Treatment of inflammatory bowel disease: medical and surgical aspects
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Decision-making in ileocecal Crohn’s disease management: surgery versus pharmacotherapy

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**SUMMARY**

Ileocecal Crohn’s disease can be treated medically as well as surgically. Both treatment modalities have been improved markedly in the last two decades, making Crohn’s disease more manageable. However, multidisciplinary research, addressing issues such as timing of surgery or medical treatment versus surgery, is scarce. Particularly in limited ileocecal Crohn’s disease, ileocolic resection might be a good alternative for long-term medical therapy. This review discusses the evidence on medical and surgical treatment options for ileocecal Crohn’s disease. It provides an aid in decision-making by discussing a treatment algorithm that can be used until further evidence on treatment is available.
INTRODUCTION

Crohn’s disease (CD) is a chronic inflammatory bowel disorder that can affect the entire gastrointestinal tract. In 25-30% of cases, disease activity is confined to the terminal ileum with or without cecal involvement. Until 10-15 years ago, options in treating ileocecal CD were limited. Treatment focused on symptom control rather than achieving long-term remission. The medical treatment options consisted of 5-aminosalicylates (5-ASA), antibiotics and steroids. At that time, immune suppressors such as methotrexate (MTX) or azathioprine (AZA) were already available. However, efficacy was not yet established and these therapies were rarely applied because of concerns of side effects. In general, treatment consisted of a course of steroids for remission induction and 5-ASA compounds as maintenance therapy. Once refractory to steroids, patients were referred to the surgeon for ileocolic resection. Recurrent disease could lead to multiple resections with the inherent risk of complications requiring a deviating stoma and development of a short bowel syndrome. As a consequence, gastroenterologists were reluctant to send their patients to the surgeon and patients were chronically or repetitively treated with steroids. Surgery was considered the last option offered to patients with steroid refractory disease.

In the last two decades treatment algorithms have changed. Evidence on the efficacy of immune suppressors has accumulated, proving to be efficient in maintaining remission in the majority of patients. Trials on 5-ASA showed that 5-ASA effectiveness is limited. However, the most important development has been the discovery of biological anti-TNF therapy. Uncovering the important role of the proinflammatory cytokine TNF-α in the immune response has led to the development of monoclonal antibodies targeting this cytokine. These compounds appeared to be highly efficacious in the treatment of CD. Infliximab (IFX; 1998), adalimumab (ADA; 2007) are registered treatments for moderate to severe CD and, in the USA, certolizumab pegol (2008) was added to the list.

During this time the surgical management of CD was also improving. Minimal invasive surgery, bowel sparing techniques and enhanced recovery programs after surgery have greatly improved the quality of surgery and the perioperative management resulting in earlier recovery, less morbidity and superior long-term results. Particularly in limited localized ileocecal disease activity, surgery is an effective treatment strategy with a quick restoration of quality of life (QOL).

In tertiary referral centres for inflammatory bowel disease (IBD) patients are often seen in joint clinics and decision-making is often done in multidisciplinary teams. However, little research has been undertaken on issues concerning the surgical and medical treatment in terms of efficacy, costs and QOL. The available literature consist of a few opinion papers concerning timing of surgery in the era of biological therapies and guidelines lacking definitive answers.

The aim of this review is to discuss the medical and surgical treatment options for ileocecal CD and to provide an aid in decision-making by discussing a treatment algorithm that can be used until further evidence on the treatment is available.
Ileoceleal Crohn’s disease

When Burril Crohn first reported the disease that we now know as CD, he described a regional ileitis. In 25-30% of CD patients, the ileocecal junction is the only region where the disease is active. Typical complaints of patients with active CD in the ileocecal region are abdominal pain in the lower right quadrant, persistent diarrhoea, fever with or without anorexia, nausea and vomiting as signs of obstruction. The stenosis is caused by a combination of irreversible fibrosis due to repetitive relapses and/or oedema caused by inflammation.

Medical options

The most commonly applied treatment algorithm in the medical management of CD is a step-up approach. In this approach, therapy is started with the least toxic agents first. If not sufficiently effective, more potent drugs will be added or started instead. Some gastroenterologists propose a more aggressive approach, arguing that with the step-up approach, agents with low efficacy are used for prolonged periods of time, while uncontrolled inflammation continues, resulting in tissue damage. The newly advocated approach is a top-down strategy with initially aggressive treatment with biologic therapy and early immune suppression. Decision-making in top-down versus step-up strategies was recently addressed in a previous issue of this journal and is beyond the scope of this review.

The American and European guidelines agree that for drug-induced remission, patients with mild ileal CD are best treated with budesonide. Budesonide is an ethylcellulose-coated steroid that is released in the ileum. Owing to the low systemic bioavailability as a result of the high first-pass metabolism (90%), budesonide optimizes the advantages of steroid therapy and at the same time minimizes the risk of systemic side effects. In the Cochrane review by Seow et al. budesonide proved to be more effective than placebo or mesalamine for induction of remission in CD. Although less effective when compared with conventional steroids, budesonide was associated with a lower rate of adverse events.

For patients with a moderate-to-severe flare of disease, oral steroids (prednisone) are indicated. In patients who require steroids to induce remission, concomitant maintenance therapy consisting of AZA or 6-mercaptopurine (6MP) must be considered, or MTX in case of intolerance for thiopurines. 6MP and its prodrug AZA are efficient for induction of remission, but have a delayed onset of action. However, when started together with a steroid remission induction course, AZA has been shown to be more effective as maintenance therapy once the steroids were tapered. MTX was shown to be significantly more effective compared to placebo in inducing and maintaining remission (remission induction: MTX 39% versus placebo 19% (p = 0.025); maintenance of remission: MTX 65% versus placebo 14% (p = 0.04)). In current treatment strategies it is mainly applied as maintenance therapy. Patients having recurrent flares despite immunomodulating maintenance therapy or showing intolerance necessitating repetitive steroid courses, require an anti-TNF agent as the next step in the medical treatment algorithm. The first biological anti-TNF agent registered for the treatment of CD was IFX. In the USA it was approved by the US FDA in 1998, followed by approval in Europe in 1999. IFX is a chimeric human-murine antibody binding membrane-bound as well as free soluble TNF, thereby neutralizing proinflammatory and regulatory...
actions of TNF. Multiple trials have established IFX for remission induction and maintenance therapy\textsuperscript{26-27}. In 2007, the fully human anti-TNF agent ADA was added to the biological drug armamentarium, showing similar results in inducing and maintaining remission in ileocolonic CD\textsuperscript{28-30}. Both IFX and ADA have shown clear efficacy in inducing remission (responses 65\% and 58\% in the large IFX trials \textsuperscript{25,27}; 59\% response at week 4 of the large ADA trial \textsuperscript{28}). However, at one year only 40-50\% of responding patients still experience benefits from these agents, as a large proportion of patients will lose response to these drugs\textsuperscript{31,32}. In patients who became intolerant to IFX or who lost response, the Gauging Adalimumab Efficacy in Infliximab Nonresponders (GAIN) trial, a double-blind randomized trial, showed that ADA was significantly more efficient compared with placebo in restoring remission\textsuperscript{33}. However, the gain was limited: after 4 weeks, remission was achieved in only 21\% of patients (34 out of 159) in the ADA group versus 7\% in the placebo group.

Safety of medical therapy
The long-term safety of medical therapy for CD remains to be determined. Since most medical therapies in CD are immune-suppressive there is a risk of developing opportunistic infections. In a large case-control study, the use of corticosteroids, AZA/6MP and IFX was shown to be associated significantly with the development of opportunistic infections in IBD patients, especially when the compounds are used in combination\textsuperscript{34}. A large cohort study recently showed that thiopurine use (AZA or 6MP) for IBD was associated with an increased risk of developing lymphoproliferative disorders (multivariate-adjusted hazard ratio between patients receiving thiopurines and those who never received thiopurines: 5.28 (95\% CI 2.01-13.9))\textsuperscript{35}. A debate on the combined therapy of immunomodulating agents such as AZA or 6MP and anti-TNF therapy is ongoing\textsuperscript{36-38}. On one hand, concomitant immunomodulating therapy showed to suppress the chance of developing antibodies against IFX, thereby preserving efficacy of IFX\textsuperscript{39} and resulting in higher response rates\textsuperscript{40}. On the other hand, emerging reports on hepatocellular T-cell lymphoma in young CD patients on anti-TNF in combination with thiopurines have made gastroenterologists reluctant to combine immune suppression for longer periods\textsuperscript{41}. A study claiming equivalent efficacy of maintenance for IFX monotherapy and combined immune suppression is flawed by lack of power\textsuperscript{42}. Other studies addressing the issue of tapering combined immune suppression are currently being undertaken\textsuperscript{43,101}.

Quality of life in medical treatment
Bernklev et al. found in a large cohort study that patients with CD have a significantly reduced QOL owing to frequent relapses, repetitive steroid courses, side effects of immunomodulating therapy or extra intestinal manifestations\textsuperscript{44}. Feagan et al. investigated the QOL of patients receiving IFX remission induction and maintenance therapy for up to one year in the patients participating in A Crohn’s Disease Clinical Trial Evaluating Infliximab in a New Long- Term Treatment Regimen (ACCENT) I trial\textsuperscript{45}. In this double blind randomized trial, patients received IFX remission induction and maintenance therapy. The authors concluded that IFX therapy significantly improved QOL compared with the QOL in responders before therapy. This QOL remained statistically improved in those patients receiving IFX maintenance therapy compared to placebo receivers. A similar study has been performed
for ADA (Crohn’s Trial of the Fully Human Antibody Adalimumab for Remission Maintenance (CHARM) trial), with similar conclusions. However, no QOL data exist for patients on maintenance therapy with IFX or ADA compared with healthy controls. It might be hypothesized that the impaired QOL in patients with long-lasting immunomodulating therapy also applies for patients on long-term biological therapy. Moreover, data of QOL in patients on anti-TNF therapy for more than 1 year are scarce. Casellas et al. measured QOL in CD patients for up to 4 years after the start of IFX maintenance therapy. However, QOL was only measured in those patients who remained in remission. The majority of patients relapsed and had a decline in quality of life but were excluded from the study, leaving the data unsuitable for interpretation.

**Costs**

Up to the point that biologicals are prescribed, costs for maintenance therapy remain low. However, a significant number of patients will require further treatment after failed steroid and immunomodulating therapy. Currently, gastroenterologists generally prescribe biological therapy.

In the Netherlands biological therapy is expensive; 100 mg of IFX costs € 591.88. This implies that costs for a patient with a weight of 75 kg who starts IFX remission induction and maintenance therapy will accumulate to a total sum of € 18,940.16 in one year, apart from costs for daycare at the hospital, estimated at € 500 per infusion. Likewise, 40 mg of ADA costs €496.94 in the Netherlands. One year of therapy (loading dose of 160 mg at week 0 and 80 mg at week 2, followed by 40 mg every 2 weeks) totals € 14,908.20 (Figure 1).

**FIGURE 1: COSTS OF ANTI-TNF THERAPY AND ILEOCOLIC RESECTION**

* Derived from the Dutch pharmaceutical compass (http://www.fk.cvz.nl)
† Maartense et al. Ann Surg 2006; IFX: costs were calculated for a person weighing 75 kg
Bodger et al. performed a Markov analysis to assess cost-effectiveness of biological therapy. They concluded that in responders, compared with standard therapy, both IFX and ADA may represent a cost-effective use of healthcare resources for up to 4 years, since costs fell below the £30,000 per quality-adjusted life years threshold for cost-effectiveness in the UK. The Canadian Agency for Drugs and Technologies in Health, however, has published a cost-effectiveness analysis regarding anti-TNF drugs for the treatment of refractory IBD, comparing them with surgery and with conventional treatments. The conclusion was that costs associated with anti-TNF treatments are high and that anti-TNF treatment might not be cost-effective.

Since anti-TNF treatment might not be cost-effective, it must be used selectively. Other alternatives like surgery become more important. A real-life comparison of anti-TNF and surgery for ileocecal CD disease in terms of costs and quality-adjusted life years is needed.

SURGICAL OPTIONS

The surgical treatment of ileocecal CD consists of an ileocolic resection. During the past few decades, surgical research has been focussing on the comparison of laparoscopic and open surgery. These studies provided evidence on short- and long-term results of both approaches. Short-term studies showed that QOL is quickly restored after the ileocolic resection. Long-term studies revealed a low recurrence rate, indicating that ileocolic resection is a very effective treatment for localised ileocecal CD.

Short- term outcomes after ileocolic resection

Four systematic reviews describing the short-term results after a laparoscopic versus open ileocolic resection have been published. These reviews were based on 12-16 studies including two randomised trials. Polle et al. reported a postoperative surgical reintervention rate of 0-8.3% in the different studies analyzed in their review (Table 1). Overall morbidity was 15.3% (Table 2). One might hypothesize that these results were achieved in specialized institutions, thereby not reflecting daily practise. A nationwide analysis of all ileocolic resections performed in France in the period 2000-2004 showed a similar overall morbidity rate of 15% in 49,609 procedures. In-hospital mortality in this cohort was 0.9% and was significantly higher after an open approach (0.9% in open operated patients compared to 0.2% after laparoscopic resection, p < 0.01).

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</tr>
<tr>
<td>anastomotic leakage</td>
<td>5**</td>
</tr>
<tr>
<td>necrotizing wound infection</td>
<td>1</td>
</tr>
<tr>
<td>small bowel obstruction</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>9 (1.5%)</td>
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* Polle et al. Dig Surg 2006 51; ** Three patients had temporary diversion
Several studies have investigated the risk of postoperative complications in the setting of prior anti-TNF therapy. A systematic review published in 2006 concluded that there was no increased rate of postoperative complications associated with immunomodulator use\(^5\). More publications have appeared since then, but these studies have shown conflicting results\(^54,55\). It is, therefore, as yet unknown whether anti-TNF or immunomodulator therapy should be avoided in the preoperative setting.

Maartense et al. measured QOL before and during the 3 months after the initial resection\(^49\). Patients had a quick restoration of QOL after surgery: a short deterioration was resolved after two weeks, and after 3 months, QOL had increased significantly (\(p < 0.001\) compared with the baseline measurement).

With regard to the comparison of laparoscopy and open surgery, all reviewers concluded that laparoscopy had short-term benefits over open surgery.

**Long-term results**

Long-term follow-up data of ileocolic resection also originate from trials that compared the laparoscopic and open techniques. The two most recent long-term studies are follow-up studies from two randomized trials\(^56,57\). In a cohort of 56 patients with a median follow-up of 10.5 years, Stocchi found an overall recurrence rate of 52%\(^56\). However, recurrence rate requiring re-resection was 28.5%, and only an additional 9% of patients required a readmission to treat the disease medically. This means that half of patients remained disease free until 10 years after the resection. Of the other half of patients, one third of patients could be managed in an outpatient setting.

<table>
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<td>wound haematoma</td>
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<td>ileus / small bowel obstruction</td>
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<td>urinary tract infection</td>
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<td>pneumonia</td>
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<tr>
<td>atelectase / pneumothorax</td>
<td>4</td>
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<tr>
<td>miscellaneous</td>
<td>4</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>91 (15.3 %)</strong></td>
</tr>
</tbody>
</table>

* Polle et al. Dig Surg 2006 51
Our own data showed an overall clinical recurrence rate of 38% with only five of 55 patients (9%) requiring re-resection. Median follow-up in this study was 6.8 years. Long-term QOL in this study was comparable to the QOL of healthy controls on most subscales subscribing the efficacy of laparoscopic ileocolic resection. Important features of laparoscopic surgery were a superior cosmesis and fewer incisional hernias.

Costs
In the study of Maartense et al., median overall costs were significantly lower after a laparoscopic approach compared with the open technique (Figure 1). The median costs, including relaparotomies, hospital stay and readmission costs, were € 6.412 for the laparoscopic procedure and € 8.196 for the open approach. Young-Fadok et al. calculated similar costs. After a follow-up of 6.8 - 10.5 years, no additional costs were made apart from the periodical out-patient visits in 50–60% of patients. The remaining patients had extra costs as result of a relapse requiring medical or surgical treatment.

Early versus late surgery
Aratari et al. retrospectively compared outcomes of patients who underwent surgery at time of diagnosis with those of patients who had surgery during the course of the disease. They concluded that the incidence of clinical recurrence requiring immunosuppressive therapy was significantly lower in the early surgery group, indicating that early surgery might lead to a prolonged clinical remission. Owing to the retrospective, nonrandomized design of the trial, the comment on this study is that the two groups were not comparable: in the early-surgery group, the surgery was often performed because of clinical need, and not to investigate a top-down approach, while the late surgery patients had more severe disease activity associated with a shorter disease free survival.

From a patient perspective, an older but interesting study is that of Scott and Hughes from 1994. A total of 80 patients who underwent an ileocolic resection were questioned if they would - in retrospect - have preferred an earlier or later resection, or at the same time as it was done. Of the 70 recipients, 74% answered that they would have wanted an earlier resection, and not one patient would have preferred their operation to have been later. Since this study lacks a control group it is a biased study. It is, however, the only evidence available about the patients’ opinion on timing of surgery and, therefore, worth mentioning.

In summary, the major short-term benefit of an ileocolic resection is the quick restoration in QOL due to the removal of the diseased bowel segment at the expense of a (small) risk on severe complications. When looking at the long-term follow-up a low recurrence rate requiring re-resection was found, but also the overall relapse rate was relatively low.

**EXPERT COMMENTARY: MEDICATION OR SURGERY?**

The treatment success of IFX in therapy-resistant CD is evident and surgical resection is commonly appreciated as a negative outcome in the treatment of CD. As a consequence, surgical resection as a treatment option is often
overlooked and patients are frequently unnecessarily treated with consecutive courses of immunosuppressant with a significant burden on the QOL. Isolated ileocecal CD in particular offers the alternative of surgical resection and may have gains in cost-effectiveness and QOL that extend far beyond the benefits of medical therapy.

Both the medical and surgical strategy can be advocated on clinical arguments. On one hand, medical treatment can prolong resection-free survival, thereby preventing the risks of surgery; on the other hand, studies have shown that resection often leads to a quick restoration of QOL with a low long-term recurrence rate. Moreover, long-term results of laparoscopic ileocolic resection are well established now, while, by contrast, little is known about the efficacy and QOL of long-term immunomodulating therapy and treatment with biologicals.

Guidelines differ in their recommendations. The European guidelines state that for severely active localized ileocecal disease not responding to conventional therapy, ‘infliximab should be considered […], although surgical options should also be considered and discussed’ 10. The American College of Gastroenterology (ACG) practice guideline states that surgery is advocated for ‘neoplastic / preneoplastic lesions, obstructing stenoses, suppurative complications, or medically intractable disease’, suggesting that all medical options should have been tried before turning to surgery 11. It is, however, noted that with the better postoperative maintenance schemes and appropriate surgery, the prolongation of ineffective medical management is no longer justified to ‘avoid’ surgery. In the decision of whether to treat surgically or medically, it is important to take several factors into consideration that preclude one of the treatment options beforehand (see algorithm, Figure 2). First, it is important to rule out disease activity elsewhere, because in these cases, an ileocolic resection will not suffice. In case of severe extraintestinal manifestations or autoimmune co morbidity, medical therapy is indicated to treat both disease entities. Patients with active perianal fistulas concomitant with ileocecal CD are best treated with anti-TNF. On the contrary, however, patients with obstructive symptoms due to a fibrotic terminal ileum are best treated surgically, since medication will have no effect. In clinical practise the distinction between a fibrotic stricture and inflammatory stenosis may be difficult. Prestenotic dilatation and absence of wall thickening and an inflammatory infiltrate on MRI indicate a predominant fibrotic component, whereas ulceration and oedema of the mucosa and the bowel wall point towards a inflammatory stenosis. Frequently, the distinction cannot be made.

To decide for patients who might benefit from both medical and surgical therapy, evidence is required regarding three major factors: the long-term efficacy, the long-term QOL and the overall costs. Finally, the patients’ preference should be taken into account, and to a lesser extent perhaps the doctor’s preference. However, the decisive factor should be evidence instead of preference. Therefore, trials are needed to determine the mutual relations of therapies.

The optimal strategy for steroid-refractory ileocecal CD is currently under investigation in the Netherlands in the Laparoscopic Ileocolic Resection Versus Infliximab Treatment of Distal Ileitis in Crohn’s Disease (LIRIC) trial 62. In this trial, a laparoscopic ileocolic resection is being compared with treatment with IFX for recurrent CD in the terminal ileum. Primary end points in this study are the costs and QOL. Patients are followed-up for one year after the start of treatment. The results of this trial can be expected in 2012 or 2013.
FIGURE 2: TREATMENT ALGORITHM FOR ILEOCECAL CROHN’S DISEASE

Ileocecal Crohn’s disease

Mild disease activity

Budesonide remission induction

Remission

Stop steroids, continue immunomodulating maintenance therapy

Mild to moderate disease activity

Remission induction with steroids + immunomodulating maintenance therapy

Remission

Steroid refractory or dependent disease

- Stenosis due to fibrosis rather than disease activity?
  Yes → Surgery: ileocolic resection
  No → Disease activity elsewhere?
    - Active perianal disease?
      Yes → Medical therapy: antiTNF (IFX / ADA)
      No → Co morbidity requiring similar medical therapy?
        Yes → Medical therapy: antiTNF (IFX / ADA)
        No → Remaining patients with ileocolic disease activity requiring additional therapy
          → Both antiTNF therapy and an ileocolic resection are optional; decide in consultation with patient
Five Year View

Thanks to the developments in basic research, a shift in the treatment paradigm might be expected in the long term. There is increasing evidence that CD is not one disease entity but that it is rather a group of diseases, all requiring different treatment. Genetic research has revealed various variants in genes such as NOD2, that are associated with CD. Possibly, by mapping the genome of a CD patient, the future phenotype of the disease can be predicted to adjust the treatment to this prediction.

However, the solution and implementation of the genomic research path will probably remain future prospects over the next 5 years. In the meantime, clinical trials investigating the best treatment options for CD patients are critically important.

At the same time, the developments of new antibodies against TNF or other cytokines may reveal interesting treatment targets. A good review of all the biologic therapies currently under investigation in different phases is presented in the article of Rutgeerts et al. All ‘-abs’ with their targets are described and an overview is given in which phase of research each of the products is.

In conclusion, no evidence is available pointing at a specific strategy, although more long-term evidence is available on surgical treatment. At present, all benefits and risks must be weighed carefully and discussed with the patient to decide what therapy path must be chosen. Trials are needed to be able to definitely answer the question ‘medical or surgical treatment?’
Reference List


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(101) Clinical trial registration site where the Azorix-trial is registered, comparing azathioprine to anti-TNF as maintenance monotherapy for CD in remission after combined therapy.
http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=1404

(102) PDF-file of the Canadian agency for Drugs and Technologies in Health about cost-effectiveness of TNF therapy in steroid refractory CD patients.
http://www.cadth.ca/media/pdf/00479_Anti_TNF_a_Drugs_for_Refractory_Inflammatory_Bowel_Disease_to_e.pdf