

# Recurrence and Impact of Postoperative Prophylaxis in Laparoscopically Treated Primary Ileocolic Crohn Disease

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**Objectives:** To define risk factors for recurrence and to determine whether postoperative prophylaxis would influence time to recurrence after primary laparoscopic ileocelectomy for Crohn disease.

**Design:** Retrospective record review.

**Setting:** Tertiary academic medical center.

**Patients:** All patients who underwent primary laparoscopic ileocelectomy for terminal ileal Crohn disease between April 28, 1994, and August 3, 2006, at the Mayo Clinic, Rochester, Minnesota.

**Main Outcome Measures:** All patients were reviewed for follow-up, recurrence, risk factors for recurrence, and use of postoperative immunosuppressive prophylaxis.

**Results:** One hundred nine patients were identified, of whom 89 were followed up postoperatively at Mayo Clinic with a median follow-up of 3.5 years (range, 1.8 months

to 11.9 years). Recurrence was discovered in 54 patients (61%) at a median of 13.1 months (range, 1.3 months to 8.7 years). Forty-four patients (49%) received postoperative immunosuppressive prophylaxis (37 [42%] received azathioprine, 8 [9%] received 6-mercaptopurine, and 3 [3%] received infliximab). In a multivariate model of various risk factors for recurrence, presence of granulomas was the only significant predictor of recurrence ( $P=.01$ ). The 2-year cumulative recurrence rates in the prophylaxis and nonprophylaxis groups were 37.5% and 52.6%, respectively (log-rank test,  $P=.87$ ).

**Conclusions:** Recurrence occurred in more than half of the patients with Crohn disease after primary laparoscopic ileocelectomy. In this highly selected patient population, use of immunosuppressive prophylaxis was not associated with a delay in recurrence. Presence of granulomas was the only significant predictor of recurrence. These findings should be further explored in larger and less selected patient populations.

*Arch Surg.* 2010;145(1):42-47

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**C**ROHN DISEASE IS A chronic transmural granulomatous process that affects 600 000 people in the United States.<sup>1</sup> Recent advances suggest that Crohn disease results from an interplay of genetic susceptibility, dysregulation of the mucosal immune system, and gut microflora; however, the etiology remains unknown.<sup>2</sup> Much of the knowledge regarding the natural history of Crohn disease predates the use of immunosuppressive and biologic agents, and thus the natural history of Crohn disease in the modern era has not been clearly defined.<sup>3</sup>

Minimally invasive surgery has gradually become an accepted approach to the surgical treatment of Crohn disease. Today, laparoscopic ileocelectomy is the preferred technique in the surgical management of medically refractory Crohn dis-

ease at our institution. This preference is based on observed improvements in short-term outcomes, earlier return of bowel function, shorter hospital stay, lower morbidity, and lower cost.<sup>4-10</sup> There are few reports on the long-term outcome of laparoscopic surgery as measured by disease recurrence, reoperative surgery, and requirement for postoperative medical therapy.<sup>8-11</sup>

## See Invited Critique at end of article

Management of postoperative Crohn disease has typically included early identification of recurrence and early initiation of medical treatment. The evidence for medical prophylactic therapy is still largely unsupported.<sup>12,13</sup> A meta-analysis suggested that postoperative 5-aminosalicylates have a modest effect in reducing

the risk of recurrence,<sup>14</sup> but a subsequent study showed no benefit.<sup>15</sup> Data on the efficacy of purine analogues (azathioprine [AZA] and 6-mercaptopurine [6-MP]) in this setting are conflicting.<sup>16,17</sup> Nitroimidazole antibiotics such as metronidazole and ornidazole have modest efficacy, but many patients cannot tolerate these drugs owing to neuropathy. Unfortunately, this inability to prevent recurrence on a large broad scale leads to clinical relapse in at least half of patients.<sup>18</sup>

Our study aims were to determine the cumulative probability of postoperative recurrence of Crohn disease following primary laparoscopic ileocolonic resection for terminal ileal disease and to determine risk factors associated with recurrence.

## METHODS

Patients undergoing laparoscopic resection for terminal ileal Crohn disease were prospectively included in an institutional database. The medical records of these patients were reviewed to retrospectively retrieve data for this study. We included all patients who underwent primary laparoscopic ileocelectomy for terminal ileal Crohn disease and were followed up at Mayo Clinic, Rochester, Minnesota, from April 28, 1994, to August 3, 2006. A total of 109 patients underwent primary laparoscopic ileocolonic resection. Eighty-nine patients were followed up at Mayo Clinic and therefore met our criteria for analysis. Institutional review board approval was obtained to review the patients' medical records.

Patient demographic characteristics and information on preoperative variables such as cigarette smoking status, previous surgical procedures, preoperative medications, and indication for surgery were recorded. Definitions for operative indications included medically refractory disease (ie, nonstricturing, nonpenetrating), fibrostenotic disease, and fistulizing disease (intraloop fistula, fistula between the ileum and left colon, bladder, or skin).<sup>19</sup> Surgical details such as type of anastomosis (stapled vs hand sewn), pathological variables such as presence of granulomas, histological activity (mild, moderate, severe) of Crohn disease, and positivity of margins were reviewed.

Data on postoperative outcomes included use of prophylactic medication, postoperative recurrence, and reoperation rates and details. Recurrence was defined as 1 or more of the following: (1) presence of endoscopic evidence of disease (eg, a Rutgeerts score<sup>20</sup> of 1 indicates  $\leq 5$  aphthous lesions; a Rutgeerts score of 2 indicates  $>5$  aphthous lesions with normal mucosa between the lesions, or skip areas of larger lesions; a Rutgeerts score of 3 indicates diffuse aphthous ileitis with diffusely inflamed mucosa; and a Rutgeerts score of 4 indicates diffuse inflammation with already larger ulcers, nodules, and/or narrowing); (2) radiological findings of Crohn disease (including on computed tomography of the abdomen and pelvis, small-bowel follow-through, or computed tomographic enterography); or (3) pathological evidence of disease at reoperation. Routine evaluation with endoscopy or other imaging modalities was typically performed for symptomatic patients and at 12 to 18 months for those without symptoms postoperatively. Postoperative prophylaxis in this study included AZA (2 mg/kg in all patients), 6-MP, infliximab (5-10 mg/kg), or a combination of these medications. The choice to administer prophylactic therapy as well as the specific medications used were left to the discretion of the patients' gastroenterologists. Patients who received prophylactic medical therapy and those who did not were compared for any significant difference among these demographic variables.

Descriptive statistics including mean (standard deviation), median (range), and frequency (percentage) were used to summarize demographic and clinical characteristics. The 2-sample *t* test,  $\chi^2$  test, and Wilcoxon rank sum test were applied to compare these baseline variables between patients who received prophylactic medication postoperatively and those who did not. The primary end point of this study was time to recurrence of Crohn disease. Univariate analysis was performed using the Kaplan-Meier method, whereas multivariate analysis was performed using a Cox proportional hazards regression model. The independent variables incorporated in the multivariate model were selected by participating clinicians. All statistical tests were 2-sided, and  $P < .05$  was considered statistically significant. All analyses were performed using SAS statistical software version 9.1.3 for UNIX (SAS Institute, Inc, Cary, North Carolina).

## RESULTS

Eighty-nine patients (71% female) with a median age of 29 years (range, 15-76 years) were included in this study. Medically refractory disease was the most common indication for surgery in our cohort (52 patients [58%]). Other indications included fibrostenotic obstruction (27 patients [30%]) and fistulizing disease (5 patients [6%]). Two patients (2%) had gross positive resection margins and 11 patients (12%) were found to have granulomas in the resection specimen.

The median postoperative follow-up was 3.5 years (range, 1.8 months to 11.9 years). All patients with follow-up of less than 1 year had either recurrence (5 patients) or colonoscopy excluding recurrence (2 patients). Endoscopic, radiological, or histological recurrence occurred in 54 patients (61%), and the median time to recurrence for those who experienced recurrence was 13.1 months (range, 1.3 months to 8.7 years). Most recurrences were symptomatic (47 patients [87%]). At the time of last follow-up, 3 patients with recurrent disease required reoperation. Among 50 patients with endoscopic findings of recurrence, 48 had a definable Rutgeerts score: 4 (8%) had a score of 1; 18 (38%) had a score of 2; 19 (40%) had a score of 3; and 7 (15%) had a score of 4. Six patients had recurrence defined by computed tomographic enterography with findings of inflammatory small-bowel disease. All patients without recurrence were evaluated with colonoscopy within the follow-up period. There were no differences in the 2 groups with regard to type (endoscopy or radiological imaging) ( $P = .45$ ) or timing ( $P = .87$ ) of this follow-up. The univariate analysis assessing the effect of each potential risk factor on time to recurrence is shown in **Table 1**. The presence of granulomas in the resection specimen was identified as a significant risk factor for time to recurrence of disease ( $P = .03$ ) (**Figure 1**). The use of postoperative prophylactic medication was not significantly associated with time to recurrence ( $P = .87$ ) (**Figure 2**).

Preoperative, operative, and pathological factors with the potential to impact recurrence were included in a multivariate Cox proportional hazards regression model to identify risk factors for recurrence (**Table 2**). After incorporating all of the univariate predictors except preoperative medication, only the presence of granulomas in the surgical specimen was identified as a significant

**Table 1. Cumulative Recurrence Rate at 2 Years Postoperatively for Demographic and Clinical Factors<sup>a</sup>**

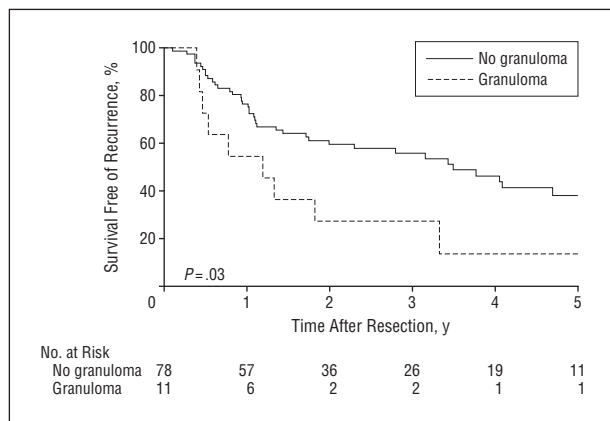
Variable	Cumulative Recurrence Rate (95% CI), %	P Value
Aged $\geq 30$ y at surgery		.63
No	42.2 (25.0-55.5)	
Yes	47.6 (29.9-60.8)	
Stapled anastomosis		.25
No	63.9 (27.4-82.0)	
Yes	41.0 (28.2-51.6)	
Medically refractory disease		.31
No	35.9 (17.1-50.4)	
Yes	49.3 (33.3-61.4)	
Current smoker		.79
No	42.2 (29.1-52.9)	
Yes	55.1 (22.8-73.9)	
Positive margins		.80
No	43.9 (31.5-54.0)	
Yes	55.0 (0.0-80.2)	
Presence of granulomas		.03
No	40.5 (28.1-50.8)	
Yes	72.7 (28.4-89.6)	
Preoperative medication <sup>b</sup>		.90
No	44.1 (15.8-62.9)	
Yes	44.8 (31.4-55.7)	
Postoperative prophylaxis <sup>c</sup>		.87
No	52.6 (34.5-65.6)	
Yes	37.5 (21.0-50.6)	

Abbreviation: CI, confidence interval.

<sup>a</sup>Univariate Kaplan-Meier analysis.

<sup>b</sup>Defined as infliximab, azathioprine, or prednisone.

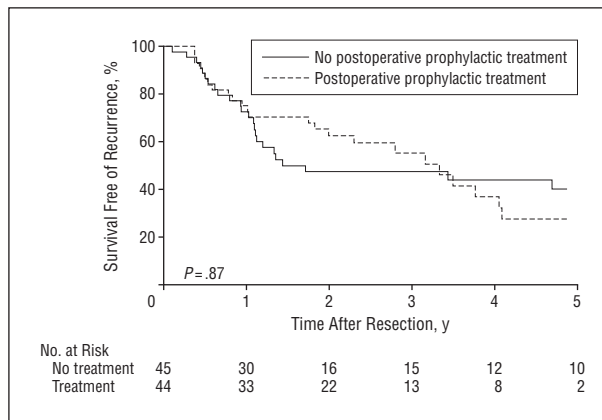
<sup>c</sup>Defined as 6-mercaptopurine, infliximab, or azathioprine.



**Figure 1.** Survival free of Crohn disease recurrence stratified by the presence of granulomas in the resection specimen.

risk factor for time to recurrence of disease (hazard ratio = 2.89; 95% confidence interval, 1.26-6.64;  $P = .01$ ). In other words, the hazard of disease recurrence for patients with granulomas in their resection specimen was almost 3 times higher than for those who did not have granulomas (Table 2).

Postoperative prophylactic medications included AZA (2 mg/kg), 6-MP, and infliximab (5-10 mg/kg). Postoperative prophylaxis was started in 44 patients (49%) (37 [42%] received AZA, 8 [9%] received 6-MP, and 3 [3%] received infliximab). Comparisons between the postop-



**Figure 2.** Survival free of Crohn disease recurrence stratified by the use of postoperative prophylactic medical therapy. Postoperative prophylactic treatment includes infliximab, azathioprine, or 6-mercaptopurine.

**Table 2. Risk of Recurrence Given Demographic and Clinical Factors<sup>a</sup>**

Variable	HR (95% CI)	P Value
Aged $\geq 30$ y at surgery	1.57 (0.86-2.86)	.14
Stapled anastomosis	0.54 (0.27-1.10)	.09
Medically refractory disease	1.28 (0.70-2.36)	.42
Current smoker	0.97 (0.46-2.03)	.93
Positive margins	1.29 (0.49-3.43)	.61
Presence of granulomas	2.89 (1.26-6.64)	.01
Postoperative prophylaxis <sup>b</sup>	1.09 (0.63-1.90)	.76

Abbreviations: CI, confidence interval; HR, hazard ratio.

<sup>a</sup>Multivariate Cox proportional hazards regression model.

<sup>b</sup>Defined as 6-mercaptopurine, infliximab, or azathioprine.

erative prophylaxis and nonprophylaxis groups identified no significant differences among preoperative variables except the preoperative use of AZA (Table 3). Preoperative use of AZA was higher in the postoperative prophylaxis group than in the nonprophylaxis group (31 patients [70%] vs 6 patients [13%], respectively;  $P < .001$ ). The time to recurrence of Crohn disease in the prophylaxis group and in the nonprophylaxis group were not significantly different ( $P = .87$ ) (Table 1). The median time to recurrence (or last follow-up if there was no recurrence) in these 2 subsets was 24.9 months in the prophylaxis group and 16.0 months in the nonprophylaxis group.

## COMMENT

Crohn disease is a chronic inflammatory gastrointestinal disorder with an unpredictable clinical course characterized by a high incidence of recurrence. In this study, the presence of granulomas in the resected specimen was the only significant predictor of recurrence among the many risk factors evaluated. It is likely that this specific cohort of patients who were amenable to laparoscopic surgery has a greater impact on recurrence than the surgical approach itself. Second, the open-label use of prophylactic medical therapy in this highly selected cohort was not associated with a delay in the time to recurrence.

This study is unique in that we focused on a highly selected cohort of patients with Crohn disease who underwent their first surgical resection for terminal ileal disease using a laparoscopic approach. Unlike previous laparoscopic series,<sup>4,5,8,9</sup> this study provides information on the largest cohort of patients with laparoscopically treated terminal ileal disease with the additional information of type and dosing of postoperative medical treatment as well as recurrence data defined by endoscopic and radiological imaging. In addition, we are not aware of studies in the literature that have evaluated both risk factors for recurrence and the impact of postoperative prophylaxis in similar patients undergoing primary laparoscopic ileocelectomy for terminal ileal Crohn disease. Although the vast majority of patients had excellent follow-up with standard definitions of endoscopic recurrence, we did lose 20 patients owing to lack of follow-up. Although this is a sizable patient group, the loss is not unexpected given our tertiary referral practice.

Patients in this trial had a 61% recurrence rate (54 of 89 patients) defined in large part by endoscopy by the time of this analysis. Endoscopic recurrence is used by most medical trials as a major study end point. In addition, most recurrences (47 patients [87%]) were symptomatic. Rutgeerts et al<sup>21</sup> noted that 73% to 93% of patients undergoing ileocolic resection had evidence of endoscopic recurrence after 1 year and 85% to 100% of patients had evidence of endoscopic recurrence after 3 years. Unlike our series, all other modern published laparoscopic surgical trials lack data regarding endoscopic recurrence.<sup>8-10</sup> This information is critical to decision making regarding further medical treatment and may ultimately affect the need for further surgical therapy. In addition, the need for further surgical resection varies widely from 15% to 45% at 3 years, 26% to 65% at 10 years, and 33% to 82% at 15 years.<sup>22</sup> Smaller, less defined laparoscopic series to date have reported rates of surgical recurrence equal to ours<sup>9</sup> or significantly higher (22%-28%).<sup>8,11</sup> The reasons for our low surgical recurrence rates are likely multifactorial and might have been influenced by our follow-up period and the process in which patients were selected for a laparoscopic approach.

Analysis of specific risk factors revealed that the presence of granulomas in the specimen was the only significant predictor of recurrence. This finding supports the belief by some that the presence of epithelioid granulomas may separate Crohn disease into 2 pathological subsets and may indicate aggressive disease.<sup>23,24</sup> In a recent study by Cullen et al,<sup>25</sup> the presence of epithelioid granulomas in the specimen was the only factor significantly associated with the incidence of symptomatic recurrences. In their study, 61% of those with symptomatic disease recurrence had granulomas compared with 34% of those who remained asymptomatic. However, earlier reports contradict this finding.<sup>26,27</sup>

Smoking status has always been considered a significant risk factor for recurrence in Crohn disease. Several studies have reported 5-year and 10-year recurrence rates that were significantly higher in smokers than in non-smokers.<sup>28,29</sup> After a multivariate analysis, Cottone et al<sup>30</sup> proposed that smoking was an independent risk factor

**Table 3. Comparison of Demographic Characteristics Based on Postoperative Prophylaxis in Crohn Disease**

Variable	No Prophylaxis (n=45)	Prophylaxis (n=44)	P Value
Age at surgery, mean (SD), y	34.9 (15.7)	34.3 (12.2)	.84
Aged ≥30 y at surgery, No. (%)	21 (47)	23 (52)	.60
Female, No. (%)	31 (69)	32 (73)	.69
BMI, mean (SD)	25.0 (5.4)	25.0 (5.9)	.97
Recurrence, No. (%)	29 (64)	25 (57)	NA
Stapled anastomosis, No. (%)	35 (78)	39 (89)	.17
Medically refractory disease as main surgical indication, No. (%)	28 (64)	24 (55)	.39
Preoperative AZA use, No. (%)	6 (13)	31 (70)	<.001
Current smoker, No. (%)	10 (22)	7 (16)	.45
Positive margins, No. (%)	5 (11)	3 (7)	.48
Presence of granulomas in pathological specimen, No. (%)	6 (13)	5 (11)	.78
Persistent disease, No. (%)	2 (4)	4 (9)	.38
Time from surgery to last follow-up, median (range), mo	48.7 (5.9-142.7)	38.1 (1.8-126.4)	NA

Abbreviations: AZA, azathioprine; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); NA, not applicable.

for endoscopic, clinical, and surgical recurrence. In our study, 17 patients (19%) were smokers and this was not a predictor of recurrence of Crohn disease after ileocelectomy ( $P=.79$ ).

Analysis of recurrence based on the use of prophylactic medications showed that there was no statistical difference in time to recurrence between those treated with postoperative medical prophylaxis and those in the no-therapy arm ( $P=.87$ ). Certainly, all factors related to treatment decisions and recurrence risk cannot be accounted for in this series. However, this is one of the only studies to actually define treatment and report on both endoscopic and operative recurrence rates. In contrast to our findings, one laparoscopic series found that medications decreased time to recurrence but did not define the specific type or dosing of prophylactic medication used.<sup>9</sup> Other laparoscopic series lack any information regarding follow-up strategy, medication used, or their impact on recurrence.<sup>4,5,8,10,11</sup> More importantly, the decision to treat patients postoperatively with AZA in our series was not influenced by operative or pathological findings that would indicate increased risk of recurrence, as nearly all patients in this series had similar disease patterns. The decision to treat patients postoperatively was likely related to the preoperative use of AZA more than any other clinical factor. Moreover, the lack of efficacy related to postoperative prophylaxis found in this series remains in alignment with much of the current medical literature, which suggests that the utility of postoperative medical treatment is unsupported.<sup>12,13</sup> An alternative explanation for our failure to observe a significant difference between the 2 treatment groups is that our study

may be underpowered to detect a clinically meaningful difference.

Previous randomized controlled trials evaluating the efficacy of a variety of postoperative prophylactic medications including mesalamine, AZA, 6-MP, infliximab, and probiotics failed to consistently demonstrate efficacy.<sup>12,13,31-37</sup> Data on the role of purine analogues specifically in maintenance of surgically induced remission are contradictory. Two randomized controlled trials involving AZA or its metabolite 6-MP failed to show any advantage in postoperative recurrence.<sup>17,38</sup> In contrast, a placebo-controlled trial by Hanauer et al<sup>16</sup> reported reduced clinical recurrence using 6-MP. However, this study has a number of shortcomings, which were highlighted by Sandborn and Feagan.<sup>39</sup> Our data provide additional confirmatory evidence that purine analogues may not be of benefit for postoperative prophylaxis in patients with Crohn disease undergoing primary laparoscopic ileocecal resection.

Data on the role of biological therapy in prevention of postoperative recurrence in Crohn disease are sparse, even though infliximab was introduced into clinical practice in 1998. A recent report on the combination of infliximab and methotrexate to prevent postsurgical recurrence after ileocelectomy showed promising results.<sup>40</sup> Only 3 patients (3%) in our study received postoperative infliximab, which limits our ability to draw meaningful conclusions as to its impact on recurrence.

As discussed earlier, this cohort of patients is highly selected and therefore may not be comparable to the more diverse patient subsets in previous open studies. Also, these data do not support the notion that prophylactic medication should not be used in selected patients with more severe disease. However, in this selected cohort of laparoscopically treated patients, the use of postoperative immunomodulating prophylaxis was not shown to be associated with a benefit in delaying recurrence. Moreover, the presence of granulomas in the surgical specimen is a strong predictor of recurrence and should stimulate a heightened level of follow-up. Future research is needed to explore the efficacy of modern medical therapy in patients with Crohn disease undergoing laparoscopic surgical resection in order to define proper treatment and follow-up programs.

Accepted for Publication: February 16, 2009.

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Financial Disclosure: Dr Sandborn has provided research support to Procter & Gamble Pharmaceuticals, Shire Pharmaceuticals, Centocor Ortho Biotech, Abbott Laborato-

ries, and UCB Pharma and has acted as a consultant for Procter & Gamble Pharmaceuticals, Shire Pharmaceuticals, Salix Pharmaceuticals, Ferring Pharmaceuticals, Centocor Ortho Biotech, Abbott Laboratories, and UCB Pharma.

Funding/Support: This work was supported by a grant from the Department of Surgery, Mayo Clinic.

Previous Presentation: This work was presented at the 2008 Annual Meeting of the American Society of Colon and Rectal Surgeons; June 6, 2008; Boston, Massachusetts.

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**INVITED CRITIQUE**

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## Preventing Crohn Disease Recurrence With Drugs After Ileocelectomy

### *An Exercise in Futility?*

**M**alireddy and colleagues from the Mayo Clinic conducted this retrospective record review to assess whether postoperative administration of anti-inflammatory agents lowered the risk of recurrence after laparoscopic ileocelectomy for Crohn disease. Of the 109 patients identified as having had the procedure, 89 were followed up postoperatively for a median of 3.5 years. The authors identified 54 patients (61%) who had recurrence at a median of 13.1 months as detected endoscopically, radiologically, or histologically. Apparently, to look for recurrence, endoscopy was performed at any time postoperatively for anyone who was symptomatic and at 12 to 18 months for anyone who was not symptomatic. Only 44 of the patients (49%) whom they followed up postoperatively received any kind of prophylaxis (most commonly AZA/6-MP). There was no significant difference in recurrence between those who received the prophylaxis (37.5%) and those who did not (52.6%), although there appeared to be a trend toward efficacy in the prophylaxis group.

This study is well written and appropriate statistical methods were used. Certainly the laparoscopic angle of the article is novel (although it is difficult to imagine that

the surgical approach or technique would alter the natural history of the disease in any way) and the series size is notable. However, the outcome does not really shed any new light on this controversial area that has been extensively studied in both retrospective studies (such as this one) and prospective, randomized studies (of which there are a significant number). The results of these studies are not predictable, not consistent, and not in agreement, leaving the thoughtful reviewer to conclude that if postoperative prophylaxis has any impact in its current state, it must be very small since it is not consistently shown to be of benefit. For example, of the 3 randomized controlled trials of sulfasalazine,<sup>1-3</sup> 2 showed no benefit and 1 showed benefit at 1 year. Seven randomized controlled trials studying mesalamine postoperatively have similarly discordant results. A meta-analysis of the first 4 studies suggested benefit of routine postoperative mesalamine administration.<sup>4</sup> However, when the fifth study<sup>5</sup> was completed and factored in, the results were no longer statistically significant. There are fewer studies on AZA/6-MP use in this setting, but they are similarly unpredictable and conflicting.<sup>6-8</sup> Thus, the evidence in support of routine postoperative adminis-