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Clinical Factors Contributing to Rapid Reoperation for Crohn's Disease Patients Undergoing Resection and/or Strictureplasty

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Abstract Although surgically induced remission of Crohn's disease following segmental resection/strictureplasty is effective and durable, a subpopulation of patients will require rapid reoperation. We reviewed our inflammatory bowel disease center's database to identify patients who underwent multiple laparotomies. A retrospective analysis of consecutive Crohn's disease patients (1998–2004) was performed, and patients requiring repeat laparotomy were identified. Rapid reoperation was defined as repeat intestinal surgery within 2 years. Demographic data and medical treatment were recorded. Clinical factors contributing to rapid reoperation were defined as (1) symptomatic adhesion, (2) residual strictures/technical error, (3) lack of effective medical therapy, and (4) severe disease despite medical treatment. Of 432 patients, 65 required two or more abdominal explorations, with 32 patients requiring rapid reoperation (50 surgeries). Residual strictures and technical error accounted for 20% of procedures; ineffective medical therapy was identified in 64%, whereas severe disease despite medical therapy was a contributing factor in 14%. Adhesions were found in a single patient. Kaplan–Meier analysis confirmed that rapid reoperation patients had significant and consistently shorter intervals between surgical procedures (i.e., interval between procedures 1 and 2 and 2 and 3). Residual strictures manifest during postop year 1, whereas recurrence of severe disease was the dominant contributing factor during year 2. Our data suggest that operative strategies emphasizing occult stricture detection and adequate medical therapy in Crohn's disease patients may improve outcome and decrease the need for rapid re-exploration.

Keywords Crohn's disease · Surgery · Strictureplasty · Azathioprine · 6-Mercaptopurine · Methotrexate · Infliximab · Adhesions · Complications

Introduction

Despite advances in medical treatment, the majority of Crohn's disease patients will require intestinal surgery during their lifetime.[1–5] Although not curative, surgery is necessary to correct complications of intestinal inflammation, including symptomatic luminal stenosis, fistula, abscess, perforation, or manage fulminant disease uncontrollable with medical treatment. For obstructing intestinal Crohn's disease, surgical approaches typically require either resection of the affected bowel with primary anastomosis or strictureplasty to reestablish patency of the intestinal lumen. Crohn's disease patients requiring segmental resection with

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reanastomosis and/or strictureplasty will invariably have recurrence of disease, with the remission and symptom-free interval varying between patients.[6,7] After their first operation, 33 to 82% of Crohn's disease patients will require further surgical intervention, which may occur at early, as well as late, time periods.[8–11]

In the setting of intestinal segmental resection and/or strictureplasty, the majority of Crohn's disease patients will experience a prolonged time period between surgeries. One third of Crohn's disease patients will require reoperation by 10 years.[12,13] However, a subgroup of Crohn's disease patients demonstrates a more problematic clinical course, requiring a rapid return to the operating room, at an interval of less than 2 years. Patients who demonstrate a pattern of rapid reoperation are arguably one of the most severe phenotypes, as the repeat resections become technically more challenging and place the individual at risk for gut failure. The percentages of Crohn's disease patients who face rapid reoperation, as well as clinical factors that contribute to a rapid return to surgery, are presently not defined.

The underlying reasons contributing to rapid reoperation in Crohn's disease are heterogeneous and may include symptomatic intra-abdominal adhesions, retained strictures not addressed at the preceding procedure, technical errors, intra-abdominal septic complications (i.e., abscess, anastomotic leak, enterocutaneous fistula) occurring rapidly after an initial abdominal procedure, and rapid recurrence of severe intestinal inflammation leading to complications and refractory disease. We hypothesized that Crohn's disease patients who undergo rapid reoperation (i.e., repeat intestinal surgery within 2 years of an operation) represent a distinct, high-risk subgroup of patients with a unique natural history. Furthermore, we sought to characterize the clinical factors that correlated with rapid reoperation in an attempt to devise improved surgical and medical algorithms for care. In this paper, we define the subgroup of Crohn's disease patients who have required rapid reoperation, as well as clinical patterns that are linked to this poor outcome. We demonstrate that technical errors, primarily linked to retained strictures not addressed at the preceding operation and insufficient medical therapy required for the maintenance of remission in Crohn's disease, are important contributing factors. Our findings suggest that surgical approaches to address occult small intestinal strictures, as well as optimizing immunomodulator therapy for maintenance of remission, may provide strategies for improved clinical outcome in this high-risk subgroup of Crohn's patients.

Methods

A review of consecutive Crohn's disease patients followed at a tertiary referral inflammatory bowel disease center between 1998 and 2004 was performed. Patients undergoing multiple abdominal procedures involving resection with primary intestinal anastamosis and/or strictureplasty were eligible for analysis. Operations performed at outside institutions and at our facility were analyzed. Crohn's disease patients undergoing colectomy in the absence of small intestinal disease were not included in our analysis as we wished to focus our review on small intestinal disease. Individuals requiring procedures limited to the perineum were excluded from this study.

We performed a retrospective review of the peri-operative clinical course and surgical outcomes. Demographic and medical treatment for the Crohn's disease was recorded. Clinical factors contributing to rapid reoperation were defined as (1) symptomatic adhesions not requiring intestinal resection, (2) technical error (re-exploration for hemorrhage or sepsis within 2 weeks and/or retained strictures and stenotic anastamoses), (3) inadequate immunomodulator therapy, or (4) severe disease in the presence of what was judged to be adequate immunomodulator therapy. Immunmodulator therapy included azathioprine or 6 mercaptopurine (6MP), methotrexate and/or infliximab, agents with demonstrated efficacy to maintain remission in moderate to severe Crohn's disease.[14–16] Crohn's disease patients on either azathioprine or 6MP therapy with insufficient 6MP metabolites (rapid metabolizers) were included as inadequate therapy. For this study, red blood cell 6-thioguanine levels of <150 pmol/8×10^8 cells were arbitrarily defined as insufficient or inadequate Crohn's disease therapy.[17]

Adequate medical therapy was not achieved due to a variety of reasons, which include drug intolerance, drug allergy, failure of compliance, rapid metabolism of purine analogs (6MP, azathioprine), and failure of the physician to prescribe immunomodulator therapy. We defined Crohn's disease with nutritional deterioration, quality of life deterioration as measured by the Short Inflammatory Bowel Disease Questionnaire,[18] or severe disease requiring surgery as moderate to severe disease. All patients treated at our center with moderate to severe disease are candidates for immunomodulator therapy, but this may not have been achieved.

For the purpose of this retrospective analysis, only one clinical factor could be designated for each rapid reoperation. The clinical factors listed above were arbitrarily ranked by priority in the following order: (1) symptomatic adhesions, (2) technical error, (3) inadequate immunomodulator therapy, and (4) severe disease in the presence of immunomodulator therapy. Therefore, a patient with adhesions listed as the postoperative diagnosis could not also be included in the category of inadequate immunomodulator therapy. A review of the operative record and discharge summary was performed initially by a neutral research member (K.R.T.) who had not participated in the care of

Table 1 Demographics Data

	Total Patients (n=65)	Surgery w/in 2 Years (n=32)	Surgeries >2 Years (n=33)	
Gender				
M	35 (54%)	18 (56%)	17 (52%)	n.s.
F	30 (46%)	14 (44%)	16 (48%)	
Smokers	23 (35%)	11 (34%)	12 (36%)	n.s.
Location of disease				
SB	36 (55%)	20 (63%)	16 (48%)	
SB/LB	20 (31%)	8 (25%)	12 (36%)	
LB	8 (12%)	3 (9%)	5 (15%)	
Upper GI	1 (2%)	1 (3%)	0	n.s.
Age of onset				
<40 years	63 (97%)	30 (94%)	33 (100%)	
>40 years	2 (3%)	2 (6%)	0	n.s.
Disease behavior				
Inflammation	0	0	0	
Stricture	58 (89%)	28 (87%)	30 (91%)	
Fistula	7 (11%)	4 (13%)	3 (9%)	n.s.

patients during the operative time period. Once the clinical factors for the rapid reoperation had been designated, experienced medical personnel (D.G.B.) and surgical staff (M.F.O.) verified the ranking.

Analysis was carried out with SAS statistical software (The SAS Institute, Cary, NC, USA) and LogXact software (Cytel Software, Cambridge, MA, USA). The Medical College of Wisconsin's human research review committee approved this study.

Results

During the study period, 432 Crohn's disease patients were identified in the database. Sixty five patients had required more than a single surgical intervention. A total of 200 abdominal surgeries had been performed in these 65 patients. Thirty two of these patients required rapid reoperation within 2 years (7% of our Crohn's disease population). A total of 50 abdominal procedures had been performed in the rapid reoperation patients. In the cohort of patients requiring rapid reoperation, the average number of surgical procedures was 3.0+1.2 (mean+SD) and the operative interval was 2.9+4.5 years (mean+SD). The 33 Crohn's disease patients in our center requiring repeat surgery who never required rapid reoperation had a mean of 2.9+1.3 surgical procedures (not significant) with an average interval of 7.6+4.9 years (p<0.05).

Analysis of demographic data revealed no significant difference between patients who had undergone rapid reoperation when compared to patients with longer time intervals between the repeat surgical procedures (Table 1).

Kaplan–Meier analysis followed by Wilcoxson testing confirmed that the intervals between procedures 1 and 2 and between procedures 2 and 3 were significantly shorter in patients who had ever been categorized as rapid reoperative patients (p<0.001, Figs. 1 and 2). The interval between procedures 3 and 4 did not reach statistical significance between these two groups due to the limited number of patients requiring four surgical procedures. We repeated the Kaplan–Meier analysis after excluding procedures that had been judged to be technical error and adhesions. Again, Kaplan–Meier analysis followed by Wilcoxson testing confirmed that the intervals between procedures 1 and 2 and between procedures 2 and 3 were significantly shorter in patients who had ever been categorized as rapid reoperative patients (p<0.001, Figs. 3 and 4).

Next, we evaluated the clinical factors that contributed to rapid reoperation. There were 27 rapid reoperation procedures in the first postoperative year. The contributing clinical factors were as follows: symptomatic adhesions (1 procedure, 4%), technical error (8 procedures, 7 missed strictures, 1 evacuation of hematoma, 30%), inadequate immunomodulator therapy (13 procedures, 2 on azathioprine with inadequate drug levels, 11 who were on no drug, 1 of the 11 had an intra-abdominal abscess, 47%), and severe disease despite immunomodulator therapy (5 procedures, 19%). Between years 1 and 2, there were 23 rapid reoperation procedures. In this group, technical error contributed to 13% (3 procedures), whereas severe disease despite immunomodulator therapy was responsible for two procedures (9%); inadequate immunomodulator therapy was linked to the majority of these rapid reoperations (18 procedures, 78%). Symptomatic adhesions were not seen during the second postoperative year in our cohort of rapid reoperation patients. In summary, during the first 2 years, adhesions were responsible for 2%, technical error for 22%, severe disease with inadequate therapy for 62%, and severe disease despite adequate therapy for 14% of rapid reoperations.

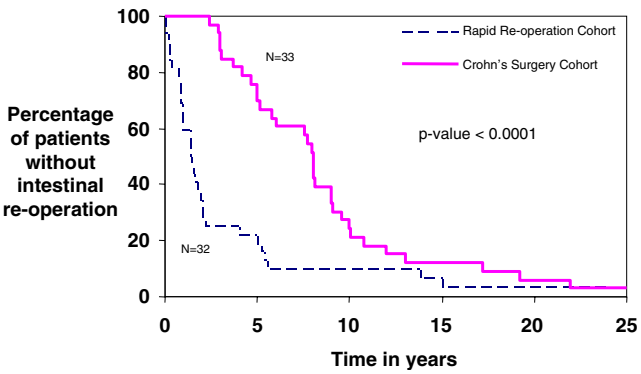

Figure 1 Intervals between surgery 1 and 2 in the rapid reoperation Crohn's surgery cohorts.

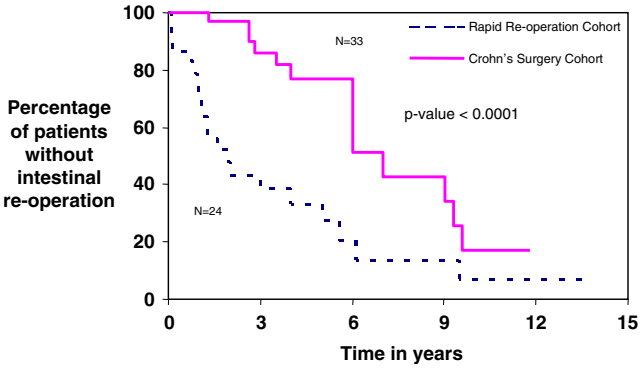

Figure 2 Intervals between surgery 2 and 3 in the rapid reoperation Crohn's surgery cohorts.

Interestingly, nine patients who were categorized in the rapid reoperation group were initiated on immunomodulator therapy for the first time (three on azathioprine, one on leflunomide,[19] and five on infliximab maintenance therapy). Since initiating immunomodulator therapy, eight out of nine patients have not required additional surgical intervention, with a mean duration of elapsed time of 4.7 years and a range of 1.4 to 9.4 years since prior surgery. Fifty two of the 65 Crohn's disease patients who required repeat abdominal operation (80%) are currently maintained on immunomodulator therapy. The remaining patients are not on immunomodulator therapy due to multiple drug intolerances or refusal to comply with therapy.

Three of the Crohn's disease patients requiring repeat abdominal operations included in this study have subsequently died, giving this population a mortality rate of 4.6%. Each of these deceased patients had at least five surgeries. One patient died at age 39 following repeat hip replacement surgery for avascular necrosis. A second patient died at the age of 71 years with a cardiac event attributed to electrolyte disturbances, and the third patient died at the age of 53 years of complications of line infection on chronic total parenteral nutrition.

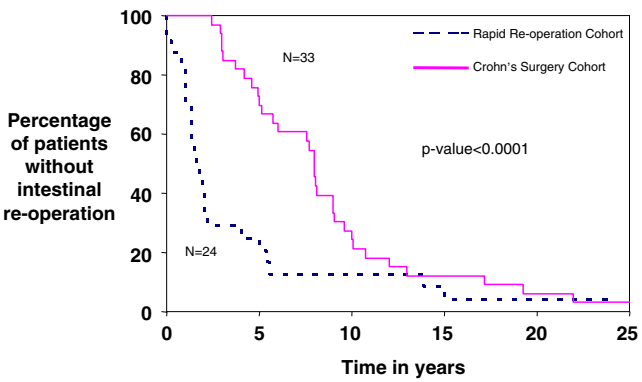

Figure 3 Intervals between surgery 1 and 2 with elimination of surgical procedures judged to be due to technical error and adhesions. These data demonstrate problems associated with lack of effective/adequate medical maintenance therapy in the rapid reoperative cohort.

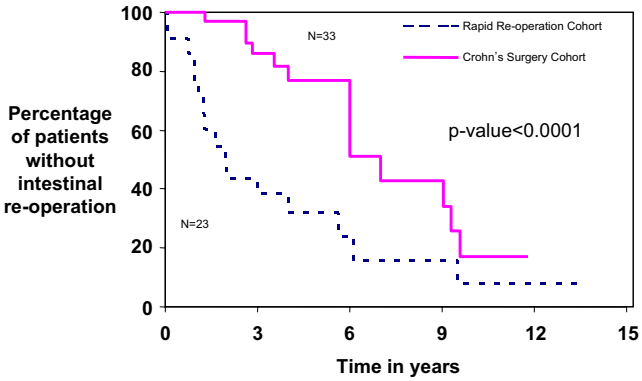

Figure 4 Interval between surgery 2 and 3 with elimination of surgical procedures judged to be due to technical error and adhesions.

Discussion

Although surgery is the most rapid treatment modality to induce remission in Crohn's disease, patients who undergo segmental resection and reanastomosis and/or strictureplasty will experience relapse at high rates. Surgically induced remission may last numerous years in fortunate individuals, whereas other patients with Crohn's disease will experience symptomatic clinical relapse within months of laparotomy. We report that a subgroup of patients who require a rapid return to surgery within 2 years of the prior procedure constitute a distinct high-risk subgroup of Crohn's disease patients who are significantly more likely to face additional rapid reoperations. In addition, we highlight clinical factors related to surgical technique and adjunctive medical therapy, which were linked to rapid reoperation. These findings suggest that improved operative strategies to address occult intestinal strictures and maximizing immunomodulator maintenance of remission therapy appropriate for moderate to severe Crohn's disease may improve clinical outcomes in this high-risk subgroup of patients.

Improved medical management strategies for Crohn's disease have established a central role for immunomodulators such as azathioprine, 6MP, and methotrexate in the management of moderate to severe Crohn's disease.[15,20] Biologic therapy with the anti-TNF-α chimeric monoclonal antibody infliximab has also been identified as effective in resolving Crohn's disease inflammation and maintaining remission.[21,22]

Our study suggests that patients whose illness is severe enough to warrant repeat surgery will benefit from the use of immunomodulator agents typically used in moderate to severe Crohn's disease. Furthermore, patients with a rapid return to the operating room represent a more ill subset of patients, and care must be taken to assure compliance, adequate therapeutic drug levels, and ongoing therapy.

Studies have estimated that postoperative complications and morbidity associated with strictureplasty or bowel

resection with anastomosis for Crohn's disease range from 13 to 22%.[23–26] The most serious immediate complications are fistula, abscess, and anastomotic leak, which typically occur within 1 month of the intestinal procedure. We recently demonstrated a lack of association between immunomodulator agents and infectious complications in the setting of Crohn's disease surgery.[27] This has been confirmed in other centers.[28] These data suggest that Crohn's disease patients requiring abdominal surgery may benefit during the initial postoperative month with immunomodulator therapy to provide medical control of the disease process. These findings also suggest that the initiation of medical treatment in patients who are facing the prospect of surgery due to symptomatic complications (i.e., intermittent partial small bowel obstruction) may benefit from the initiation of immunomodulator treatment in the short term, as well as with the potential benefit of preventing postoperative recurrence of disease.[29]

In our analysis, we also defined a subgroup of patients where technical issues during the initial procedure contribute to a rapid return to surgery. We broadly categorized stenotic anastamoses and retained strictures as technical error. Much has been written in the literature about the superiority of either stapled or hand sewn anastamoses; however, our technical errors included both types of anastamoses and no meaningful conclusion can be made regarding that argument from these data.[30–32] There were no prior laparoscopic surgical procedures for Crohn's disease in the cohort that we evaluated. However, it must be noted that the frequency of laparoscopic resections for Crohn's disease is very small in our region.

Small intestinal Crohn's disease may manifest with "skip" areas scattered in the intestine, as well as diffuse disease throughout the small bowel. In patients with these more extensive patterns of disease, the capability to accurately determine a "dominant" stricture(s) that requires surgical treatment is difficult. The ability to adequately gauge the level of severity of strictures may be made more challenging by laparoscopic approaches. Surgeons have historically relied on small bowel barium radiographs to provide an accurate map of the pathologic intestinal anatomy, which will require resection or strictureplasty. Previous studies have suggested that radiographic imaging may underestimate up to 1/3 of strictures in 1/3 of the patients.[33] This high rate of occult strictures may play a contributing role in the Crohn's patients who required rapid reoperation in our study, particularly those who required repeat surgery within 1 year. The adoption of intraoperative plans to diagnose and correct all luminal stenoses with resection/strictureplasty will potentially address this mechanism linked to rapid reoperation.

We realize that our study was limited by its retrospective design and was not the ideal method for demonstrating the direct therapeutic effect of regimens. We depended upon documentation of the previous surgeon and analyzed results with incomplete knowledge of the prior pathology. In spite of this, retrospective analysis can demonstrate significant correlations, which may generate hypotheses that can be further defined with prospective trials.

Our analysis of Crohn's disease patients requiring rapid reoperation has attempted to characterize a high-risk subgroup of patients who have a relatively defined starting point for an analysis of their natural history (i.e., postoperative clinical course). Unfortunately, clinical trials in patients with Crohn's disease have been severely hampered by the heterogeneity of the disease process, where interpatient variability regarding anatomic location of disease, duration of disease, unique histories of drug treatment and medication intolerance, and variable strategies employed with surgical intervention are typically not taken into consideration. The result of this comingling of patients with different levels of disease severity, at various stages in their natural history of illness, is typically a nonsignificant clinical result. We believe that the identification of this rapid reoperation Crohn's disease cohort is an important contribution of this study.

By limiting the population of postoperative patients to those who have undergone segmental resection and/or strictureplasty, we were able to both identify a unique natural history, which is linked again to heterogeneous clinical contributing factors (i.e., occult strictures, lack of early immunomodulator therapy, and lack of effective maintenance immunomodulator therapy over the initial two postoperative years). Using our criteria for patients with a history of rapid reoperation, we identified 7% of the total Crohn's disease cohort followed in our center. Although this is not the majority of Crohn's disease, this approximation appears to be consistent with the subgroup that has extensive small intestinal disease and will be at risk for intestinal failure due to repeated surgery. Our study suggests that this cohort of patients can be readily identified based on their clinical history (repeated small intestinal surgery at rapid intervals) and should have continuous medical treatment with more potent immunomodulator agents maintained on a long-term basis. The argument that medical treatment may be successfully weaned off in postoperative Crohn's disease patients does not apply to the rapid reoperation subgroup, where surgical risk (i.e., intra-abdominal septic complications), as well as an aggressive form of disease that rapidly recurs with clinically symptomatic illness, is highly likely. Our study suggests that a surgical approach which strives to diagnose and repair intestinal strictures in combination with a medical approach which emphasizes maintenance immunomodulator therapy will lead to improved outcomes in the management of this high-risk Crohn's disease population.

Our case series suggests that Crohn's disease patients who require rapid reoperation represent a subset who require greater health care resources. Early identification of these patients as being at risk may allow improved strategies for medical interventions. Maintaining remission with immunomodulator therapy may represent a key variable that can be optimized to improve surgical outcome in these Crohn's disease patients.

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Discussion

694. Rapid Re-Operation for Crohn's Disease. Paper presented by Mary Otterson, M.D., Milwaukee, WI.

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Discussion by Susan Gearhart, M.D., Maryland.
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Dr. S. Gearhart (Baltimore, MD): I want to thank the authors, first of all, for the opportunity to discuss this paper and for their timely submission. I also want to congratulate you on an interesting and important study examining the clinical risk factors associated with reoperation for Crohn's disease. I have questions on several specific aspects of your study.

First, the aim of your study was to identify clinical factors that are associated with the rapid reoperation for Crohn's disease. Yet the clinical data with regards to the initial surgery type as it directly related to the need for rapid reoperation, for example, strictureplasty or no strictureplasty, laparoscopic, which you touch on in your manuscript, emergent or elective, is missing. Could you please elaborate on that? It also would be important to list factors which may affect healing in Crohn's disease, such as nutritional status of the patient or steroid use. Furthermore, in your mention in the manuscript about patients with colonic disease you decided to exclude them, and I didn't understand why you did, and then you did actually mention them when you described demographic data. Could you just touch on whether or not you were discussing colonic disease?

Second, you defined one of your clinical factors contributing to rapid reoperation for Crohn's disease as inadequate immunomodulator therapy. I agree with you that there is certainly data to support the use of immunomodulator therapy in active Crohn's disease and preventing clinical recurrence of the disease. However, the data is not compelling in the support of the use of immunomodulators in the prevention of surgical recurrence and the need to go back to the operating room for surgery for Crohn's disease. And could you comment on your data with respect to randomized clinical trials and the use of immunomodulator therapy on the prevention of recurrence of Crohn's disease postoperatively?

Finally, in your conclusions you suggest that this study supports the use of immunomodulators in patients who require rapid reoperation for Crohn's disease. This study is retrospective and lacks a control group and therefore this claim may be a bit premature. Do you have plans to look at this in a more prospective fashion?

Thank you.

Dr. Otterson: Thank you very much for your comments. I hope I remember all the questions in the appropriate order.

Regarding strictureplasty versus resection, we have looked at strictureplasty versus resection with recurrence and not seen any issues in the past. I think that the majority of the outside procedures are performed as resections and a very small minority are done as strictureplasties. At our institution most of our procedures are actually a combination of both strictureplasty and resection. So it is going to be difficult for us to give a conclusive result on that.

We do routinely pull a Foley catheter and inflate it to 2 cm through our intestine looking for missed strictures. In a paper that we wrote several years ago, we found that radiology underestimated a third of the strictures in a third of the patients. So if you have single strictures in first-time resections, the data is pretty good for radiology, but after that, if they have multiple resections or if they have had multiple strictures identified, you really need to look for additional strictures.

The nutritional factors, I don't have data on that. We have looked in the past, and we did not see a difference with albumins down to a level of 3. The VAH study suggests that 2.5 is the magic number. We didn't see any difference at a level of 2.5 for complications, postoperative intra-abdominal septic complications, but we did not specifically look at that with this.

Steroid use, most of the patients who came in with partial obstructive issues were on steroids to try to control their obstructive symptoms, but the majority of our patients, 80%, are on immunomodulator therapy before they come to the operating room. The patients who are not on drug therapy are those patients who are multiply drug intolerant, leading to novel concoctions of drugs, or who are noncompliant.

As far as randomized clinical trials, methotrexate, azathioprine, or 6-MP have all been shown in randomized prospective trials to be the only drugs that are capable of inducing prolonged remission with Crohn's disease. The ACCENT II trials with infliximab and REMICADE are also supporting the data that good medical care prior to the surgical procedures are the way to go as far as maintaining disease-free intervals.