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Demographic and Clinical Parameters Influencing the Short-Term Outcome of Anti-Tumor Necrosis Factor (Infliximab) Treatment in Crohn's Disease

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Objective: Infliximab is an effective treatment for refractory or fistulizing Crohn's disease (CD). However, about 30% of patients do not respond to infliximab for unknown reasons. Identifying predictive factors of response is important for optimizing clinical management and for better understanding infliximab's mechanisms of action. The aim of this study was to assess whether demographic or clinical parameters influence short-term response to infliximab.

Methods: The first 240 CD patients of the Belgian Infliximab Expanded Access Program were studied for response to infliximab treatment and assessed at 4 (refractory luminal CD) or 10 wk (fistulizing CD) after the first infusion. Detailed demographic and clinical information on age, sex, type of disease (fistulizing or refractory), Crohn's Disease Activity Index score, C-reactive protein (CRP), smoking habits, disease duration, localization of disease, concomitant medication, and previous surgery were obtained from all patients. Logistic regression and decision tree analysis were performed.

Results: There were 73.5% responders and 26.5% nonresponders to treatment. Stepwise logistic regression identified age (OR = 0.971, 95% CI = 0.947-0.995, $p = 0.018$), isolated ileitis (OR = 0.359, 95% CI = 0.177-0.728, $p = 0.004$), and previous surgery (OR = 0.429, 95% CI = 0.233-0.787, $p = 0.006$) as inversely correlated with response, whereas isolated colitis (OR = 1.905, 95% CI = 1.010-3.597, $p = 0.046$) and concomitant immunosuppressive treatment (OR = 2.670, 95% CI = 1.430-5.016, $p = 0.0022$) were positively correlated with response to infliximab. Surprisingly, smoking habits were not retained as predictors for response. Decision tree analysis provided a working algorithm based on age and immunosuppressive treatment that warrants further exploration.

Conclusions: In this large cohort of infliximab-treated CD patients, young age, Crohn's colitis, and concomitant immunosuppressive treatment were identified as independent variables favoring short-term response to infliximab.

INTRODUCTION

Without a definitive cure for Crohn's disease (CD), the current management (*i.e.,* a combination treatment of 5-aminosalicylates, corticosteroids, immunomodulating drugs, and antibiotics) aims at suppressing intestinal inflammation. The search for new drugs mainly focuses on the immune cascade and cytokine interactions, and a number of new immune modulating agents have been clinically investigated. In 1994, the efficacy of the murine-human monoclonal chimeric antibody against tumor necrosis factor-α (TNF-α, infliximab, Remicade) in the treatment of severe refractory rheumatoid arthritis was reported (1); soon afterward, this therapy also proved to be effective in severe refractory CD (2). Meanwhile, three placebo-controlled, double blind, randomized trials in CD have been published that show overall response rates of 65% (3-5). Infliximab has proved to be a major breakthrough in the management of both refractory and fistulizing CD. Although long-term efficacy and safety results remain unknown, the short- and medium-term clinical efficacy are very good; the duration of response after a single infusion ranges between 6 wk to 24 months, with a median of 12 wk (6-8). When patients are

retreated with one infusion every 8 wk, sustained remission is observed in 50% of patients (5). Treatment with infliximab is also associated with significant healing of endoscopic lesions and disappearance of the mucosal inflammatory infiltrate at the histological level (9, 10). However, some concerns remain. The lack of efficacy in about one third of patients as well as the high cost of the repeated infusions support the need for the identification of patient subgroups who will clearly benefit from the drug.

Response does not seem to be a matter of dosing (3), although selected patients may benefit from higher doses (11). Patients who do not respond to one infusion are unlikely to do so after another; however, the prognosticators that determine response or lack of response are still unknown. Targan *et al.* (3) could not identify any clinical parameters predictive of response to infliximab. In the study of Present *et al.* (4), concomitant use of azathioprine (AZA) seemed to encourage healing of fistulas. Also, in the retreatment study (5), a trend toward a positive influence of concomitant AZA treatment on infliximab response was seen, as 75% of patients taking AZA were still in remission 8 wk after the last infusion (at 44 wk), compared with 50% of patients who were not taking AZA. Besides clinical characteristics, demographic parameters have also been studied with respect to response prediction. However, published trials so far have not included smoking habits, one of the best known environmental risk factors influencing the clinical course of CD (3-8).

In general, defining demographic and clinical parameters that could predict response would contribute to a better understanding of the pathogenesis of the disease. In addition, they may provide insight into the mechanisms of action of infliximab, and may also lead to improved cost-effectiveness. Therefore, in this study, we assessed whether demographic or clinical parameters could predict short-term response in a large cohort of infliximab-treated CD patients.

MATERIALS AND METHODS

Patients

The first 240 CD patients of the Belgian Infliximab Expanded Access Program (Schering-Plough NV/SA, Study number P01246-1) were included in this study. Demographic characteristics, clinical parameters, and outcome data were recorded. Of this cohort, 137 (57.1%) patients received infliximab for refractory luminal disease and 103 (42.9%) for fistulizing disease. The demographic data and baseline clinical characteristics obtained are summarized in Table 1. Approval for the study was given by the Ethical Committees of the respective institutional boards where the study was ongoing, and all patients gave written informed consent before enrolling in the trial.

Treatment

Infliximab (Remicade; Centocor, Malvern, PA) was given as an *i.v.* infusion of 5 mg/kg in all patients. Eligible patients had to belong to one of the following groups: 1) they had to have single or multiple enterocutaneous draining fistula(s) as a complication of CD resistant to conventional treatment for at least 3 months ("severe" fistula patients); 2) they had to have moderately to severely active CD of at least 6 months' duration, with colitis, ileitis, or ileocolitis confirmed by radiography or endoscopy, and refractory or dependent on oral corticosteroid therapy (>8 mg/day prednisone equivalent); or 3) they were refractory or intolerant to methotrexate (MTX), AZA, 6-mercaptopurine (6-MP), or cyclosporine (started at least 12 wk before enrollment in the trial). Patients defined as dependent on corticosteroids were patients who failed all attempts to wean steroids completely. According to the protocol of the Expanded Access Program, patients with refractory luminal disease received a single infusion at wk 0. For fistulizing disease, three consecutive infusions at weeks 0, 2, and 6 were administered.

Evaluation of Efficacy

Response was determined at 4 or 10 wk after first infusion for refractory luminal or fistulizing CD, respectively. According to the criteria used in the study by Targan *et al.* (3) for luminal disease, patients were scored as cpmplete responders (remission) or partial responders when the Crohn's Disease Activity Index score (12) was <150 or when a reduction of ≥70 points in the Crohn's Disease Activity Index score was obtained, respectively. For fistulizing disease, response was defined as complete in the case of complete cessation of draining of the fistula despite gentle finger compression, and as partial in the case of an at least 50% decrease of the number of draining fistulae from baseline at two consecutive visits, respectively (4).

Table 1. *Demographic and Baseline Clinical Characteristics of the Study Population (N = 240)*

	Refractory CD (n = 137)	Fistulizing CD (n = 103)	All Patients (N = 240)
Mean baseline CDAI (range)	294 (72-609)	200 (51-526)	261 (51-609)
Mean baseline CRP (mg/L)	24.5	24.9	24.7
Median age (yr) (IQR)	34 (28-44)	37 (30-46)	36 (28-4475)
Female/male (%)	84/53 (61.3/38.7)	69/34 (67.0/33.0)	153/87 (63.8/36.2)
Smoking (%)	68 (49.6)	39 (37.8)	107 (44.6)
Mean disease duration (yr)	10.7	13.0	11.7
Involved intestinal area			
Ileitis (%)	23 (16.8)	17 (16.5)	40 (16.7)
Ileocolitis (%)	70(51.1)	35 (34.0)	105 (43.8)
Colitis (%)	43 (31.4)	46 (44.7)	89 (37.1)
Localization of fistulas			
Perianal		69	
Rectovaginal		23	
Enterocutaneous		19	
Into bladder		1	
Enterocolic		1	
Concomitant treatment			
Aminosalicylates (%)	59 (43.1)	47 (45.6)	106 (44.2)
Steroids (%)	75 (54.7)	33 (32.0)	108 (45.0)
6-MP/AZA/MTX (%)	76 (55.5)	64 (62.1)	140 (57.9)
Oral contraceptives	31 (22.6)	21 (20.4)	52 (21.7)
NSAIDs	8 (5.8)	5 (4.9)	13 (5.4)
Previous abdominal surgery	51 (37.2)	31 (30.1)	82 (34.2)

CDAI = Crohn's Disease Activity Index; NSAID = nonsteroidal anti-inflammatory drugs.

Statistical Analysis

Data were analyzed by means of a stepwise logistic regression and decision tree analysis (DTA), both implemented in SAS/STAT, release 8.01 (SAS Institute, Cary, NC). Whereas logistic regression enables the identification of independent variables associated with the defined target, decision tree analysis allows adding a weight to these variables. DTA (SAS Enterprise Miner) splits data into binary branches (CART option) according to the values of variables and continues splitting branches in an iterative process that leads to the target value. Each split depends on the value of only one variable *x*. Suppose that there are *M* variables: at each node, the tree algorithm searches through the variables one by one, beginning with x_1 up to x_m. For each variable, the best split is found, and the *M* best single variable splits are compared to select the best of the best. DTA will reject variables that play no role in arriving at the target. SAS Enterprise Miner divides the data set randomly into a training data set (±70% of data) used for model fitting, and a validation data set (±30% of data) to assess the adequacy of the model. In this way, DTA generates a working algorithm that, in turn, can be applied to new data and be scored. In contrast with a regression model, DTA does not allow for deducing significant interactions between variables. The results reported in the next section were obtained with a significance level of $\alpha = 0.05$; all reported *p* values are two-sided.

RESULTS

Six patients of the total cohort (2.5%) could not be evaluated for response because of confounding factors (psychiatric disorders, n = 2; short bowel syndrome, n = 1; acute surgery, n = 2; liver transplant and need for new concomitant immune suppressive treatment, n = 1) and were therefore excluded from further analysis. Of the remaining 234 patients evaluable for response, 172 of 234 (73.5%) were responders (of whom 110 of 234 (47.0%) entered remission and 62 of 234 (26.5%) showed partial response), whereas 62 of 234 (26.5%) did not respond to infliximab. Response rates for fistulous and luminal disease were 74.3% and 72.9%, respectively. The following noteworthy adverse events were seen: seven patients experienced acute infusion reactions, two patients developed a lupus-like syndrome, three patients developed hematological problems (one autoimmune hemolytic anemia, one leukopenia, one pancytopenia), and three patients developed a malignancy (one prostate cancer, one cervical cancer, and one desmoid tumor).

Stepwise logistic regression identified the following variables: age (OR = 0.971, 95% CI = 0.947-0.995, p = 0.018), presence of isolated ileitis (OR = 0.359, 95% CI = 0.177-0.728, p = 0.004), and previous surgery (OR = 0.429, 95% CI = 0.233-0.787, p = 0.006) were inversely correlated with response, whereas isolated colitis (OR = 1.905, 95% CI = 1.010-3.597, p = 0.046) and concomitant immunosuppressive treatment (OR = 2.670, 95% CI = 1.430-5.016, p = 0.0022) were positively correlated with response to infliximab (Table 2). There were 140 patients taking concomitant immunomodulating drugs, 127 AZA or 6-MP, and 13 MTX. Among the 13 patients taking MTX, nine of 13 were responders and four of 13 were nonresponders. However, no significant results were reached when this subgroup was analyzed separately, possibly because of the small number of patients. The significant influence of concomitant immunosuppressive medications on response is mainly due to AZA. Subanalysis with only those patients taking AZA/6-MP (leaving out those patients on MTX) was even more significant (OR = 2.773, 95% CI = 1.485-5.178, p = 0.0014).

If outcome was defined on the basis of remission rather than response, comparable results were obtained: namely, colitis (p = 0.019) and immunosuppressive treatment (p = 0.001) were positively associated with remission. More advanced age (p = 0.061), ileitis (p = 0.008), and previous surgery (p = 0.001) were associated with poor response.

Table 2. *Comparison of Responders (Remission or Partial) Versus Nonresponders for the Demographic and Clinical Characteristics Studied (Logistic Regression—SAS/STAT)*

	Response (n = 172)	Nonresponse (n = 62)	OR (95% CI)	p Value
Mean baseline CDAI	254	268	0.99 (0.996-1.002)	0.48
Mean baseline CRP (mg/L)	25.6	22.5	1.00 (0.988-1.020)	0.63
Median age (yr) (IQR)	33 (27-41.25)	41.5 (32-49)	0.971 (0.947-0.995)	0.018
Female/male (%)	108/64 (62.8/37.2)	40/22 (64.5/35.5)	0.993 (0.505-1.953)	0.98
Smoking (%)	80 (46.5)	26 (41.9)	1.38 (0.674-2.809)	0.38
Type of disease: fist/refractory	75/97 (43.6/56.4)	26/36 (41.9/58.1)	0.707 (0.319-1.568)	0.39
Mean disease duration (yr)	10.8	13.1	1.006 (0.972-1.041)	0.74
Involved intestinal area				
Ileitis (%)	22 (12.8)	18 (25.0)	0.359 (0.177-0.728)	0.004
Ileocolitis (%)	78 (45.3)	27 (43.5)	1.071 (0.595-1.927)	0.82
Colitis (%)	72 (41.9)	17 (23.6)	1.905 (1.010-3.597)	0.046
Concomitant treatment				
Aminosalicylates (%)	81 (47.0)	23 (37.1)	1.721 (0.880-3.363)	0.11
Steroids (%)	77 (44.8)	30 (48.4)	0.866 (0.443-1.691)	0.67
6-MP/AZA/MTX (%)	110 (63.9)	25 (40.3)	2.670 (1.430-5.016)	0.0022
Oral contraceptives	40 (23.3)	12 (19.4)	0.859 (0.432-1.700)	0.66
NSAIDs	8 (4.6)	5 (8.1)	0.800 (0.237-2.700)	0.72
Previous abdominal surgery	51 (29.6)	31 (50.0)	0.429 (0.233-0.787)	0.006

Abbreviations as in Table 1.

The regression model allowed us to look for interactions between certain variables. There was no interaction between age and colonic involvement, or between age and concomitant immunosuppressive drugs. However, a positive interaction of concomitant immunosuppressive drugs on colonic involvement was seen: of 191 patients with Crohn's colitis who were evaluable for response, 95 of 147 (64.6%) responders were taking AZA, compared to only 18 of 44 (40.9%) of nonresponders (OR = 0.394, 95% CI = 0.197-0.789, p = 0.009). Inversely, the presence of colitis did not have any additional beneficial effect on concomitant immunosuppressive intake toward treatment response.

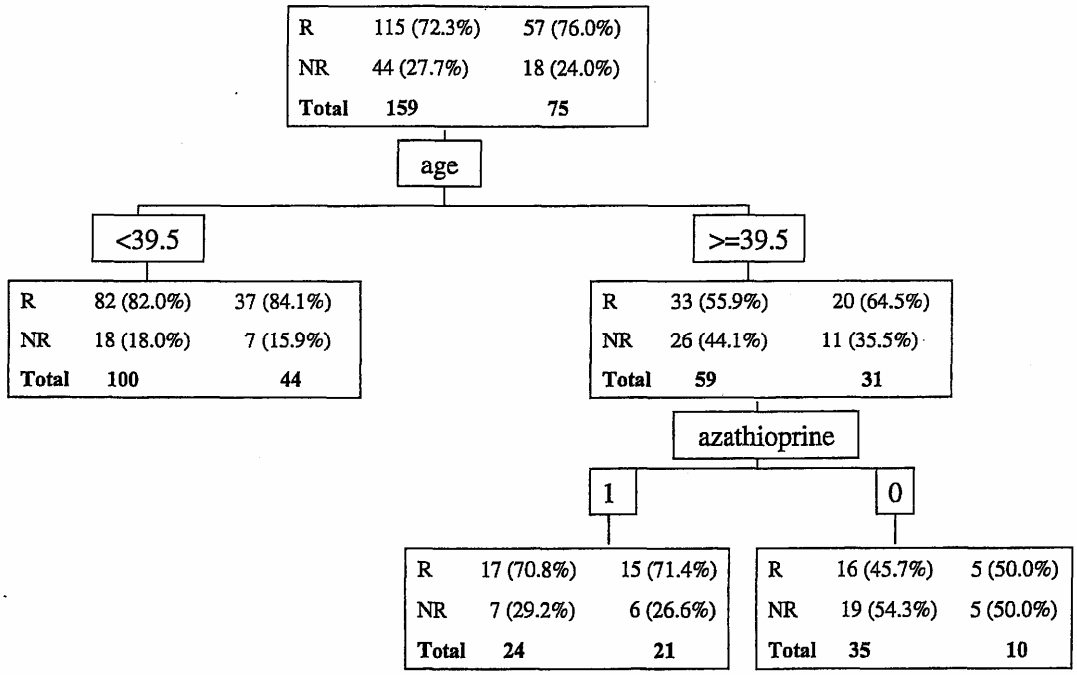
Smoking habits did not influence response to infliximab; 80 of 106 (75.5%) smokers showed response, which was not significantly different from the response seen in nonsmokers (89 of 128, 69.5%) (OR = 1.376; 95% CI = 0.674-2.809, p = 0.38). Furthermore, in smokers, the same ratio for response/nonresponse was observed, regardless of concomitant immunosuppressive intake. This implied that there was no interaction between smoking and immunomodulator therapy, as suggested in other studies (13).

Subsequently, patients with fistulizing and luminal disease were analyzed separately. For refractory luminal disease only, the following variables were significantly related with response: age (OR = 0.961, 95% CI = 0.929-

0.995, $p = 0.024$), ileitis (OR = 0.325, 95% CI = 0.128-0.824, $p = 0.018$), and concomitant immunosuppressive treatment (OR = 2.917, 95% CI = 1.292-6.587, $p = 0.010$). In the subgroup of fistulizing disease, young age and previous surgery were the only significant parameters (OR = 0.961, 95% CI = 0.926-0.998, $p = 0.037$ and OR = 0.345, 95% CI = 0.128-0.930, $p = 0.035$, respectively). The concomitant intake of immunosuppressive treatment was borderline significant (OR = 2.48, 95% CI = 0.997-6.17, $p = 0.0508$).

The same input variables were used in the decision tree analysis (Fig. 1). For the whole data set, age was the first splitting variable: for a cut-off of age <39.5 yr, 82% of the training and 84% of the validating data set would be correctly classified toward infliximab response. The purity of the node age <39.5 yr could not be improved further by the program and, hence, the splitting stopped. For the node age >39.5 yr, only 55.9% and 64.5% would correctly be classified toward response for the training and validation data set, respectively. However, AZA was defined as the second splitting variable in this node, and prediction of response improved to 70.8% and 71.4%, respectively, with concom itant AZA therapy. No other variables, including disease localization or previous surgery, could be identified in this decision tree that could further improve our model. Given the fact that DTA is created for large data sets of information, no subanalysis of fistulizing and luminal CD was performed.

Figure 1. *Decision tree analysis (using SAS enterprise Miner; see text) on the total study population (n = 240). Absolute numbers as well as percentage of response (R) and nonresponse (NR) for the training data set (left column) and validation data set (right column) are given. Age was selected as the first splitting variable to predict the target, whereas use of azathioprine was selected as second splitting variable in the group of patients >39.5 yr.*



DISCUSSION

Treatment refractoriness is a serious problem for a chronic disorder such as CD. Because the pathogenesis of CD is still unknown, there is no cure for the disease, and current treatment focuses on suppressing the intestinal inflammation. Therapy refractoriness is not a new problem in the clinical management of inflammatory bowel disease (IBD). From the very first introduction of corticosteroids, it was shown that 20% of patients do not respond, and 36% of responders develop steroid dependency (14). AZA/6-MP is effective in up to 50% of patients who are dependent on or refractory to corticosteroids (15); however, 25% of patients still do not respond. MTX is an alternative for patients who do not respond or who are intolerant to AZA/6-MP (16). Recently, the introduction of monoclonal antibodies against TNF-α was a major achievement in the treatment of diseases such as IBD and rheumatoid arthritis. Approximately 170,000 patients worldwide have since been

treated (two thirds of patients for rheumatoid arthritis and one third of patients for IBD) worldwide and results are promising, with overall response rates around 65%. However, again we are confronted with a group of nonresponding patients. Therefore, it is of great importance to find clinical, biochemical, or immunological parameters to predict treatment failure. Indeed, if treatment fails, patients remain symptomatic and are at increased risk for complications, hospital admissions, and even surgery.

To our knowledge, the present study is the largest to date on demographic and clinical parameters influencing short-term response to initial infliximab infusions. We observed 74% responders to treatment and 26% nonresponders. These data are similar to findings of three large published trials (3-5) as well as subsequently published cohort-studies (6-8). In our study, response to infiximab in the total cohort was associated with a young age, colitis, and—probably most importantly—the concomitant intake of immunomodulating drugs. In only those patients with refractory luminal CD, young age and concomitant use of immunomodulators were associated with response, whereas isolated ileitis was associated with poor response. For fistulizing CD, young age also favored response, whereas previous abdominal surgery was associated with poor response. Probably colonic disease did not hold up in these stratified analyses because of widened confidence intervals resulting from decreased sample size. We did not observe a change in the point estimates of the OR when comparing OR of the total regression model, as compared to the model stratified according to disease type.

None of the randomized trials or the three recent retrospective studies showed any significant association between, for example, AZA/6-MP treatment and initial response to infliximab, probably because of a lack of statistical power. Although in the retreatment study it was suggested that concomitant immunosuppressive treatment may favor response, no significance was reached (5). It must be noted that in the present study we looked at the response to initial infiximab infusions; this is different from maintenance of remission with repeated infiximab treatment, in which case AZA/6-MP treatment may be beneficial by preventing attenuation of response to repeated infliximab infusions.

The study by Cohen *et al.* also found that concurrent therapy with 6-MP or AZA (but not MTX) resulted in a higher response and remission rates to initial infliximab infusion when compared to patients not receiving any of these additional immunomodulators; but, again, no significance was reached (6). Although the results of that study should be treated with caution (given that this was a retrospective study rather than a randomized trial), the efficacy data in rheumatoid arthritis clearly demonstrate the synergistic effect of concomitant immunosuppressive treatment on infliximab response (17).

Decision tree analysis selected age, with a cut-off of 39.5 yr, as the best variable to predict response. Patients under this age are more likely to respond. In the older group of patients, in contrast, the response was lower but could substantially be improved by concomitant use of AZA. Whether use of infliximab should be advocated in these elderly patients who are not taking immunosuppressive drugs remains to be determined. A first step is to confirm our results in independent patient cohorts to see whether treatment guidelines can be optimized further in the future. It is not clear why younger patients would have a better response. One hypothesis is that the better outcome in younger patients could be related to a shorter duration of their disease. However, our results could not prove this. It is well known that there is a functional decline in both the adaptive and innate immune systems with increasing age (18). Several hypotheses try to explain this so-called immune senescence: reduction in the synthesis and release of hormones or neurotransmitters; alterations in the number, density, and affinity of receptors; diminished receptor responsiveness; and/or alterations in biochemical events distal to the hormone/receptor site. Maybe the question why older patients respond less well should be focused in this direction.

Although logistic regression identified disease localization and previous abdominal surgery as other independent variables associated with response, in the decision tree model, these variables were less important than age and concomitant AZA treatment, and could not further improve the predictive model.

Interestingly, smoking habits were not retained as predictive factors from our analysis. It has been shown that smoking is associated with a more severe course of CD and with an increased risk for surgery. The same authors found that immunosuppressive therapy neutralizes the influence of smoking on surgical rates (13). However, the possibility that the negative results for smoking in our study were caused by the neutralizing effect of concomitant immunosuppressive treatment could not be demonstrated.

Because CD results from an interaction among environmental, genetic, and immunological factors, anti-TNF treatment may tackle only part of the etiopathogenesis of CD. Other factors are still present that will also define clinical outcome. Biological availability of infliximab in the serum, among other factors, seems to be an

important determinant of response. It is mandatory to continue the search for clinical parameters that can identify those patients who are more likely to benefit from current or new treatments. In this respect, studies on genetic polymorphisms, serological markers, and cytokine profiles could add more insight into the problem and could improve our understanding in the mechanisms of action of drugs. More importantly, however, the insights derived from such studies would enable practitioners to better serve our patients with CD by offering them a more efficacious, individually tailored therapeutic management.

In conclusion, in this large cohort of infliximab-treated patients with CD, young age, concomitant immunosuppressive treatment, and isolated colitis were independent variables of response to infliximab, whereas previous abdominal surgery and isolated ileitis were associated with poor response. These results may have important clinical implications for future management of CD with infliximab. Decision tree analysis further provided a working algorithm to be prospectively tested.

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