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To cite this version:

Philippe Zerbib, Dine Koriche, Stéphanie Truant, Ahmed Fouad Bouras, Gwenola Vernier-Massouille, et al.. Pre-operative management is associated with low rate of post-operative morbidity in penetrating Crohn's disease. Alimentary Pharmacology and Therapeutics, 2010, 32 (3), pp.459. 10.1111/j.1365-2036.2010.04369.x . hal-00552578

HAL Id: hal-00552578

https://hal.science/hal-00552578v1

Submitted on 6 Jan 2011

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Alimentary Pharmacology & Therapeutics

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Journal:	*Alimentary Pharmacology & Therapeutics*
Manuscript ID:	APT-0179-2010.R1
Manuscript Type:	Original Scientific Paper
Date Submitted by the Author:	29-Apr-2010
Complete List of Authors:	Zerbib, Philippe; CHU de Lille, Digestive Surgery and Transplantation Koriche, Dine; CHU de Lille, Digestive Surgery and Transplantation Truant, Stéphanie; CHU de Lille, Digestive Surgery and Transplantation Bouras, Ahmed Fouad; CHU de Lille, Digestive Surgery and Transplantation Vernier-Massouille, Gwenola; CHU de Lille, Hepatogastroenterology Seguy, David; CHU de Lille, Hepatogastroenterology Pruvot, François-René; CHU de Lille, Digestive Surgery and Transplantation Cortot, Antoine; CHU de Lille, Hepatogastroenterology Colombel, Jean-Frédéric; Centre Hospitalier Universitaire de Lille, Service d'Hépato-gastroentérologie
Keywords:	Crohn's disease < Disease-based, Small intestine < Organ-based, General practice < Topics, Nutrition < Topics, Surgery < Topics

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Pre-operative management is associated with low rate of post-operative morbidity in penetrating Crohn's disease.

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Short running title: Pre-operative management for penetrating Crohn's disease.

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Abstract

Background and Aim: Ileocecal resection for penetrating Crohn's disease is still challenging with a high rate of post-operative morbidity and faecal diversion. We report retrospectively the results of pre-operative management for penetrating Crohn's disease focusing on the rate of post-operative major morbidities and need for faecal diversion.

Methods: Between 1997 and 2007, 78 patients with penetrating Crohn's disease underwent a first ileocecal resection after a pre-operative management consisting in bowel rest, nutritional therapy, intravenous antibiotics, weaning off steroids and immunosuppressors, and drainage of abscesses when appropriate.

Results: Resection was performed for terminal ileitis associated with fistula (n = 41), abscesses (n = 37) or both (n = 5). A pre-operative nutritional therapy was performed in 50 patients (68%) for 23 days (range, 7 - 69 days) along with a weaning off steroids and immunosuppressors. A diverting stoma was performed for 6 patients (7.7%). There was no post-operative death. Post-operative complications were classified as minor in 10 patients (12.8%), and major in 4 patients (5%). Overall, the post-operative course was uneventful in 58 patients (74%).

Conclusion: Pre-operative management for penetrating Crohn's disease allowed ileocecal resection with low rate of post-operative morbidity and faecal diversion.

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Introduction

Crohn's disease (CD) is a chronic inflammatory disease associated with significant morbidity. The introduction of anti-TNF agents has improved outcome in CD [1, 2] but there are still few data on their long-term efficacy beyond one year and their impact on the long-term outcome [3]. Despite improvement in medical care the rate of surgery remains high in CD [4]. Penetrating CD, defined as subacute perforation with abscess formation and chronic perforation with internal fistula formation, is still a prominent indication for surgery [5]. Patients who had abdominal surgery for penetrating CD still experience a high rate of post-operative complications [6, 7]. A two-stage procedure including a temporary diverting stoma is often required in up to 39% to 51% of patients [8, 9]. Several risk factors have been associated with a poor outcome of surgery for penetrating CD such as the presence of an abscess at the time of surgery, the use of chronic corticosteroid medication and an impaired nutritional status.

We have implemented in our institution a systematic pre-operative management for penetrating CD consisting in bowel rest, nutritional therapy, intravenous antibiotics, weaning of steroids and percutaneous drainage of abscesses when appropriate. We here report the results of this approach focusing on the rate of post-operative major morbidities and need for faecal diversion for primary penetrating ileocecal CD.

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Methods

Patients

We reviewed retrospectively the files of all consecutive patients who underwent a first ileocecal resection (ICR) for penetrating CD from December 1997 to January 2007 in a unique surgical department. Penetrating CD was defined according to Montreal's classification [10]. In addition to medical history and physical examination, all patients were assessed before surgery with colonoscopy and computed tomography scanning (CT-scan). Data collection included the following: patient characteristics such as gender, age, body mass index, smoking history, familial history of inflammatory bowel disease, and serum albumin level ; CD features such as extent of the disease, perianal involvement, time from diagnosis, indication for surgical treatment (i.e. abscess, fistula or both), medical treatment (i.e. steroids, immunosuppressors (azathioprine, methotrexate), anti-TNFα).

Pre-operative management

- Nutritional therapies

Enteral nutrition (EN) using preferentially elemental diet was applied for 2 weeks before surgery in 2 situations depending on the existence of an intestinal sub-occlusion: night enteral nutrition in addition to ordinary food if transit persisted or exclusive enteral nutrition (>30 kcal/kg ideal body weight / day) in sub-occluded patients. Patients with complete intestinal occlusion and complete food intolerance, patients with clinically or endoscopically severe colitis and patients with abdominal or pelvic abscesses received a Total Parenteral Nutrition (TPN) for 3 weeks before surgery.

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- Drainage of abscesses

Abdominal, pelvic or retroperitoneal abscesses > 5 cm in diameter were drained percutaneously under sonography or CT-scan guidance whenever possible or surgically drained. Repeat CT-scans were not systematically performed after drainage. Subsequently, ICR was performed 2 to 3 weeks after drainage of an abscess.

- Medical treatment

All patients received intravenous broad spectrum antibiotherapy for 15 days (metronidazole and fluoroquinolone or cephalosporin) directed against anaerobic bacteria and adapted to bacteriologic results. Presence of an abscess led to immediate withdrawal of immunosuppressors and/or anti-TNFα therapy and weaning of steroids was achieved before surgical resection. Steroids were decreased quickly before surgery i.e. at a rhythm of 10 mg of prednisolone / day until half dose and 5 mg / day after until 0. For patients being under a mean dose of 45 mg / day, the mean time for a complete weaning was 7 days. As patients were weaned of steroids at least 1 week before surgical resection, no steroid cover during the peri-operative period was necessary. Azathioprine and methotrexate were stopped as soon as the patient was hospitalized as well as Anti-TNFα therapy.

Surgical procedure

Ileocecal resection was performed using laparoscopic or open surgical resection.

Laparoscopic-assisted ileocecal resection

Patients were placed in the French position. A 3-trocar approach was used (subumbilical, 10 mm; right and left fossa, 5 mm). After full intracorporeally mobilization of the right colon, the distal ileum and the cecum were exteriorized through a 4- to 5-cm vertical midline incision. The whole small bowel was thoroughly

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examined extracorporeally from the duodeno-jejunal flexure to the ileum. Vascular ligation, bowel division and a sutured end-to-end, or end-to-side anastomosis were performed extracorporeally with a handsewn technique using a single layer of interrupted resorbable sutures (Vicryl® or Monocryl® 4/0). In cases of fistula, the ileum and the victim organ (bowel or bladder) were divided intracorporeally. The defect of the victim organ was then closed laparoscopically or extracorporeally. Conversion to open surgery was defined as whenever any unplanned incision was performed, when any longer than 5 cm planned incision was made or earlier in the procedure than anticipated.

Open surgical resection

Through a sus- and sub-umbilical midline incision, the right colon was mobilized. After vascular and bowel division, end-to-end or end-to-side ileo-colic anastomosis was performed with a handsewn technique using a single layer of interrupted resorbable sutures (Vicryl® or Monocryl® 4/0).

Faecal diversion by end ileocolostomy exteriorized in the right flank was performed after ICR, instead of the anastomosis, if an abscess was still present at the time of surgery or in case of complex ileo-sigmoid fistula requiring a large sigmoidectomy. In these cases, delayed ileo-colic anastomosis was performed 3 months later. Oral intake was started after surgery with clear liquids and enlarged as long as tolerated. Patients were discharged when a normal diet was possible.

Outcomes definitions

Post-operative morbidity and mortality were defined as any complication or death occurring within 3 months after ICR. Post-operative complications were classified using the morbidity scale proposed by Dindo et al. (Table 1) [11]. Hospital stay was defined as the time from the surgical intervention to hospital discharge. The

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post-operative course was considered as uneventful when ICR was performed with primary anastomosis, without any post-operative complication.

Statistical analysis

Continuous variables were expressed as mean (standard deviation, range). Categorical variables, expressed as frequencies and percentages, were compared using the chi-square test or Fisher's exact test, as appropriate. All analyses were performed using SPSS, version 13.0 (SPSS Inc. Chicago, IL).

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Results

Seventy eight patients (48 males) with a mean age of 29 years (SD, 8.8; 16 - 70) underwent elective ICR for penetrating CD. Patients' characteristics are listed on Table 2. Mean follow-up for the entire patient cohort was 23.2 months (SD, 24.9; 1 - 86). Indications for resection were terminal ileitis associated:

- With fistula in 41 patients: entero-cutaneous fistula (n = 11), entero-bladder fistula (n = 11), ileo-sigmoid fistula (n = 21), entero-colic fistula (n = 3), ileo-ileal fistula (n = 7)
- With abscesses in 32 patients
- Or both abscesses and fistula in 5 patients.

Pre-operative management and surgical procedure are reported in Table 3. For 50 patients (64%), a pre-operative TPN (n = 45) or EN (n = 5) was performed for 23 days (7 - 69). Among 37 patients presenting with an abscess, percutaneous CT scan or surgical drainage was performed in 11 (29.7%) in association with antibiotic therapy. Eighteen patients were on steroids at their admission (mean dose, 45 mg/day). Sixteen patients were on immunosuppressors (azathioprine, methotrexate) and one patient on anti-TNFα therapy. All patients were weaned off steroids, immunosuppressors and anti-TNFα therapy at the time of surgery.

Mean operating time was 155 minutes (SD, 45.7; 60 - 300). Among 78 patients, 35 underwent laparoscopic ICR (45 %) of whom 11 (31.4 %) were converted to an open approach for the following reasons: inflammatory pelvic adhesions ± complex fistula (n = 6), large inflammatory mass (n = 3), and ileo-sigmoid fistula (n = 2). Additional surgical procedures reported in Table 3, included liver biopsy (n = 2), cholecystectomy (n = 3), temporary faecal diversion (n = 6), closure of a fistula directed toward a victim organ (n = 29), additional small bowel

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resection (n = 4), sigmoidectomy (n = 3), stricturoplasties (n = 4), cesarean (n = 1) and closure of stoma (n =1). A temporary diverting stoma was performed in 6 patients (7.7%) due to presence of residual abscess at the time of surgery or in case of complex ileo-sigmoid fistula requiring a large sigmoidectomy. Faecal diversions were all temporary and always performed at time of open ICR and never for anastomotic leakage in post-operative period. Faecal diversions were all and always performed in open ICR.

There was no post-operative death. According to the Dindo's classification[11], post-operative morbidities were classified as 3 grades I, 7 grades II (including 3 patients who had conservative management of anastomotic leakage), 1 grade IIIa (percutaneous drainage of intra-abdominal collection) and 3 grade IIIb (cholecystitis, hemoperitoneum, occlusion that needed re-operation). Anastomotic leakage management never necessitated post-operative faecal diversion and was always managed through conservative treatment. The 6 patients necessitating diverting stoma were not included in the uneventful outcomes. Overall, the post-operative course was uneventful in 58 patients (74 %) (Table 4).

By univariate analysis, seven factors were tested in order to identify predictive factors of postoperative outcome, i.e the need for faecal diversion and/or occurrence of postoperative complications: previous laparotomy, BMI ≤ 20, albumin ≤ 30 before nutrition, preoperative enteral and/or parenteral nutrition, surgical approach (laparoscopic / open), abscess and/or fistula as indication for resection, additional surgical procedures. None of these factors was associated with the need for faecal diversion or occurrence of postoperative complications. Nevertheless, this could be a type-2 error due to the relatively small size of our population.

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Discussion

The aim of this retrospective study on a large cohort of ICR for penetrating CD at a tertiary referral center was to assess the results of a standardized therapeutic strategy i.e. surgery after 2 to 3 weeks of pre-operative management consisting in bowel rest, nutritional therapy with intravenous antibiotics, weaning off steroids, immunosuppressors and anti TNFα therapy, and drainage of abscesses > 5 cm. This management is feasible and associated with low rate of post-operative morbidity of 18% and no mortality and had similar outcomes than those operated on for uncomplicated Crohn's ileitis.

The weakness of this current series is that it was uncontrolled. However, during the study period, our strategy of preoperative management was adopted as a standard of care based on our experience with Crohn's disease surgery resulting in a low number of patients undergoing planned ileo-colic resection for penetrating CD without preoperative management. Furthermore, such a prospective comparative trial or even a retrospective case-matched study seems in any case difficult if not impossible to perform.

These results are indeed comparable to those reported in a recent meta-analysis pooling data from 12 studies, in which the post-operative morbidity rate for surgery in CD was 12.8 % for laparoscopic surgery compared with 20.2 % for open surgery [12].

The low rate of temporary diverting stoma (7.7 %) is also remarkable. All of them were voluntarily performed in patients with residual abscess at the time of surgery or complex ileo-sigmoid fistula necessitating large sigmoidectomy. Indeed stoma diversion rate reported in previous series of ICR for penetrating CD was five times more elevated than in our series. In a retrospective study of ileosigmoid fistula

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in CD where 93% of patients underwent ICR, a stoma diversion was voluntarily performed in 51% of patients (53/104 patients) and was secondarily performed in 4% of patients (4/104 patients) due to anastomotic leakage [9]. In another recent prospective study comparing complicated and uncomplicated CD undergoing laparoscopic ICR, a two-stage procedure with a temporary diverting stoma was performed in 39 % for complex fistulizing CD (all of them being voluntarily performed) [8]. Operative findings evidenced that the inflammatory process in patients who initially had an abscess or phlegmon diminished after 2 weeks of bowel rest. It is therefore likely that our strategy of pre-operative management allowed ICR to be performed with primary anastomosis in circumstances that might have otherwise required a two-stage procedure with diverting stoma. However, the optimal duration for bowel rest with nutritional assistance is yet unknown, the period of 2 to 3 weeks having been pragmatically chosen.

We believe that the good surgical outcome in this series is also linked to the impact of the pre-operative management on important risk factors for post-operative complications. Patients were weaned off corticosteroids, immunomodulators and anti-TNFα agents during the pre-operative period. The deleterious impact of steroids on the outcome of surgical resections in CD is well documented. A recent meta-analysis showed that pre-operative corticosteroids increased the likelihood of all post-operative complications (OR 1.41, 95% CI: 1.07-1.87) and of infectious complications (OR 1.68, 95%CI: 1.24-2.28). This higher risk of complications is dose dependent and therefore it is suggested to stop corticosteroids preoperatively or taper doses lower than 40 mg/day [13]. Our policy was also to stop immunomodulators and anti-TNFα even though it is still debated whether or not they increase the likelihood of anastomotic leakage and infectious complications in CD patients [14-16]. Thiopurines

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can be related to a decrease in epithelial cell proliferation and T-cell-mediated suppression of the inflammatory reaction which could interfere with adequate collagen synthesis and wound healing resulting eventually in an impairment of anastomotic healing. In a recent prospective analysis, patients under thiopurine therapy had a significant increased risk for anastomotic leakage especially in case of intra-abdominal sepsis leading the authors to advice a two-stage procedure in this setting [17]. In a retrospective study, thiopurines alone and the addition of thiopurines for patients under steroids was not found to significantly increase the risk of post-operative infectious complications [18].

Another important point of our preoperative management was to improve nutritional status when altered. Poor nutritional state and low serum albumin certainly increase post-operative morbidity and the risk of a two-stage procedure [7, 19, 20]. Pre-operative nutritional therapies can improve nutritional parameters and wound healing even before nutritional parameters show any change [21, 22]. Recent calorie intake may be more important than nutritional status [23]. Nutritional therapies alone in pre-operative situation are probably insufficient to treat active CD [24], but, in association with antibiotherapy (and abscess drainage when appropriate) they seem to improve wound healing with a low rate of faecal diversion. In a prospective population-based study comparing handsewn and stapling anastomosis in patients with CD (where 98% of patients underwent ICR), the same preoperative management was reported before intestinal resection [25]. The authors reported a very low complications rate (no anastomotic leakage) and conclude that the choice of anastomotic technique is not the most important factor for anastomotic healing but the crucial point is that patient was operated on under the optimal general conditions in terms of nutritional and

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healing capacity. Our study is, to our knowledge, the first which evaluated this preoperative management in a large series of penetrating CD.

The modalities of nutritional assistance have changed along our study. Initially, TPN appeared more fitted to the situation of penetrating CD since it insured a better bowel rest than EN, but with greater risks. Thus, in our initial experience, we attempted to put as much as possible patients under EN, but some of them aggravated their abscess under EN. Then, we decided to reserve EN to patients with a fistulizing form only (without abscess) and with a persistent intestinal transit.

This series further confirm that the laparoscopic-assisted approach to complex CD is feasible and safe. Abscess, phlegmon or fistulas are not contraindications to a successful laparoscopic ICR [8, 26]. Several authors have reported fewer complications associated with the laparoscopic approach [26-28]. Nevertheless, the nature of complicated CD can render surgery challenging, and the technical difficulties encountered are more pronounced with laparoscopic surgery [29-32]. Penetrating CD (i.e., intra-abdominal abscess and fistula) was independent factors predicting conversion to open surgery [33]. Our conversion rate of 34% was comparable to previous studies [8, 34, 35]. According to other authors, the main reasons for conversion were the presence of complex inflammatory masses or fistula [12, 36, 37].

In conclusion, pre-operative management for penetrating CD allowed to decrease dramatically faecal diversion rate than previously reported after ICR for penetrating CD with a low rate of post-operative morbidity. Most patients (64%) received intensive medical therapy including total parenteral nutrition or an elemental diet for more than 2 weeks. This policy might result in a longer hospital stay and higher overall costs. However, this needs to be balanced with a low rate of faecal diversion which is associated with decrease of quality of life and iterative

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hospitalisations [38-41] and the low rate of post-operative morbidity with no need for re-admissions.

Consensus incorporating this strategy and discussing the relative place of surgery and medical treatment is required. This attitude should be confirmed by prospective studies before being considered as a gold standard for penetrating CD.

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Table 1. Classification of surgical complications [11].

Grade	Definition
Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics, electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside
Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications Blood transfusions and total parenteral nutrition are also included
Grade III	Requiring surgical, endoscopic or radiological intervention
Grade IIIa	Intervention not under general anesthesia
Grade IIIb	Intervention under general anesthesia
Grade IV	Life-threatening complication requiring IC/ICU management
Grade IVa	Single organ dysfunction (including dialysis)
Grade IVb	Multiorgan dysfunction
Grade V	Death of a patient
Suffix “d”	If the patient suffers from a complication at the time of discharge, the suffix “d” (for “disability”) is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication.

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Table 2. Patient's characteristics

SD: Standard deviation; BMI: Body mass index

Age, years, mean (SD, range)	29 (8.8, 16 - 70)
Gender (male / female)	48 / 30
BMI, kg/m^2, mean (SD, range)	20 (3.4, 14 - 34)
Time from diagnosis of CD to surgery, days (SD, range)	48 (57, 0 - 330)
Smoking history, n (%)	14 (18)
Previous laparotomy, n (%)	18 (23.1)
Median laparotomy	13
Appendectomy	5
Perianal Crohn's disease, n (%)	9 (11.5)
Indications for resection, n (%)	
Fistula	41 (53)
Abscess	32 (41)
Abscess and fistula	5 (6)
Serum albumin, mean (SD, range)	33.9 (6.1, 20 – 46)

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Table 3. Pre-operative management and surgical procedure

TPN: Total parenteral nutrition; EN: Enteral nutrition ; ICR : Ileocecal resection ; IV : Intravenous ; SD : Standard deviation

Penetrating ileitis, n	78
Pre-operative Management	
• Nutritional therapies (2 weeks) and IV antibiotic therapy (15 days)	
○ TPN, n (%)	45 (58)
○ EN, n (%)	5 (6)
• Drainage of abscess > 5cm, n (%)	11 (30)
○ Surgical, n	5
○ Radiological, n	6
• Weaning of steroids, immunossupressors and anti TNFα therapy, n	35
Surgical procedure	
• Laparoscopic ICR, n (%)	35 (45)
• Open ICR, n (%)	43 (55)
• Temporary diverting stoma, n (%)	6 (7.7)
• Additional surgical procedures, n	
○ Liver biopsy	2
○ Cholecystectomy	3
○ Closure of a victim organ	29
○ Additional small bowel resection	4
○ Sigmoidectomy	3
○ Stricturoplasties	4
○ Cesarean	1
○ Closure of a stoma	1

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Table 4. Operative's outcomes.

SD: Standard deviation

Conversion rate, n (%)	11 (34)
Mean operating time, min (SD, range)	155 (45.7, 60 - 300)
Death, n	0
Faecal diversion by temporary stoma, n	6
Overall morbidity, n (%)	14 (18)
Post-operative morbidity according to Dindo's classification, n (%)	
Grade I	3 (4)
Grade II	7 (9)
Grade IIIA	1 (1.3)
Grade IIIB	3 (4)
Mean hospital stay, days (SD, range)	10 (3.7, 6 - 24)
Uneventful operative outcomes, n (%)	58 (74)

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