IBD TREATMENTS

IBD TREATMENTS

TREATMENT GOALS

Treatment of inflammatory bowel disease (IBD) involves a three-step approach:

1. INDUCE REMISSION OF SYMPTOMS

Treatment relieves acute symptoms, such as diarrhoea, abdominal pain, rectal bleeding and fever, and reduces inflammation, allowing intestinal tissue to heal. Once symptoms have been resolved, patients may gain weight and experience significant improvement in their level of fatigue and quality of life.

2. MAINTAIN REMISSION OF SYMPTOMS

Once symptoms are brought under control, patients typically remain on medication to suppress intestinal inflammation and maintain healing. This prevents disease flares and limits disease progression.

3. PREVENTION OF COMPLICATIONS

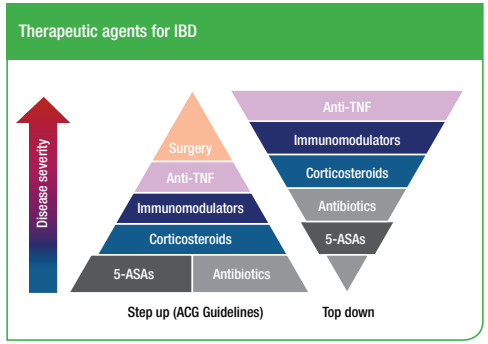
Medications need to keep inflammation tightly controlled, even when no symptoms are present, to avoid the narrowing of the digestive tract (stenoses), abscesses and abnormal connections between the anal canal and the perianal skin (fistulae). Surgery may be required to resolve some of these complications.

PHARMACEUTICAL TREATMENT OF IBD

Every patient with IBD is different, so their treatment needs to be tailored to treat their individual disease and to suit their own preferences. Several classes of pharmaceuticals are used to treat IBD. The most frequently used medications are discussed below; however, other treatment options may also be considered.

AMINOSALICYLATES

Mesalamine, ozalazine, balsalazide and sulfasalazine are drugs that have 5-aminosalicylic acid (5-ASA) as their active ingredient and are often used as first-line treatment for inducing and maintaining symptom remission in mild-to-moderately active ulcerative colitis (UC).[1] Their effectiveness in inducing and maintaining remission in active Crohn's disease (CD) has not been clearly established,[2] although they may be of benefit in preventing relapse of CD following surgery.[3]



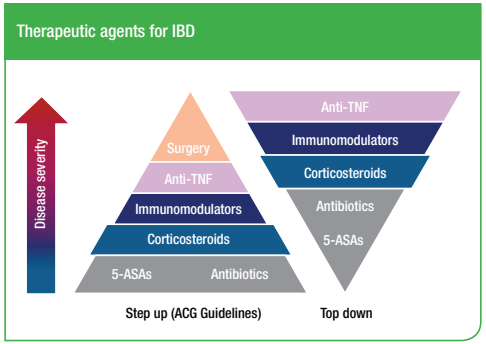
Side effects of 5-ASA agents include headache, anorexia, nausea, vomiting, heartburn, inflammation of the pancreas and a variety of hypersensitivity reactions. In rare cases, it has been reported that they can impair kidney function and affect the production of blood cells.

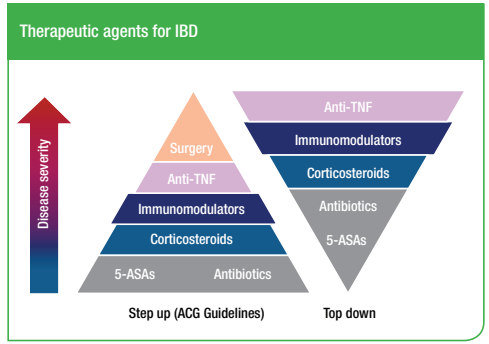
Different formulations of 5-ASA agents are available to minimise adverse effects including enteric-coated tablets (which do not dissolve until they pass through the stomach), enemas and suppositories.

CORTICOSTEROIDS

Corticosteroids (e.g. budesonide, prednisolone, prednisone, dexamethasone, hydrocortisone and methylprednisolone) reduce inflammation and suppress the body's immune system. They are considered the primary therapy treating flare-ups in moderate-to-severe and fulminant UC and moderate-to-severe active CD.[4] However, they are not effective at maintaining long-term remission and should be used only in planned short courses.[5]

Side effects of corticosteroids include fluid retention, weight gain, acne, insomnia, tremors, night sweats and emotional disturbances. Other serious effects include elevated blood pressure, osteoporosis and psychosis. Long-term use can cause cataracts and glaucoma. Due to their side-effect profile, the corticosteroid dose should





be gradually reduced within no more than 4 weeks of starting treatment and the drug discontinued once clinical remission has been induced.[5]

Corticosteroids can be given orally, intravenously or rectally, depending on the location and severity of the inflammation.

IMMUNOMODULATORS

Immunomodulators such as azathioprine (AZA) and 6-mercaptopurine (6-MP) suppress the immune system and are used to maintain remission in patients with UC6 and induce and maintain remission in patients with CD.[7,8] In CD, they may also be used in combination with anti-tumour necrosis factor (TNF) agents to increase response rates and prolong the duration of benefit[9,10] (refer to the following section on Anti-TNF agents).

Common side effects of AZA and 6-MP include nausea, vomiting, fatigue, liver inflammation and increased sensitivity of the skin to sunlight. They may also cause pancreatitis, in which case the drug must be stopped. For this reason, and because of the risk of immunosuppression due to a reduction in circulating white blood cells, regular blood tests are required for all patients receiving these drugs. It should also be noted that these drugs are associated with a small but definite increased risk of skin cancers and lymphoma.[11,12]

Methotrexate is an alternative immunomodulator to AZA and 6-MP for patients with CD. Trials to assess its benefit in UC are ongoing. As methotrexate can cause liver inflammation and fibrosis of the lungs, careful monitoring is required. Other immunomodulators include ciclosporin, tacrolimus and mycophenolate mofetil.

ANTIBIOTICS

In CD, antibiotics are used to treat bacterial overgrowth in the small intestine, abscesses and fistulas and may also be used to treat intestinal inflammation itself, although the evidence to support their use in this setting alone is weak.[13] Frequently used antibiotics include metronidazole, ciprofloxacin and rifaximim.

Antibiotics do not have a role in the management of UC, unless there is an infection, such as Clostridium difficile.

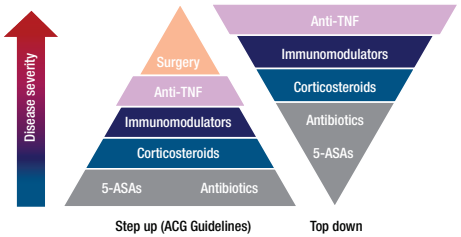
ANTI-TNF AGENTS (BIOLOGICS)

Adalimumab and infliximab are agents that block the action of TNF-alpha, a potent molecule involved in the intestinal inflammation and damage inherent to IBD.They are approved for the treatment of moderate-to-severe CD and UC in patients who have failed conventional immunomodulators and corticosteroids.

Anti-TNF agents are associated with an increased risk of serious infections such as tuberculosis or other infections caused by viruses, fungi or bacteria that have spread throughout the body. Other serious adverse events can be associated with anti-TNF agents. Patients should speak with their doctor to fully understanding the benefit risk profile of anti-TNF agents.

Anti-TNF agents have been shown to induce and maintain remission of symptoms and heal the lining of the digestive tract in CD[9,10,14–16] and UC.[17–20] This reduces the need for surgery and hospitalisation, as well as improving patients' quality of life.[21–24]

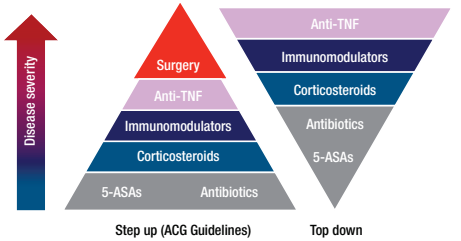
Therapeutic agents for IBD



Anti-TNF agents are more effective when used early in the course of the disease before complications, such as stenoses and abscesses, have occurred. Furthermore, they may be more effective when given together with AZA or 6-MP therapy.[9,10] Adalimumab is administered as an injection under the skin and infliximab is administered as an intravenous infusion. They should be given as a planned course and not simply in response to symptoms.

SURGERY FOR IBD

Therapeutic agents for IBD



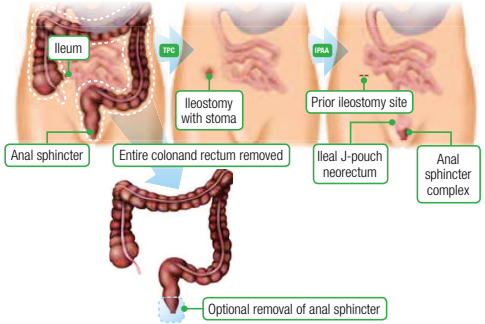
ULCERATIVE COLITIS

Surgery to remove part of the large bowel (colectomy) may be required in patients with UC, particularly those with a poor response to long-term medical treatment, emergency complications (such as toxic or fulminant colitis in which the colon becomes dilated, life-threatening hemorrhage and intestinal perforation) or colonic dysplasia (an early sign of bowel cancer).

The goal of surgery for UC is to cure the disease with as little alteration of normal physiological functions and lifestyle as possible.

The most common procedures are:

- **Total proctocolectomy with ileostomy:**
  the whole large intestine is removed, together with the rectum and anal canal. The end of the small intestine is then brought out through an opening in the skin of the abdominal wall, creating a stoma or ileostomy. An external bag is fitted to the stoma to collect digestive waste.



- **Subtotal colectomy and ileal pouch anal anastomosis (IPAA or pouch surgery):**
  the whole large intestine and rectum are removed, but the anus is retained. A pouch is then made with the end of the small intestine, which is joined to the anus. It is usual for a temporary stoma to be created to divert the flow of digestive waste and allow the pouch to heal.

The choice of operation is based on an assessment of the benefits and risks of each procedure in the individual patient and includes consideration of the reason for surgery, patient age, associated medical conditions and the presence of malignancy.

CROHN'S DISEASE

Surgery is generally reserved for patients with CD who have complications such as obstruction, stricture, abscess or fistulae, or if the disease does not respond to pharmacological therapy. In general, the surgeon will aim to remove as little bowel as possible as surgery is not a cure for the disease.

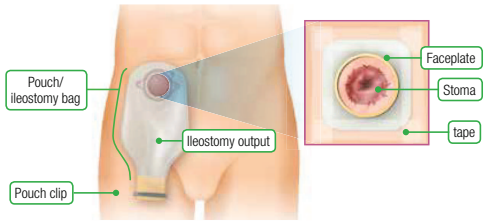
The most common procedures are:

- **Resection and anastomosis:**
  this procedure is used in patients with strictures and severe or penetrating inflammation of the bowel or who have a perforated bowel. The diseased section of the bowel is removed and the healthy ends reattached (anastomosis). However, disease often recurs near the site of anastomosis.
- **Strictureplasty:**
  patients with tight simple narrowings of the bowel (strictures) that do not respond to medical treatment may undergo this procedure, which opens the narrowed area and reshapes it without removing any part of the intestine.
- **Perianal drainage:**
  patients with perianal disease often require surgery to drain sepsis. Often a thin thread (seton) is left in place to aid drainage of pus while medical therapy and antibiotics are started.

SURGICAL COMPLICATIONS

Postoperative surgical complications include dehydration, adhesion formation, small-bowel obstruction, intra-abdominal infections, sexual dysfunction, and impaired fertility in women.

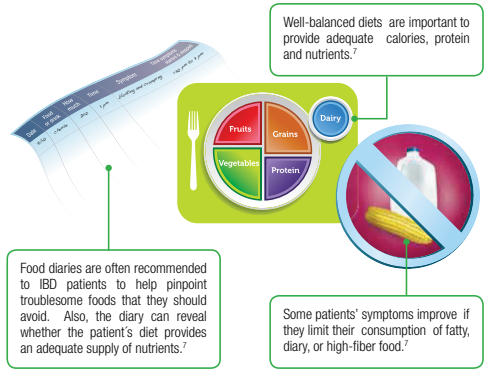
Pouchitis, or inflammation of the ileal pouch due to bacterial overgrowth, is a common complication of the IPAA procedure and will present with increased stool frequency and urgency, as well as abdominal or pelvic pain. It is often easily treated with a course of antibiotics. Cuffitis, or inflammation of the residual rectal cuff, is another inflammatory complication associated with the IPAA procedure.



NUTRITIONAL SUPPORT

Nutritional support is an essential part of the management of all patients with IBD who have lost weight or become nutrient-deficient.

The most common nutrient deficiency among IBD patients is iron deficiency, which causes anemia and may result in fatigue and reduced quality of life. Iron can be replaced with iron tablets (if tolerated) or an iron infusion.



Patients with IBD may also find that some food types increase their symptoms. This is likely to reflect fermentation of the food rather than worsening of the disease, but it may be helped by removing some foods from the diet. This should always be done with the support of a dietitian to ensure that the diet remains balanced with appropriate calories.

A specific liquid-only diet can be used to induce remission in children (and some adults) with CD affecting the small bowel. This has the advantage of avoiding the side effects associated with corticosteroids.

A NEW & EVOLVING TREATMENT APPROACH TO IBD

A NEW & EVOLVING TREATMENT APPROACH TO IBD

Ongoing inflammation of the digestive tract in patients with IBD results in cumulative tissue damage that can lead to stenoses and fistulae. This increases the likelihood that the patient will require surgery and become progressively more disabled.

Management of IBD involves appropriate and timely use of pharmaceutical treatments, monitoring of patients and early identification of complications.

Important principles in treating IBD are outlined below:[25,26]

OPTIMISE CONVENTIONAL TREATMENT QUICKLY

Patients should receive aminosalicylates or immunomodulators early in the disease course to promote tissue healing and allow corticosteroid use to be limited.

Patients may receive corticosteroids to treat a disease flare-up; however, the toxicity of these agents makes them unsuitable for long-term use. Therefore it is important that the dose of these drugs is quickly tapered and the patient to able to achieve corticosteroid-free remission.

TREAT EFFECTIVELY, EARLY IN THE DISEASE COURSE

It is important to get inflammation under control early in the disease course to avoid corticosteroids and their potential complications, allow the lining of the digestive tract to heal and alter the natural destructive course of the disease.

STEP UP TREATMENT TO ANTI-TNF THERAPY EARLY IF REQUIRED

Anti-TNF treatment should be initiated without delay if patients are not responding to conventional immunosuppressives or corticosteroids, or who are steroid-refractory, -dependent or –intolerant.

If one anti-TNF agent is not tolerated or is not effective, then the patient may be switched to an alternative anti-TNF agent.

TREAT BEYOND SYMPTOMS

Inflammation and lesions in the digestive tract can continue to persist, even in patients without any symptoms. It is becoming increasingly recognised that the long-term prognosis is improved in those patients who have healing of inflammation in their digestive tract – known as deep remission – as well as resolution of symptoms.[27]

TREAT TO TARGET

Disease location and activity varies considerably among patients; therefore, there is no "one size fits all" strategy for treating patients with IBD. Instead, management needs to be adapted to match the patient's individual disease activity, with clear targets for treatment.

Treating to target involves regular assessment of the patient, together with regular review of medicine dose or medicine type to ensure that clinical symptoms and underlying inflammation remain tightly controlled.

MONITOR PATIENTS REGULARLY

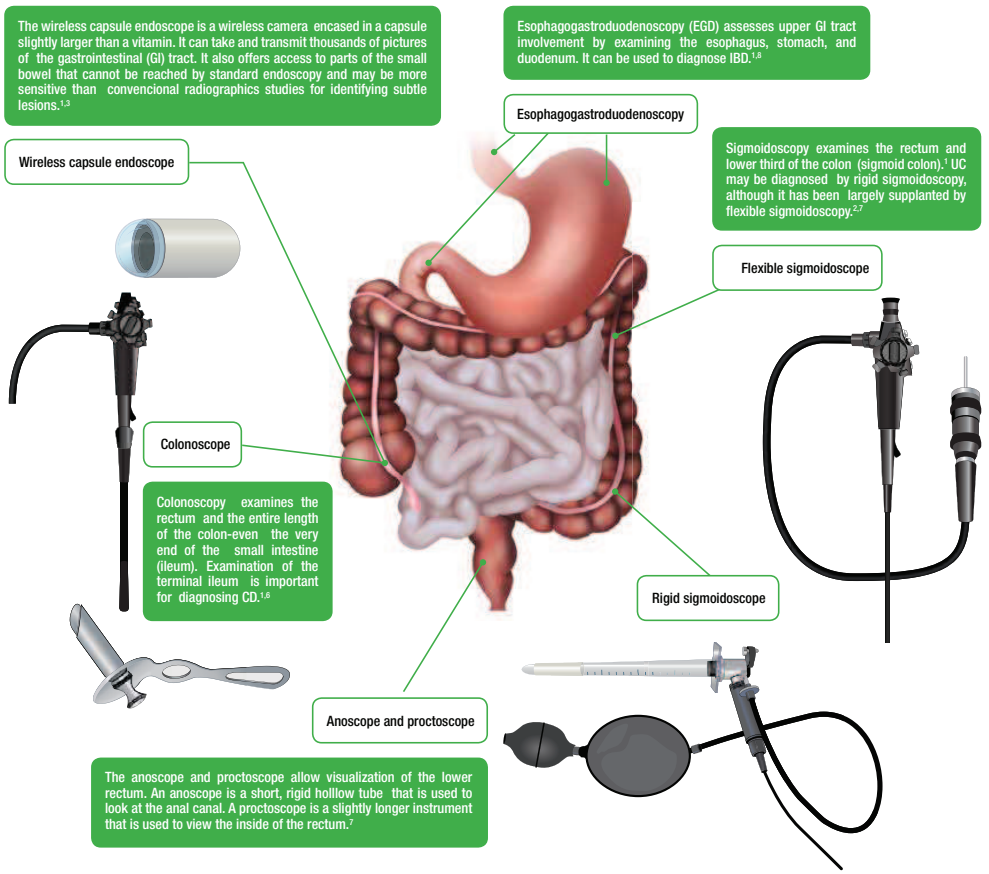
Patients with IBD need to undergo regular monitoring to assess their symptoms, measure their degree of intestinal inflammation and check for any complications.

Symptom severity can be assessed by tools and questionnaires, such as the Crohn's Disease Activity Index, the Harvey–Bradshaw Index and the Inflammatory Bowel Disease Questionnaire. These tools also allow an assessment of the patient's general well-being and quality of life and are often used in clinical trials of medical therapy for IBD.

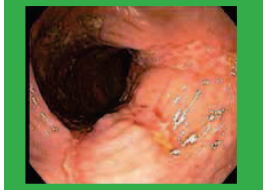
Endoscopy (the insertion of a thin tube with a light and camera into the digestive tract to allow visualisation of the inside of the tract) enables the physician to determine the extent of inflammation and tissue damage due to disease.

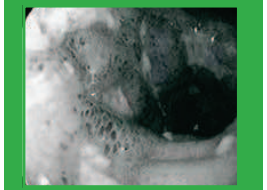
Imaging, such as magnetic resonance imaging and ultrasonography, is an important tool for determining disease severity and extent, assessing treatment effects and ruling out complications such as strictures and abscesses.

Biomarkers are substances in the blood or stool that can reflect the presence of inflammation that may be due to IBD. Regular monitoring of these markers is a non-invasive way of alerting the physician to any disease activity.



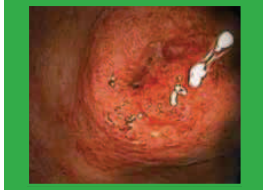
Endoscopic findings in CD

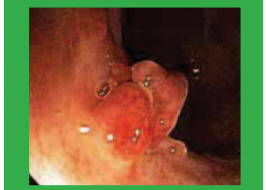




- Longitudinal Crohn's ulcer with normal surrounding mucosa; CD ulcers are characteristically discrete, with normal tissue between the ulcers, whereas UC ulcers are diffuse.[9]
- A cobblestone appearance with submucosal hemorrhages and deep linear ulcers; the cobblestone appearance most frequently occurs in the small bowel.[5,10]

Endoscopic findings in UC





- Mucosal friability (hemorrhage from the mucosa) with superficial ulceration of the rectosigmoid colon;9 friability is often associated with course granularity due to mucosal redness (erythema) and edema.[4]
- Pseudopolyps in active UC; they also are found in inactive UC.[9]

PATIENT–PHYSICIAN COMMUNICATION

It is important that treatment goals are understood and agreed by patients so that they feel that they play a role in medical decisions and continue to take the treatment prescribed for them.

Physicians need to explain to patients that symptom relief is not necessarily an indication that treatment is no longer required. Many patients will have to continue taking medication to remain symptom free and to allow inflammation to remain controlled.

It is important that patients have realistic expectations of treatment. For some patients with early disease, their symptoms may be resolved quickly and disease flare-ups may be infrequent; however, if the disease is already in a late stage, existing damage could be too severe to reverse and symptoms may persist.

REFERENCES

1. Ford AC, Achkar JP, Khan KJ, et al. Efficacy of 5-aminosalicylates in ulcerative colitis: systematic review and meta-analysis. Am J Gastroenterol 2011;106:601–16.
2. Ford AC, Kane SV, Khan KJ, et al. Efficacy of 5-aminosalicylates in Crohn's disease: systematic review and meta-analysis. Am J Gastroenterol 2011;106:617–29.
3. Ford AC, Khan KJ, Talley NJ, et al. 5-aminosalicylates prevent relapse of Crohn's disease after surgically induced remission: systematic review and meta-analysis. Am J Gastroenterol 2011;106:413–20.
4. Ford AC, Bernstein CN, Khan KJ, et al. Glucocorticosteroid therapy in inflammatory bowel disease: systematic review and meta-analysis. Am J Gastroenterol 2011;106:590–9.
5. Ferrante M, Karmiris K, Newnham E, et al. Physician perspectives on unresolved issues in the use of conventional therapy in Crohn's disease: results from an international survey and discussion programme. J Crohns Colitis 2012;6:116–31.
6. Gisbert JP, Linares PM, McNicholl AG, et al. Meta-analysis: the efficacy of azathioprine and mercaptopurine in ulcerative colitis. Aliment Pharmacol Ther 2009;30:126–37.
7. Prefontaine E, Macdonald JK, Sutherland LR. Azathioprine or 6-mercaptopurine for induction of remission in Crohn's disease. Cochrane Database Syst Rev 2010:CD000545.
8. Prefontaine E, Sutherland LR, Macdonald JK, et al. Azathioprine or 6-mercaptopurine for maintenance of remission in Crohn's disease. Cochrane Database Syst Rev 2009:CD000067.
9. Colombel JF, Sandborn WJ, Reinisch W, et al. Infliximab, azathioprine, or combination therapy for Crohn's disease. N Engl J Med 2010;362:1383–95.
10. Colombel JF, Sandborn WJ, Rutgeerts P, et al. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. Gastroenterology 2007;132:52–65.
11. Herrinton LJ, Liu L, Weng X, et al. Role of thiopurine and anti-TNF therapy in lymphoma in inflammatory bowel disease. Am J Gastroenterol 2011;106:2146–53.
12. Peyrin-Biroulet L, Khosrotehrani K, Carrat F, et al. Increased risk for nonmelanoma skin cancers in patients who receive thiopurines for inflammatory bowel disease. Gastroenterology 2011;141:1621–28 e1–5.
13. Khan KJ, Ullman TA, Ford AC, et al. Antibiotic therapy in inflammatory bowel disease: a systematic review and meta-analysis. Am J Gastroenterol 2011;106:661–73.
14. Rutgeerts P, Van Assche G, Sandborn WJ, et al. Adalimumab induces and maintains mucosal healing in patients with Crohn's disease: data from the EXTEND trial. Gastroenterology 2012;142:1102–1111 e2.
15. Rutgeerts P, Feagan BG, Lichtenstein GR, et al. Comparison of scheduled and episodic treatment strategies of infliximab in Crohn's disease. Gastroenterology 2004;126:402–13.
16. Hanauer SB, Sandborn WJ, Rutgeerts P, et al. Human anti-tumor necrosis factor monoclonal antibody (adalimumab) in Crohn's disease: the CLASSIC-I trial. Gastroenterology 2006;130:323–33.
17. Sandborn WJ, van Assche G, Reinisch W, et al. Adalimumab induces and maintains clinical remission in patients with moderate-to-severe ulcerative colitis. Gastroenterology 2012;142:257–65 e1–3.
18. Reinisch W, Sandborn WJ, Hommes DW, et al. Adalimumab for induction of clinical remission in moderately to severely active ulcerative colitis: results of a randomised controlled trial. Gut 2011;60:780–7.
19. Rutgeerts P, Sandborn WJ, Feagan BG, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. N Engl J Med 2005;353:2462–76.
20. Sandborn WJ, Rutgeerts P, Feagan BG, et al. Colectomy rate comparison after treatment of ulcerative colitis with placebo or infliximab. Gastroenterology 2009;137:1250–60.
21. Lichtenstein GR, Yan S, Bala M, et al. Infliximab maintenance treatment reduces hospitalizations, surgeries, and procedures in fistulizing Crohn's disease. Gastroenterology 2005;128:862–9.
22. Feagan BG, Panaccione R, Sandborn WJ, et al. Effects of adalimumab therapy on incidence of hospitalization and surgery in Crohn's disease: results from the CHARM study. Gastroenterology 2008;135:1493–9.
23. Lichtenstein GR, Yan S, Bala M, et al. Remission in patients with Crohn's disease is associated with improvement in employment and quality of life and a decrease in hospitalizations and surgeries. Am J Gastroenterol 2004;99:91–6.
24. Lofberg R, Louis EV, Reinisch W, et al. Adalimumab produces clinical remission and reduces extraintestinal manifestations in Crohn's disease: results from CARE. Inflamm Bowel Dis 2012;18:1–9.
25. Dignass A, Van Assche G, Lindsay JO, et al. The second European evidence-based Consensus on the diagnosis and management of Crohn's disease: Current management. J Crohns Colitis 2010;4:28–62.
26. Dignass A, Lindsay JO, Sturm A, et al. Second European evidence-based consensus on the diagnosis and management of ulcerative colitis Part 2: Current management. J Crohns Colitis 2012.
27. De Cruz P, Kamm MA, Prideaux L, et al. Mucosal healing in Crohn's disease: A systematic review. Inflamm Bowel Dis 2012.