Biologic Therapy and Surgery for Crohn Disease

E. Carter Paulson, MD, MSCE[1]

[1] Department of Surgery, Philadelphia VA Medical Center, Philadelphia, Pennsylvania

Clin Colon Rectal Surg 2013;26:128–134.

Address for correspondence E. Carter Paulson, MD, MSCE, Philadelphia VA Medical Center, 3900 Woodland Avenue, 5th Floor – Surgical Business Office, Philadelphia, PA 19104 (e-mail: paulsone@uphs.upenn.edu).

Abstract

In 1998, infliximab, an antitumor necrosis factor alpha (anti-TNF-α) antibody, was approved for use in the treatment of Crohn disease (CD). Since then, other biologic therapies, including adalimumab and certolizumab pegol (newer anti-TNF-α antibodies), and natalizumab, an antibody against alpha-4 integrin, have also been approved. Here, we review the published studies that examine the relationship between pre- and postoperative biologic therapy and postoperative complications in patients with CD. This body of literature is composed of numerous small, retrospective, heterogeneous studies that demonstrate conflicting and varied results. Overall, the receipt of biologic therapy in the pre- or postoperative period does not appear to significantly increase the risk of postoperative complications. It is, however, difficult to draw any firm conclusions based on the existing level of data. In the future, larger prospective studies are needed to better elucidate the true risks, if any, that the use of biologic therapy poses to patients with CD requiring operation.

Keywords
- Crohn disease
- surgery
- biologic therapy
- postoperative complications

Objectives: Upon completion of this article, the reader should be able to (1) understand the overall risks and benefits of preoperative biologic therapy in Crohn disease based on the available literature, (2) understand the overall risks and benefits of postoperative biologic therapy in Crohn disease based on the available literature, and (3) identify select groups of patients with Crohn disease at highest risk of postoperative complications to modify preoperative medical therapy.

Background

Crohn disease (CD) is an inflammatory disorder characterized by relapsing and remitting inflammation of the entire GI tract. Until the end of the last century, the mainstay of medical therapy for CD included corticosteroids and immunomodulators such as methotrexate, azathioprine, and cyclosporine. Although these medical therapies can often be effective in treating CD, they all have relatively significant side effects.

Well-known side effects of long-term corticosteroid use include weight gain, osteoporosis, Cushing syndrome, glucose intolerance, glaucoma, and increased risk for infections.[1–3] These all pose significant limitations in the ability to use chronic corticosteroid therapy to treat recalcitrant and recurrent CD. Additionally, many people receiving corticosteroids for CD require surgical intervention for treatment of their disease. It has been reported by several authors that preoperative corticosteroid use increases the risk of perioperative complications after surgery for CD.[4–7] More recent reports have reported a mixed picture, with many studies finding no increased risk of perioperative complication with preoperative corticosteroid use.[8–11] However, given the long-term risks of chronic corticosteroid use and the possibility of increased perioperative complications in patients with CD who require surgery, minimizing corticosteroid usage in this patient population is clearly beneficial.

The immunomodulators, including methotrexate, azathioprine, and cyclosporine, have also played a key role in the treatment of CD. They are often used as steroid sparing agents to maintain remission in CD patients. Like steroids, however, they are not without serious potential drawbacks. They are known to increase the risk of spontaneous infection, myelotoxicity, and pneumonitis.[12–14] Additionally, certain immunomodulators have well-recognized organ toxicities; for example, methotrexate is hepatotoxic and cyclosporine is nephrotoxic. As with steroids, studies evaluating the impact

Issue Theme Crohn Disease; Guest Editor, Brian R. Kann, MD, FACS, FASCRS

DOI http://dx.doi.org/10.1055/s-0033-1348052.
ISSN 1531-0043.

of immunomodulators on the risk of postoperative complications have reported varied and conflicting results. However, most studies have failed to demonstrate that preoperative immunomodulator use clearly increases the risk of postoperative complications in patients undergoing surgery for CD.[6,8,11,15–18] There are a few small studies that suggest an increased risk of postoperative infection in patients receiving methotrexate therapy who have undergone a variety of non-CD-related surgery.[19,20] Based on this, some recommend holding methotrexate for a week prior to surgery for CD.

Given the significant short- and long-term side effects of corticosteroid and immunomodulator therapy, efforts have long been underway to develop safer therapies for CD. Both corticosteroids and immunomodulators have broad effects on the immune system that may contribute to their increased risk for serious infection. Newer drugs were created intended to target specific aspects of the immune system thought to be responsible for the inflammation responsible for certain autoimmune disorders. By targeting specific aspects of the immune response, it was thought that the risk of some of the more significant infectious complications could be reduced. From these efforts, biologic therapies targeting TNF-α were developed; these were first approved for use in rheumatoid arthritis, but are now approved for use in a myriad of inflammatory diseases, including CD as well as chronic ulcerative colitis.

In the past 20 years, a new age of biologic therapy for CD has emerged. Infliximab is a monoclonal antibody against the tumor necrosis factor alpha (TNF-α) receptor, and was the first drug of its type approved for use in the treatment of CD in 1998. In recent years, several other biologic agents have been approved for use in the treatment of CD, including adalimumab and certolizumab pegol, two newer anti-TNF-α antagonists, and natalizumab, an alpha-4 integrin blocker. These newer therapies have proven efficacious, but are much less well studied than infliximab. In particular, an observed increased risk for progressive multifocal leukoencephalopathy in patients receiving natalizumab has limited its use, so it remains the least well studied.

Although the use of biologic therapies is not a panacea in the management of CD, many studies have demonstrated an increased response rate patients treated with these biologic therapies.[21,22] A Cochrane Review published in 2009 reviewed nine randomized studies evaluating the use of TNF-α blocking agents for maintenance of remission in CD.[23] The conclusion of this review was that infliximab given every 8 weeks is effective for maintenance of remission and fistula healing in patients who respond to induction therapy. Similar conclusions were drawn for adalimumab and certolizumab pegol.

A similar review article was published in 2011.[24] This study included 27 controlled trials comparing biologic therapy (anti-TNF α antibodies or natalizumab) with placebo for treatment of active or quiescent CD or ulcerative colitis. The result of the meta-analysis indicated that the biologic therapies were superior to placebo in inducing remission of luminal CD (Relative risk [RR] of no remission = 0.87; 95% confidence interval [CI], 0.80–0.94) and in preventing relapse of luminal CD (RR of relapse = 0.71; 95% CI, 0.65–0.76). These authors concluded that based on analysis of the existing trials, biologic therapies were superior to placebo in inducing remission of active CD and in preventing relapse of quiescent CD.

Like the other therapies for CD, however, biologic therapies are not without the potential for significant side effects. There is evidence of an increased rate of spontaneous infection in patients receiving anti-TNF-α blockers.[21,25–28] Some of the specifics risks that have been documented include reactivation of tuberculosis, increased risk of sepsis and opportunistic infections, and reactivation of hepatitis B. However, the Therapy, Resource, Evaluation, and Assessment Tool study, which is the largest prospective study to date evaluating the safety of infliximab compared with placebo in CD, showed that in multivariate analysis, infliximab was not an independent risk factor for serious infection in multivariate analysis.[2]

Although there is no consensus on the overall safety of the biologic therapies, there are factors that appear to increase the risk of infectious complications in patients being treated with biologic therapies for CD. For instance, the risks appear to be higher when patients are on combination therapy, such as biologic therapy along with either corticosteroids or immunomodulators.[3] Additionally, several studies have demonstrated that older patients are at an increased risk of opportunistic infection when treated with immunologic therapy, including biologic therapy.[3,29]

Preoperative Biologic Therapy and Surgery

Given the prevalence of their use, it is very common to perform both elective and emergent operations on patients with CD who have been receiving biologic therapy. Accordingly, there has been a great deal of interest in the relationship between the use of preoperative biologic therapy and postoperative complications in such patients. Currently, the only biologic therapy that has been well studied to any significant extent in this setting is infliximab, as the other drugs have only recently become more commonplace in the treatment of CD. To date, there has not been a prospective trial evaluating preoperative biologic therapy and postoperative complications. All of the published studies are retrospective and most are from single institutions, involving small, heterogeneous patient populations. Not unexpectedly, the results of these studies are varied and conflicting. We will review the most significant of these studies here.

In 2004, Colombel et al published a study evaluating the relationship between immunosuppressive and infliximab therapy with early postoperative complications in patients with CD.[8] They identified 270 patients who underwent abdominal surgery for CD between 1998 and 2001. Of these patients, 107 received preoperative corticosteroids, 106 received immunomodulator therapy (6-mercaptopurine, azathioprine, or methotrexate), and 50 received infliximab within 8 weeks of their surgery. They analyzed septic and nonseptic complications that occurred within 30 days of surgery, proposing that complications occurring outside this window are likely due to recurrent CD and not postsurgical problems. Due to the limited patient population, they

performed only univariate analysis between multiple risk factors, including use of corticosteroids, immunomodulators, and infliximab, as well as multiple other possible disease-related risks factors, such as length of diagnosis, location of disease, type of surgery, and nature of surgery (elective vs. emergent). In the multiple univariate analyses, no factor was significantly related to an increased risk of 30-day complications. For patients treated with infliximab, the odds ratio (OR) for complications was 0.9 (95% CI, > 0.4–1.9). The authors acknowledged that their analysis was restricted by small sample size and a large number of predictor variables making multivariate analysis impossible, thus limiting their ability to draw firm conclusion regarding the relationship between preoperative immunosuppression or infliximab therapy and postoperative complications.

Also in 2004, Marchal et al published a study specifically examining the relationship between infliximab therapy and the risk of postoperative complications.[30] They compared 40 patients who received one or more infusions of infliximab prior to intestinal surgery for CD with 39 patients who underwent surgery and had never received infliximab therapy. The two groups were similar in almost all aspects, except that infliximab patients were much more likely than the infliximab-naïve cohort to be on concomitant therapy, particularly corticosteroids (73 vs. 41%, $p < 0.001$). In this study, there was a trend toward higher rates of early (12.5 vs. 7.7%) and late (17.5 vs. 12.8%) postoperative complications in the infliximab group compared with the infliximab-naïve group, but no difference reached statistical significance. Although no significant differences were found, this could be the result of the small, heterogeneous patient population in this study limiting their ability to reach statistical significant. It is possible that the same differences, if borne out in a larger cohort, could be significant. Additionally, no adjustment was made for the difference in corticosteroid use between the groups. The small increase in postoperative complications could have, at least in part, been due to differences in corticosteroid use, not infliximab use, but this is not addressed in their methods.

In 2008, two articles were published in the same issue of the *Journal of Gastrointestinal Surgery*, both evaluating the relationship between preoperative infliximab therapy and complications following surgery for CD. Kunitake et al studied 413 patients, 188 with CD, 156 with ulcerative colitis, and 69 with indeterminate colitis, who underwent abdominal surgery between 1993 and 2007.[9] Of these, 101 patients (24.5%) received infliximab therapy within 12 weeks of their surgery. Cumulative and individual postoperative complications were compared between the infliximab and the infliximab-naïve patients adjusting for preexisting infection, pathologic diagnosis, comorbidities, and steroid use. In this study, the infliximab and noninfliximab groups had similar rates of cumulative postoperative complications (IFX = 16.8%, non-IFX = 15.7; $p = 1.0$). Rates of individual complications (postoperative death, anastomotic leak, thrombotic complications) trended toward higher rates in the infliximab group in univariate analysis, but there was no difference that was statistically significant. They did note a statistically significant increased in length of stay in the infliximab group (IFX—12.2 d vs. non-IFX 10.2 d, $p < 0.0001$). Their multivariate analysis revealed no significant difference in postoperative complications between the infliximab and noninfliximab groups (OR 2.5; $p = 0.14$). As with prior studies, these authors acknowledge that the lack of statistical significance may be due to insufficient statistical power related to the small sample size. Again, there are trends noted in this study toward higher complication rates in the infliximab group, but the authors' ability to draw any conclusions regarding these trends is limited.

In the same journal issue, Appau et al published another study looking at postoperative complications and infliximab use in patients with CD.[31] They compared 60 patients with CD undergoing ileocolonic resection with primary anastomosis after 1998 who received infliximab in the 3 months prior to surgery to 329 contemporary cohort patients who underwent ileocolonic resection having never received infliximab. The authors believed that patients treated with infliximab might be generally sicker than patients who did not require infliximab, and they hypothesized that this might bias the results against infliximab. To address this concern, they also compared the infliximab group to an additional historical cohort of 69 patients who underwent ileocolonic resection before 1998, as infliximab was not available for CD before that date. They felt that this group would more accurately represent a comparative group with similar patient characteristics. The outcomes they evaluated included 30-day mortality, wound infection, anastomotic leak, sepsis, intraabdominal abscess, and readmission rate. After multivariate adjustment for differences in medication (corticosteroids, immunomodulator) use, age, gender, comorbidity, disease phenotypes, and the presence of an abscess at or before surgery, the infliximab group appeared to have an increased risk of 30-day postoperative readmission (OR 2.33; $p = 0.045$), sepsis (OR 2.62; $p = 0.027$), and intraabdominal abscess (OR 5.78; $p = 0.005$). They also noted that infliximab patients who had a diverting loop ileostomy created at the time of ileocolonic resection had a lower incidence of sepsis when compared with infliximab patients not undergoing loop stoma (0 vs. 27.9%; $p = 0.13$). The strength of this study is the more homogeneous nature of their patient population. All patients had terminal ileal CD and all underwent the same type of surgery, an ileocolic resection with anastomosis, with or without a diverting loop ileostomy. Many of the prior studies included patient populations that were very heterogeneous with respect to indication for surgery, type of IBD, and type of surgery performed. Using this well-defined patient population, these authors concluded that preoperative use of infliximab is associated with increased postoperative sepsis, abscess, and readmission. Again, however, the authors are forced to acknowledge that this is a retrospective study with relatively small sample size, only 60 patients in the IFX group, which limits their ability to draw firm conclusions regarding the true risk of preoperative use of IFX.

More recently, in 2009, Indar et al published a small study examining preoperative immunosuppression, including corticosteroids, immunomodulators, and/or infliximab, and

postoperative complications.[10] They analyzed 112 patients who underwent intestinal resection for CD. Given the small sample size, only univariate analysis was performed. Of the 112 patients, there were 12 different operations performed and eight different combinations of preoperative medical therapy identified. Not surprisingly, there was no association between any preoperative medical therapy and the risk of developing a postoperative complication.

In 2011, Canedo et al published another study evaluating the relationship between immunosuppressive medication and postoperative infection rates following surgical resection for CD.[11] They compared patients who had received infliximab within 3 months of their operation to patients who had received corticosteroids or other immunomodulators within 60 days of surgery and to patients who had received no drug therapy in the 3 months prior. Overall, 225 patients underwent surgical resection during their study period, 65 received infliximab either alone or in combination with corticosteroids or immunomodulators, 85 patients received only corticosteroids or immunomodulators, and 85 received no drug therapy. After multivariate adjustment for several patient and surgery related factors, neither the use of infliximab nor the use of steroids or immunomodulators was associated with the complications of anastomotic leak, wound infection, or reoperation. This small, retrospective study with a heterogeneous patient population suffers from the same limitations as almost all others published in this field.

Finally, in 2012, White et al published a study evaluating the effect of preoperative immunosuppression, including corticosteroids, immunomodulators, and biologics, on unplanned hospital readmission after surgery for CD.[32] Three hundred thirty-eight patients were included in this retrospective study. Eighteen percent received preoperative biologic therapy, 44% of the patients received monotherapy; 32% received two drugs and 6% received three drugs. Nineteen percent received no preoperative medical therapy. The authors found that combination immunosuppression was associated with an increased risk of readmission. The incidence of readmission was 3, 7, 11, and 16% in patients treated with 0, 1, 2, and 3 preoperative medication classes, respectively (trend analysis $p = 0.02$). They concluded that, although one specific type of preoperative therapy did not appear to increase risk of readmission, combination therapy might increase this risk.

Conclusions

It is clear that there is no consensus regarding the risk that preoperative biologic treatment poses to patients requiring surgery for CD. However, it does appear that biologic agents, by themselves, do not significantly increase risk of postoperative complications. Only one of the studies discussed demonstrates a significantly increased risk of postoperative complications following preoperative receipt of infliximab; a few others indicate slightly higher risks in the patients receiving preoperative biologic therapy, but small size limits their ability to achieve statistical significance. Clearly, larger multicenter prospective studies would provide valuable information regarding the true risk that these commonly used therapies pose to patients undergoing surgery for CD. There have been two review articles previously published examining the perioperative use of biologic therapies in CD.[33,34] Both conclude, based on the existing literature at the time of publication, that delaying surgery to stop biologic therapy is most likely not indicated.

Infliximab is clearly the most well studied of the existing anti-TNF antibodies, but the few studies that included adalimumab and certolizumab did not reveal any significant differences in their perioperative safety profile. Again, more studies are needed evaluating these newer anti-TNF-α antibodies, as well as natalizumab.

As the above studies indicate, delaying surgery in an effort to remove patients from biologic therapy for a given time period may not be necessary. There are certain groups of preoperative patients, however, who should give a practitioner pause. For instance, there is evidence that combination therapy might increase the risk of complications. As such, it might be prudent, if it is possible, to wean therapy to only one class of immunosuppressant preoperatively. Additionally, there is evidence that elderly patients undergoing surgery for CD are at higher risk for complications in general. As such, practitioners should use extra caution when operating on elderly patients who are on biologic therapy, and consider the use of diverting ostomies to protect distal anastomoses in these high-risk populations.

Postoperative Biologic Therapy and Surgery

Unfortunately, even with good preoperative therapy and a well-performed operation, the recurrence rate of CD is still remarkably high. Approximately 90% of patients will have endoscopic evidence of recurrence of disease 1 year after surgery, and 50% of patients will require an additional surgery.[35,36] In an effort to reduce recurrence of CD postoperatively, practitioners have tried many different medication regimens. Unfortunately, there is still endoscopic evidence of CD in up to 60% of patients treated postoperatively with steroids, 5-aminosalicylate, antibiotics, and immunomodulators.[37] There have been a few small studies recently indicating that postoperative recurrence of CD is lower in patients treated postoperatively with anti-TNF-α antibodies.[38,39] In one recent randomized study, the histologic recurrence of CD was observed in only 27.3% of patients treated postoperatively following ileocolonic resection with infliximab versus 84.6% of patients treated with placebo.[39]

As this is a relatively new treatment regimen, little is known about the effect of early postoperative biologic therapy on postoperative complications. In the randomized trial mentioned above, 11 patients undergoing ileocolonic resection were randomized to IV infliximab administered within 4 weeks or surgery and continued for 1 year, and 13 patients undergoing resection were randomized to receive a placebo injection. In this study, the occurrence of adverse events and postoperative complications was similar between the two groups.

In another study evaluating the safety of postoperative infliximab, 12 patients undergoing intestinal resection for CD were randomized to infliximab 2 to 4 weeks after surgery,

followed by infusions at 2 and 6 weeks, then every 8 weeks for a year.[40] Twelve patients were randomized to placebo infusions on the same schedule. In this small study, there were no differences noted in adverse events or postoperative complications between the two groups. The authors conclude that initiation of infliximab therapy within 4 weeks of intestinal surgery for CD is not associated with an increase in postoperative complications.

Conclusions

Although this is a nascent area of study, there is no evidence at this time to indicate that early institution of infliximab in the postoperative period increases the risk of complications. On the contrary, early initiation of infliximab therapy may reduce the recurrence of CD and help eliminate future surgeries in this patient population. As with preoperative therapy, there are very few published studies looking specifically at the other biologic therapies, such as adalimumab, certolizumab peg, and natalizumab. As these drugs become more widespread, it is expected that more data will be published regarding their safety in the postoperative period.

References

1 Rutgeerts PJ. Review article: the limitations of corticosteroid therapy in Crohn's disease. Aliment Pharmacol Ther 2001;15 (10):1515–1525
2 Lichtenstein GR, Feagan BG, Cohen RD, et al. Serious infections and mortality in association with therapies for Crohn's disease: TREAT registry. Clin Gastroenterol Hepatol 2006;4(5):621–630
3 Toruner M, Loftus EV, Harmsen WS, et al. Risks factors for opportunistic infections in patients with inflammatory bowel disease. Gastroenterol 2008;134:929–936
4 Post S, Betzler M, von Ditfurth B, Schürmann G, Küppers P, Herfarth C. Risks of intestinal anastomoses in Crohn's disease. Ann Surg 1991;213(1):37–42
5 Yamamoto T, Allan RN, Keighley MR. Risk factors for intra-abdominal sepsis after surgery in Crohn's disease. Dis Colon Rectum 2000;43(8):1141–1145
6 Aberra FN, Lewis JD, Hass D, Rombeau JL, Osborne B, Lichtenstein GR. Corticosteroids and immunomodulators: postoperative infectious complication risk in inflammatory bowel disease patients. Gastroenterology 2003;125(2):320–327
7 Tzivanakis A, Singh JC, Guy RJ, Travis SPL, Mortensen NJ, George BD. Influence of risk factors on the safety of ileocolic anastomosis in Crohn's disease surgery. Dis Colon Rectum 2012;55(5):558–562
8 Colombel JF, Loftus EV Jr, Tremaine WJ, et al. Early postoperative complications are not increased in patients with Crohn's disease treated perioperatively with infliximab or immunosuppressive therapy. Am J Gastroenterol 2004;99(5):878–883
9 Kunitake H, Hodin R, Shellito PC, Sands BE, Korzenik J, Bordeianou L. Perioperative treatment with infliximab in patients with Crohn's disease and ulcerative colitis is not associated with an increased rate of postoperative complications. J Gastrointest Surg 2008;12(10):1730–1736, discussion 1736–1737
10 Indar AA, Young-Fadok TM, Heppell J, Efron JE. Effect of perioperative immunosuppressive medication on early outcome in Crohn's disease patients. World J Surg 2009;33(5):1049–1052
11 Canedo J, Lee SH, Pinto R, Murad-Regadas S, Rosen L, Wexner SD. Surgical resection in Crohn's disease: is immunosuppressive medication associated with higher postoperative infection rates? Colorectal Dis 2011;13(11):1294–1298
12 Connell WR, Kamm MA, Ritchie JK, Lennard-Jones JE. Bone marrow toxicity caused by azathioprine in inflammatory bowel disease: 27 years of experience. Gut 1993;34(8):1081–1085
13 Arts J, D'Haens G, Zeegers M, et al. Long-term outcome of treatment with intravenous cyclosporin in patients with severe ulcerative colitis. Inflamm Bowel Dis 2004;10(2):73–78
14 Gutierrez-Ureña S, Molina JF, García CO, Cuéllar ML, Espinoza LR. Pancytopenia secondary to methotrexate therapy in rheumatoid arthritis. Arthritis Rheum 1996;39(2):272–276
15 Mahadevan U, Loftus EV Jr, Tremaine WJ, et al. Azathioprine or 6-mercaptopurine before colectomy for ulcerative colitis is not associated with increased postoperative complications. Inflamm Bowel Dis 2002;8(5):311–316
16 Subramanian V, Pollok RC, Kang JY, Kumar D. Systematic review of postoperative complications in patients with inflammatory bowel disease treated with immunomodulators. Br J Surg 2006;93 (7):793–799
17 Pinna-Pintor M, Arese P, Bona R, et al. Severe steroid-unresponsive ulcerative colitis: outcomes of restorative proctocolectomy in patients undergoing cyclosporin treatment. Dis Colon Rectum 2000;43(5):609–613, discussion 613–614
18 Grennan DM, Gray J, Loudon J, Fear S. Methotrexate and early postoperative complications in patients with rheumatoid arthritis undergoing elective orthopaedic surgery. Ann Rheum Dis 2001;60 (3):214–217
19 Bridges SL Jr, Moreland LW. Perioperative use of methotrexate in patients with rheumatoid arthritis undergoing orthopedic surgery. Rheum Dis Clin North Am 1997;23(4):981–993
20 Perhala RS, Wilke WS, Clough JD, Segal AM. Local infections complications following large joint replacement in rheumatoid arthritis patients treated with methotrexate versus those not treated with methotrexate. Arthritis (Egypt) 1991;34(2):146–152
21 Sands BE, Anderson FH, Bernstein CN, et al. Infliximab maintenance therapy for fistulizing Crohn's disease. N Engl J Med 2004;350(9):876–885
22 Hanauer SB, Feagan BG, Lichtenstein GR, et al. Maintenance infliximab for Crohn's disease: the ACCENT I randomized trial. Lancet 2002;359:15411549
23 Behm BW, Bickston SJ. Tumor necrosis factor-alpha antibody for maintenance of remission in Crohn's disease. Cochrane Database Syst Rev 2008;23(1):CD006893
24 Ford AC, Sandborn WJ, Khan KJ, Hanauer SB, Talley NJ, Moayyedi P. Efficacy of biological therapies in inflammatory bowel disease: systematic review and meta-analysis. Am J Gastroenterol 2011; 106(4):644–659, quiz 660
25 Rutgeerts PJ, D'Haens G, Targan S, et al. Efficacy and safety of retreatment with anti-tumor necrosis factor antibody (infliximab) to maintain remission in Crohn's disease. Gastroenterology 1999;117(4):761–769
26 Keane J, Gershon S, Wise RP, et al. Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent. N Engl J Med 2001;345(15):1098–1104
27 Colombel JF, Loftus EV Jr, Tremaine WJ, et al. The safety profile of infliximab in patients with Crohn's disease: the Mayo clinic experience in 500 patients. Gastroenterology 2004;126(1):19–31
28 Hansen RA, Gartlehner G, Powell GE, Sandler RS. Serious adverse events with infliximab: analysis of spontaneously reported adverse events. Clin Gastroenterol Hepatol 2007;5(6):729–735
29 Cottone M, Kohn A, Daperno M, et al. Advanced age is an independent risk factor for severe infections and mortality in patients given anti-tumor necrosis factor therapy for inflammatory bowel disease. Clin Gastroenterol Hepatol 2011;9(1):30–35
30 Marchal L, D'Haens G, Van Assche G, et al. The risk of post-operative complications associated with infliximab therapy for Crohn's disease: a controlled cohort study. Aliment Pharmacol Ther 2004;19(7):749–754
31 Appau KA, Fazio VW, Shen B, et al. Use of infliximab within 3 months of ileocolonic resection is associated with adverse

postoperative outcomes in Crohn's patients. J Gastrointest Surg 2008;12(10):1738–1744
32 White EC, Melmed GY, Vasiliauskas E, et al. Does preoperative immunosuppression influence unplanned hospital readmission after surgery in patients with Crohn's disease? Dis Colon Rectum 2012;55(5):563–568
33 Kumar A, Auron M, Aneja A, Mohr F, Jain A, Shen B. Inflammatory bowel disease: perioperative pharmacological considerations. Mayo Clin Proc 2011;86(8):748–757
34 Beddy D, Dozois EJ, Pemberton JH. Perioperative complications in inflammatory bowel disease. Inflamm Bowel Dis 2011;17 (7):1610–1619
35 Rutgeerts P. Review article: recurrence of Crohn's disease after surgery - the need for treatment of new lesions. Aliment Pharmacol Ther 2006;24(Suppl 3):29–32
36 Michelassi F, Balestracci T, Chappell R, Block GE. Primary and recurrent Crohn's disease. Experience with 1379 patients. Ann Surg 1991;214(3):230–238, discussion 238–240
37 El-Hachem S, Regueiro M. Postoperative Crohn's disease: prevention and treatment. Expert Rev Gastroenterol Hepatol 2009;3 (3):249–256
38 Fernandez-Blanco I, Monturiol J, Martinez B, et al. Adalimumab in the prevention of postoperative recurrence of Crohn's disease. Gastroenterology 2010;138:S-692
39 Regueiro M, Schraut W, Baidoo L, et al. Infliximab prevents Crohn's disease recurrence after ileal resection. Gastroenterology 2009;136 (2):441–450, e1, quiz 716
40 Regueiro M, El-Hachem S, Kip KE, et al. Postoperative infliximab is not associated with an increase in adverse events in Crohn's disease. Dig Dis Sci 2011;56(12):3610–3615