

# Surgery Versus Medical Management for Crohn's Disease Limited to the Distal Ileum

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## ABSTRACT

Patients presenting for first time with Crohn's disease limited to the distal ileum are usually treated with medical therapy. When relapse occurs, there is the option of further medical treatment including strapping up to a biological agent or surgery in the form of a localized resection of the diseased segment of intestine.

The surgery is followed by recurrence in many cases, with rates for clinical recurrence of 30% to 50% and for surgical recurrence of 20% to 30% at five years. Reoperation rates rise to 30% to 60% at 10 years. The majority of patients with Crohn's disease treated medically will require surgery at some time during their illness. During the period of medical treatment, before a resection is performed, patients may have a reduced quality of life due to side effects of therapy or to disease activity. Several factors have been proposed for recurrence of Crohn's disease: the type of Crohn's disease (perforating versus obstructing) and the type of anastomosis constructed with the existence of luminal factors that produce early recurrence of Crohn's disease at a preanastomotic site.

In Crohn's disease of distal ileum, surgery is an alternative to medical treatment early in the course of the disease, taking into account the following: benefits and risks of medical treatment and surgery; risk of recurrence after surgery.

Surgery has the capacity both to induce and maintain remission for unpredictable length of time via a single procedure, but the complications which develop cannot be considered easy as is the case with medical therapy, which can be stopped.

**Key words:** Crohn's disease; Distal ileum; Perforating; Obstructing; Early recurrence

## INTRODUCTION

A World Congresses of Gastroenterology in Vienna 1998 designed a simple classification system of Crohn's disease based on the clinical variables, which include age at diagnosis, anatomic location and disease behavior [1]. The anatomic location is classified as upper gastro-intestinal tract, terminal ileum, ileo-colon and colon.

In Montreal classification of inflammatory bowel disease [2], Crohn's disease is classified on the basis of three predominant parameters: age at diagnosis (age below 17 years, 17-40 years and >40 years), anatomical location of disease (ileal, colonic, ileocolonic and upper gastro-intestinal tract) and behavior (non-stricturing and non-penetrating, stricturing, penetrating) [2,3]. The investigators for Montreal classification recognize that Crohn's disease isolated to the colon may represent a distinct pathological, clinical, serological and molecular subtype.

Distal ileal disease is the one limited to the lower third of the small bowel with or without cecal involvement. Ileo-colon disease affects both the colon and distal ileum. Colon disease represents any colonic involvement between the rectum and cecum without small-bowel disease and upper gastro-intestinal disease is any disease located proximal to the distal ileum. The disease behavior is classified as stricturing, nonstricturing, penetrating and nonpenetrating (inflammatory) [4]. Patients who require surgery for disease of the distal ileum should usually undergo resection of the affected bowel. The procedure can be performed through an open or a laparoscopic approach.

## MATERIAL AND METHODS

We identified potentially relevant studies for each review question by analyzing titles and abstracts and full papers were then obtained. Two independent MEDLINE and EMBASE searches were performed to identify relevant papers published between 2000 and 2014.

The following medical subject headings terms were used in the researches: Crohn's disease, time to recurrence postmedical treatment or post surgery, anatomical location, age, sample size, length of follow-up, ileocolic surgery compared with infliximab therapy, overall recurrence rate, clinical recurrence rate, surgical recurrence rate, mucosal recurrence rate. The search terms were identified in the title, abstract or medical subject. Initially 23772 abstracts of the retrieved studies were reviewed and screened for exclusion criteria. At the end of the search 459 abstract that

fulfilled the inclusion criteria were selected. Finally, 7 full papers which addressed the relevant clinical question of the research were admitted.

We reviewed full papers against pre-specified inclusion/exclusion criteria to identify relevant studies and extracted key information about the study's methods and results into evidence (Table 1 and Table 2).

**Table 1:** Time to recurrence postmedical treatment and post surgery.

Author	Time to recurrence postmedical treatment	Time to recurrence post surgery
Singh Ranger et al., 2006 [5]	Median time to glucocorticoid-treated recurrence 20,1 months (5 to 61 months)	Mean surgery-free period 14,6 months (11 to 21 months )
Sayfan et al., 2000 [6]	NR	NR

NR=not reported

**Table 2:** Recurrence rates for elective surgery of Crohn`disease of the distal ileum after first resection and time to recurrence-elective surgery of distal ileum.

Author	Sample size	Site	Length of follow-up (years)	Overall recurrence rate %	Clinical recurrence rate %	Surgical recurrence rate %	Mucosal recurrence rate	Time to recurrence	Time to reoperation
Baldassano, 2001 [7]	39	IC	4,4	36	NR	NR	NR	Median recurrence free survival 3,94 years	NR
Cook, 2007[8]	37	NR	3,8	NR	NR	28	NR	NR	Median times to second laparotomy 12 months
Stocchi, 2008[9]	56	NR	10,5	52	NR	28,5	NR	NR	NR
Ng, 2009[10]	99	IC	1	NR	28	5	NR	At one year 28% had clinical recurrence and 5% surgical recurrence	Median time to surgical relapse 11,8 months
Eshuis, 2010[11]	55	IC	6,8	NR	38	9	NR	NR	NR

IC=ileocecal; NR=not reported

In Second Surgical Clinic of Emergency Hospital of Craiova between 2000 – 2014, 11 patients underwent surgery for Crohn's disease. 8 cases of penetrating (inflammatory) type later diagnosed due Crohn's disease on histopathological examination. The diagnosis was based on histopathological features of non-caseating granulomas with Lanngerhan's giant cells and absence of mycobacterium.

# RESULTS

Among 11 patients, 6 were male and 5 were female. The ages of patients ranged from 21 to 63 years. 5 patients were in the age group of 30-45 years

Operation was tailored in individual patients depending on the general condition of the patients, degree of peritoneal soiling, time since symptoms, conditions of the intestine, expertise of the operating surgeon and temporary diagnosis made on laparotomy. Resection followed by anastomosis was done in 6 cases, including cases of known Crohn’s disease, while resection followed by end ileostomy with mucous fistula was done in 5 cases. Resected specimens were sent for histopathological examination in all cases.

Out of 11 cases, only 1 patient died postoperatively. This patient had various co-morbidities, including diabetes and hypertension and developed MODS on second postoperative day. All patients with ileostomy underwent closure of ileostomy after 3-6 months of medical therapy for Crohn’s disease

The age at diagnosis, anatomic location, the disease behavior, type of surgical intervention and complications were retrospectively evaluated. All patients gave their written and informed consent prior to surgery.

The patient characteristics (age, location, and the disease behavior, early and late complications) are summarized in (Table 3).

**Table 3:** The patient characteristics: age, location, the disease behavior, early and late complications.

Age in years	Anatomic location	The disease behavior	Type of the surgical intervention	Complications
21	Ileocolonic	Penetrating (inflammatory)	Ileocolic resection +anastomosis	Wound infection
36	Ileocolonic	Penetrating (inflammatory)	Open ileocolic resection+ temporary ileostomy	Postoperative abscess
63	Ileal	Strictureing	Strictureplasty	MODS, died postoperatively
43	Ileocolonic	Penetrating (inflammatory)	Ileocolic resection +anastomosis	Anastomotic leak
37	Ileocolonic	Penetrating (inflammatory)	Ileocolic resection +anastomosis	Anastomotic leak
45	Ileocolonic	Penetrating (inflammatory)	Open ileocolic resection+ temporary ileostomy	Postoperative abscess
58	Ileal	Strictureing	Strictureplasty	Wound infection
25	Ileocolonic	Penetrating (inflammatory)	Ileocolic resection +anastomosis	Wound infection
56	Colonic	Strictureing	Subtotal colectomy + temporary ileostomy	Wound infection
29	Ileocolonic	Penetrating (inflammatory)	Ileocolic resection +anastomosis	-
32	Colonic	Strictureing	Subtotal colectomy+ anastomosis	-

MODS= multiple organ dysfunction syndrome

## DISCUSSION

The management of Crohn's disease remains controversial and complicated. The initial management of uncomplicated Crohn's disease should be medical and only when complications are apparent is surgery indicated. The increasing use of Anti-Tumour Necrosis Factor (**TNF**) antibody and interleukin 10, corticosteroids and 5-ASAs fails to appreciate the benefits of early surgery.

Weston et al. reported a series of 34 patients who underwent surgery for suspected appendicitis, but instead they were diagnosed with incidental Crohn's disease of the ileum [12]. After 12 years of follow up, half of 10 patients who had an immediate ileo-colic resection required no further intervention and out of the 24 patients with Crohn's disease of the ileum treated conservatively, 20 patients required surgery for debilitating symptomatology

The recurrence of disease following surgery has been used as an argument for not operating in Crohn's disease. Lochs et al. suggested the use of 5-ASA compounds in the early postoperative period may reduce recurrence rates [13]. Rutggerts et al., reported early reduction in recurrence rates following the use of metronidazole [7]. Hulten et al., demonstrates that operating in the presence of complicated disease increased postoperative morbidity from 12% to 48% and early resection prior to complicated disease was beneficial [15]. Andrews et al. reported 184 ileocolic resections for Crohn's disease [16] and factors associated with postoperative complications (wound infection, postoperative abscess and anastomotic failure) were steroid use, low serum albumin and presence of preoperative sepsis (abscess and fistula).

Treatment of Crohn's disease and other IBD varieties can include improvement in diet and nutrition, the use of medication and sometimes surgical procedures to remove or repair affected portions of gastro-intestinal tract.

In patients with progressive Crohn disease can occur fistulae between bowel loops (cologastric, coloduodenal, enterocutaneous, enterovesicular, ileosigmoid, ileocecal and ileoileal). Surgical intervention may be required because untreated fistulae can cause complications such as abdominal pain, abscess formation or unexplained diarrhea. Radiologic studies should be performed to rule out concomitant abscesses, which can be drained when present. In cases of persistent sepsis, the affected bowel is excised when an abscess is present or not.

Urgent surgery may be required in cases of perforation, abscess, recurrent hemorrhage and toxic megacolon. If medical therapy for active Crohn's disease fails (anti-inflammatory, immunosuppressant therapy and anti-tumor necrosis factor agents: infliximab, adalimumab, certolizumab pegol and natalizumab) surgical resection of the inflamed bowel with restoration of continuity is indicated.

Patients who have surgery for Crohn's disease remain at risk of developing recurrent disease and rates of second surgery were 33% at five years and 44% at ten years after the first intestinal resection [17]. Following intestinal intervention, inflammation develops in previously normal bowel or can occur close to the anastomosis [18,19]. Different drugs have been used with the scope of reducing chance of recurrence after surgery included immune suppressives, corticoid treatment, 5-ASA and metronidazole [20].

At times passes, the disease can progress to a slow perforation of the intestinal wall with abscess formation [21,22] that may require surgery.

Usually a surgical anastomosis prevails the necessity for stoma. In the last years, laparoscopic surgery has been increasingly used.

## **PATHOLOGY**

### **Macroscopic Features**

The intestinal wall in patients with advanced Crohn's disease is rigid and markedly thickened by edema and fibrosis resulting in narrowing of the lumen (Figure 1). The distension of the intestine may take a secular form with eccentric intestinal disease and the proximal intestine may be dilated. Multiple or single strictures are common and may be associated with complete or partial obstruction. The serosa is covered in varying degrees with engorged vessels, lymphatics and exudates. The serosa is often granular and minute nodules of lymphoid tissue may be seen on the surface.



**Figure 1:** The colon has been opened to show thickening of the wall and narrowing to the lumen. The mucosal surface is ulcerated and partially covered by necrotic slough. The serosal surface has granular appearance and mesentery is thickened and oedematous because of a transmural inflammatory process.

The adjacent mesentery, is usually inflamed, shortened, swollen and contains enlarge, juicy lymph nodes. The mesenteric fat tends to creep onto the serosal surface of the intestine and occasionally extends to wrap around the intestine, a finding that is frequently associated with transmural inflammation [23].

The difficulties of distinguishing Crohn's disease from tuberculos enteritis have been repeatedly emphasized [24-27]. In tuberculosis the luminal narrowing may be tubular [27]. Granulomas are a feature common to intestinal tuberculosis and Crohn's disease. In tuberculosis, granulomas account for a greater variability in size and stage of evolution and in contrast, the granulomas in Crohn's disease, remain discrete and represent the same stage of evolution. The

cracks and fissures emphasized by Lockhard-Mummery and Morson (1964) [28], Williams (1964) [29] and Morson (1968) [30] as are important diagnostic feature for Crohn's disease.

Deep fissures may penetrate through the intestinal wall and give rise to sinuses or fistulas. These sinuses may extend into the mesentery and end as blind abscesses, adding to the inflammation and resulting in formation of a mass. The ureter may become encased by retroperitoneal inflammatory process causing a hydronephrosis. Inflamed loops of intestine may adhere to uninvolved loops of the intestine with the development of ileocecal and ileosigmoid fistulas [31,32]. This fistula may extend to the skin, particularly to the healed surgical scar, and to genitourinary tract (the ureter, the bladder and the vagina). Psoas abscesses secondary Crohn's disease have been described as has extension of such abscesses into the right hip [33].

On section, the whole diseased intestinal wall is thickened especially the submucosal layer. The wall of the intestine is infiltrated transmurally with edema, inflammatory cells and degrees of fibrosis. The mucosal surface may be edematous, hyperemic and ulcerated usually. The aphthous ulcer begins as a minute micro abscess in a lymphoid follicle and grows to become a focal superficial ulceration surrounded by normal or edematous mucosa [34]. In more advanced disease, the mucosal ulceration is fissured and may extend deeply into the submucosa.

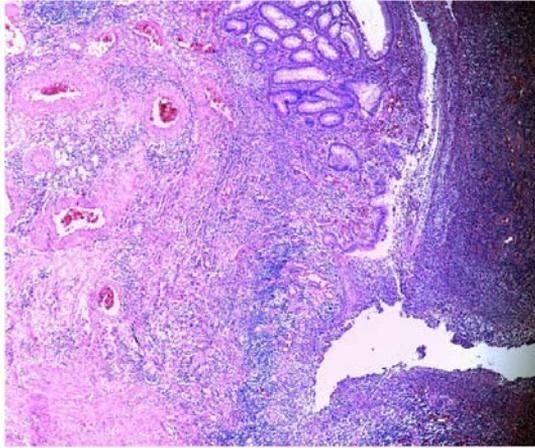
The ulcers run in a longitudinal or transverse direction, which gives rise to the cobblestone appearance of the edematous mucosal islands between the ulcers (Figure 2). Rarely, the inflammatory process is limited to the superficial layer of the intestine mucosa and submucosa [35].



**Figure 2:** Cobblestone of the mucosa of the transvers colon in the 32-year-old patient with Crohn's disease. Communicating fissures and crevices in the mucosa and separate islands of intact edematous epithelium.

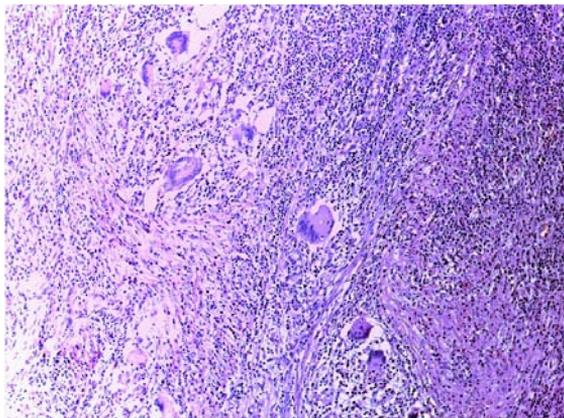
## Microscopic Features

The most common forms of Inflammatory Bowel Disease (**IBD**) are ulcerative colitis and Crohn's disease (Figure 3). Ulcerative colitis is considered in general a mucosal disease whereas Crohn's disease is both a mucosal and mural disorder [36,37]. In 1989, McQuillan and Appelman describe superficial Crohn's disease, characterized by inflammatory changes limited to mucosa and submucosa. These patients had only minimal transmural inflammation and absence of fissures extending beyond the submucosa [38].



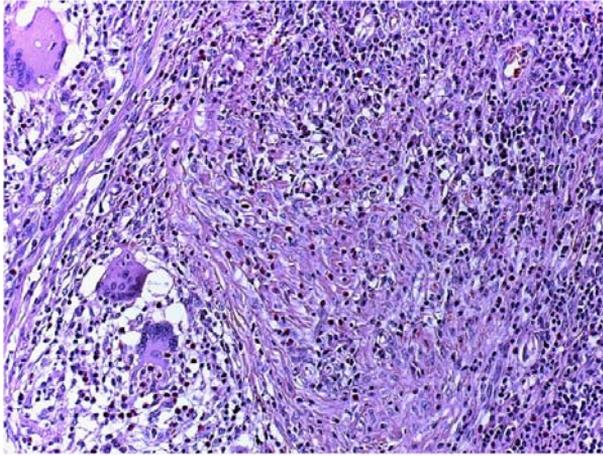
**Figure 3:** Hematoxylin & Eosin stain 40x - Areas of mucosal ulceration associated with non specific inflammation. The colon mucosa has been lost and its place is an exudates consisting of fibrin and neutrophils.

Microscopically, Crohn's disease is characterized by transmural granulomatous inflammation which includes the presence of obstructive lymphedema, plasma cells and lymphocytes most prominent in submucosal layers of the intestinal wall (Figure 4). These features are also noted in serosal and in the muscular layers and are responsible for the thickening of the wall. The histological features of Crohn's disease are granulomas, deep fissuring ulcers, transmural lymphoid aggregates and small intestine involvement [3].



**Figure 4:** Hematoxylin & Eosin stain 100x - Granulation tissue associated with mixed inflammatory cell infiltrate.

Noncaseating granulomas which are composed of lymphocytes and epithelial cells with Langerhans giant cells are found in the diseased intestines of 60% of patients with tend to localize to submucosa (Figure 5). In 25-30% of patients they are noted in the mesenteric lymph nodes [39].



**Figure 5:** Hematoxylin & Eosin stain 200x - Central granulomata with epithelioid macrophages.

On the microscopic examination may be seen mucosal ulcers which are often serpiginous and extend to a variable depth through the intestinal wall, as well as fistulas, perforation and abscesses [40].

Fibrosis of the muscularis mucosa and submucosa in severe disease is responsible for stenosis of the intestinal lumen.

## **SURGICAL CONSIDERATIONS**

### **Choice of Incision**

The incision should provide adequate exposure for performance of the necessary procedure and the incision should avoid traversing potential primary sites of ostomy construction

The midline abdominal incision with extension superiorly or inferiorly provides adequate visualization of all portions of the abdomen and pelvis, and its locations avoids all potential sites for ostomy placement. Although the transverse abdominal incision has been espoused as ideal in providing access to all quadrants of the abdomen [41] its placement below the umbilicus may fail to fulfill second requirement. Supraumbilical transverse incisions in an infant or child provide adequate access to entire abdomen [42] but this approach in adults may severely limit exposure of the lower abdomen and pelvis. Midline incision is associated with a low incidence of closure complications and if those complications may occur they represent failures in surgical technique rather than of the closure method [43]. Closure of the midline incision is straightforward, but the use of retention sutures produced by these sutures frequently produces pressure necrosis on the parts of the abdominal wall.

## Resection Margins, Margin Lengths and Lymphadenectomy

Efforts to reduce recurrence rates and anastomotic dehiscence after operations for Crohn's disease have generated diverse opinions regarding the adequate length of specimen margins after resection. In case of extended resection, histologic evidence for active Crohn's disease occasionally may be identified at resection margins and this has led some surgeons to request frozen-section analysis of the margins and consider additional resection of the margins and to consider additional resection if margins are not free of disease [37-39]. Other surgeons opt for a more limited resection of grossly normal intestine adjacent to the involved segment because the incidence of postoperative complications and recurrence may not be influenced by the presence of microscopic disease at the resection margins [47,48].

The sensitivity of frozen-section examination of active Crohn's disease is approximate 50% and it may not be available when an emergency operation is performed [49]. The use of frozen-section examination to assess adequate resection margins is unreliable because of focal nature of inflammation in Crohn's disease or from insufficient sampling. Resections should be performed only for symptomatic lesions in patients with extensive multiple areas of involved intestine and resection of 80 cm or more of terminal ileum may result in steatorrhea [50]. Clinical patterns of disease, prior resections and multiple skip may influence recurrence at a specific anastomosis. If an isolated segment of intestine is responsible for surgical intervention, macroscopically uninvolved margins can be easily obtained.

Resection margins of 2 cm should be adequate and the mesenteric dissection should be limited to whatever is necessary to perform the appropriate resection. The enthusiasm for wide lymphadenectomy [51,52] in preventing recurrence is supported by little evidence of efficacy.

There is no correlation between recurrent anastomotic disease and residual endoscopic lesions [53] or even microscopic Crohn's disease abnormalities at the resection margin [54].

## Surgical Procedures

The majority of patients affected by Crohn's disease require surgical interventions. It is well known that surgical resection is superior to bypass when technically feasible. For ileal disease extending to or within 10 cm of ileocecal valve, the cecum is resected in continuity. Most surgeons perform bowel resection for Crohn's disease. A bypass operation is still considered a reasonable procedure in specific situations. For certain types of ileocecal Crohn's disease with associated abscess or phlegmon densely adherent to the retroperitoneum, exclusion bypass with extraperitoneal abscess drainage is reasonable. Most forms of ileocecal Crohn's disease, even with such septic complications, can still be handled well by resection. In continuity (simple) bypass procedures can be done for the rarely seen Crohn's disease patient with fibrotic rather than inflammatory stenosis of the ileum, especially when the patient's condition is poor.

Stapled side-to-side anastomosis might be better than handsewn end-to-end anastomosis in ileocolic resection for Crohn's disease [55]. In Crohn's disease the submucosal plexus of macroscopically normal bowel is compromised by vasculitis [56,57] and reduced of collateral flow caused by transaction and anastomosis may lead to stenosis. The use of stapling devices provides to construct intestinal anastomosis and side-to-side technique it allow to surgeon to control the size of anastomotic lumen [58,59] and the use of staplers may cause less tissue reaction and may be associated with low recurrence rates [60].

Reconstruction after resection is generally by end-to-end anastomosis, but the size discrepancy between the two ends is so great that an end-to-side anastomosis is done with the ascending colon to maintain the water-absorbing capacity of the right colon. Right colectomy is performed only when colonic disease necessitates it. Usually a surgical anastomosis prevails the necessity for stoma. In the last years, laparoscopic surgery has been increasingly used.

The laparoscopic approach is associated with longer operative time but shorter length stay and more rapid resolution of the ileus [9]. Limited disease-free (2 cm) resection margins are adequate and anastomosis can be constructed with suture or mechanical stapling device. Stapled anastomosis is safer assuming the bowel wall is not thickened [61,62] and side-to side anastomosis may provide a lower risk of recurrence [63,67].

The laparoscopic management of ileocolic Crohn's disease is a safe and technically feasible, with a low complication rate and low conversion rate. Initially laparoscopic surgery was not attempted from Crohn's disease due to extensive inflammation, thickened mesentery, enteric fistulae and skin lesions through-out the bowel [68]. Benefits from a laparoscopic approach are that reduces scar and adhesion formation, shorter hospital stay, decreased wound infection and quicker return to bowel function. The patient selection and surgeon experience are important factors for successful laparoscopic surgery. Long term studies following laparoscopic and open ileocolic resection patients showed no difference in recurrent rates [9,69].

Laparoscopy is emerging as the standard approach for patients with Crohn's disease for initial surgery and even in selected case of patients with recurrent and complicated Crohn's disease [70].

## Ileotransverse Colostomy

Ileotransverse colostomy, the standard bypass procedure for ileocecal Crohn's disease, was developed because ileocolic resection in era before antibiotics, blood banking and other support techniques often carried out mortality about 20% [71]. To reduce mortality was advocated a two-stage approach. The first step was bypass ileocolostomy who was accomplished with little mortality and the second step was the resection. The ileotransverse colostomy with exclusion is associated with probably risk for development of adenocarcinoma. The retrospective study with 15 years follow-up, recurrence rates were 65% for resection, 82% for bypass with exclusion and 94% for a

simple bypass [72]. In patients with difficult resection secondary to retroperitoneal involvement by a septic process, extraperitoneal drainage and bypass with exclusion is recommended [73].

The proximal end of the excluded segment is brought to the skin because the closure of the proximal end of the excluded segment may lead to perforation or to development of a large infected mucocele. Resection of the excluded segment can be performed at a later date.

Cameron et al. [74] demonstrate that patients who have a side-to-end ileocolonic anastomosis have recurrent involvement of portion of ileum adjacent to the colon. Rutgeerts et al. [75] have shown that proximal diversion above an ileocolonic anastomosis prevents recurrence at anastomotic site.

Simple bypass may be performed for chronic obstruction in patients with jejunoileal disease [76]. In patients with short-bowel syndrome, in an effort to preserve intestinal length, minimal surgical intervention consisted in combinations of short-segment minimal resection, side-to-side enteroanastomosis and stricturoplasty: technique of short stricturoplasty in the manner of a Heineke-Mikulicz or technique of longer stricturoplasty in the manner of Finney piloroplasty for strictured segments more than 10 cm long.

Resection with primary anastomosis is still the treatment of choice for primary ileal or ileocecal Crohn's disease unresponsive to medical management.

## Temporary Loop Ileostomy

Temporary loop ileostomy may be particularly valuable in emergency situations [77] and may be helpful in certain circumstances to permit diversion of fecal stream in setting of Crohn's disease of the distal small intestine and proximal colon.

In case of the free perforation, resection of the diseased segment and primary anastomosis should not be done. In these circumstances construction of an end ileostomy and mucous fistula is recommended [78] or construction of a double-barreled cutaneous ileostomy [79]. In more favorable circumstances permitting performance of an anastomosis, a proximal diverting loop ileostomy may be used as a complementary procedure to protect anastomosis.

Patients with ileocecal Crohn's disease and perforations of the intestine at the mesenteric border with formation of a mesenteric abscess, the initial treatment might consist of drainage and loop ileostomy, resection being deferred until the patient's general condition improve. With resolution of the abscess, a more conservative resection may be possible only the intestine involved with the Crohn's disease being resected.

A loop ileostomy may be necessary as a temporary measure in the unusual circumstances of emergency intervention for obstruction when extent of disease is not clear [77,80].

The ileostomy is used as an adjunct to complicated procedures when the risk of anastomotic leakage is high.

In situations with multiple simultaneous resections, difficult subtotal colectomy with ileoproctostomy, resection and anastomosis performed in the presence of gross infection or contamination, presence of multiple fistulas, the ileostomy is used for temporary diversion proximal to an anastomosis after definitive resection.

Temporary loop ileostomy may serve occasionally as the initial procedure for patients with fulminant disease that is in poor nutritional condition and for patients with extensive perianal disease.

## CONCLUSIONS

Implementing appropriate and timely surgical intervention can lead to significantly decreased of pre- and postoperative morbidity and significant improvement in quality of life in Crohn's disease.

Infliximab and adalimumab are recommended as treatment option for adults with severe active Crohn's disease which has contraindications or are intolerant and has not responded to immunosuppressive and/or corticosteroid treatments.

Infliximab is a chimeric huma-murine monoclonal antibody that binds with high affinity to TNF $\alpha$  and inhibits its functional activity and is indicated for treatment of severe and fistulising active Crohn's disease.

Adalimumab is recombinant human monoclonal antibody that binds specifically to TNF $\alpha$ , blocking interaction with its cell-surface receptors and limiting the promotion of inflammatory pathways.

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