

Inflammatory bowel disease surgery in the biologic era

Linda Ferrari, Mukta K Krane, Alessandro Fichera

Linda Ferrari, Mukta K Krane, Alessandro Fichera, University of Washington Medical Center, Seattle, WA 98195-6410, United States

Author contributions: All the authors designed the study and wrote the manuscript.

Conflict-of-interest statement: Authors declare no conflict of interest.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Alessandro Fichera, MD, FACS, FASCRS, University of Washington Medical Center, 1959 NE Pacific Street, Box 356410, Seattle, WA 98195-6410, United States. afichera@uw.edu
Telephone: +1-206-6165709

Received: September 29, 2015
Peer-review started: October 2, 2015
First decision: November 4, 2015
Revised: January 13, 2016
Accepted: March 9, 2016
Article in press: March 14, 2016
Published online: May 27, 2016

Abstract

Anti-tumour necrosis factor (TNF)- α therapy has revolutionized inflammatory bowel disease (IBD) treatment. Infliximab and adalimumab either as monotherapy or in combination with an immunomodulator are able to induce clinical and biological remission in patients with moderate and severe Crohn's disease (CD) and ulcerative colitis (UC). These new therapies have led to a shift in the goals of IBD management from just

controlling clinical symptoms to preventing disease progression. However, despite these advances in medical therapy, surgery is still required in 30%-40% of patients with CD and 20%-30% of patients with UC at some point during their lifetime. While biologics certainly play a major role in the medical treatment of IBD, there is concern about the effects of these anti-TNF- α agents on postoperative complications and morbidity. The purpose of this article is to review the role of surgery in the treatment of IBD in the age of biologics and the impact of these medications on per-operative outcomes. In this manuscript we review the relationship between biologic agents and surgery in the treatment of IBD. We also discuss in detail the perioperative risks and complications.

Key words: Inflammatory bowel disease; Anti-tumour necrosis factor alpha agents; Ulcerative colitis; Crohn's disease; Infliximab

© **The Author(s) 2016.** Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: We review the relationship between biologic agents and surgery in the treatment of inflammatory bowel disease. We also discuss in detail perioperative risks and complications in this setting.

Ferrari L, Krane MK, Fichera A. Inflammatory bowel disease surgery in the biologic era. *World J Gastrointest Surg* 2016; 8(5): 363-370 Available from: URL: <http://www.wjgnet.com/1948-9366/full/v8/i5/363.htm> DOI: <http://dx.doi.org/10.4240/wjgs.v8.i5.363>

INTRODUCTION

Anti-tumour necrosis factor (TNF)- α therapy has revolutionized inflammatory bowel disease (IBD) treatment. Infliximab (IFX) and adalimumab (ADA) either as monotherapy or in combination with an immuno-

modulator are able to induce clinical and biological remission in patients with moderate and severe Crohn's disease (CD)^[1-6] and ulcerative colitis (UC)^[7,8]. These new therapies have led to a shift in the goals of IBD management from just controlling clinical symptoms to preventing disease progression.

The concept of composite or deep remission based on clinical and biological remission and mucosal healing has recently emerged. The ability to achieve composite remission seems to be correlated with better long-term outcomes, improved quality of life, and fewer surgical operations^[6].

However, despite these advances in medical therapy, surgery is still required in 30%-40% of patients with CD and 20%-30% of patients with UC at some point during their lifetime^[9,10]. In CD patients, the risk for surgery seems to be related to stenosing phenotype, perianal disease, smoking, younger age at diagnosis, and delay in biologic therapy^[11]. Surgery in patients with CD is not curative but is necessary when medical therapy is unable to achieve symptomatic control. For patients with UC, surgery is curative and indicated for failure of medical management, acute complication including fulminant colitis, perforation, severe bleeding and toxic megacolon, and chronic conditions such as development of dysplasia or malignancy.

While biologics certainly play a major role in the medical treatment of IBD, there is concern about the effects of these anti-TNF- α agents on postoperative complications and morbidity. The purpose of this article is to review the role of surgery in the treatment of IBD in the age of anti-TNF- α agents and the impact of these medications on peri-operative outcomes.

CD

Luminal disease

Medical treatment for luminal CD focuses on the achievement of composite remission, which is best obtained thorough initiation of combination therapy with anti-TNF- α agents (IFX or ADA) and immunomodulators within 18-24 mo of diagnosis in patients with moderate to severe CD. Composite remission is correlated with fewer-hospitalization and CD-related surgeries and better quality of life. In the ACCENT I trial^[12] scheduled IFX was associated with a two-fold lower rate of surgery at 54 wk compared with on demand treatment (3% vs 7.5% respectively, $P = 0.01$). In the CHARM trial^[5] the rate of surgery at one year was 9 times lower in the group treated with ADA than in the placebo group (0.6% vs 3.8% respectively, $P = 0.001$).

However, despite improvements in medical management at least 30%-40% of patients with CD require surgery at some point during their lifetime^[9,10]. Schnitzler *et al*^[12] found that of 614 patients treated with IFX, 24% had required major abdominal surgery at a median follow-up of 4.6 years. Peyrin-Biroulet *et al*^[13] followed 296 patients diagnosed with CD and reported that 26% underwent at least one major abdominal surgical

procedure at a median follow-up of 57 mo. In addition, among patients treated with ADA as a second line therapy after IFX failure, the rate of surgical intervention was 18% at 130 wk^[14]. Given the continued role of surgery and the increasing use of biologic therapy in the management of CD, it is imperative to understand how these treatments influence each other.

Postoperative complications

Studies on the effect of biologic agents on postoperative complications have yielded conflicting results^[15-29]. Appau *et al*^[15] analyzed 389 patients who underwent ileocolonic resection for CD, 60 patients had been treated with IFX within 3 mo of surgery and 329 patients had not. The IFX group appeared to have a higher rate of postoperative sepsis (20% vs 5.8%, $P = 0.021$), anastomotic leak (10% vs 1.4%, $P = 0.049$) and hospital readmission (20% vs 2.9%, $P = 0.007$).

On the contrary, a recent multicenter trial including 6 tertiary referral centers^[21] encompassing 298 patients with CD treated with IFX or ADA showed no differences in major or minor complications between patients who received biologics within 2 mo of surgery compared to patients who received biologics more than 2 mo before surgery. The rate of anastomotic leak was similar between the two groups, 7.2% in the biologic group and 8% in the non-biologic group ($P = 0.976$), and they concluded that the use of anti-TNF- α agents within 2 mo of surgery for CD with intestinal anastomosis did not increase the risk of anastomotic, infectious, or other complications. Canedo *et al*^[17] studied 225 CD patients who underwent surgery and divided them into 3 categories based on exposure to IBD medications within 90 d of surgery: IFX, other drugs including steroids and/or immunosuppressive agents (OD), and no drugs (ND). Ileocolonic resection was the most common procedure followed by total colectomy and proctectomy. Laparoscopy was performed in 47.7%, 45.9% and 29.3% of patients in the IFX, OD and ND groups respectively ($P = 0.04$). There was no statistically significant difference in the incidence of intra-operative complications or length of hospital stay in the three groups. In addition rates of postoperative pneumonia ($P = 0.14$), wound infection ($P = 0.35$) and abscess ($P = 0.34$) were similar between the three groups. Anastomotic leak was reported in 5.7%, 6.66% and 2.43% of patients respectively for the IFX, OD and ND groups ($P = 0.39$).

Kasperek *et al*^[22] recently analyzed their experience in 96 patients with CD of which 48 patients had received IFX within 3 mo of a Crohn's related abdominal surgery, with a median of 60 d (range 1-90 d) between the last IFX dose and surgery and compared them to a control group who had undergone abdominal surgery for CD without prior IFX treatment. They evaluated minor complications, including wound infections, urinary tract infections and paralytic ileus, and major complications such as anastomotic leak, intra-abdominal abscess, postoperative hemorrhage, small bowel enterocutaneous fistula, and death. There was a trend toward a greater

rate of anastomotic leaks and intra-abdominal abscesses in the control group (13% vs 4%, $P = 0.27$), but it did not reach statistical significance. Analysis of the interval between the last administered dose of IFX and surgery demonstrated no difference in complication rates. They recommended scheduling elective surgery halfway between infusions, 4 wk after IFX infusion assuming an 8-wk interval for maintenance therapy, and re-initiating IFX 4 wk post-operatively in the absence of complications.

We recently published our experience^[29] of 518 IBD patients, 143 treated with IFX within 12 wk of surgery (IFX group) and affected by CD (63), UC (71) and indeterminate colitis (8), and 376 not treated with biologics [non-IFX (NIFX) group]. Total abdominal colectomy followed by proctocolectomy and ileocolonic resection was the most frequent operations performed and all procedures were done laparoscopically. Operative time and blood loss were similar between the 2 groups ($P = 0.50$ and $P = 0.34$ respectively). In addition the incidence of infectious complications (12% vs 11.2%, $P = 0.92$), anastomotic leak (5.2% vs 2.9%, $P = 0.69$), and thrombotic complications (3.5% vs 5.6%, $P = 0.46$) was not statistically different between the IFX and NIFX groups. Subgroup analysis confirmed similar rates of overall, thromboembolic, anastomotic, and infections complications regardless of whether the patients had CD or UC.

With the emerging trend toward initiating biologic therapy early in the course of disease and a resultant increase in the proportion of patients on these agents pre-operatively, there has been increased debate regarding not only whether anti-TNF- α therapy needs to be discontinued prior to elective surgery but if so what the minimum interval should be between the last dose of the biologic agent and the surgery. Depending on individual metabolism, the half-life of IFX is 7-18 d^[28] and serum antibodies disappear at 3 mo.

In a series of 195 patients with IBD Waterman *et al*^[19] compared postoperative complications and infections between patients exposed to biologics (IFX or ADA) within 14 d, 15-31 d, and 31-180 d before surgery. Most of these patients receive concomitant thiopurine (double therapy) or thiopurine and corticosteroids (triple therapy). They found that biologic therapy alone was not associated with an increased rate of 30-d postoperative infectious complications, hospital stay, readmission, reoperation or anastomotic leak. However, combination therapy with thiopurine and biologics increased rates of postoperative complications including urinary tract infection, wound infection, bacteremia and the need for postoperative antibiotics. In addition, a shorter interval between the last dose of anti-TNF- α therapy and surgery did not increase postoperative complications. They concluded that it is not necessary to delay surgery until anti-TNF- α washout has been achieved. Several other recent trials have been demonstrated no correlation between overall postoperative infections or anastomotic leaks and the interval (ranging from 1-12 wk) between

last IFX administration and surgery^[17,21,22,29].

Postoperative recurrence

Several factors are related to recurrence: smoking, the *NOD2/CARD15* gene mutation, young age at diagnosis, short duration of disease prior to an operation and multiple sites of disease^[11,30-34]. Rate of recurrence may also be influenced also by surgical technique^[30,34] including the type of anastomosis, resection margin and the decision to perform a stricturoplasty vs a resection^[35]. The role of biologic therapy in reducing the incidence of surgical recurrence is yet unknown but we can infer the impact that anti-TNF- α agents may have based on mucosal healing. Early observational studies have demonstrated reduced rates in endoscopic and clinical recurrence in patients post-operatively treated with IFX^[36], Regueiro *et al*^[37] demonstrated in a placebo-controlled randomized trial that endoscopic recurrence was significantly lower in the IFX group compared to controls at 1 year (9.1% vs 84.6%, $P = 0.0006$) but the sample size was too small to detect differences in clinical recurrence. Yoshida *et al*^[38] also conducted a randomized control trial comparing IFX to placebo and found the clinical remission rate with IFX was 100% vs 68% in the placebo group ($P < 0.03$) at one year^[38].

Recently, Savarino *et al*^[39] published the results of a prospective randomized study in which 51 patients with CD who had undergone an ileocolonic resection were assigned to receive ADA at a dose of 160/80/40 mg every two weeks, azathioprine (AZA) at 2 mg/kg per day, or mesalamine at 3 g/d starting 2 wk after surgery. Patients were followed for 2 years. The rate of endoscopic recurrence was lower in the ADA group (6.3%) compared with both the AZA (64.7%; OR = 0.036; 95%CI: 0.004-0.347) and mesalamine groups (83.3%; OR = 0.013; 95%CI: 0.001-0.143). In addition patients in ADA arm had a lower rate of clinical recurrence (12.5%) compared with the AZA (64.7%; OR = 0.078; 95%CI: 0.013-0.464) and mesalamine groups (50%; OR = 0.143; 95%CI: 0.025-0.819).

The role of IFX in preventing relapse of CD after surgical resection is currently being evaluated in the multicentric randomized prevent trial^[40,41]. In this study, patients are post-operative assigned to receive either IFX or placebo. Patients in both groups are treated according to their treatment arm at week 0 and then every 8 wk through week 200. However if a patient initially randomized to the placebo group relapses, IFX therapy may be initiated. Data collection for this trial has been completed and the results are being awaited.

Perianal disease

Perianal CD (PCD) is considered an aggressive and disabling phenotype, which manifests in about 40% of patients diagnosed with CD. Quality of life is often compromised due to anal pain, discharge and fecal incontinence^[41]. Before the introduction of biologics, 40% of patients with PCD underwent proctectomy. Recently anti-TNF- α agents have been demonstrated

to induce and maintain perianal fistula closure in two randomized control trials^[42,43].

Perianal fistulas may be classified as simple if a single, low, transphincteric tract without abscess, stenosis or inflammation is present, or complex if there is more than one tract, granulomatous inflammation, presence of an abscess or it is rectovaginal^[44]. The majority of Crohn's patients experience complex fistulas during their disease course.

Treatment of perianal fistula requires a multidisciplinary approach between surgery, gastroenterology, and radiology. Initial management begins with assessment of the extent and complexity of disease^[45]. Endoscopy evaluates the presence of proctitis, which is predictive of a non-healing fistula tract. Rectal examination under anesthesia helps identify and classify fistulas and enables control of the infection through drainage of the abscess and insertion of a seton. Magnetic resonance imaging (MRI) is considered the gold standard for imaging of PCD with higher specificity compared to transrectal ultrasound. It enables evaluation of the abscess volume and maximum fistula length and can be used to restage and assess response to treatment^[46].

Once the extent and nature of the PCD is characterized combination treatment consisting of surgical and medical therapy (TNF- α with or without immunomodulator) results in improved rates of fistula healing compared with surgery or medical therapy alone^[46-50]. Depending on the study, the endpoint may be fistula healing, usually defined as absence of fistula or drainage by medical examination, or clinical improvement, defined as reduction of symptoms or drainage.

Initially, the role of surgery is to control sepsis and define the anatomy of the fistula track after which definitive treatment can be planned. Surgical options for the treatment of perirectal abscesses or fistulas in patients with CD favor conservative approaches including incision and drainage and placement of non-cutting setons. Non-cutting setons preserve the integrity of the anal sphincter, drain fistula tracts and limit abscess formation and recurrences^[45]. More aggressive procedures including fistulotomy or advancement flap may be appropriate in certain circumstances but are generally avoided because they are associated with increased morbidity and risk of fecal incontinence.

According to recent literature the most effective approach for PCD consists of seton placement prior to starting medical treatment with anti-TNF- α agents or anti-TNF- α agents plus thiopurine^[50-53]. El-Gazzaz *et al*^[50] showed complete healing in 36.6% of patients treated with biologic agents plus surgery vs 26.5% for patients treated with surgery alone with a median follow-up of over 3 years but this was not statistically significant ($P = 0.1$). Bouguen *et al*^[51] reported a study of 156 patients with PCD treated with IFX. Sixty-two percent of patients also underwent seton placement and 56% were on concomitant immunomodulators. At a median follow-up of 57 mo, 46% of total patients and 69% of patients treated with IFX and seton placement for a

median of 8 mo had sustained complete fistula closure. Haennig *et al*^[52] reported data on 81 IBD patients with perianal fistula, 62 (80.5%) underwent drainage with loose seton plus IFX therapy and 73 (90%) received treatment with immunomodulators (either Azathioprine or Methotrexate) in addition to anti-TNF- α . At a median follow-up of 64 mo fistula closure was achieved in 75% of patients.

The need and timing of seton removal and the appropriate duration of anti-TNF therapy remain debated topics^[53]. Bouguen *et al*^[51] found improved outcomes when the seton was removed within 34 wk of starting biologic therapy. Haennig *et al*^[52] hypothesize that the optimal time for seton removal should be determined by the surgeon based on clinical characteristics and recommend that it be left *in situ* between 2 and 8.5 mo. Most series evaluate the status of the fistula by clinical examination, however there is increasing data that MRI may be the more accurate instrument to guide decisions regarding timing of seton removal. MRI often shows residual inflammation and disease activity even when the external tract is closed, which is the basis for recurrence^[45,46]. In terms of how long biologic therapy should be maintained, no consensus can be found in literature but there is a suggestion that long-term anti-TNF- α therapy is associated with better long-term results.

UC

Anti-TNF- α agents are approved to treat moderate to severe UC as second line treatment in patients refractory to corticosteroids and immunomodulators^[54-56]. IFX was approved for UC refractory to standard medications in 2006^[7], adalimumab was approved in 2012^[57,58] and recently, golimumab received approval in Europe and the United States^[59,60].

A recent meta-analysis^[8] demonstrated that anti-TNF- α therapy is more effective than placebo in reducing UC-related hospitalizations. The study analyzed results of IFX^[54], ADA^[55,56] and golimumab^[7,57] trials and found that IFX and ADA achieve long-term mucosal healing at 52-54 wk in 35.6% of patients compare to 16.8% in the placebo group. In addition IFX and ADA were able to reduce UC-related hospitalizations^[61-64] and IFX alone was superior to placebo in reducing the need for colectomy.

Postoperative complications

Unlike CD, in UC a proctocolectomy is curative and removes the risk of developing colorectal cancer. In the era of conservative management, the timing of surgery vs medical therapy with biologics or other medications is challenging^[65]. A colectomy for UC may be done as an emergent/urgent or elective procedure depending on the clinical scenario. An emergent/urgent colectomy is indicated for significant hemorrhage, perforation, megacolon, and severe colitis refractory to medical management. Elective colectomies may be performed in patients with UC that experience chronic symptoms

refractory to medical therapy, those who can't tolerate the adverse effects of medication^[66] and patients with high-grade dysplasia, multifocal low-grade dysplasia or cancer^[53]. There is increasing evidence that in current practice the threshold for surgery is too high and that it is important to consider surgery an alternative therapy rather than a failure of medical therapy^[65,67,68]. Roberts *et al*^[67] compared 3 years mortality for patients who had urgent or elective surgery vs medical management in over 28000 patients hospitalized with UC. The elective colectomy group had the lowest mortality rate (3.7%), while the medical management and urgent colectomy groups had similar mortality rates (13.6% and 13.2% respectively, $P = 0.001$).

In terms of the postoperative effects of anti-TNF therapy on surgery in UC patients, studies of IFX have shown differing results^[20,29,69-76]. The Cleveland Clinic group reported that patients undergoing restorative proctocolectomy with ileoanal pouch anastomosis (IPAA) who were treated pre-operatively with IFX had a 3.54 times greater risk of developing early complications ($P = 0.004$), with the rate of sepsis increased by 13.8 fold ($P = 0.011$), even though the majority of cases were done in 3 stages^[72]. However, Gainsbury *et al*^[69] demonstrated that preoperative IFX use was not associated with an increased risk of short-term postoperative complications after IPAA performed in 2 or 3 stages. They evaluated 81 patients, 29 treated with IFX within 12 wk of surgery and 52 not exposed to IFX. Overall short-term postoperative complications were similar between the IFX and NIFX groups (44.8% vs 44.2%, $P = 0.960$). Infections complications, defined as pelvic/intra-abdominal abscess or wound infection, were similar between the IFX and NIFX groups (17.2% vs 26.9%, $P = 0.32$). In multivariate analysis the risk of wound infection while correlated with a higher body mass index (odds ratio = 0.88, 95%CI: 0.78-0.9, $P = 0.049$) was not related with biologic treatment. Similar results were found by Ferrante *et al*^[70] who analyzed 119 patients undergoing restorative proctocolectomy with IPAA in 1 or 2 stages with 22 of the patients having received IFX 12 wk before surgery. Short-term post-operative complications were not significantly different between the two groups. The two predictors of short-term postoperative complications were use of moderate to high dose corticosteroids (> 20 mg of methylprednisolone for > 2 mo) and absence of a diverting ileostomy.

A recent meta-analysis^[73] of 5 studies including 132 patients on IFX who underwent a restorative proctocolectomy with IPAA in either 2 or 3 stages demonstrated an increase in total postoperative complications (OR = 1.80, 95%CI: 1.12-2.87), but not short-term infectious complications (OR = 2.24, 95%CI: 0.63-7.95) or non-infectious complications (OR = 0.85, 95%CI: 0.50-1.45) in the IFX group.

In our experience^[29], we found no correlations between exposure to IFX within 12 wk of surgery and the rate of postoperative adverse events in 237 UC patients (71 in the IFX group and 166 in NIFX group).

The majority of patients in our study underwent a three stage restorative proctocolectomy with IPAA with only 15 (10.6%) patients in the IFX group and 37 (9.8%) patients in the NIFX group undergoing a two stage procedure ($P = 0.94$).

Higher levels of IFX are associated with increased rates of remission and improved endoscopic outcomes but there is concern that it may be correlated with postoperative complications as well. Waterman *et al*^[19] analyzed 108 IBD patients who underwent a colectomy (94/108 for UC), 51 patients had received biologics before surgery and 57 patients had not and they found that preoperative biological therapy was not associated with increased rates of infectious complications or poor wound healing. Preoperative serum levels of IFX were measured within 2 mo of surgery using a microplate Enzyme linked ImmunoSorbent Assay with a cut-off value of 1.4 mg/mL for detectable levels and the association between serum IFX levels and short-term complications was assessed in 19 patients with UC. Of those 19 patients, 10 had detectable levels of IFX and 9 were undetectable. As expected, the group with detectable levels had a shorter time interval between the last dose of IFX and surgery (median 18 d vs 34 d, $P = 0.03$) and while the rate of wound infection trended higher in the detectable group, this was not statistically significant (3/10 vs 0/9 respectively, $P = 0.21$); there was no difference in the rates of any other complications. A limitation of the study is that the sample size was quite small and data from larger populations is needed to draw more definitive conclusions.

In a recent study published by Lau *et al*^[25] anti-TNF- α levels were measured in 217 IBD patients treated with biologic therapy prior to surgery. An anti-TNF- α value of ≥ 0.98 mg/mL was considered a detectable level even though a cutoff of ≥ 3 μ g/mL is usually used for clinical efficacy. Patients were stratified into: Low (0.98-3 μ g/mL), medium (≥ 3 μ g/mL ≤ 8 μ g/mL), and high (≥ 8 μ g/mL) level groups. Ninety-four of the 217 patients were diagnosed with UC of which 42 patients had a three stage and 52 had a two stage restorative proctocolectomy with IPAA. The infectious complication rate between the undetectable and detectable serum anti-TNF- α drug level groups was not significantly different (9% vs 12%, $P = 0.78$). The rates of overall postoperative morbidity (40% vs 47%, $P = 0.59$) and hospital readmission (19% vs 24%, $P = 0.67$) also did not differ. They concluded that even detectable levels of anti-TNF- α agents were not associated with adverse outcomes postoperatively.

CONCLUSION

Anti-TNF- α therapy for the treatment of IBD has improved long-term outcomes including symptom management, mucosal healing, and endoscopic recurrence and is being used earlier in the course of the disease and with increased frequency. However, surgery continues to be an important part of the management of both UC

and CD. While the data is mixed, increasing evidence is emerging that surgery can safely be performed while patients are undergoing biologic therapy. More data is needed on the impact that anti-TNF- α agents will have on the rates of surgical recurrence in CD.

REFERENCES

- 1 **Targan SR**, Hanauer SB, van Deventer SJ, Mayer L, Present DH, Braakman T, DeWoody KL, Schaible TF, Rutgeerts PJ. A short-term study of chimeric monoclonal antibody cA2 to tumor necrosis factor alpha for Crohn's disease. Crohn's Disease cA2 Study Group. *N Engl J Med* 1997; **337**: 1029-1035 [PMID: 9321530]
- 2 **Hanauer SB**, Feagan BG, Lichtenstein GR, Mayer LF, Schreiber S, Colombel JF, Rachmilewitz D, Wolf DC, Olson A, Bao W, Rutgeerts P. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. *Lancet* 2002; **359**: 1541-1549 [PMID: 12047962]
- 3 **Colombel JF**, Sandborn WJ, Reinisch W, Mantzaris GJ, Kornbluth A, Rachmilewitz D, Lichtiger S, D'Haens G, Diamond RH, Broussard DL, Tang KL, van der Woude CJ, Rutgeerts P. Infliximab, azathioprine, or combination therapy for Crohn's disease. *N Engl J Med* 2010; **362**: 1383-1395 [PMID: 20393175 DOI: 10.1056/NEJMoa0904492]
- 4 **Sandborn WJ**, Hanauer SB, Rutgeerts P, Fedorak RN, Lukas M, MacIntosh DG, Panaccione R, Wolf D, Kent JD, Bittle B, Li J, Pollack PF. Adalimumab for maintenance treatment of Crohn's disease: results of the CLASSIC II trial. *Gut* 2007; **56**: 1232-1239 [PMID: 17299059]
- 5 **Colombel JF**, Sandborn WJ, Rutgeerts P, Enns R, Hanauer SB, Panaccione R, Schreiber S, Byczkowski D, Li J, Kent JD, Pollack PF. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. *Gastroenterology* 2007; **132**: 52-65 [PMID: 17241859]
- 6 **Colombel JF**, Reinisch W, Mantzaris GJ, Kornbluth A, Rutgeerts P, Tang KL, Oortwijn A, Bevelander GS, Cornillie FJ, Sandborn WJ. Randomised clinical trial: deep remission in biologic and immunomodulator naïve patients with Crohn's disease - a SONIC post hoc analysis. *Aliment Pharmacol Ther* 2015; **41**: 734-746 [PMID: 25728587 DOI: 10.1111/apt.13139]
- 7 **Rutgeerts P**, Sandborn WJ, Feagan BG, Reinisch W, Olson A, Johanns J, Travers S, Rachmilewitz D, Hanauer SB, Lichtenstein GR, de Villiers WJ, Present D, Sands BE, Colombel JF. Infliximab for induction and maintenance therapy for ulcerative colitis. *N Engl J Med* 2005; **353**: 2462-2476 [PMID: 16339095]
- 8 **Colombel JF**, Sandborn WJ, Ghosh S, Wolf DC, Panaccione R, Feagan B, Reinisch W, Robinson AM, Lazar A, Kron M, Huang B, Skup M, Thakkar RB. Four-year maintenance treatment with adalimumab in patients with moderately to severely active ulcerative colitis: Data from ULTRA 1, 2, and 3. *Am J Gastroenterol* 2014; **109**: 1771-1780 [PMID: 25155227 DOI: 10.1038/ajg.2014.242]
- 9 **Bouguen G**, Peyrin-Biroulet L. Surgery for adult Crohn's disease: what is the actual risk? *Gut* 2011; **60**: 1178-1181 [PMID: 21610273 DOI: 10.1136/gut.2010.234617]
- 10 **Hancock L**, Mortensen NJ. How often do IBD patients require resection of their intestine? *Inflamm Bowel Dis* 2008; **14** Suppl 2: S68-S69 [PMID: 18816762 DOI: 10.1002/ibd.20600]
- 11 **Cleynen I**, González JR, Figueroa C, Franke A, McGovern D, Bortlik M, Crusius BJ, Vecchi M, Artieda M, Szczypiorska M, Bethge J, Arteta D, Ayala E, Danese S, van Hogezaand RA, Panés J, Peña SA, Lukas M, Jewell DP, Schreiber S, Vermeire S, Sans M. Genetic factors conferring an increased susceptibility to develop Crohn's disease also influence disease phenotype: results from the IBDchip European Project. *Gut* 2013; **62**: 1556-1565 [PMID: 23263249 DOI: 10.1136/gutjnl-2011-300777]
- 12 **Schnitzler F**, Fidler H, Ferrante M, Noman M, Arijis I, Van Assche G, Hoffman I, Van Steen K, Vermeire S, Rutgeerts P. Long-term outcome of treatment with infliximab in 614 patients with Crohn's disease: results from a single-centre cohort. *Gut* 2009; **58**: 492-500 [PMID: 18832518 DOI: 10.1136/gut.2008.155812]
- 13 **Peyrin-Biroulet L**, Oussalah A, Williet N, Pillot C, Bresler L, Bigard MA. Impact of azathioprine and tumour necrosis factor antagonists on the need for surgery in newly diagnosed Crohn's disease. *Gut* 2011; **60**: 930-936 [PMID: 21228429 DOI: 10.1136/gut.2010.227884]
- 14 **Oussalah A**, Babouri A, Chevaux JB, Stancu L, Trouilloud I, Bensenane M, Boucekkine T, Bigard MA, Peyrin-Biroulet L. Adalimumab for Crohn's disease with intolerance or lost response to infliximab: a 3-year single-centre experience. *Aliment Pharmacol Ther* 2009; **29**: 416-423 [PMID: 19035976 DOI: 10.1111/j.1365-2036.2008.03902.x]
- 15 **Appau KA**, Fazio VW, Shen B, Church JM, Lashner B, Remzi F, Brzezinski A, Strong SA, Hammel J, Kiran RP. Use of infliximab within 3 months of ileocolonic resection is associated with adverse postoperative outcomes in Crohn's patients. *J Gastrointest Surg* 2008; **12**: 1738-1744 [PMID: 18709420 DOI: 10.1007/s11605-008-0646-0]
- 16 **Colombel JF**, Loftus EV, Tremaine WJ, Pemberton JH, Wolff BG, Young-Fadok T, Harmsen WS, Schleck CD, Sandborn WJ. Early postoperative complications are not increased in patients with Crohn's disease treated perioperatively with infliximab or immunosuppressive therapy. *Am J Gastroenterol* 2004; **99**: 878-883 [PMID: 15128354]
- 17 **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**: 1294-1298 [PMID: 20969715 DOI: 10.1111/j.1463-1318.2010.02469.x]
- 18 **Kopylov U**, Ben-Horin S, Zmora O, Eliakim R, Katz LH. Anti-tumor necrosis factor and postoperative complications in Crohn's disease: systematic review and meta-analysis. *Inflamm Bowel Dis* 2012; **18**: 2404-2413 [PMID: 22467533 DOI: 10.1002/ibd.22954]
- 19 **Waterman M**, Xu W, Dinani A, Steinhart AH, Croitoru K, Nguyen GC, McLeod RS, Greenberg GR, Cohen Z, Silverberg MS. Preoperative biological therapy and short-term outcomes of abdominal surgery in patients with inflammatory bowel disease. *Gut* 2013; **62**: 387-394 [PMID: 22619367 DOI: 10.1136/gutjnl-2011-301495]
- 20 **Narula N**, Charleton D, Marshall JK. Meta-analysis: peri-operative anti-TNF α treatment and post-operative complications in patients with inflammatory bowel disease. *Aliment Pharmacol Ther* 2013; **37**: 1057-1064 [PMID: 23581515 DOI: 10.1111/apt.12313]
- 21 **Myreldid P**, Marti-Gallostra M, Ashraf S, Sunde ML, Tholin M, Oresland T, Lovegrove RE, Tøttrup A, Kjær DW, George BD. Complications in surgery for Crohn's disease after preoperative antitumour necrosis factor therapy. *Br J Surg* 2014; **101**: 539-545 [PMID: 24615529 DOI: 10.1002/bjs.9439]
- 22 **Kasperek MS**, Bruckmeier A, Beigel F, Müller MH, Brand S, Mansmann U, Jauch KW, Ochsenkühn T, Kreis ME. Infliximab does not affect postoperative complication rates in Crohn's patients undergoing abdominal surgery. *Inflamm Bowel Dis* 2012; **18**: 1207-1213 [PMID: 21928373 DOI: 10.1002/ibd.21860]
- 23 **El-Hussuna A**, Andersen J, Bisgaard T, Jess P, Henriksen M, Oehlenschläger J, Thorlacius-Ussing O, Olaisen G. Biologic treatment or immunomodulation is not associated with postoperative anastomotic complications in abdominal surgery for Crohn's disease. *Scand J Gastroenterol* 2012; **47**: 662-668 [PMID: 22486168 DOI: 10.3109/00365521.2012.660540]
- 24 **Mascarenhas C**, Nunoo R, Asgeirsson T, Rivera R, Kim D, Hoedema R, Dujovny N, Luchtefeld M, Davis AT, Figg R. Outcomes of ileocolic resection and right hemicolectomies for Crohn's patients in comparison with non-Crohn's patients and the impact of perioperative immunosuppressive therapy with biologics and steroids on inpatient complications. *Am J Surg* 2012; **203**: 375-378; discussion 378 [PMID: 22364904 DOI: 10.1016/j.amjsurg.2011.11.001]
- 25 **Lau C**, Dubinsky M, Melmed G, Vasiliauskas E, Berel D, McGovern D, Ippoliti A, Shih D, Targan S, Fleshner P. The impact of preoperative serum anti-TNF α therapy levels on early postoperative outcomes in inflammatory bowel disease surgery.

- Ann Surg* 2015; **261**: 487-496 [PMID: 24950263 DOI: 10.1097/SLA.0000000000000757]
- 26 **Rosenfeld G**, Qian H, Bressler B. The risks of post-operative complications following pre-operative infliximab therapy for Crohn's disease in patients undergoing abdominal surgery: a systematic review and meta-analysis. *J Crohns Colitis* 2013; **7**: 868-877 [PMID: 23466411 DOI: 10.1016/j.crohns.2013.01.019]
 - 27 **Ehteshami-Afshar S**, Nikfar S, Rezaie A, Abdollahi M. A systematic review and meta-analysis of the effects of infliximab on the rate of colectomy and post-operative complications in patients with inflammatory bowel disease. *Arch Med Sci* 2011; **7**: 1000-1012 [PMID: 22328883 DOI: 10.5114/aoms.2011.26612]
 - 28 **Cornillie F**, Shealy D, D'Haens G, Geboes K, Van Assche G, Ceuppens J, Wagner C, Schaible T, Plevy SE, Targan SR, Rutgeerts P. Infliximab induces potent anti-inflammatory and local immunomodulatory activity but no systemic immune suppression in patients with Crohn's disease. *Aliment Pharmacol Ther* 2001; **15**: 463-473 [PMID: 11284774]
 - 29 **Krane MK**, Allaix ME, Zoccali M, Umanskiy K, Rubin MA, Villa A, Hurst RD, Fichera A. Preoperative infliximab therapy does not increase morbidity and mortality after laparoscopic resection for inflammatory bowel disease. *Dis Colon Rectum* 2013; **56**: 449-457 [PMID: 23478612 DOI: 10.1097/DCR.0b013e3182759029]
 - 30 **De Cruz P**, Kamm MA, Prideaux L, Allen PB, Desmond PV. Postoperative recurrent luminal Crohn's disease: a systematic review. *Inflamm Bowel Dis* 2012; **18**: 758-777 [PMID: 21830279 DOI: 10.1002/ibd.21825]
 - 31 **Zallot C**, Peyrin-Biroulet L. Clinical risk factors for complicated disease: how reliable are they? *Dig Dis* 2012; **30** Suppl 3: 67-72 [PMID: 23295694 DOI: 10.1159/000342608]
 - 32 **Yamamoto T**, Watanabe T. Strategies for the prevention of postoperative recurrence of Crohn's disease. *Colorectal Dis* 2013; **15**: 1471-1480 [PMID: 23809911 DOI: 10.1111/codi.12326]
 - 33 **Reese GE**, Nanidis T, Borysiewicz C, Yamamoto T, Orchard T, Tekkis PP. The effect of smoking after surgery for Crohn's disease: a meta-analysis of observational studies. *Int J Colorectal Dis* 2008; **23**: 1213-1221 [PMID: 18762954 DOI: 10.1007/s00384-008-0542-9]
 - 34 **Michelassi F**, Sultan S. Surgical treatment of complex small bowel Crohn disease. *Ann Surg* 2014; **260**: 230-235 [PMID: 24743631 DOI: 10.1097/SLA.0000000000000697]
 - 35 **Fichera A**, Lovadina S, Rubin M, Cimino F, Hurst RD, Michelassi F. Patterns and operative treatment of recurrent Crohn's disease: a prospective longitudinal study. *Surgery* 2006; **140**: 649-654 [PMID: 17011913]
 - 36 **Sorrentino D**, Terrosu G, Avellini C, Maiero S. Infliximab with low-dose methotrexate for prevention of postsurgical recurrence of ileocolonic Crohn disease. *Arch Intern Med* 2007; **167**: 1804-1807 [PMID: 17846401]
 - 37 **Regueiro M**, Schraut W, Baidoo L, Kip KE, Sepulveda AR, Pesci M, Harrison J, Plevy SE. Infliximab prevents Crohn's disease recurrence after ileal resection. *Gastroenterology* 2009; **136**: 441-450.e1; quiz 716 [PMID: 19109962 DOI: 10.1053/j.gastro.2008.10.051]
 - 38 **Yoshida K**, Fukunaga K, Ikeuchi H, Kamikozuru K, Hida N, Ohda Y, Yokoyama Y, Iimuro M, Takeda N, Kato K, Kikuyama R, Nagase K, Hori K, Nakamura S, Miwa H, Matsumoto T. Scheduled infliximab monotherapy to prevent recurrence of Crohn's disease following ileocolic or ileal resection: a 3-year prospective randomized open trial. *Inflamm Bowel Dis* 2012; **18**: 1617-1623 [PMID: 22081474 DOI: 10.1002/ibd.21928]
 - 39 **Savarino E**, Bodini G, Dulbecco P, Assandri L, Bruzzone L, Mazza F, Frigo AC, Fazio V, Marabotto E, Savarino V. Adalimumab is more effective than azathioprine and mesalamine at preventing post-operative recurrence of Crohn's disease: a randomized controlled trial. *Am J Gastroenterol* 2013; **108**: 1731-1742 [PMID: 24019080 DOI: 10.1038/ajg.2013.287]
 - 40 **Janssen Biotech, Inc.** A Multicenter Trial Comparing REMICADE (Infliximab) and Placebo in the Prevention of Recurrence in Crohn's Disease (CD) Patients Undergoing Surgical Resection Who Are at an Increased Risk of Recurrence. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Available from: URL: <http://clinicaltrials.gov/ct2/show/results/NCT01190839>
 - 41 **Schwartz DA**, Loftus EV, Tremaine WJ, Panaccione R, Harmsen WS, Zinsmeister AR, Sandborn WJ. The natural history of fistulizing Crohn's disease in Olmsted County, Minnesota. *Gastroenterology* 2002; **122**: 875-880 [PMID: 11910338]
 - 42 **Sands BE**, Anderson FH, Bernstein CN, Chey WY, Feagan BG, Fedorak RN, Kamm MA, Korzenik JR, Lashner BA, Onken JE, Rachmilewitz D, Rutgeerts P, Wild G, Wolf DC, Marsters PA, Travers SB, Blank MA, van Deventer SJ. Infliximab maintenance therapy for fistulizing Crohn's disease. *N Engl J Med* 2004; **350**: 876-885 [PMID: 14985485]
 - 43 **Present DH**, Rutgeerts P, Targan S, Hanauer SB, Mayer L, van Hogezaand RA, Podolsky DK, Sands BE, Braakman T, DeWoody KL, Schaible TF, van Deventer SJ. Infliximab for the treatment of fistulas in patients with Crohn's disease. *N Engl J Med* 1999; **340**: 1398-1405 [PMID: 10228190]
 - 44 **Sandborn WJ**, Fazio VW, Feagan BG, Hanauer SB. AGA technical review on perianal Crohn's disease. *Gastroenterology* 2003; **125**: 1508-1530 [PMID: 14598268]
 - 45 **Gecse KB**, Bemelman W, Kamm MA, Stoker J, Khanna R, Ng SC, Panés J, van Assche G, Liu Z, Hart A, Levesque BG, D'Haens G. A global consensus on the classification, diagnosis and multi-disciplinary treatment of perianal fistulising Crohn's disease. *Gut* 2014; **63**: 1381-1392 [PMID: 24951257 DOI: 10.1136/gutjnl-2013-306709]
 - 46 **Shenoy-Bhangle A**, Nimkin K, Goldner D, Bradley WF, Israel EJ, Gee MS. MRI predictors of treatment response for perianal fistulizing Crohn disease in children and young adults. *Pediatr Radiol* 2014; **44**: 23-29 [PMID: 24005981 DOI: 10.1007/s00247-013-2771-5]
 - 47 **Yassin NA**, Askari A, Warusavitarne J, Faiz OD, Athanasiou T, Phillips RK, Hart AL. Systematic review: the combined surgical and medical treatment of fistulising perianal Crohn's disease. *Aliment Pharmacol Ther* 2014; **40**: 741-749 [PMID: 25115149 DOI: 10.1111/apt.12906]
 - 48 **Antakia R**, Shorthouse AJ, Robinson K, Lobo AJ. Combined modality treatment for complex fistulating perianal Crohn's disease. *Colorectal Dis* 2013; **15**: 210-216 [PMID: 22672653 DOI: 10.1111/j.1463-1318.2012.03124.x]
 - 49 **Duff S**, Sagar PM, Rao M, Dolling S, Sprakes M, Hamlin PJ. Infliximab and surgical treatment of complex anal Crohn's disease. *Colorectal Dis* 2012; **14**: 972-976 [PMID: 21899707 DOI: 10.1111/j.1463-1318.2011.02811.x]
 - 50 **El-Gazzaz G**, Hull T, Church JM. Biological immunomodulators improve the healing rate in surgically treated perianal Crohn's fistulas. *Colorectal Dis* 2012; **14**: 1217-1223 [PMID: 22251452 DOI: 10.1111/j.1463-1318.2012.02944.x]
 - 51 **Bouguen G**, Siproudhis L, Gizard E, Wallenhorst T, Billioud V, Bretagne JF, Bigard MA, Peyrin-Biroulet L. Long-term outcome of perianal fistulizing Crohn's disease treated with infliximab. *Clin Gastroenterol Hepatol* 2013; **11**: 975-981.e1-4 [PMID: 23376316 DOI: 10.1016/j.cgh.2012.12.042]
 - 52 **Haennig A**, Staumont G, Lepage B, Faure P, Alric L, Buscail L, Bournet B, Moreau J. The results of seton drainage combined with anti-TNF α therapy for anal fistula in Crohn's disease. *Colorectal Dis* 2015; **17**: 311-319 [PMID: 25425534 DOI: 10.1111/codi.12851]
 - 53 **Tanaka S**, Matsuo K, Sasaki T, Nakano M, Sakai K, Beppu R, Yamashita Y, Maeda K, Aoyagi K. Clinical advantages of combined seton placement and infliximab maintenance therapy for perianal fistulizing Crohn's disease: when and how were the seton drains removed? *Hepatogastroenterology* 2010; **57**: 3-7 [PMID: 20422862]
 - 54 **Dignass A**, Eliakim R, Magro F, Maaser C, Chowers Y, Geboes K, Mantzaris G, Reinisch W, Colombel JF, Vermeire S, Travis S, Lindsay JO, Van Assche G. Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 1: definitions and diagnosis. *J Crohns Colitis* 2012; **6**: 965-990 [PMID: 23040452 DOI: 10.1016/j.crohns.2012.09.003]
 - 55 **Dignass A**, Lindsay JO, Sturm A, Windsor A, Colombel JF, Allez

- M, D'Haens G, D'Hoore A, Mantzaris G, Novacek G, Oresland T, Reinisch W, Sans M, Stange E, Vermeire S, Travis S, Van Assche G. Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 2: current management. *J Crohns Colitis* 2012; **6**: 991-1030 [PMID: 23040451 DOI: 10.1016/j.crohns.2012.09.002]
- 56 **Van Assche G**, Dignass A, Bokemeyer B, Danese S, Gionchetti P, Moser G, Beaugerie L, Gomollón F, Häuser W, Herrlinger K, Oldenburg B, Panes J, Portela F, Rogler G, Stein J, Tilg H, Travis S, Lindsay JO. Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 3: special situations. *J Crohns Colitis* 2013; **7**: 1-33 [PMID: 23040453 DOI: 10.1016/j.crohns.2012.09.005]
- 57 **Reinisch W**, Sandborn WJ, Hommes DW, D'Haens G, Hanauer S, Schreiber S, Panaccione R, Fedorak RN, Tighe MB, Huang B, Kampman W, Lazar A, Thakkar R. Adalimumab for induction of clinical remission in moderately to severely active ulcerative colitis: results of a randomised controlled trial. *Gut* 2011; **60**: 780-787 [PMID: 21209123 DOI: 10.1136/gut.2010.221127]
- 58 **Sandborn WJ**, van Assche G, Reinisch W, Colombel JF, D'Haens G, Wolf DC, Kron M, Tighe MB, Lazar A, Thakkar RB. Adalimumab induces and maintains clinical remission in patients with moderate-to-severe ulcerative colitis. *Gastroenterology* 2012; **142**: 257-265.e1-3 [PMID: 22062358 DOI: 10.1053/j.gastro.2011.10.032]
- 59 **Sandborn WJ**, Feagan BG, Marano C, Zhang H, Strauss R, Johannis J, Adedokun OJ, Guzzo C, Colombel JF, Reinisch W, Gibson PR, Collins J, Järnerot G, Hibi T, Rutgeerts P. Subcutaneous golimumab induces clinical response and remission in patients with moderate-to-severe ulcerative colitis. *Gastroenterology* 2014; **146**: 85-95; quiz e14-15 [PMID: 23735746 DOI: 10.1053/j.gastro.2013.05.048]
- 60 **Sandborn WJ**, Feagan BG, Marano C, Zhang H, Strauss R, Johannis J, Adedokun OJ, Guzzo C, Colombel JF, Reinisch W, Gibson PR, Collins J, Järnerot G, Rutgeerts P. Subcutaneous golimumab maintains clinical response in patients with moderate-to-severe ulcerative colitis. *Gastroenterology* 2014; **146**: 96-109.e1 [PMID: 23770005 DOI: 10.1053/j.gastro.2013.06.010]
- 61 **Sandborn WJ**, Rutgeerts P, Feagan BG, Reinisch W, Olson A, Johannis J, Lu J, Horgan K, Rachmilewitz D, Hanauer SB, Lichtenstein GR, de Villiers WJ, Present D, Sands BE, Colombel JF. Colectomy rate comparison after treatment of ulcerative colitis with placebo or infliximab. *Gastroenterology* 2009; **137**: 1250-1260; quiz 1520 [PMID: 19596014 DOI: 10.1053/j.gastro.2009.06.061]
- 62 **Lopez A**, Ford AC, Colombel JF, Reinisch W, Sandborn WJ, Peyrin-Biroulet L. Efficacy of tumour necrosis factor antagonists on remission, colectomy and hospitalisations in ulcerative colitis: Meta-analysis of placebo-controlled trials. *Dig Liver Dis* 2015; **47**: 356-364 [PMID: 25661014 DOI: 10.1016/j.dld.2015.01.148]
- 63 **Colombel JF**, Rutgeerts P, Reinisch W, Esser D, Wang Y, Lang Y, Marano CW, Strauss R, Oddens BJ, Feagan BG, Hanauer SB, Lichtenstein GR, Present D, Sands BE, Sandborn WJ. Early mucosal healing with infliximab is associated with improved long-term clinical outcomes in ulcerative colitis. *Gastroenterology* 2011; **141**: 1194-1201 [PMID: 21723220 DOI: 10.1053/j.gastro.2011.06.054]
- 64 **Feagan BG**, Sandborn WJ, Lazar A, Thakkar RB, Huang B, Reilly N, Chen N, Yang M, Skup M, Mulani P, Chao J. Adalimumab therapy is associated with reduced risk of hospitalization in patients with ulcerative colitis. *Gastroenterology* 2014; **146**: 110-118.e3 [PMID: 24067881 DOI: 10.1053/j.gastro.2013.09.032]
- 65 **Windsor A**, Michetti P, Bemelman W, Ghosh S. The positioning of colectomy in the treatment of ulcerative colitis in the era of biologic therapy. *Inflamm Bowel Dis* 2013; **19**: 2695-2703 [PMID: 23846487 DOI: 10.1097/MIB.0b013e318292fae6]
- 66 **Kornbluth A**, Sachar DB. Ulcerative colitis practice guidelines in adults: American College Of Gastroenterology, Practice Parameters Committee. *Am J Gastroenterol* 2010; **105**: 501-523; quiz 524 [PMID: 20068560 DOI: 10.1038/ajg.2009.727]
- 67 **Roberts SE**, Williams JG, Yeates D, Goldacre MJ. Mortality in patients with and without colectomy admitted to hospital for ulcerative colitis and Crohn's disease: record linkage studies. *BMJ* 2007; **335**: 1033 [PMID: 17977817]
- 68 **Randall J**, Singh B, Warren BF, Travis SP, Mortensen NJ, George BD. Delayed surgery for acute severe colitis is associated with increased risk of postoperative complications. *Br J Surg* 2010; **97**: 404-409 [PMID: 20101648 DOI: 10.1002/bjs.6874]
- 69 **Gainsbury ML**, Chu DI, Howard LA, Coukos JA, Farraye FA, Stocchi AF, Becker JM. Preoperative infliximab is not associated with an increased risk of short-term postoperative complications after restorative proctocolectomy and ileal pouch-anal anastomosis. *J Gastrointest Surg* 2011; **15**: 397-403 [PMID: 21246415 DOI: 10.1007/s11605-010-1385-6]
- 70 **Ferrante M**, D'Hoore A, Vermeire S, Declerck S, Noman M, Van Assche G, Hoffman I, Rutgeerts P, Penninckx F. Corticosteroids but not infliximab increase short-term postoperative infectious complications in patients with ulcerative colitis. *Inflamm Bowel Dis* 2009; **15**: 1062-1070 [PMID: 19161179 DOI: 10.1002/ibd.20863]
- 71 **Coquet-Reinier B**, Berdah SV, Grimaud JC, Birnbaum D, Cougard PA, Barthet M, Desjeux A, Moutardier V, Brunet C. Preoperative infliximab treatment and postoperative complications after laparoscopic restorative proctocolectomy with ileal pouch-anal anastomosis: a case-matched study. *Surg Endosc* 2010; **24**: 1866-1871 [PMID: 20108148 DOI: 10.1007/s00464-009-0861-0]
- 72 **Mor IJ**, Vogel JD, da Luz Moreira A, Shen B, Hammel J, Remzi FH. Infliximab in ulcerative colitis is associated with an increased risk of postoperative complications after restorative proctocolectomy. *Dis Colon Rectum* 2008; **51**: 1202-1207; discussion 1207-1210 [PMID: 18536964 DOI: 10.1007/s10350-008-9364-7]
- 73 **Yang Z**, Wu Q, Wu K, Fan D. Meta-analysis: pre-operative infliximab treatment and short-term post-operative complications in patients with ulcerative colitis. *Aliment Pharmacol Ther* 2010; **31**: 486-492 [PMID: 19925496 DOI: 10.1111/j.1365-2036.2009.04204.x]
- 74 **Bregnbak D**, Mortensen C, Bendtsen F. Infliximab and complications after colectomy in patients with ulcerative colitis. *J Crohns Colitis* 2012; **6**: 281-286 [PMID: 22405163 DOI: 10.1016/j.crohns.2011.08.014]
- 75 **Selvaggi F**, Pellino G, Canonico S, Sciaudone G. Effect of preoperative biologic drugs on complications and function after restorative proctocolectomy with primary ileal pouch formation: systematic review and meta-analysis. *Inflamm Bowel Dis* 2015; **21**: 79-92 [PMID: 25517596 DOI: 10.1097/MIB.0000000000000232]
- 76 **Uchino M**, Ikeuchi H, Matsuoka H, Bando T, Ichiki K, Nakajima K, Tomita N, Takesue Y. Infliximab administration prior to surgery does not increase surgical site infections in patients with ulcerative colitis. *Int J Colorectal Dis* 2013; **28**: 1295-1306 [PMID: 23604447 DOI: 10.1007/s00384-013-1700-2]

P- Reviewer: Actis GC, Decorti G, Hokama A **S- Editor:** Qiu S

L- Editor: A **E- Editor:** Liu SQ





Published by **Baishideng Publishing Group Inc**

8226 Regency Drive, Pleasanton, CA 94588, USA

Telephone: +1-925-223-8242

Fax: +1-925-223-8243

E-mail: bpgoffice@wjgnet.com

Help Desk: <http://www.wjgnet.com/esps/helpdesk.aspx>

<http://www.wjgnet.com>

