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The changing landscape of surgery for Crohn's disease

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Abbreviations: Crohn's Disease (CD), Inflammatory Bowel Disease (IBD), Anti-Tumor Necrosis Factor (aTNF), Immunomodulators (IM), Azathioprine (AZA), Mercaptopurine (MP), Methotrexate (MTX), Ileal Pouch Anal Anastomosis (IPAA), Continent Ileostomy (CI), Multidisciplinary team conference (MDT)

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Abstract

The incidence of Crohn's disease is increasing world-wide and the disease location and behavior is changing towards more colonic as well as inflammatory behavior. As previous data have spoken towards ileal disease and stricturing and penetrating disease to be the indications most in need of surgery, one could expect the surgical load to decrease. As these changes are relative, the absolute numbers of surgical interventions are less affected. There are also data showing an increasing complexity among patients at time of surgery. Finally, a new role for surgery as initial therapy to induce remission instead of biologic therapy in ileal or ileocaecal disease has been suggested. In order to improve the care for patients with Crohn's disease in general, and the peri-operative phase in particular, the use of multidisciplinary team discussions is essential. In conclusion, the role of surgery is changing. Fewer patients need surgery, but when they do they have more complex disease. In the future, ileocaecal resection may be used increasingly as initial therapy to induce remission in a true top-down approach.

Introduction

Crohn's disease (CD) is an inflammatory bowel disease (IBD) characterized by discontinuous (often referred to as skip lesions) transmural inflammation involving any portion of the gastrointestinal tract^{1 2}. The original description by Crohn *et al* was of a regional ileitis³ and the classical ileocecal type of the disease was affecting the ileum and cecum. There is quite often a time lag between the first symptoms and the eventual CD diagnosis⁴. Symptoms are dominated by crampy abdominal pain, bowel obstructions and diarrhoea. However, fistulas, intestinal as well as perianal, are quite frequent and after 20 years disease duration up to 50% of patients may have suffered of at least one episode of fistulation⁵⁻⁷. The disease sometimes causes growth retardation and/or delayed puberty in children and adolescents and weight-loss and malnutrition in adults, both due to less food intake but also due to the inflammatory activity and sometimes by-passes created by fistulas^{6 8 9}.

There is as yet no gold standard diagnosing CD¹⁰, hence it remains a test of clinical skill depending on relevant patient history, thorough physical examination, laboratory testing, and detailed review of radiographic, endoscopic, and pathologic reports¹⁰. The disease is nowadays classified according to the Montreal classification (Table 1) aiming to describe the different forms of severity in CD¹¹. In general terms, younger age at diagnosis, wider spread in the intestinal tract and more complicated disease predicts worse long-term outcome.

As CD is a chronic disease with no definite cure, it may have a severe impact on quality of life compared with the general population due to lack of energy, pain, diarrhea, malnutrition, perianal disease, ostomy-related concerns and the uncertain nature of disease in general¹²⁻¹⁴. Previous studies have shown that such impairment in quality of life is more associated

with severe disease activity rather than the disease itself or even the localization or behavior of the disease^{13 15-20}. The different therapies for CD are focused on relief of symptoms and dealing with complications to the disease. In active disease, induction of remission can be achieved either through medical therapy or surgery. When patients have no or limited symptoms therapies are aimed at maintenance of remission and to prevent relapsing of symptoms and need of further surgery. It is important to remember that most patients spend most of their life in remission²¹ and that medical therapy and surgery are used as *complementary* therapies can achieve remission with low symptomatic load in many patients^{22 23}. The correlation between remission and quality of life is strong, regardless if remission was achieved medically or surgically^{24 25}.

The disease has for a long time had a very high incidence and prevalence in western and northern countries with Sweden, Canada and northern US having among the highest incidences, but is today getting more common also in previously low incident regions²⁶. The location of CD within the gastrointestinal tract seems to have changed somewhat over time. Originally described as a segmental ileitis (L1, Table 1) this location has, in relative measures, decreased in favour of CD colitis (L2) and ileocolitis (L3)^{27 28}. Apart from the change in the location of the disease there are also a number of reports on a shift towards more patients diagnosed either very early (A1) or late in life (A3)^{27 29} as well as less frequent occurrence of stricturing (B2) or penetrating disease (B3)²⁷.

Primary medical therapy

Originally steroids were the only drug used in CD. Later on slow-release formulas and development of budesonide, with a high first passage metabolism in the liver, has improved

the effect and with somewhat less side-effects. Long term use of steroids do however have severe side effects and in modern CD therapy the basis of medical therapy has shifted to immunomodulators (e.g. azathioprine (AZA) and mercaptopurine (MP)), methotrexate (MTX) and so-called biological therapies. The first type of biological therapy was the antibodies targeted at the tumor necrosis factor receptor (aTNF), e.g. infliximab (IFX), adalimumab and golimumab. These have since been followed by other antibodies targeting other receptors involved in the inflammatory cascade, i.e. vedolizumab and ustekinumab³⁰. Vedolizumab is an antibody targeted against the $\alpha 4\beta 7$ receptors of circulating lymphocytes that normally migrate into the gastrointestinal tract, and thus preventing them from reaching their goal, while the antibody ustekinumab diminishes the intestinal inflammation by targeting receptors for interleukins 12 and 23.

The medical treatment has also in some ways gone from a gradual step-up of medication³¹ to a more rapid step-up, or even a “top-down-approach” in selected patients^{32 33}. Whether this change in strategy really has modified the course of the disease or the need of surgery is still debated^{34 35} and at the same time there has been a vast change in the costs for the healthcare of IBD patients. Up to the turn of the millennium, hospitalization and surgery were the major cost drivers in IBD care, but a recent Dutch study found aTNF use to be the main costs driver currently, accounting for 64% of the total cost in CD, while surgery accounted for less than 1% of the healthcare costs in CD³⁶.

Surgical therapy

The disease was first treated with extensive resection³⁷, with the inherent risk of developing short bowel syndrome and intestinal failure^{38 39}. The extent of surgical resection has since repeatedly been shown to be of less importance for treatment outcome⁴⁰⁻⁴², and today

bowel-preserving techniques are preferred, such that inflamed areas are not always surgically removed (unless engaged in fibrotic strictures and/or fistulas) and short strictures may be treated by strictureplasty instead of resection⁴³⁻⁴⁶.

Surgical therapy should be applied according to both location and behavior of the disease but also to where in their life span the patients is as well as the effect on the patient, e.g. delayed growth or puberty in children and adolescents. In general, indications for surgery in CD has been the treatment of complications of the disease, e.g. stricturing and/or penetrating disease (Table 1). Prior to the end of the last millennium, and before the wider spread of immunomodulating and biological therapy, about 50% of patients underwent abdominal surgery within 10 years of their CD diagnosis^{47 48}. Decreasing surgical rates have been reported during the last 50 years down to 24-27% after 5 years from diagnosis after 1990⁴⁹. The studies included in the meta-analysis by Frolkis *et al* are however heterogeneous and a vast majority of the included patients were diagnosed prior to the introduction of IM and aTNF, with scarce or no information on type of surgical procedures. In a more recent study from Sweden the cumulative incidence for first abdominal surgery within ten years of CD diagnosis were as low as 21% for patients diagnosed between 2004 and 2009 and the cumulative incidence of a repeated abdominal procedure five years following the primary procedure was only 15% among those patients diagnosed with CD in 1996–2000⁵⁰. A similar finding was presented by Jeuring *et al* from the Netherlands who found decreasing trends in need of hospitalization as well as use of surgery in CD while no change was seen in disease progression⁵¹. The use of IM and aTNF increased significantly over time but in a matched control using propensity-score no differences in hospitalization, surgery, or phenotype progression were found between patients with or without IM or aTNF therapy. In another

study the occurrence of bowel resections were compared in patients with long-term (>12 months) and short-term use (<12 months) of aTNF and no difference was found between the two groups³⁵.

Ileocecal resection is today still the most common procedure in CD and in a recent study from the US no decrease could be seen in the period 1993-2004 regarding the frequency of ileocecal resections or right hemicolectomies in CD ⁵². More recent data from Sweden on the other hand show a very different picture, with the 10-year cumulative incidence of an ileocecal resection having decreased from 40% in patients diagnosed between 1990 and 1995 to 16% in patients diagnosed between 2004 and 2009. Furthermore, the need of a repeated ileocolic resection was as low as 5% after five years, but with no significant temporal changes in ileocolic resection rates seen over the whole time period 1990 to 2014⁵³.

Location

Ileitis and terminal ileitis

A recent landmark randomized controlled study compared laparoscopic ileocecal resection with IFX therapy in non-stricturing terminal ileitis and found surgery to be equally good as IFX therapy in regards of quality of life, complications, repeat hospital admissions and complications to the given therapy⁵⁴ but at a lower cost already after one year⁵⁵.

During a median follow-up of four years 37% of patients in the IFX group went through a resection, while 26% patients in the resection group were put on aTNF later on. Altogether laparoscopic surgical resection in terminal ileitis may be an alternative to aTNF in inducing remission in unifocal disease. In most cases both therapies may be reasonable options as

first line therapy, and it may therefore be down to the choice of the patient which therapy is used firsthand. Even though the risk of repeat ileocolic resection is low⁵³ there is however a subsequent risk of needing either surgery or aTNF as secondary therapy at a later stage and patients should be informed of this as well.

Endoscopic recurrence is apparent in a majority of patients already within the first year after resectional surgery for ileal CD⁵⁶ and the severity of the endoscopic recurrence may in some way also give information on the risk of clinical and/or surgical recurrence^{57 58}. Some patients are more prone to have a recurrence of their ileocolic disease, e.g those who continue to smoke^{59 60}, have perforating disease^{60 61}, a short duration between CD diagnosis and surgery as well as between primary and repeat surgery⁶²⁻⁶⁴, or have peri-anal disease^{62 64}. Moreover, some studies have found histopathological factors like presence of granulomas in the resection margin of the small bowel⁶⁵ or mesentery⁶⁶ as well as myenteric plexitis^{67 68} to be associated with a higher risk of post-operative recurrence.

An alternative to surgical resection of a strictured small bowel segment may be strictureplasty. The method was initially described by Emanoel Lee, Oxford, who transferred the technique from tuberculosis surgery to CD surgery⁶⁹. In the beginning the technique was mainly used in patients with multiple short strictures in order to diminish the risk of developing intestinal failure in the long run. Later a number of more advanced methods have been developed with long ileal segments of skipped lesions and strictures, the Michelassi isoperistaltic side-to-side strictureplasty being the most well-known⁷⁰. A recent addition to strictureplasties is the method described by de Buck van Overstraeten *et al*⁷¹. In patients with a wide-spread ileal disease, a long side-to-side isoperistaltic strictureplasty involving the ileocecal valve is used in order to save bowel length.

In patients with short strictures of the terminal ileum balloon dilation may also be an option in order to defer surgery⁷². There is a risk of perforation at time of dilation and it has been suggested that it would be safer in an anastomosis compared with a de novo stricture but a meta-analysis could not verify this and both seems safe⁷³. Like in resectional surgery, smokers have a less favorable outcome of an endoscopic dilation⁷⁴ and this emphasises the importance of stopping smoking in CD⁷⁵. There seems, however, to be an increased risk of surgical complications in patients failing a balloon dilatation of anastomotic strictures in comparison with those going straight to repeat resection, and the endoscopist as well as the patient should be aware of this⁷⁶. In strictures of the colon the risk of colorectal cancer has to be considered^{77 78} and resection is recommended rather than strictureplasty or dilation⁷⁹
80.

Colitis

Crohn's disease of the colon can be widespread like ulcerative colitis but quite often more limited to only one or more segments. Historically, proctocolectomy or colectomy with an ileorectal anastomosis was the gold standard⁸¹, while today segmental resections have gained ground⁸²⁻⁸⁴ and indication for surgery is dependent on the extent and location of the disease. Before the 1990's approximately half of all patients with colonic CD would have had surgery within 10 years of their diagnosis and a quarter will have had an ileostomy⁸⁵. More recent numbers from Sweden show a 5-year risk of colonic segmental resection in all CD patients to be around 8% while the risk of colectomy or proctectomy is 1% and 0.6% respectively⁵⁰. There seems to be similar risks of repeat surgery regardless of whether subtotal colectomy or segmental resection is performed, but with better quality of life and bowel function in the latter case^{83 84 86}. However, in the case of two or more involved

segments there seems to be an increased risk for repeat surgery among patients with segmental resection⁸⁷. A possibly important factor in the long-term chance of keeping the colon and avoiding a permanent stoma is the use of IM and aTNF as the increasing use of these drugs have coincided with a decrease in left colectomies and subtotal colectomies due to CD^{34 52 82 88 89}.

In the acute setting of a severe CD colitis and/or severe perianal disease a diverting stoma may be a good option to colectomy and/or proctectomy^{90 91}. This may have advantages as it is a less invasive procedure in the very ill patient and also adds the possibility to let medications like IM and aTNF to anecdotally work better in a defunctioned bowel. It is however important to realize that only a third of the patients will have their stoma reversed and that in the long term only one of four reversed patients will keep their bowel continuity⁹¹. Also, the outcome of a diverting stoma is somewhat worse in the era of aTNFs, both in the early response rate and long-term outcome⁹¹. This is possibly due to the selection of a group of more ill patients today as most of them will have failed both IM and aTNF therapy before being offered a diversion, while a diversion was offered a lot earlier previously and possibly to patients who today would have responded well to medical therapy⁹¹.

In the case of proctocolectomy, end ileostomy is the gold standard but in highly selected cases restorative surgery may be offered to CD patients as well. Panis *et al* have shown that it is not unreasonable to offer the well-informed CD patient an ileal pouch anal anastomosis (IPAA)⁹². Our unit have been more prone to offering these patients a Kock's continent ileostomy (CI)⁹³ as complications are somewhat less difficult to deal with in the abdomen compared within the pelvis. Apart from a well-informed patient strict criterions should be

used and only offering it to patient without signs of CD in small bowel for a minimum of five years (verified with capsule endoscopy and/or small bowel MRI) and tolerance to IM and/or aTNF⁹⁴ and in the case of IPAA also no history or signs of perianal disease⁹².

In some instances, a proctectomy, or pouchectomy, is still needed in the end and it is a well-known fact that these patients may have a complicated perineal wound healing in up to 55% and around 50% have not healed within three months⁹⁵⁻⁹⁷. A recent study by Li *et al* has shown the importance of dealing with the perianal sepsis prior to the proctectomy letting the area to cool down, preferably with a stepwise approach with first a diverting stoma⁹⁶ and then possible also the use of aTNF⁹⁸.

Disease behavior

There are epidemiologic studies suggesting that CD has evolved towards earlier detection and is associated with less complications²⁷. Yet, contradictory to this, other studies show that the indication to surgery in CD has shifted to more complicated procedures with fistulizing disease⁵². There is an inherent risk of trying medical therapy too long in the non-responding patient and this has been shown to be associated not only with deterioration of the patient, with weight loss and development of perforating disease, but also with more surgical complications and need of a stoma (Figure 1)^{99 100}.

It has been shown that apart from smoking, anemia, weight-loss and hypo-albuminemia, also perforating disease and colonic CD have an increased risk of anastomotic complications¹⁰¹⁻¹⁰⁴. Moreover, the risk of anastomotic complications increases with the number of risk factors present at time of surgery, approaching 50% in the event of three or four risk factors^{101 102}. It is important to evaluate the patient prior to surgery and optimize

with enteral nutrition (or parenteral if enteral nutrition is ineffective) and treat abdominal sepsis with drainage and antibiotics¹⁰⁵⁻¹⁰⁹. In the few cases where such optimization is not possible, it is safer to do a staged procedure with a split stoma, or possibly a diverting stoma, with closure a few months later when the patient has recovered¹¹⁰. Some patients will however be less prone to accept even a temporary stoma, and in this situation it is of utmost importance to evaluate the risks for the individual patient in case of an anastomotic dehiscence. Some patients may be well fit to tolerate a major complication and severe secondary morbidity (with repeat laparotomy, defunctioning stoma and possibly intensive care) and a calculated risk may be justified. Other patients will not have enough reserves, e.g. due to impaired general condition and/or old age, to manage such complication and there will be risk of mortality in case of a dehiscence¹¹¹. All patients, but especially high-risk patients, deserve to be discussed in a multidisciplinary team conference (MDT) prior to surgery and thereafter have an informed consent on a surgical and perioperative plan¹¹². The team however must always remember that calculated risks must be the decision of the patient, as he/she is the one who will suffer the possible consequences.

The MDT is important in the care of patients with IBD, and especially the severely ill patients with a more complicated disease¹¹²⁻¹¹⁴. There is a general consensus that the IBD MDT require presence of IBD oriented gastroenterologist/gastroenterologists and colorectal surgeon/surgeons, radiologist, IBD nurse and preferably also a pathologist^{112 113}

In the preoperative setting patients should be evaluated not only to have the proper indications for surgery, including a proper radiological and endoscopic investigation, but also regarding risk factors and nutritional, medical and surgical optimization. The next step should be the surgical planning, making sure the right procedure is done at the right time

and by the right team¹¹⁴. At time of surgery it is important to understand the importance of not only the experience of the surgical team but the whole IBD team of the unit¹¹⁵. In the uncomplicated setting laparoscopic surgery is gold standard but far more important is that the appropriate approach is used depending on the complexity of the disease and the experience of the surgeon^{79 116}.

Unless there already has been a post-operative medical plan for the patient at time of surgery there should be a new discussion at the MDT¹¹⁵. As mentioned before, penetrating disease^{60 61}, short duration between CD diagnosis and surgery^{62 63} and repeated surgery⁶⁴ are associated with an increased risk of further disease recurrence, but the most important factor is smoking. In a meta-analysis a twofold increased risk of clinical recurrence and a 2.5-fold increase in surgical recurrence was found among smokers⁵⁹. Endoscopic recurrence is apparent in a majority of patients already within the first year after resectional surgery for CD⁵⁶ and in the case of ileal disease a general rule is ileocolonoscopy within 6-12 months in order to evaluate the need of and tailor post-operative therapy with IM and/or biologicals⁷⁹. Less is known in regards of the best post-operative management but active endoscopic monitoring leads to better outcome¹¹⁷ and the value of stop smoking must be made clear for the patient.

Conclusion

Crohn's disease is yet without a medical, as well as surgical cure which is why the therapeutic aim still is symptom control. There is an increasing incidence and prevalence and some evidence is suggesting more colonic location and inflammatory behavior than previously but at the same time there are signs of more complicated disease among patients in need of surgery. Medical and surgical therapies should be used as complementary

methods and multidisciplinary discussions are essential in achieving minimal symptomatic load and highest possible quality of life.

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Tables and figures

Table 1

Montreal classification of Crohn's disease¹¹. The "worst" type of the classification ever taking part in a patient's life will be the one used in the classification, i.e. a patient diagnosed at age 12 with inflammatory ileocolic disease will at first get the classification A1 L1 B1. When the same patient later in life develops colonic disease as well and develops an ileosigmoidal fistula and also a perianal fistula the new classification will be A1 L3 B3p.

	Montreal classification of Crohn's Disease			Disease modifier
Age at diagnosis (A)	A1 ≤16 years of age at diagnosis	A2 17-40 years of age at diagnosis	A3 >40 years of age at diagnosis	N/A
Location of the disease (L)	L1 Ileal or ileocecal disease	L2 Colonic disease	L3 Ileocolonic disease (other than ileocecal)	L4 Isolated upper gastrointestinal disease
Behavior of the disease (B)	B1 Inflammatory, non-stricturing, non-penetrating disease	B2 Stricturing disease	B3 Penetrating disease	p Perianal disease

In pediatric Crohn's disease the modified Paris classification is used dividing e.g. small bowel disease to L1 if the last 1/3 of the ileum is affected and L4b if the small bowel is affected in the proximal 2/3 of ileum up to the ligament of Treitz. Upper gastrointestinal Crohn's disease proximal of the ligament of Treitz is classified as L4a¹¹⁸.

The vicious route of severe Crohn's disease refractory to medical therapy. With increasing non-responsive attempts with medical therapies (e.g. steroids, immunomodulators and/or biologicals) patients may develop clinical impairment with increasing number of surgical risk factors (e.g. weight loss, hypo-albuminemia, perforating disease). Before deciding on a primary anastomosis the risk of an anastomotic dehiscence should be evaluated as well as if the patient is fit enough to survive such complication or not. The patient must be fully aware of such risks as there is risk of severe post-operative morbidity and mortality.