to a lower risk of CD^[13].

The pathogenesis is unclear^[5]. An excessive immune response against intraluminal bacteria occurs in the mucosa in susceptible patients and leads to a chronic

inflammation that can involve all the gastrointestinal tract^[7]. Anyway, it is localized in the small intestine or proximal right colon with a preference of the terminal ileum in most cases^[14]. The histologic findings that characterized the disease are ⁷ non-caseating granulomas and discontinuous transmural lesions with inflammation penetrating to the muscularis propria, resulting in structuring and fistulization^[15].

Due to the high variability of localization and severity of inflammation, the disease can have different clinical manifestations that range from very mild to severe. Sometimes, the disease can present as an acute and severe form since the beginning^[7, 14, 16, 17].

⁵ A cure remains elusive and efficient management of CD is essentially multidisciplinary.^[18, 19] Surgery is still required even if the number of operations has decreased in recent years mainly for the introduction of biological therapy^[19, 20].

Uncomplicated forms identified patients with prevalent inflammatory phenotype^[7, 19]. On the other hand, patients affected by a form of CD with a progressive complicated phenotype present with stenosis (structuring phenotype) or abscesses/fistulas (penetrating phenotype). Elective surgery comes into play when patients are refractory to medical treatment if they have an obstructive phenotype. According to the existing literature, the ⁴ risk of surgery at 1, 5 and 10 years after diagnosis of CD is 16.3%, 33.3% and 46.6%, respectively^[21]. It is still controversial whether medical treatment reduces the need for surgery^[22] or not^[23, 24].

The indications for operative management of CD also include acute and chronic disease complications. Since CD is characterized by periods of exacerbation and remission, it is not uncommon an acute presentation of complications that requires urgent/emergency surgery in 6-16% of cases^[24]. Patients requiring emergency surgery are generally in critical conditions and present with intra-abdominal sepsis and a pre-operative status of immunosuppression and malnutrition which exposes them to a higher risk of complications and mortality. Although most CD acute complications ² are managed nonoperatively, it is important to recognize those that require surgical approach. In this review, we aimed to discuss the acute complications of CD and their treatment,

focusing on the recent results of surgical, endoscopic and percutaneous treatments, as individual treatments and as integrated therapy.

DIAGNOSIS

Patients with CD, who present to emergency department with symptoms of acute complications, must be properly framed to formulate an accurate diagnosis and decide what is the best possible treatment. Firstly, a blood chemistry panel must be obtained. It must include full blood count, electrolytes, liver enzymes, renal function, and inflammatory biomarkers, such as C-reactive protein (CRP), serum albumin and fecal calprotectin level. It is fundamental to rule out possible infections carrying out blood and stool cultures and toxin test for *Clostridium difficile*^[7, 19].

Typically, the laboratory panel of a patient with acute CD complications is characterized by anemia, increased leukocytosis, thrombocytosis, altered liver and kidney function and increased inflammatory markers. Neutrophil/Lymphocyte ratio (NLR), obtained by dividing the absolute number of neutrophils by the absolute number of lymphocytes, is described, by many authors, as a good predictor of sepsis and, in case of CD, as an index of acute disease complicated by the presence of abscesses. In this context, Khoury *et al*^[25] have developed a clinical score to predict the presence of intra-abdominal abscess (Table 1). For patients with a low score (≤ 7) the probability of an intra-abdominal abscess is very low and therefore an urgent computerized tomography (CT)-scan can be avoided. On the other hand, a high score (> 9) would warrant urgent imaging for the elevated risk of this intra-abdominal finding. In this scenario, also useful are the disease severity indices, such as Harvey-Bradshaw Index^[26] (Table 2), Crohn's Disease Activity Index (CDAI, Table 3)^[27-29] and Prognostic Nutrition Index^[30]. This last index, calculated using the formula $PNI = 10 \times \text{albumin (g/dL)} + 0.005 \times \text{total lymphocyte count}/\mu\text{l}$ measured in peripheral blood with a reference value ≤ 40 , is widely used to evaluate the nutritional status of the patient and to predict the risk of postoperative complications after gastrointestinal surgery^[30, 31]. A

preoperative low nutritional prognostic index¹⁹ is a useful predictor of postoperative infectious complications in patients with CD-related bowel resection^[31, 32].

Abdominal CT-scan with intravenous contrast is the examination of first choice for the diagnosis^[33]. It allows to evaluate the presence of complications such as bleeding, perforation, obstruction due to strictures and presence of abscesses. The procedure is essential to decide whether to proceed with a surgical treatment or opt for an initial nonoperative management^[34]. A frequent use of CT-scan¹⁴ has been reported for all patients who were admitted to emergency department for abdominal pain^[35], but CD are irradiated more often for diagnostic purpose, with a higher exposure to X-rays^[36]. Several studies evidenced that CD patients are exposed to CT-scan radiation up to 2-3 times per year^[36-39]. It is also described that children who are early exposed to CT-scan, have an increased risk of brain tumor and leukemia^[40, 41].⁵ Craig *et al*^[41] evaluated a low dose CT protocol, reaching radiation levels as low as a plain abdominal X-ray which provided similar diagnostic efficacy even if with low-quality images. The diagnostic accuracy of Magnetic Resonance Imaging (MRI) enterography/enteroclysis is like CT-scan and prevents exposure to ionizing radiations. Anyway, it has a few cons such as limited availability, high cost and time consumption^[27].

As recommended by recent guidelines for the management of CD in the emergency setting^[7],¹ point of care ultrasonography can have a role in showing free fluid, abscess, or intestinal distension, especially when CT-scan is not available. Bettenworth *et al*^[42] in their review showed that sensitivity of the ultrasonography for stricture diagnosis runs from 80 to 100% with specificity rates of 63-75%.⁵ A systematic review by Panes *et al* revealed that the sensitivity and specificity for ultrasound in the detection of complication are high and comparable to MRI^[43].

INITIAL OPTIMIZATION

Since urgent surgery in patients with CD is burdened by a high rate of complications, due to intra-abdominal sepsis, immunosuppression, and malnutrition, it is necessary to

optimize their general conditions and nutritional status, preferring, if feasible, a delayed surgery.

Preoperative corticosteroid use is associated with increased risk of postoperative complications^[44, 45]. ⁵Reduction of corticosteroid doses may decrease postoperative complications but should be carefully monitored to avoid increasing CD burden^[19]. Meta-analyses of prospective and retrospective studies ⁵reported up to a doubling of surgical site infection for patients on steroids^[46, 47].

The application of biologic therapy before urgent surgery is still unclear. The PUCCINI trial showed no effect of anti-Tumor Necrosis Factors α on postoperative complications^[48]. Current evidence suggests that preoperative treatment with vedolizumab ⁵or ustekinumab does not increase the risk of postoperative complications in patients with CD having abdominal surgery, and cessation of these therapies prior to surgery is not mandatory^[49-51].

Malnutrition is an independent risk factor for postoperative poor outcomes^[52, 53]. ⁵Preoperative nutritional assessment should be performed for all patients with CD who need surgery^[19]. The ¹European Society for clinical nutrition and metabolism referred that serum albumin of < 3 g/dL, BMI < 18.5 kg/m², and weight loss > 10-15% within 6 mo are the best indicators of severe malnutrition in CD patients^[54]. The nutrition of choice should be the enteral nutrition which can be replaced with the parenteral one only in those patients who cannot tolerate the first or have severe contraindications such as a high flow intestinal fistula, intestinal perforation, or intestinal ischemia^[55, 56]. Brennan *et al*^[57] observed that patients who received pre-operative nutritional support had a rate of postoperative complications of 20% compared with 61.3% in the group without nutritional support. ¹Zhu *et al*^[58] suggest that enteral nutrition is feasible in CD patients with non-radiologically-drainable abdominal abscess.

INDICATIONS TO EMERGENCY SURGERY

Acute bowel obstruction, intra-abdominal sepsis, hemorrhage, acute toxic colitis, perianal sepsis are the indications to an emergency procedure in patients with CD. The incidence of acute complications of CD are shown in Table 4.

Acute surgical emergencies in patients with CD are associated with high morbidity and mortality. Postoperative mortality rates for nonelective surgeries in CD have decreased but remain significantly higher than the mortality rate following elective surgery (3.6 vs 0.6 percent)^[59, 60]. Although most acute complications of CD are managed nonoperatively, it is important to recognize those that require surgical management. Another issue is the prevention of recurrence which is still much debated.

INTESTINAL OBSTRUCTION

Acute intestinal obstruction is the most frequent complication in patient with CD, especially in patients with ileo-colic localization (35-54%), while in jejunal (22-36%) or colic (5-17%) localizations the frequency is lower^[19, 61-63]. Gastroduodenal obstruction is rare, occurring in 0.5 to 13% of patients^[62, 64]. Patients with gastroduodenal strictures present with postprandial fullness, early satiety, vomiting, and upper abdominal pain^[65, 66]. Patients with obstruction of the small intestine present with nausea, vomiting, dehydration, crampy abdominal pain, bloating, obstipation, and constipation. Patients with colonic obstruction may present without nausea and vomiting, but with bloating, distension, and abdominal pain, in addition to constipation. Initial management of bowel obstruction includes bowel rest, intravenous hydration, and nasogastric decompression in the presence of vomiting^[42].

Strictures complicating CD can be classified as inflammatory or fibrostenotic^[67]. Patients with inflammatory disease deserve medical therapy, such as steroids for reducing inflammation. Patients who do not improve with medical therapy and in whom an occlusion due to fibrosis can be hypothesized, need to go for a CT-scan or an MRI. In these patients, an interventional approach, endoscopic or surgical, is usually needed^[7]. Deferred surgery is the preferred option in adult patients with small-bowel obstruction without bowel ischemia or peritonitis. Endoscopic balloon dilatation (EBD) is a suitable

treatment option for patients with short (< 5 cm) strictures^[68]. For fibrotic strictures, EBD has a technical success rate of 89 to 92%, with 70 to 81% patients presenting free of occlusive symptoms in the short term^[69]; differently in the long period 73.5% of patients require to repeat a dilatation and 43% a surgical intervention within 2 years^[70]. Fully covered self-expandable metal stents (FCSEMS) have been used for endoscopic treatment of patients for whom EBD was unsuccessful. In a multicenter, open-label, randomized trial^[71], 80 patients were randomly assigned to treatment: 39 (49%) patients to the FCSEMS group and 41 (51%) patients to the EBD group. 33 (80%) of 41 patients in the EBD group and 20 (51%) of 39 patients in the FCSEMS group could avoid a new therapeutic intervention in 1 year (OR 3.9 95%CI 1.4-10.6; $P = 0.0061$). Two of 80 patients had perforations (one patient in the EBD group and one patient in the FCSEMS group)^[71]. EBD is more effective than FCSEMS for CD strictures, with a good safety profile for both the treatments.

Surgery is mandatory for intestinal obstruction with potential impending perforation, with long or multiple strictures, when the strictures are not endoscopically accessible endoscopically, when medical or endoscopic treatment does not result in an adequate reduction of clinical symptoms, or when there is a suspicion of an underlying malignancy^[7, 72, 73]. If emergency surgery is indicated, a laparoscopic approach is recommended when appropriate expertise exists^[74, 75].

The surgical treatment of choice is a segmental resection of the involved segment with primary anastomosis. In fact, the most important principle in the surgical management of CD is to resect only the segment of bowel affected by the complication to prevent short bowel syndrome. Even if adjacent areas of bowel are clearly diseased, that should be ignored^[76]. Furthermore, when two intestinal segments are involved, but with a healthy segment in between, the resection of the healthy segment depends on its length, too^[77]. If it is 10 cm or longer, it probably should be saved. If it is 5 cm or shorter it should be included. In the other cases, the surgical attitude will depend on previous resection, configuration of blood supply and mobility of the mesentery. The anastomosis could be both hand-sewn or stapled, end-to-end or side-to-side^[78]. The

literature does not describe a superiority of one technique over another and the final decision can be left to the surgeon preference^[78-80]. If a stapled anastomosis is performed, some authors advise to do it with an isoperistaltic configuration just to allow an easier subsequent endoscopic surveillance. If the bowel wall is edematous, due to chronically inflammation, a hand-sewn anastomosis would be better^[80]. The general conclusion favours stapled side-to-side anastomosis. The diameter of the anastomosis plays a role as well, with the assumption that a wider anastomosis will have a lower rate of clinical and surgical complications^[81, 82].

Other surgical options include stricturoplasty, intestinal bypass and creation of ileostomy. Short fibrous strictures, multiple strictures, short bowel syndrome, rapid recurrence of obstruction due to CD, duodenal CD are indication for stricturoplasty. Contraindications to stricturoplasty comprehend multiple strictures in a short intestinal segment, a long stricture (> 20 cm), or stricture close to resection site^[83]. Bypass operation have largely been abandoned because of the subsistence of disease activity^[83]. An ileostomy is required when it is not safe to perform an anastomosis, such as in case of patient severe instability, malnutrition, intra-abdominal sepsis, chronic immunosuppression or when a small bowel resection is performed together with colonic or rectal resection^[76, 79].

INTRA-ABDOMINAL SEPSIS

Abscess

The presence of an abscess occurs in up to 20% of CD patients^[84-86]. It typically results from a penetrating disease phenotype with a distal stricture^[80]. An abscess categorized CD as active at Harvey-Bradshaw Index^[26] and severe with a CDAI > 450^[27-29]. Abscess is defined as an inflammatory mass consequent to bowel perforation promptly covered by fibrin which adheres to the loops' surface causing adhesions among them. It can be associated with other CD complications such as fistulas (40%) and stenosis (51%)^[14, 85]. Usually, these patients present to emergency department with fever associated to abdominal pain, palpable masses, rebound tenderness. In 28% cases they can have a

generalized sepsis^[84]. So, it is crucial they receive a proper clinical evaluation. If an abscess is suspected cross-sectional imaging is recommended. CT-scan is the gold standard for their detection in the emergency setting and it also consents to identify concomitant fistulae or bleedings. MRI has a similar accuracy with a lower ionizing radiation exposure, but it is not always accessible in the emergency department. Point of care US can have a role in the initial assessment and it is extremely useful in rural hospitals where CT is not available^[7, 87, 88]. Moreover, if there is an indication to the positioning of a percutaneous drainage, both ultrasonography and CT, can be used as guides^[86, 89]. In selected cases, also endoscopic ultrasound can be employed for draining the cavity by a transvaginal or transrectal approach^[90, 91].

When the abscess diagnosis is confirmed, the best patient tailored treatment must be defined. In stable patients with abscesses smaller than 3 cm, early empiric antimicrobial therapy is recommended with a close clinical and biochemical monitoring. If the abscess is > 3 cm percutaneous drainage associated to antibiotics is endorsed^[7, 89]. The drainage approach depends on the abscess' site. It can be transgluteal for pelvic abscesses, but also transabdominal. The catheter, whose size must be chosen considering the viscosity of the fluid collected, is left in place and the daily quantity and quality of the drain must be recorded, carefully^[84, 92].

Percutaneous drainage is a validated procedure because it may avoid an immediate operation, allowing to delay elective surgery^[93, 94]. Inflammation will have enough time to resolve, making possible limited intestinal resections and reducing the need of a diverting stoma creation. In addition, the nutritional status could be optimized, and steroids interrupted before surgery, reducing the risk of anastomotic leak^[53, 84]. According to some studies, percutaneous drainage is just a bridge to the definitive surgical treatment. On the other hand, more recent studies, have demonstrated that most patients do well with only percutaneous drainage and do not need any other surgical treatment with success rates that vary from 50 to 95%. Anyhow, the risk of recurrence, more often within 3 years, must be considered^[95-97]. Immediate surgery should be considered in case of patients with septic shock or failure of percutaneous

drainage due to multiple and multilocular abscesses and those associated with a fistula (Figure 1)^[84, 98].

Another key factor in the conservative treatment in CD patients with abscess is the antibiotic therapy. Therefore, it is important to collect a sample of drained fluid and send it for a microbiological test. The culture can reveal the type of microorganisms in the pus, allowing the optimization of the antimicrobial therapy, increasing the chances of conservative treatment success. In Reuken study, culture was positive in about 88% of patients and usually polymicrobial^[99]. The most common pathogens were *E. coli*, *Streptococcus* spp., *Enterococci*, *Candida* and anaerobes. The most used empirical first-line antibiotics were broad spectrum penicillins, followed by cephalosporins and quinolones^[99]. These treatments revealed to be inadequate in patients on immunosuppression or with a prolonged hospitalization and that could be linked to a higher risk of failure^[80]. The appropriate duration of antibiotic therapy is unclear. Also, anti-TNF therapy can have a role in the treatment of an abscess, but only if associated to antimicrobial treatment that must be continued for three months^[100].

After antimicrobial treatment and percutaneous drainage clinical improvement is expected in 3–5 days, with a gradually decrease in the drains output. According to the American Society of Colon and Rectal surgeons, after a successful resolution of an abscess with percutaneous drainage and antibiotics, a drain study to exclude a concomitant fistula could be beneficial^[80]. If patient's condition does not improve, a re-evaluation is mandatory^[84], and if the abscess has not been adequately drained, repositioning of the drain or an operation must be considered.

When a surgical exploration must be performed for conservative treatment failure or for concomitant other Crohn's complications, some issues need to be considered. First, if the patient is unstable, an open approach is recommended, considering the damage control surgery principles. There is also room for open abdomen use. An operation with a bowel resection gives better results than an operative drainage alone which determines a higher rate of reoperation and enterocutaneous fistulas' formation. In case of septic shock, it may be appropriate to perform bowel resection with stapled off bowel

stumps, peritoneal lavage, and open abdomen with a planned second exploration in the next 24-48h after the patient has been stabilized in ICU. At this point, surgeons must decide if creating a stoma or anastomosing the stumps^[89, 101]. In case of stable patient and technical skills available, laparoscopy is recommended to reduce hospital stay and morbidity. Both in open and laparoscopic surgery extensive resections must be avoided because they can lead to immediate or future short-bowel syndrome in these patients^[80]. Even after success of conservative treatment, ¹⁶ patients with a concomitant stenosis, an enterocutaneous fistula or refractory active disease are likely to require surgery^[102]. It is believed that a window of 6 to 8 wk after the resolution of the acute clinical scenario, could permit a good improvement of the clinical and nutritional status, but also a proper imaging and endoscopic work-up. This work-up aims to avoid unexpected findings during the elective operation^[93]. Moreover, as already discussed, the surgical outcomes will be better and comparable to CD patients with non-penetrating disease, as it is also confirmed by recent research^[103]. In their study, on 592 patients, Collard *et al* compared patients who underwent an ileocolonic resection after a conservative treatment for an abscess to CD patients without a penetrating disease who had the same operation^[103]. In the first group, all the patients underwent a CT-scan after the percutaneous drainage to demonstrate a complete resolution of the abscess. Nevertheless, the persistent of an abscess, defined by the presence of a pus-like or purulent collection in site of the original abscess, was found in 25% of cases. Anyway, there were no differences between the two groups for rate of primary anastomosis, need of additional intestinal resection, incidence of intraoperative and postoperative complications and length of hospital stay.

Free perforation

Free peritoneal perforation in CD, is a rare condition that ¹ occurs in 1-3% of CD patients as a first manifestation, or in the course of the disease^[104, 105]. It is one of the main indication for emergency surgery with an high rate of morbidity and mortality in case of delayed surgery^[104]. Greenstein *et al*^[106] reported that perforation can occur in the ileum or in the colon indifferently, without a preference for location. Instead, the

Connect study of Doh *et al*^[105] found that ileal perforation had a higher incidence (86.2%), while colonic perforation occurred in only 7.4% of the patients. Some authors described that steroids increase the risk of free perforation^[107-110]. The role of anti TNF agents in the etiopathogenesis of free perforation, instead, is not clear yet^[111]. The mechanism leading to free perforation is still unclear, but there are two most likely hypotheses. The first and more conceivable is that the increase of intraluminal pressure proximal to a stenosis causes a bowel distension which can perforate the thin layer overlying a deep ulcer, while the second suggests that the perforation is consequent to intestinal ischemia due to inflammation of the small vessels^[105].

The intestinal segment affected by the perforation should be resected deciding whether to directly perform a primary anastomosis or proceed with an enterostomy. According to our practice, in case of severe abdominal contamination (Figure 2), we recommend not to close the laparotomy, but to perform a second look, as already described by Liu *et al*^[112], using the technique of open abdomen with negative pressure wound therapy (Figure 3). In this way, it is possible to prevent intra-abdominal sepsis and during the second look, optimize the resection. In some selected cases, a primary anastomosis could be feasible as the vacuum system allows a good intra-abdominal clearance. We also recommend this technique in the setting of damage control surgery with a hemodynamically unstable patient, when also the decision to perform an enterostomy will be postponed to the second look.

Acute appendicitis

Appendiceal CD is a rare condition, whose incidence varies from 0.1% to 2.0%^[113]. After the first case described in 1953,^[114] there was an initial interest in the topic with most of the cases described in the late 80s–early 90s^[115, 116]. In 1990, Ruiz *et al* identified 85 cases of CD limited to the appendix^[117]. The disease was found most in the second and third decades. The authors suggest that a prolonged preoperative history of symptoms should alert the surgeon to this possibility^[117]. Lindhagen *et al* identified 50 cases and added 12 of their own^[118]. The indication for surgery in their patients were appendicitis in eight patients, appendiceal abscess in two, suspected pyosalpinx in one, and ovarian

cyst in one. All but two of the eight appendicitis underwent appendectomy; the others underwent a more extensive resection. There were no postoperative complications. The authors concluded that when CD is confined to the appendix the prognosis is very favorable^[118].

When considering acute appendicitis in CD patients, it is essential to differentiate between patients admitted to emergency department with a possible appendicitis who already have been diagnosed with CD and patients who underwent an appendectomy, and the histopathology reveals the disease. In a recent study, a group from Seoul analyzed 2179 appendectomies. Among these only 12 (0.55%) were compatible with CD at the histology^[113]. The twelve patients presented to emergency department with right lower quadrant pain, abdominal pain, and diarrhea. The duration of symptoms varied from 2 to 5 mo^[113]. They did not present systemic manifestations such as uveitis, arthralgia, and arthritis. The histological examination revealed transmural inflammation, lymphoid aggregates and epithelioid granulomas as peculiar features present in all the cases, followed by appendiceal wall thickening and mucosal ulceration. When the diagnosis is made, the patient must be referred to a tertiary center for the future gastroenterology follow-up.

Sometimes, the appendix inflammation is consequent/reactive to terminal ileitis in patients affected by CD. Since the acute presentation is like common appendicitis, it is crucial to focus on symptoms like recurrent abdominal pain or diarrhea, lack of fever, weight loss, microcytic anemia, hypoalbuminemia, and hypoproteinemia. In fact, these symptoms are more typical of CD rather than appendicitis. If there is a suspect of CD, the entire small and large bowel should be carefully examined to verify the presence of the disease and its extent.

In patients with a known CD, it is recommended a medical treatment for ileocecal CD. In fact, if in the rare cases of CD localized only in the appendix, the appendectomy can be performed safely. The clinical scenario is completely different when there is active ileocecal disease. In this situation, there are some issues that need to be considered. The main goal is to avoid an ileocecal resection, when possible, for limiting the unnecessary

excision of intestinal segments. Anyhow, an ileocecal resection is the operation of choice in case of cecum involvement to reduce the risk of leak from the appendix stump and formation of enterocutaneous fistula. Furthermore, if the patient has experienced severe symptoms due to his ileitis, an ileocecal resection is the treatment of choice, followed by biologic therapy. Otherwise, the patient will continue suffering CD symptoms with 38% requiring a resection within one year. Finally, it is not necessary to remove a macroscopically normal appendix during an exploration for suspected appendicitis, if there are findings that raise doubts of CD^[119].

ACUTE COLITIS

Toxic colitis represents a potentially fatal condition that may occur in patients affected by inflammatory bowel disease. Studies have demonstrated that as many as 50% of all toxic colitis cases may be secondary to Crohn's colitis^[72, 120, 121]. Diagnostic criteria include: severe diarrhea (6 or more bloody bowel movements per day), temperature higher than 37.8°C, heart rate > 90 beats/minute, anemia (hemoglobin <10.5 g/dL), an elevated erythrocyte sedimentation rate (<30 mm/h), hypoalbuminemia (<3.0 g/L), and leukocytosis (>10.5 x 10⁹ cells/L)^[122]. Toxic megacolon is defined when a radiographic imaging demonstrating dilation of the transverse colon to at least 6 cm is associated to the previously mentioned criteria^[7, 72]. Cytomegalovirus infection has been identified in 25% to 36% of patients with steroid-refractory acute colitis. Studies have demonstrated that *Clostridium difficile* infection in the setting of severe or toxic colitis is associated with increased morbidity and mortality.

When toxic colitis is diagnosed, intensive medical therapy should be promptly administered. Intravenous methylprednisolone, 60 mg per day, or hydrocortisone, 300 mg, are the medications of choice^[123]. Treatment with higher doses of intravenous corticosteroids have not been demonstrated to reduce colectomy rate and, thus, should not be considered. In general, a response to steroid therapy includes improvement or resolution of the systemic inflammatory response syndrome and a decrease in stool frequency. In case of overall clinical improvements over the course of the following 3

days, maintenance therapy could be considered. If there is no response to corticosteroid therapy, rescue therapy is used. Infliximab has now emerged as the most widely used rescue therapy due to its low toxicity, ease of administration, and, consequently, the possibility to be used for maintenance therapy. One recent literature review demonstrated immediate response rates to infliximab as a rescue therapy agent range between 50% and 83%, with long-term response rates slightly lower at 50% to 63%^[124].

Contrarily, in case of worsening of clinical condition or failure to improve a transition to either rescue therapy or an urgent colectomy should be taken into account. If a patient presents with peritonitis or evidence of free perforation on imaging, surgical exploration is mandatory. Perforation in patients with toxic megacolon is associated with a high mortality rate (27–57%), regardless of whether the perforation is contained or free^[7]. The transverse colon is the area of greatest concern in toxic megacolon. The surgical option of choice is subtotal colectomy with end ileostomy which allows for future reconstructive options avoiding permanent stoma by ileorectal anastomosis (Figure 4). This could be suggested for patients without rectal or perianal involvement. A total proctocolectomy should be avoided since it is associated with greater postoperative morbidity and mortality due to increased operative time, risk of blood loss, pelvic sepsis, pelvic nerve damage, even if total proctocolectomy with permanent stoma is the safest option to avoid further operation in high-risk patients^[72]. The patient typically improves over the ensuing few days. An ileoproctostomy can be recommended 6 mo later in selected patients who demonstrate minimal mucosal inflammation, adequate rectal compliance, absence of significant anoperineal disease, and sufficient sphincter strength^[72].

BLEEDING

Gastrointestinal bleeding is a common complication in patients affected by CD. Inflammation/ulceration of the bowel are the basis of its onset. Usually, conservative treatment and endoscopy are sufficient to resolve this condition which rarely requires an emergency surgical procedure. Severe intestinal hemorrhage, on the other hand, is a

rare occurrence in CD, with reported incidence between 0% and 6%^[125, 126]. The underlying pathophysiology of the hemorrhage most often is a result of focal erosion into an intestinal vessel. Due to the infrequency of significant bleeding in Crohn's disease, as stated before, all common causes of upper and lower gastrointestinal bleeding should be assessed. Localization of the bleeding site is essential regardless of the planned therapy.

Management of gastrointestinal bleeding related to CD begins with hemodynamic assessment. In a stable patient the localization of the lesion could be identify by endoscopy or radiology. Nasogastric tube, in case of hematemesis, should be inserted to protect the airway and decompress the stomach. Gastroscopy could be required to rule out an upper gastrointestinal bleeding. If a lower gastrointestinal source is suspected, a retrospective study^[127] reported that the detection rate for vascular lesions was higher for colonoscopy following contrast-enhanced CT scan than for colonoscopy alone.

The role of angiography and of angioembolization must be still clarified. Most of the data suggest that angiography/angioembolization could be feasible in stable patients, but further studies are needed to better define outcomes in the emergency setting^[7]. The major advantage is that it can control severe bleeding without bowel preparation. Disadvantages include the risk of bowel ischemia and the administration of intravenous contrast. In particular the rate of bowel ischemia following embolization was 1–4% in recent studies^[128].

In case of hemodynamic instability, resuscitation by intravenous fluid/blood products administration is fundamental aiming to normalize blood pressure and heart rate prior to endoscopic evaluation/intervention. Packed red blood cells should be transfused to maintain the hemoglobin above 7g/dL. A threshold of 9g/dL should be considered in patients with massive bleeding, significant comorbidities (especially cardiovascular ischemia) or possible delay in receiving therapeutic interventions^[7]. The decision to perform a surgical urgent procedure depends on bleeding source itself, the hemodynamic condition of the patient and on the availability/feasibility of less invasive therapeutic options (i.e., endoscopy or angiography). In case of persistent

hemodynamic instability operative management is necessary. The most challenging situation is represented by patients ² who have a primary or recurrent hemorrhage without an identifiable source of bleeding. In these cases, the likelihood of successfully eradicating the source of hemorrhage through a “blind” intestinal resection must be weighed against the risk of recurrent bleeding and of creating a short bowel syndrome in patients with extensive disease or multiple previous resections.

POST-OPERATIVE RECURRENCE

Post-operative recurrence is the appearance of new lesions after surgery for CD. After the first intestinal resection, 25-45 % of patients are likely to need further operations within 10 years^[129]. ⁸ One year after an initial resection, 60-80% of patients possess endoscopic recurrence, 10-20% experience clinical relapse, and 5% demonstrate operative recurrence^[130]. Diagnosis of postoperative recurrence is primarily based on clinical symptoms and endoscopic findings. Rutgeers *et al* developed an endoscopic scoring system to assess endoscopic recurrence (Table 5)^[131].

Therefore, ileocolonoscopy is the gold standard to identify the presence and severity of CD recurrence, so it is recommended within the first year after surgery^[20]. An emerging and less invasive method to identify postoperative recurrence is the small intestine contrast ultrasonography, which is comparable to ileocolonoscopy to detect lesions related to CD^[132]. Fecal calprotectin is another non-invasive diagnostic and monitoring tool because a later correlation was found between endoscopic severity and calprotectin levels^[133].

In the last few decades, the ⁴ risk of major abdominal surgery within the first 5 years of diagnosis has declined, due to the advances in medical treatment of CD. However, there is still a great debate in literature about risk factors for postoperative recurrence in Crohn' disease (Figure 5). According to ECCO guidelines, smoking, prior intestinal surgery, penetrating disease, ²¹ absence of prophylactic treatment, perianal location, presence of granulomas in surgical specimen and myenteric plexitis are considered predictors of early post-operative recurrence after ileocolonic resection^[20]. Santiago *et al*

identify the presence of colic disease as an independent risk factor for postoperative recurrence and reoperation, while colectomy or proctocolectomy performed during the first surgery have a protective role against reoperation in patients with CD^[134]. Liu *et al* in 2020 published a series on the comparison between primary anastomosis and staged surgery in emergency treatment of complicated CD. The results of this study showed a lower surgical recurrence rate for staged surgery, probably linked to the reduction of inflammatory activity when a fecal diversion is performed^[112]. ¹⁷ A young age, less than 16 years, was identified as another risk factor for repeated abdominal surgery in CD patients by a multicenter study of Korean Inflammatory Bowel Disease Study Group, as well as the presence of stricturing disease behavior^[135].

Other recent fields of investigation focus on the role of anastomotic technique in the pathogenesis of postoperative recurrence. In 2014 and 2018, two meta-analyses were performed to define the optimal surgical technique of anastomosis. The conclusions were that stapled isoperistaltic side-to-side anastomosis, because of its larger lumen, can significantly reduce incidence of postoperative complications and recurrence^[136, 137]. In 2011, Kono introduced a new anastomotic technique. The Kono-S is an antimesenteric functional end-to-end hand sewn anastomosis, with the two stumps sutured to create a “supporting column”, which allows to preserve the diameter and to prevent stenosis and distortion of the anastomosis^[138]. ²² The SuPREMe-CD Study, a randomized clinical trial which compares Kono-S anastomosis and stapled side-to-side anastomosis, confirms the reduction of postoperative recurrence when the Kono-S anastomosis is performed^[139].

Few studies in literature analyze the correlation between emergency surgery for CD and postoperative recurrence. However, emergency surgery would seem to be another independent risk factor for surgical recurrence^[140]. ¹¹ Urgent surgery may be related to more aggressive disease, and greater variation in the anastomotic technique in urgent surgery may affect the risk of recurrence^[81]. Furthermore, a recent paper highlights that an end-to-end anastomosis is associated with an increased risk of early postoperative

recurrence in the subset of patients undergoing an emergency operation, as well as does smoking and the failure to commence early medical prophylaxis^[141].

Another important topic about the risk of recurrence in CD is represented by the role of the mesentery. Patients with CD are characterized by a peculiar form of adipose tissue hypertrophy, known as “creeping fat”^[142], which seems to be an independent predictor of early clinical recurrence of CD when there is an advanced mesenteric involvement in the surgical specimen^[143]. An international, multicenter, randomized controlled trial by Li *et al*^[144], is ongoing to compare conservative limited resection and surgery with mesenteric excision in CD, and its results may provide important insights about the most appropriate surgical technique. ⁹ One of the most common components of CD that manifests itself after proctocolectomy is the recurrence of disease in the ileostomy or remaining small bowel.

PERIANAL SEPSIS

Perianal fistulas and abscesses are common in CD with an incidence up to 43% and are more frequent in patients with distant colonic or rectal disease^[145, 146]. They require a multidisciplinary - both medical and surgical - approach to achieve a complete fistula healing and reduce the negative effect on patient's lifestyle^[147, 148].

Abscess is a consequence of cryptoglandular inflammation/infection as described by Eisenhammer in 1956 and can be the first sign of CD^[149]. It may result in a fistula, that is classified based on its location as described by Parks and Gordon, in up to 40% of cases^[150]. Both abscesses and fistulas are manifestations that can bring the patient to emergency physicians' attention (Table 6)^[151].

Most patients with a perianal abscess present with pain, swelling and redness of the interested area. High abscesses also known as supralevator abscesses do not extend to the more superficial perianal tissues and are not associated to visible and palpable inflammatory signs, but more often to systemic signs like fever and malaise^[7, 149]. If a supralevator source is suspected a CT scan or MRI is useful cause it gives more

information about the abscess extension, but also on eventual associated intrabdominal findings^[7].

When approaching a patient with a perianal abscess or fistula, the initial goal must be the sepsis control. The early drainage is the only accepted treatment for this purpose, eventually associated to gram negative and anaerobic spectrum antibiotics in patients on immunosuppression and in those with septic shock^[152, 153]. It is recommended to leave a Petzer or a Malecot catheter in wide ischiorectal abscesses^[147, 153]. It is better to perform the drainage in general anesthesia, especially if the patient is in pain, because this will allow a better exploration.

As a result of the inflammation, it could be challenging to find the underlying fistula and unsuccessful attempts could cause tissue destruction and create an iatrogenic track. There is no evidence on support of wound packing following the drainage. Nevertheless, it could have a hemostatic role in case of bleeding. If the fistula track is evident, a loose draining seton should be inserted. ¹ There should be no attempt to lay the fistula open at the same time, to preserve future anal function whose damage would negatively impact on patient lifestyle^[153].

In the emergency setting, there is no room for treatment such as fibrin glue, fistula plug, ligation of the intersphincteric fistula tract, advancement flap, and stem cells. These will be considered when the acute process is completely solved. At this point, patient will be referred to a tertiary center and a multidisciplinary team will decide which is the best treatment for him^[154]. The decisional work-up will also include a sigmoidoscopy to define if perianal sepsis was associated to an active proctitis^[147].

A recent UK survey summarize the state of the art on acute management of perianal sepsis in CD. 32% of the responding surgeons (133/179) confirmed that they ²³ would drain sepsis, 31.1% would consider placement of a seton and only 0.6% would consider excision of the fistula track. That is in accordance with the previous evidence. When further investigations are needed, MRI is the imaging of choice (96.1%). Most respondents (42.2%) would start antimicrobial therapy preoperatively and the antibiotic of choice is metronidazole (77.9%). In case of recurrent sepsis, most respondents are

used to create a diverting stoma. In fact, as demonstrated in other studies, it may improve quality of life in patients with severe and recurrent perianal CD^[155].

CONCLUSION

CD is a chronic and recurrent inflammatory disease that can present with acute complications. The patient's clinical status and assessment of the background disease location and severity must be considered to guide diagnosis and treatment of the acute complications. CD is unremitting and incurable, and, therefore, treatment aims to induce a deep and prolonged remission, prevent and address complications of the disease, avoid extensive bowel resections, and improve quality of life. Acute surgical emergencies in patients with CD are associated with a high morbidity and mortality. Although most acute complications of CD are managed nonoperatively, it is important to recognize those that require surgical management.

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