Intestinal perforation in Crohn’s disease
Factors predictive of surgical resection

Hélène BRIHIER, Isabelle NION-LARMURIER, Pauline AFCHAIN, Emmanuel TIRET, Laurent BEAUGERIE, Jean-Pierre GENDRE, Jacques COSNES

SUMMARY
New medical therapeutic options challenge the usual surgical management of Crohn’s disease patients with intestinal perforation.

Objectives — To determine factors predictive of surgery for perforation in Crohn’s disease and define a group of patients that may benefit from non-surgical treatment.

Methods — One hundred and sixty-two patients (69 males, 93 females, mean age 39) with perforated Crohn’s disease (fistula, abscess, inflammatory mass) between January 1995 and September 2003 were studied retrospectively.

Results — One hundred and fifty-one patients (93%) underwent surgery; 70 had planned surgery and 81 had surgery for symptomatic deterioration. At two years, the cumulative probability of intestinal resection was 0.89 ± 0.03, and the cumulative probability of unplanned intestinal resection was 0.72 ± 0.05. Predictive factors of unplanned surgery were elevated platelet count (adjusted hazard ratio 3.15; 95% CI 2.21-4.50) and absence of fistula (adjusted hazard ratio 3.14; 95% CI 2.48-3.99). The rate of postoperative complications, the need for a stoma, and the length of bowel resection were not significantly different whether the surgery was planned or not.

Conclusion — A significant proportion of patients with intestinal perforation complicating Crohn’s disease, particularly those with a fistula, might benefit from non-surgical treatment.

RÉSUMÉ
Perforation intestinale au cours de la maladie de Crohn : facteurs prédictifs de chirurgie

Hélène BRIHIER, Isabelle NION-LARMURIER, Pauline AFCHAIN, Emmanuel TIRET, Laurent BEAUGERIE, Jean-Pierre GENDRE, Jacques COSNES

La maladie de Crohn perforée est classiquement traitée chirurgicalement mais l’apparition de nouveaux traitements médicaux remet en cause cette attitude.

Objectifs — Évaluer dans la maladie de Crohn les facteurs prédictifs de chirurgie pour perforation intestinale et définir les malades pouvant bénéficier d’un traitement non chirurgical.

Malades et méthodes — Cent soixante-deux malades consécutifs atteints de maladie de Crohn (69 hommes, 93 femmes, âge moyen 39 ans) ayant développé une perforation intestinale (fistule, abcès, plastron ou pseudo-tumeur inflammatoire) entre 1995 et 2003 ont été étudiés rétrospectivement.

Résultats — Cent cinquante et un malades (93 %) ont été opérés, 70 de façon programmée et 81 pour échec du traitement médical (probabilités cumulées à 2 ans de chirurgie quelle qu’elle soit 0,89 ± 0,03, de chirurgie non programmée 0,72 ± 0,05). Les facteurs prédictifs de chirurgie non programmée étaient l’hyperplasie (HRA 3,15; IC 95 % 2,21-4,50) et l’absence de fistule (HRA 3,14; IC 95 % 2,48-3,99). Le taux de complications et de stômes et la longueur d’exérèse du tube digestif n’étaient pas significativement différents que la chirurgie ait été programmée ou non.

Conclusion — Environ un quart des malades non opérés d’emblée pour perforation intestinale sur maladie de Crohn, surtout ceux porteurs de fistule, pourraient bénéficier d’un traitement non chirurgical.

Introduction
Intestinal perforation is one of the most frequent and most severe complication of Crohn’s disease (CD). Aside from anoperineal manifestations, 30 to 40% of CD patients develop perforation complications after a 10-year disease course [1, 2]. It is widely considered that surgery is generally indicated for CD patients who develop intestinal perforations because such manifestations are considered as advanced-stage lesions unresponsive to medical treatment. The advent of new treatments active in the acute [3] or chronic phases of the disease (immunosuppressors, repeated infusion of infliximabs) [4, 5] challenge this approach based on the irreversibility of intestinal perforation. It is known however that if the perforation is localized, elective treatment such as radio-guided percutaneous drainage of abscess formations, can be successful [6-8].

The purpose of the present work was to determine whether surgery can be avoided in certain CD patients who develop intestinal perforation and to attempt to ascertain which patients could benefit from a conservative treatment.

Patients and methods
Medical files of patients with CD seen between January 1995 and September 2003 who developed during this period an intestinal perforation related to their CD were studied retrospectively. This consecutive series was selected from a database (MICISTA) which includes all patients with inflammatory bowel disease followed in the Gastroenterology Unit of the Rothschild then Saint-Antoine Hospitals in Paris France. During the period under consideration, 2740 patients with CD were seen in the Unit. Among them, 269 developed intestinal perforation (figure 1). Perforations arising from the anus or the rectum (fistulæ and perianal or anoperineal abscesses), repeated intestinal perforations, and limited perforations without apparent communication with neighboring organs...
Diagnosis of intestinal perforation

Intestinal perforation was defined according to the Vienna classification [9]. According to this classification, intra-abdominal perforations include: fistulae, inflammatory masses, and abscesses. We thus considered that patients had intestinal perforation if they presented a fistula between the intestine and a neighboring organ, an intra-abdominal abscess, agglutination of the intestinal loops in contact with an inflammatory focus, or an inflammatory pseudo-tumor (tumor-like mass resulting from an inflammatory process). The date of the perforation was noted as the date of morphological proof, i.e. formal identification of an abscess, loop agglutination, inflammatory mass or internal or enterocutaneous fistula.

Treatment modalities

The treatment protocol applied in the unit for patients with CD has been presented elsewhere [10]. In patients with serious clinical signs (abdominal pain, sepsis), treatment of intestinal perforation included interruption of oral food intake (solids and fluids), enteral (EN) or parenteral nutrition (PN) of variable duration, and intravenous antibiotics. Voluminous abscesses were evacuated whenever possible via transperitoneal puncture with drainage. It was considered that intestinal perforation was a sign of advanced disease which would not regress with medical treatment; surgery was thus the rule. Patients underwent surgery within a variable delay after discovery of the perforation. Surgery was clearly favored as stated in the medical file. This therapeutic attitude was termed “planned surgery”. Despite this protocol, several patients were treated medically because they declined surgery or had an unfavorable clinical situation. These patients underwent surgery only if their symptoms worsened or if new complications developed; they were considered to have undergone “necessary surgery”.

Variables defining perforation

The following data were recorded from the medical file: a) clinical symptoms at diagnosis of intestinal perforation: pain, diarrhea, fever, weight loss greater than 5% of usual body weight, clinical palpation of an abdominal mass, intestinal obstruction; b) laboratory results at the time of perforation: cell counts, serum C-reactive protein (CRP), serum albumin, c) type of imaging (ultrasonography, computed tomography, barium study, barium enema) used to establish the diagnosis of perforation; d) type of perforation: fistula, abscess, loop agglutination, inflammatory pseudo-tumor; e) size of abscess defined as the greatest diameter if greater than 3 cm; f) segment (jejunum, ileum, colon, rectum, anus) presenting active lesions at the time of the perforation.

We also noted ongoing treatments (corticosteroids, immunosuppressors or infliximab given within the three months preceding diagnosis of intestinal perforation), and therapeutic modalities applied secondarily (EN, PN, antibiotics, percutaneous abscess drainage). Patients given EN or PN for more than eight days were considered to have received nutritional support. Patients given antibiotics for more than 48 hours were considered to have received antibiotic therapy.

Disease course

Abdominal surgery and time from discovery of perforation to surgery were noted to describe the disease course. For the present analysis, we distinguished “planned surgery” from “necessary surgery”. When surgery was undertaken, we noted the length of bowel resection, use of a temporary stoma, and the development of major or minor postoperative complications. Major complications were defined as: sepsis, peritonitis, pneumonia, abscess formation, anastomotic fistulization, anastomotic disunion requiring surgical revision. Minor complications were: anastomotic disunion not requiring surgical revision, stomal prolapse, pancreatitis, and fever without clinically identified focus [11, 12]. Median follow-up after the diagnosis of intestinal perforation was 22 months (range 0-103).

Statistical analysis

Statistical comparisons between groups were performed with the chi-square test or the Student t test as appropriate. The probability of not undergoing surgery after demonstration of intestinal perforation was calculated according to the Kaplan-Meier method using two end points: intestinal surgery irrespective of the reason, and “necessary surgery”. For the second survival curve, patients who had undergone “planned surgery” were considered to be non-operated patients and were censored at the date of surgery. Explanatory variables, dichotomized when appropriate, were: gender, age, history of appendicectomy, smoking, date of perforation (before or after 1/1/99), duration of CD, clinical symptoms (fever > 38° C, abdominal pain, diarrhea, intestinal obstruction, palpable mass), biological data (anemia < 10 g/L, polymorphonuclear neutrophil count > 10000/mm³, platelet count > 400000/mm³, elevated CRP > 50 mg/L, low serum albumin < 30 g/L), type of perforation (fistula, abscess, loop agglutination, pseudo-tumor), segment involved (jejunum, ileum, colon, rectum, anus), ongoing treatment (corticosteroids, immunosuppressors). These variables were included in the univariate analysis and submitted to the long rank test. Variables exhibiting P < 0.10 at univariate analysis were retained for multivariate analysis using the Cox model. Multivariate analyses were performed for examination variables (clinical and biological data, ongoing treatment) available for only 102 patients and for history and morphological variables (gender, age, appendicectomy, smoking, date and type of perforation, duration of CD, segment involved) which were available for all patients. Results are expressed as adjusted hazard ratio with 95% confidence interval (95CI).

Data were noted on an Excel spreadsheet and processed with GB-STAT software (Silver Spring, MD, USA).
Results

Diagnosis and treatment of intestinal perforation

Perforation was often identified in patients with abdominal pain (92%), weight loss greater than 5% of usual body weight (77%), fever (41%), worsening diarrhea (18%), or intestinal obstruction (22%). Radiological diagnosis of perforation was achieved with computed tomography in 65% of patients. The perforation was an isolated fistula in 54 patients (33%) (49 enterocutaneous fistulae, 5 bowel-bladder fistulae), fistulization with abscess formation in 23 (14%) (16 enterointestinal, 2 bowel-bladder, 5 enterocutaneous fistulae), isolated abscess without identified fistula in 59 (36%), an inflammatory pseudotumor in 22 (14%), and an isolated loop agglutination in 4 (2%). The clinical presentation was poorly correlated with the type of perforation. Patients with an isolated fistula (N = 54) had a painful abdominal syndrome (N = 42, 78%), weight loss (N = 24, 44%), fever (N = 11, 20%), worsening diarrhea (N = 8, 15%) and intestinal obstruction (N = 10, 19%). None of the fistulae were fortuitous discoveries in patients with few or no symptoms. The lesions were located in the ileum in 146 patients (90%), the colon in 57 (35%), and the rectum in 14 (9%). Immediate treatment of the perforation depended on the anatomic type as indicated in table I. After treatment of the perforation, medical treatment of CD included corticosteroids (N = 74 patients, treatment initiated after perforation for 50), immunosuppressors (azathioprine or 6-mercaptopurine for 56, treatment initiated after perforation for 42) and infliximab perfusion (N = 4 patients). Patient outcome is summarized by type of perforation in figure 1. Most patients underwent surgical treatment of their perforation, but fistulae were operated less often. Enterocutaneous fistulae were an exception; all were treated by “planned surgery”. “Necessary surgery” was performed for isolated fistulae because of septic complications (N = 7 patients with peritonitis or abscess formation), obstruction (N = 8 patients) or disease aggravation (N = 6 patients). Patient characteristics are presented by final surgical treatment in table II.

Surgery irrespective of indication

One hundred fifty one patients (93%) underwent surgery, 70 planned and 81 necessary (figure 1, table II). In figure 2, the probability of not undergoing surgery is presented as a function of time after demonstration of perforation. This probability was 0.83 at one month, 0.50 at six months and 0.28 at two years. The clinical and biological variables associated with early surgery at univariate analysis were absence of palpable mass, elevated polymorphonuclear neutrophil count, elevated platelet count, elevated CRP level and corticosteroid therapy. At multivariate analysis, associated variables were high platelet count (OR 1.95; 95CI 1.56-2.44) and corticosteroid therapy (OR 1.54; 95CI 1.24-1.91). Historical and morphological variables associated with early analysis were jejunal lesions, healthy ileum, presence of an abscess, and absence of fistula. At multivariate analysis, associated variables were jejunal lesions (OR 4.45; 95CI 2.54-7.79) and absence of fistulae (OR 2.18; 95CI 1.83-2.59).

Necessary surgery

Necessary surgery was performed in 91 patients because of secondary worsening of symptoms: 15 emergency procedures (sepsis, peritonitis, obstruction) and 66 procedures for treatment failure. In figure 3, the probability of not undergoing necessary surgery is presented by time since discovery of the perforation. This probability was 0.83 at one month, 0.50 at six months and 0.28 at two years. In figure 4, the probability of necessary surgery is presented by anatomic type of perforation. The patients were classified by increasing gravity of the lesions (inflammatory pseudotumor, loop agglutination, fistula, abscess. Necessary surgery was performed less frequently for fistulae than for abscess formation or pseudotumors. The clinical and biological variables associated with unfavorable course leading to necessary surgery were, at univariate analysis, absence of a palpable mass, weight loss, elevated polymorphonuclear neutrophil count, anemia, and elevated platelet count. At multivariate analysis, there was one associated variable: elevated platelet count (OR 3.15; 95CI 2.21-4.50). Historical and morphological variables associated with necessary surgery were, at univariate analysis, ileal lesions, presence of an abscess, presence of an inflammatory mass, and absence of fistula. At multivariate analysis, there was one associated variable: absence of fistula (OR 3.14, 95CI 2.48-3.99). In other words, the presence of a fistula was protective against necessary surgery.

Postoperative period and length of intestinal resection

The rate of major postoperative complications was 9.2%; the rate for minor complications was 4.6%. In the group of patients who underwent planned surgery, 61 patients did not develop postoperative complications (87%), two had a minor complica-

Table I. – Treatment modalities of intestinal perforation according to the type of perforation.

<table>
<thead>
<tr>
<th>Type of perforation</th>
<th>Antibiotic therapy</th>
<th>Enteral/Parenteral nutrition</th>
<th>Puncture/drainage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isolated enterocutaneous fistula</td>
<td>15</td>
<td>7</td>
<td>-</td>
</tr>
<tr>
<td>(N = 49)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isolated enterovesical fistula</td>
<td>3</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>(N = 5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abscess without identified fistula</td>
<td>47</td>
<td>18</td>
<td>21</td>
</tr>
<tr>
<td>(N = 59)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abscess with fistula (N = 23)</td>
<td>20</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Pseudo-tumor (N = 22)</td>
<td>8</td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td>Loop agglutination (N = 4)</td>
<td>2</td>
<td>1</td>
<td>-</td>
</tr>
</tbody>
</table>

Fig. 2 – Cumulative probability of not undergoing surgery, whatever the indication of surgery, during the three years following intestinal perforation (N=162).

Probabilité de ne pas subir de résection intestinale quelle qu’en soit l’indication dans les 3 ans suivant le diagnostic de perforation intestinale (N = 162).
In the group of patients who underwent necessary surgery, there were 69 patients (85%) who did not develop postoperative complications, five who had minor complications and seven who had major complications. These rates were not significantly different. A temporary stoma was fashioned for 13 patients who underwent planned surgery.

Table II. – Characteristics of Crohn’s disease patients with intestinal perforation according to surgical outcome.

<table>
<thead>
<tr>
<th>Surgery</th>
<th>Planned (%)</th>
<th>Necessary (%)</th>
<th>Not operated (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>70</td>
<td>81</td>
<td>11</td>
</tr>
<tr>
<td>Men</td>
<td>28 (40)</td>
<td>36 (44)</td>
<td>5 (45)</td>
</tr>
<tr>
<td>Age over 40 years</td>
<td>18 (26)</td>
<td>29 (36)</td>
<td>4 (36)</td>
</tr>
<tr>
<td>Smokers</td>
<td>45 (64)</td>
<td>46 (57)</td>
<td>8 (73)</td>
</tr>
<tr>
<td>CD for more than 4 years</td>
<td>35 (50)</td>
<td>38 (47)</td>
<td>7 (64)</td>
</tr>
</tbody>
</table>

Symptoms:
- Fever                        | 26 (37)     | 37 (46)       | 3 (27)          |
- Palpable mass                 | 24 (34)     | 23 (28)       | 5 (45)          |
- Obstruction                   | 17 (24)     | 19 (23)       | 0               |

Laboratory results:
- Elevated PMN count            | 17 (37)     | 19 (45)       | 0               |
- Anemia                         | 7 (14)      | 11 (24)       | 0               |
- Elevated platelet count        | 30 (59)     | 27 (60)       | 0               |
- Low serum albumin             | 30 (71)     | 26 (67)       | 1 (20)          |
- Elevated CRP                   | 36 (71)     | 29 (66)       | 3 (38)          |

Radiological diagnosis:
- Scanner                       | 50 (71)     | 51 (63)       | 5 (45)          |
- Barium                        | 13 (19)     | 18 (22)       | 5 (45)          |
- Others                        | 6 (9)       | 12 (15)       | 1 (9)           |

Type of perforation:
- Isolated abscess              | 26 (37)     | 32 (40)       | 1 (9)           |
- Isolated fistula              | 25 (36)     | 21 (26)       | 8 (73)          |
- Abscess and fistula           | 11 (16)     | 11 (14)       | 1 (9)           |
- Inflammatory pseudo-tumor     | 7 (10)      | 15 (19)       | 1 (9)           |
- Loop agglutination            | 1 (1)       | 3 (4)         | 0               |

CD involvement:
- Ileum                          | 62 (89)     | 73 (90)       | 11 (100)        |
- Colon                         | 28 (40)     | 26 (32)       | 3 (27)          |
- Rectum                        | 6 (9)       | 6 (7)         | 2 (18)          |
- Extensive (> 50 cm)            | 11 (16)     | 13 (16)       | 4 (36)          |
- Anus and perineum             | 4 (6)       | 5 (6)         | 2 (18)          |

Treatment before perforation:
- Corticosteroids                | 41 (59)     | 30 (37)       | 3 (27)          |
- Immunosuppressors              | 16 (23)     | 13 (16)       | 0               |
- Infliximab                     | 1 (1)       | 0             | 0               |

*Laboratory data were not available for all patients.
The major difficulty in the interpretation of our results is that the study included patients who underwent surgery because the decision was directly related to the type of perforation. For example, no attempt was made to delay surgery in patients with enterovesical fistulae while surgery was generally retarded in other patients because of the initially favorable course. Surgery was a planned decision in the first category of patients and a final solution which had to be employed in the second. We attempted to eliminate the weighting implied by the medical decision by limiting our second analysis to “necessary surgery” cases, i.e. patients for whom surgery was undertaken not because of a prior decision but because the clinical course was unsatisfactory under medical treatment. This second analysis demonstrated that a considerable proportion of the patients who developed an intestinal perforation can be successfully treated without surgery. The presence of an abscess or loop agglutination was not found to be associated with early surgery and the localization of the lesions did not have an effect on the clinical course under medical treatment. This finding confirms recent data in the literature suggesting that medical treatment using antibiotic therapy plus radiological or surgical drainage can be proposed as the first-intention treatment. A few recent studies have compared radiological or surgical drainage but the results are discordant [21]. Radiological drainage is proposed for two different reasons, depending on the team. Some propose radiological drainage as a curative treatment to avoid surgery while others use it to bide time until a less aggressive surgery can be undertaken [22, 23]. The initial apprehension about draining complicated abscesses, i.e. those associated with fistulization, multiple abscesses or abscesses at several localizations, has declined [24]. The reported rates of success of radiological drainage (26-50%) average about 40% [7, 21, 22, 25-29]. Casola et al. reported a high success rate of 60%, possibly related to a large proportion of retroperitoneal abscesses [30]. Success rates have been similar for surgical drainage (12-38% recurrence free) [21-85% of patients] [14, 19, 31, 32], but with a greater number of enterocutaneous fistulae [19,22,30,33].

Conversely, fistulization, complicated or not by abscess formation, was more often associated with favorable outcome with medical treatment. The fistula and its associated infectious complications were associated with necessary surgery in a minority of patients, most undergoing surgery because of intestinal obstruction or renewed disease activity independent of the fistula. In other words, fistulization per se is not a factor favoring the need for surgery. Studies investigating immunosuppressor or
infliximab treatments have included a small number of patients but have reported fistula improvement or closure. Two studies evaluating 6-mercaptopurine [34, 35] were published by the same team. The first reported improvement or closure of enterocutaneous fistulae in eight patients (75%) and of entero-enteral fistulae in seven (86%) at three months. The second study showed that 31% of the fistulae closed in the treated group versus 6% in the placebo group, but the initially programmed crossover was only implemented in a few patients. A meta-analysis of five studies [36] on azathioprine or 6-mercaptopurine treatment showed that 22 of 41 treated patients were responders compared with 6 of 29 in the placebo group. Treatment with cyclosporine has enabled clear improvement in two of four patients [37]. The first publication investigating infliximab demonstrated a significant improvement in enterocutaneous fistulae: 52% in the infliximab group versus 2% in the placebo group; there were only a few abdominal fistulae (N=9) in this study which did not demonstrate a statistical difference [38]. The second study reported a response after three injections of infliximab in 22 of 39 patients with enterocutaneous abdominal fistulae [39].

Our study also revealed that high platelet count was a factor predictive of early surgery, particularly "necessary" procedures. High platelet count probably reflects a long-standing inflammatory process which is too advanced to respond to medical treatment. This factor should be taken into consideration when deciding on the treatment strategy in CD patients with intestinal perforation.

Another important finding in this study was the absence of negative consequences of a non-surgical strategy. The rates of postoperative complications and the length of bowel resection were not different between patients who underwent "planned surgery" or an emergency resection because of failure to respond to medical treatment. Although this could be related to a selection bias, scheduled surgery being favored in patients with more active disease at the time of the diagnosis of perforation, comparison of the baseline data (Table II) did not demonstrate any statistical difference. Furthermore, immunosuppressive treatment does not increase postoperative morbidity [11]. Abscess drainage associated with antibiotic therapy reduces the inflammation and adherent tissue which can complicate emergency surgical procedures. We had rates of major, minor, and septic postoperative complications similar to those reported by other groups [9%, 7% and 6-13%] [12, 14, 40]. Unlike Hurst et al. [12] postoperative complication rates were similar in our series for planned and emergency procedures. The mean length of the bowel resection was somewhat shorter than reported by Hurst et al. and Yamamoto et al. [38 and 20 cm respectively] [12, 41].

In conclusion, our study demonstrated that surgical resection is generally favored for the treatment of intestinal perforation in CD patients, but that certain patients can benefit from conservative treatment without surgery. A medical strategy, preferably with immunosuppressors and infliximab in the event of fistulization, can be favored without an excessive risk of complication in patients who do not have bowel-bladder involvement.

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