PO Box 2345, Beijing 100023, China
www.wjgnet.com
wjg@wjgnet.com

World J Gastroenterol 2006 August 14; 12(30): 4794-4806
World Journal of Gastroenterology ISSN 1007-9327

TOPIC HIGHLIGHT

Paolo Gionchetti, MD, *Series Editor*

Conventional therapy for Crohn's disease

Carsten Büning, Herbert Lochs

Carsten Büning, Herbert Lochs, Department of Gastroenterology, Hepatology & Endocrinology, Charité Campus Mitte, Universitätsmedizin Berlin, Berlin, Germany
Correspondence to: Carsten Büning, MD, Department of Gastroenterology, Hepatology & Endocrinology, Charité Campus Mitte, Universitätsmedizin Berlin, Schumannstrasse 20/21, Berlin 10117, Germany. carsten.buening@charite.de
Telephone: +49-30-450614237 Fax: +49-30-450514906
Received: 2006-02-17 Accepted: 2006-03-10

Abstract

Crohn's disease (CD) is a multifactorial disorder of unknown cause. Outstanding progress regarding the pathophysiology of CD has led to the development of innovative therapeutic concepts. Numerous controlled trials have been performed in CD over the last years. However, many drugs have not been approved by regulatory authorities due to lack of efficacy or severe side effects. Therefore, well-known drugs, including 5-ASA, systemic or topical corticosteroids, and immunosuppressants such as azathioprine, are still the mainstay of CD therapy. Importantly, biologicals such as infliximab have shown to be efficacious in problematic settings such as fistulizing or steroid-dependent CD. This review is intended to give practical guidelines to clinicians for the conventional treatment of CD. We concentrated on the results of randomized, placebo-controlled trials and meta-analyses, when available, that provide the highest degree of evidence. We provide evidence-based treatment algorithms whenever possible. However, many clinical situations have not been answered by controlled clinical trials and it is important to fill these gaps through expert opinions. We hope that this review offers a useful tool for clinicians in the challenging treatment of CD.

Key words: Crohn's disease; Conventional treatment; Review; Therapy

Büning C, Lochs H. Conventional therapy for Crohn's disease. *World J Gastroenterol* 2006; 12(30): 4794-4806

http://www.wjgnet.com/1007-9327/12/4794.asp

INTRODUCTION

Crohn's disease (CD) is a chronic bowel disease characterised by a relapsing inflammatory process. It can affect any part of the gastrointestinal tract and is associated with discontinuous, transmural lesions of the gut wall. The current working hypothesis suggests that CD results from an aberrant immune response towards fecal bacteria in a genetically susceptible host[1].

While medical treatment of the acute flare is successful in most patients, one of the most difficult tasks in general medicine is to treat complications such as strictures, abscesses, fistulae and chronic disease activity. In this review, we describe the conventional treatment of CD depending on different clinical situations, such as an acute flare, maintenance of remission, fistulizing or chronically active disease behaviour.

Apart from the below discussed medical and surgical treatment of CD, other factors including changes in lifestyle should be recommended. Herein, probably the most important aspect is smoking cessation. Smoking has shown to be a risk factor for CD relapse after medically or surgically induced remission[2] and is associated with the need for higher doses of corticosteroids and immunosuppressants[3]. Importantly, a prospective trial showed that only one year of smoking cessation leads to a more benign course of disease with a lower rate of relapses[4]. This trial also showed that the ability to quit smoking clearly depended on the physician's role. So the conventional treatment of CD should start, if neccessary, with convincing the patient to quit smoking.

ACTIVE DISEASE

Definition

The activity of CD can be assessed clinically, endoscopically or by other indices[5]. The most established way is through the BEST activity index (CDAI), where symptoms and objective criteria such as anemia and body weight are included[6]. Index values of 150 and below are associated with quiescent disease; values above that indicate active disease, and values above 450 are seen with extremely severe disease. In addition other diagnostic values such as blood sedimentation rate, C-reactive protein (CRP) and thrombocytes should also be taken into account. Endoscopic inflammatory evaluation, however, is not necessary in every exacerbation of the disease but might offer important information with respect to disease localisation. This is especially important for the use of topically acting agents such as budesonide in terminal ileal or right colonic CD. Exacerbation of CD through infectious agents should always be considered and

Table 1 Drugs for the treatment of CD

Drug	5-ASA (mesalamine or sulfasalazine)
Dosage	3.2-4 g/d
Indications	Mild to moderately active disease, postoperative maintenance
Important side effects	Headache, nausea and abdominal pain, often during treatment with sulfasalazine (in up to 45% of patients); thrombopenia; interstitial nephitis, pancreatitis;
Monitoring	Liver function, full blood count and especially renal function
Pregnancy	Suggested to be safe in conventional doses

excluded if possible.

In addition, the American College of Gastroenterology has defined the different disease activities in clinical practise as follows[7]: mild to moderately active disease is defined as "ambulatory patients able to tolerate oral alimentation without manifestation of dehydration, toxicity (high fevers, rigors, prostration), abdominal tenderness, painful mass, obstruction or > 10% weight loss. In contrast, moderate to severe disease applies to patients that have failed to respond to treatment for mild to moderate disease or those with more prominent symptoms such as fever, significant weight loss, abdominal pain or tenderness, intermittent nausea or vomiting (without obstructive findings), or significant anemia. Severe disease refers to patients with persisting symptoms despite the introduction of steroids as outpatients, or individuals presenting with high fever, persistent vomiting, evidence of intestinal obstruction, rebound tenderness, cachexia, or evidence of an abscess.

5-ASA

No debate has been as longstanding and controversial as whether the use of 5-ASA containing drugs in CD is justified or not. Numerous studies regarding this aspect have been performed over the last 25 years. However, data from current studies do not clearly support either point of view. Different study designs and drug dosages have been used that make comparison of the results rather difficult.

Sulfasalazine is the original compound in this class consisting of 5-ASA linked by an azo-bond to sulfapyridine, which is split off in the colon. Therefore efficacy of sulfasalazine was expected to be limited to colonic disease. Furthermore up to 50% of patients are not able to tolerate sulfasalazine due to nausea, headache, vomiting and epigastric pain. These side effects are suggested to be caused by the sulfapyridine moiety. Therefore, other 5-ASA formulations (mesalamine formulations and the pro-drugs olsalazine and balsalazide) without sulfapyridine have been introduced into the market with different pharmacodynamic and pharmacokinetic profiles (Table 1). These different preparations are therefore suggested to be non-interchangeable.

Sulfasalazine: Sulfasalzine has been shown to be significantly better than placebo in randomized clinical trials in inducing remission in active CD[8-10]. Subgroup analyses suggested that patients with only colonic disease seem to benefit the most from sulfasalazine therapy[8,9], whereas patients treated previously with prednisone failed to respond[8]. Sulfasalazine has not shown to have steroid-sparing properties[9,11]. Since 5-ASA was identified to be the active moiety in sulfasalazine, other 5-ASA containing formulations (such as mesalamine) have been tested in CD.

Mesalamine: Different pharmacological preparations allow relase of the active drug in different parts of the intestine. Therefore mesalamine, in contrast to sulfasalazine, may also be used in CD including small bowel CD. However, studies on the induction of remission in active CD with mesalamine yielded conflicting results. In total, six placebo-controlled trials with varying dosages of mesalamine have been performed to date. Two earlier studies did not detect a benefit of mesalamine over placebo in inducing remission[12,13]. Tremaine and colleagues observed a significantly greater number of patients that responded (defined as either a decrease of CDAI $\geqslant$ 70 or CDAI < 150), but this benefit was rather small (9 patients with mesalamine treatment *vs* 4 patients in the placebo group). However, no significant differences were found when clinical remission (defined as CDAI < 150) was analyzed[14]. Singleton and colleagues conducted three different trials with mesalamine (Pentasa) that were recently combined in a meta-analysis although two of the three trials were never published in full[15]. This analysis found a statistically significant benefit of mesalamine over placebo. However, this benefit was rather small (CDAI reduction of 18 points for the intention-to-treat-analysis).

In summary the clinical benefit of mesalamine in the treatment of active CD seems to be rather low. However, mesalamine is well tolerated and has a favourable side effect profile compared to sulfasalazine. The latter factor is probably the main reason why mesalamine is significantly used more often compared to sulfasalazine although data from randomized trials are in favor of sulfasalazine. Furthermore, many patients with mild to moderately active disease try a more harmless drug at first before taking corticosteroids.

Budesonide

The introduction of the topically-acting steroid budesonide has become a very potent alternative in the treatment of patients with CD located in the terminal ileum or right colon. Due to rapid metabolism by cytochrome P-450 enzymes in the liver, budesonide has less sytemic bioavailibility than systemic corticosteroids. A recent meta-analysis combined the data from 5 published studies investigating budesonide in comparison to placebo, 5-ASA and systemic corticosteroids[16]. A significant advantage of budesonide in inducing remission was observed in comparison to placebo (odds ratio of 1.85) and mesalamine (odds ratio of 1.73). Accordingly, a patient is 73% more likely to achieve remission with budesonide than mesalamine. Corticosteroids induced remission even more often as compared to budesonide with an odds ratio of 0.87, but in patients with mild and moderate disease (CDAI 200-300), no difference in remission rates was found. Treatment with budesonide was associated with similar side effects compared to mesalamine and placebo. Importantly, fewer side effects, such as acne, moon face

Table 2 Drugs for the treatment of CD

Drug	Systemicorticosteroids (prednisone equivalent) or budesonide
Dosage	Corticosteroids: 30-60 mg/d or 1-1.5 mg/kg per day; Budesonide: 9 mg
Indications	Corticosteroids: moderate to severe disease. Budesonide: terminal ileal and right colonic disease in mild to moderate disease, low dose budesonide eventually for maintenace therapy
Important side effects	Weight gain, hypertension, fluid retention, myopathy, mood changes, infections, glaucoma, skin changes including acne, adrenal suppresion. Long term side effects: osteoporosis, cataract, aseptic bone necrosis
Pregnancy	Lower doses seem to be relatively safe
Comments	Avoid long-term use

Table 3 Drugs for the treatment of CD

Drug	Azathioprine (6-mercaptopurine)
Dosage	2-2.5 mg/kg (1-1.5 mg/kg)
Indications	Maintenance, chronically active disease, steroid-refractory and steroid-dependency, fistulae, concomittant therapy with infliximab;
Important side effects	Pancreatitis, bone marrow supression, allergic reactions, drug heptatitis, nausea, malaise, bacterial and viral infections; in patients intolerant to azathioprine due to gastrointestinal symptoms, 6-mercaptopurine is suggested (not in side effects such as pancreatitis and bone marrow suppression)
Monitoring	Liver function, lipase and full blood count biweekly for the first three months, if normal then every three months throughout therapy
Pregnancy	Should be avoided, although available studies suggest a potential use especially in patients where maintaining remission is essential
Comments	Entire therapeutic efficacy is observed mostly after 2-4 mo; consider testing for thiopurine methyltransferase (TPMT) genotypes to identify patients with high-risk of bone marrow suppression; consider metabolite monitoring for adaequate dosing; ensure adequate birth control; allow 3 mo time before pregnancy or conceiving

and osteoporosis, were observed compared to systemic corticosteroids. The recommended dose of budesonide is 9 mg/d and should be tapered 3 mg every 2-4 wk unless a maintenance therapy with budesonide is suggested (see below).

Systemic corticosteroids

For moderate to severe CD, and especially if therapy with 5-ASA has failed, systemic corticosteroids are the treatment of choice (Table 2). Corticosteroids are fast and effective and induce remission in approximately 70% of patients. In active CD, corticosteroids have been shown to be superior to sulfasalazine, azathioprine and placebo[8,9]. No dose finding studies have yet been performed. Reported doses range from 30 mg/d to 1 mg/kg per day, however most clinicians start with 60 mg/d, although it seems to be favourable to apply a body weight dependent dosage (1 mg/kg). Tapering should be performed according to improvement of clinical symptoms and is usually done in steps of 5-10 mg/wk. At lower dosages, tapering might be reduced to 2.5-5 mg/wk. Whether i.v. application has an advantage over oral in severe acute flares is not clear, although it is frequently used when oral treatment has not been effective.

Table 4 Drugs for the treatment of CD

Drug	Methotrexate
Dosage	25 mg/wk i.m., if remission is achieved reduce to 15 i.m. (or s.c.)
Indications	Maintenance, chronically active disease, steroid-refractory and steroid-dependency, fistulae
Important side effects	Nausea, abdominal pain, diarrhea, stomatitis; hepatitis, liver fibrosis; hypersensivity pneumonitis
Monitoring	Liver function and full blood count monthly for the first two months, if normal then every two months throughout therapy
Pregnancy	Strictly prohibited
Comments	Entire therapeutic efficacy is observed mostly after 2-4 mo; consider folic acid supplementation with 2.5-5 mg/d; ensure adequate birth control; allow 3 mo time before pregnancy or conceiving

Azathioprine/6-Mercaptopurine

The most common-ly used immunomodulators are the thiopurines, 6-mercaptopurine and its prodrug azathioprine (Table 3). Numerous clinical trials studied the efficacy of these immunomodulators in active CD. The most convincing data were obtained in the early trial by Present and colleagues where 67% *vs* 8% of the patients in the 6-mercaptopurine group *vs* placebo, respectively, achieved remission[17]. However, other trials did not observe a significant difference in the use of azathioprine compared to placebo[8,18]. Despite these conflicting data, a meta-analysis reported an odds ratio of 3.09 favoring azathioprine/6-mercaptopurine therapy over placebo[19] to induce remission. In addition, a recent Cochrane analysis reported an overall response in active CD of 54% *vs* 33% for azathioprine *vs* placebo, respectively[20].

Thiopurines are slow acting drugs and an effect can be observed after 2-3 mo. Thus thiopurines are less frequently used to induce remission in an acute exacerbation but rather to maintain remission. However, they have been shown to have steroid sparing properties[19,20] and furthermore the combination of prednisolone and azathioprine has shown to be superior over prednisolone monotherapy[21]. Therefore it is suggested to add azathioprine to corticosteroids in severe CD.

Methotrexate

In the pivotal trial by Feagan and collea-gues, methotrexate given intramuscularly 25 mg once a week was more likely to induce remission compared to placebo (Table 4). In addition, steroid-sparing properties were noted[22]. However, side effects were more common with methotrexate therapy than with placebo. Other studies using low dose methotrexate did not show a significant benefit[23,24]. In addition, no benefit was obserevd when high intravenous methotrexate was compared to oral

Table 5 Drugs for the treatment of CD

Drug	Metronidazole
Dosage	10-20 mg/kg
Indications	Mild to moderately active disease; fistulae (usually prolonged treatment)
Important side effects	Nausea, metallic taste in the mouth, coating of the tongue, peripheral neuropathy
Monitoring	See side effects
Pregnancy	Long term treatment not yet evaluated, short term treatment appears to be safe

Table 6 Drugs for the treatment of CD

Drug	Ciprofloxacin
Dosage	1-2 g/d
Indications	Mild to moderately active disease, fistulae
Important side effects	Taste disturbance, gastrointestinal events, tendopathies
Monitoring	Generelly well tolerated, see side effects
Pregnancy	Probably safe

azathioprine[25]. Like azathioprine/6-mercaptopurine, intramuscular methotrexate is only rarely used to treat an acute exacerbation of CD but is used more frequently in chronic active CD[26]. Importantly, side effects with methotrexate, specifically liver dysfunction, are common and need to be monitored. In addition, methotrexate is contradicted during pregnancy and should be used very cautiously in women of child-bearing potential.

Antibiotics

Although antibiotics are frequently used to treat CD, this practice is not supported by strong evidence from randomized trials. However, increasing knowledge of the impotance of mucosal bacteria for the pathogenesis of CD gives a good rationale for investigating antibiotic approaches[27]. In addition, distinguishing an acute flare from an infectious gastroenteritis/colitis can be difficult. Thus antibiotics provide a therapeutic alternative, which might benefit both an acute flare and a gastrointestinal infection. However, further studies are warranted to establish the role of antibiotics in the treatment of CD and at this time they cannot be recommended as standard therapy.

Metronidazole: Metronidazole (20 mg/kg per day) has been shown to be superior over placebo in reducing the CDAI but not with respect to the induction of remission[28] (Table 5). Furthermore, this benefit was only seen in patients with colonic or ileocolonic disease, whereas no benefit was found with disease location in the ileum. Similar findings were reported from another trial where few patients with colonic involvement showed an improvement[29]. Another study reported no benefit *vs* placebo[30]. Compared to sulfasalazine, a cross over study reported no difference in the first 4 mo. However, in the cross over design, patients switched to metronidazole showed an improvement of CDAI, whereas in the sulfasalazine group this was not the case[31,32].

Table 7 Drugs for the treatment of CD

Drug	Infliximab
Dosage	5 mg/kg per infusion; usually started at wk 0, 2, and 6 and then repeated every 8 wk if necessary
Indications	Chronically active disease, steroid-refractory and steroid-dependency, maintenance, fistulae
Important side effects	Nausea, headache, abdominal pain, infections, sepsis; infusions reactions (early or delayed), reactivation of tuberculosis
Monitoring	Vital signs around infusion
Pregnancy	Unknown
Comments	Exclude tuberculosis before infusions, consider concommittant use of imunosuppressants (azathioprine) to reduce antibody formation

Ciprofloxacin: Ciprofloxacin is often used in a clinical routine, especially in combination with metronidazole (Table 6). Ciprofloxacin was significantly better compared to placebo in inducing remission in a smaller trial[33] and was shown to be similarly effective compared to mesalamine[34]. In contrast, corticosteroids resulted in higher rates of clinical remission compared to ciprofloxacin and metronidazole[35]. In patients with chronically active disease on budesonide, the addition of metronidazole and ciprofloxacin was not superior over budesonide monotherapy, although in patients with colonic CD a trend towards a significant benefit was observed[36].

Infliximab

Infliximab is a chimeric IgG1 monoclonal antibody against TNF-α (Table 7). Apart from inhibiting TNF-α, recent data suggest that the induction of apoptosis in T cells through infliximab might be an important mechnism of action[37]. Infliximab has shown to be superior over placebo in inducing remission in patients with moderate to severe CD resistance to standard therapy[38]. In this trial, after four weeks 33% of patients went into remission after one single infliximab infusion as compared to 4% of the patients given placebo.

Summary: Treatment of active CD

In mild and moderately active CD, 5-ASA or budesonide may be used as first line therapy, despite the limited efficacy of 5-ASA shown in randomized, placebo-controlled trials. The presently available budesonide preparations are only efficacious in disease primarily located within the terminal ileum or right colon. In non-responders, systemic corticosteroids should be used. Severe CD should be treated with systemic corticosteroids. If corticosteroids given orally do not lead to improvement, intravenous application should be considered since enteral absorption might be decreased due to severe intestinal inflammation. Enteral nutrition should also be added particularly in malnourished patients (see below chapter on nutrition for details). If an infectious complication is suspected, the additional therapy with antiobiotics (e.g. ciprofloxacin plus metronidazole) might be beneficial. The combination of systemic corticosteroids and azathioprine is superior to prednisolone monotherapy and this combination might be beneficial in severe cases. In patients

refractory to corticosteroids, treatment with infliximab should be considered. Surgery might be neccessary in patients with severe and refractory CD not responding to above mentioned strategies. Intravenous cyclosporin and tacrolimus should only be used in selected severe and refractory cases.

MAINTENANCE OF REMISSION

Maintaining a medically or surgically induced remission of disease is one of the most important but yet most difficult therapeutic goals in the treatment of CD. Maintenance therapy in CD is characterized as treatment with only a few available drugs, moderately high rates of efficacy and frequent side effects. In total, 40%-70% of CD patients will experience a symptomatic relapse in 1 year after a medically or surgically indused remission[8,9]. Silverstein and colleagues reported that a surgically induced remission lasts a mean of 766 d whereas a non-surgically induced remission lasts only 120 d indicating that a surgically induced remission is more stable[39]. It was frequently recommended that the indication for a relapse-preventing therapy should be based on the prospective risk of an individual patient to relapse. Although the estimation of risk for relapse, based on the phenotype or genotype, is still controversial, single well known risk factors like smoking, frequent relapses in the past, a chronic active disease *etc*. have been described. To stop smoking is a very important therapeutic goal[2,40]. Systemic corticosteroids should not be used for maintaining remission due to lack of efficacy and severe long-term side effects. Since randomized, placebo-controlled trials suggest a different approach in medically or surgically induced remissions, we will handle them separately.

Medically induced remission

5-ASA: Numerous randomized, placebo-controlled studies, including four meta-analyses, have attempted to establish a role for 5-ASA in the maintenance of remission. Different study regimens and durations were performed and a substantial number of trials included only small numbers of patients. The two most recent meta-analyses failed to show a benefit for mesalamine over placebo in the maintenance of medically induced remission[41,42]. However, the preferable side effect profile of 5-ASA, especially mesalamine compared to azathioprine/6-mercaptopurine or methotrexate, is probably the reason why mesalamine is still used frequently to maintain a medically-induced remission. Many clinicians therefore try to maintain remission with mesalamine at least one time, especially in young women of childbearing potential. In addition many patients are in favour of trying a rather harmless drug at first for long-term therapy.

Azathioprine/6-Mercaptopurine: Azathioprine/6-mercaptopurine is the treatment of choice for patients with high risk of relapse. The effectiveness of azathioprine has been described in a recent meta-analysis including five randomized, placebo-controlled trials. In addition, a steroid-sparing effect was observed[43]. No clear direction has been given as to when to start the treatment with azathioprine/6-mercaptopurine. The following indications are most commonly accepted: frequent flares (more than two per year), chronically active disease, and steroid dependence (e.g. if two attempts of tapering steroids have failed). The thiopurines are slow acting drugs and an effect is usually observed after 2-3 mo with approximately 90% of patients responding within the first 4 mo[17].

An earlier open study suggested that azathioprine is no longer effective after 3.5 years[44]. In contrast, the same group reported, in a very recent placebo-controlled trial, that azathioprine is still effective with prolonged use[45]. However, a small increase in the frequency of malignancy, especially lymphoma, cannot be excluded in the long term treatment with azathioprine/6-mercaptopurine[46,47]. This must be weighed against the improved quality of life due to both drugs for patients with CD.

Methotrexate: The potential of methotrexate to induce remission was investigated in a study by Feagan and colleagues. Herein the patients who had achieved remission after weekly 25 mg intramuscularly were randomized to 15 mg methotrexate or placebo. Methotrexate was found to be significantly better than placebo in maintaining remission[26]. However, side effects were more significant than placebo. Methotrexate has not been studied in surgically or medically induced remission by other drugs (e.g. corticosteroids). In summary, methotrexate is suggested to be the alternative to azathioprine/6-mercaptopurine in the maintenance of remission. It has also shown to have steroid-sparing properties with the mean time to respond at about 2 mo.

Budesonide: Lower doses of budesonide (3 or 6 mg) have also been studied for their potential to be effective in the maintenance of remission. Although earlier meta-analyses have not shown that budesonide was superior over placebo[16,48], a recent randomized, placebo-controlled trial found a trend towards a longer quiescent disease in budesonide treated patients compared to placebo[49]. In this trial, no significant difference in total adverse events or corticosteroid-associated events was demonstrated between placebo and budesonide. In addition, a very recent paper by Sandborn and colleagues combined the data of four double-blind, placebo-controlled trials with identical protocols analyzing the efficacy of 6 mg budesonide. Budesonide was shown to be effective for prolonging the time to relapse and for significantly reducing the rates of relapse at 3 and 6 mo but not at 12 mo. Herein no difference in the frequency of adverse events and glucocorticosteroid associated side effects between budesonide and placebo was found[50]. Thus, the current data suggest that budesonide at a dosage of 6 mg seems to have the effect of prolonging remission in CD in terminal ileal or right colonic disease. Budesonide might thus offer a potential alternative in the maintenance of a medically-induced remission, especially in steroid-dependent patients.

Infliximab: Two studies have shown that infliximab is effective in maintaing remission in CD[51,52]. In the Accent I trial, infliximab was shown to be superior over placebo in the maintenance of remission in CD patients that responded to one single infusion of infliximab. Herein, about 20% of patients in remission after the first infusion of infliximab were maintained in remission for one year with repeated infusions every eight weeks[52]. Infliximab

was also shown to have steroid-sparing properties. Repeated infusions of infliximab should thus be considered for chronically active or steroid-dependent patients where standard immunosuppressants are not effective or where surgical interventions are not considered. However, repeated infusions of infliximab are costly and data on long-term safety, including the occurrence of malignancies, are limited. Infliximab has been shown to lead to mucosal healing, which was associated with reduced surgical interventions and lower hospitalization rates[53]. However, at this time it is debated whether mucosal healing is an important goal in CD therapy. Further studies are warranted regarding this matter. The development of antibodies against infliximab is frequently found and is associated with reduced efficacy and increased numbers of infusion reactions. The concommitant use of immunosuppressants has been shown to reduce the incidence of antibody formation[54].

Summary: Maintenance after medically induced remission

After a medically-induced remission, maintenance therapy should be initiated based on the individual situation. No medical therapy may be considered in patients with low risk of relapse. However, in patients with high risk for relapse (frequent relapses, colonic involvement and severe disease behaviour), therapy with azathioprine or 6-mercaptopurine should be initiated. In patients with terminal ileal or right colonic disease, low-dose budesonide might offer an alternative especially in steroid-dependent patients. In patients who are not responding or are intolerant to azathioprine/6-mercaptopurine, therapy with methotrexate may be used. If not successful, patients should be considered for maintenance treatment with infliximab.

Postoperative CD (surgically-induced remission)

About 75% of CD patients will require surgery within the first 20 years after the onset of symptoms[55,56]. In addition, recurrence rates after surgical resection are high: after the first resection, up to 80% of patients show an endoscopic recurrence within the first year although most patients are not symptomatic[55-57]. Furthermore, up to 20% have clinical symptoms and 5% require another surgical intervention within the first year. After 5 years, about 50% of patients have a clinical relapse. Systemic corticosteroids and budesonide are not effective in preventing postoperative relapse[58-61], whereas methotrexate, ciprofloxacin and infliximab have not been studied for this indication. Various risk factors for postoperative recurrence have been described but most of these risk factors have not been studied in a prospective manner. Currently smoking is the most consistently described risk factor for postoperative relapse[40,62]. In addition, Rutgeerts and colleagues showed that preoperative disease activity and endoscopic lesions at the neoterminal ileum within the first year after surgery are also associated with higher risk for postoperative recurrence[57]. In addition, a recent study suggested that CD patients with CARD15 mutations have a higher risk of postoperative relapse compared to patients without mutated CARD15. Thus genotyping for CARD15 mutations might offer a potential alternative to identify patients with high risk of postoperative relapse[63]. Further studies are warranted to consider this approach.

5-ASA: As opposed to the controversial discussion about the efficacy of 5-ASA in the treatment of CD, the results on the prevention of postoperative recurrence are quite solid. Camma and colleagues described in a meta-analysis a risk reduction of 13.1% by mesalamine treatment compared to placebo[41]. A more recent placebo-controlled trial reported that mesalamine did not significantly affect the postoperative course of CD, but some relapse-preventing effect was found in patients with isolated small bowel disease[64]. In summary, 5 ASA is the only treatment with an evidence-based relapse preventing effect after a surgically induced remission and is therefore recommended according to recent guidelines[65].

Azathioprine/6-Mercaptopurine: The two largest studies regarding the effect of azathioprine/6-mercaptopurine to prevent postoperative recurrence were recently published. In the first trial, Hanauer and colleagues compared 6-mercaptopurine at the low fixed dose of 50 mg/d to mesalamine 3 g/d and placebo after ileocolic resection[66]. There was a significant benefit of 6-mercaptopurine compared to placebo in preventing clinical and endoscopic recurrence over two years. However, this study has been criticized since it was underpowered and also had a high drop-out rate of patients. Ardizzione and colleagues observed no benefit of azathioprine at standard dosing (2 mg/kg) in preventing clinical relapse after two years in comparison to mesalamine[67]. In summary, although none of these studies offer robust data to support the use of azathioprine/6-mercaptopurine in the prevention of postoperative recurrence, many clinicians use these drugs for this indication.

Antibiotics: In a randomized, placebo-controlled trial a significant decrease was observed in the incidence of severe endoscopic recurrence with metronidazole treatment as compared to placebo after ileal resection[68]. In addition, metronidazole therapy statistically reduced the clinical recurrence rates at 1 year. Metronidazole is still only rarely used on this occasion since long term intake is not tolerated by most patients due to side effects such as metallic taste, nausea and peripheral neuropathy. Ciprofloxazin has not been studied in a randomized, placebo-controlled trial regarding the prevention of postoperative recurrence. Rifaximin, which is a non-absorbable drug with good tolerability covering most Gram-positive and Gram-negative bacteria, might offer a very promising alternative since long term application is tolerated much better[69]. At the moment, although frequently used in clinical practice, none of these antibiotics will be considered standard therapy until more controlled trials provide clear results.

Rutgeerts and colleagues investigated the efficacy of ornidazole, a nitroimidazole antibiotic, for the prevention of clinical recurrence after curative ileocolonic resection in a recent placebo-controlled trial. They found that ornidazole significantly reduced the clinical and endoscopic recurrence rate at 1 year compared to placebo. However, significantly more patients in the ornidazole group dropped out of the study because of side effects. In summary, these data indicate that ornidazole might offer a therapeutic alternative in preventing postoperative recurrence[70].

Summary: Treatment of postoperative CD

No standard treatment algorithm prevents postoperative relapse. Despite the controversial discussion on its efficacy, mesalamine over a period of two years is recommended as the treatment of choice in the prevention of postoperative relapse. However, many patients who undergo surgical resection have already been treated with mesalamine so that alternative regimes should be initiated. Although robust data are lacking, most clinicians use azathioprine/6-mercaptopurine at standard dosing in patients with higher risk of postoperative relapse. To estimate the risk of clinical relapse the diagnosis of endosciopic lesions at the anastomosis 6 mo after resection may be used. Azathioprine/6-mercaptopurine may be started if severe or moderate lesions at the anastomosis are found[71]. Although this regime has never been studied in a randomized trial, it seems to be a reasonable approach. Antibiotics, such as metronidazole or ornidazole, might offer a potential alternative although the long term use is limited due to side effects. In addition, prospective studies investigating infliximab in this setting are warranted.

COMPLICATIONS IN CD

Fistulizing disease behaviour

The treatment of fistulizing CD remains probably the most difficult clinical challenge. Treatment is complicated since very few drugs have proven efficacy whereas most agents used in CD therapy (5-ASA, systemic corticosteroids, budesonide) are ineffective. Fistulae are reported to occur in up to 50% of patients after 20 years of disease[72]. Especially enterocutaneous and enterovaginal fistulae have a severe impact on the quality of live of CD patients. Enterovesical fistulae require surgical intervention due the potential development of an urosepsis. Perianal fistulae are the most common form and are often complicated by an abscess where surgical drainage must be performed. Since complete long term closure of fistulae cannot be achieved in many patients with the available therapies, reduction of fistula drainage and closure of part of the fistulae have been accepted therapeutic goals. Apart from medical treatment approaches as discussed below, surgical interventions such as fistulotomy and insertion of non-cutting setons should be part of the management. A close cooperation between the gastroenterologist and the surgeon is required.

Azathioprine/6-Mercaptopurine: Robust data summarized in the meta-anaylsis by Pearson[19] show a positive effect of azathioprine/6-mercaptopurine on fistula closure with an odds ratio of 4.44 (CI 1.50-13.20). Thus azathioprine/6-mercaptopurine is the basis of long-term treatment of fistulae.

Methotrexate: No randomized trial has been performed using methotrexate to investigate the healing of fistulae. However, retrospective data showed complete or partial response in 56% (9/16) of patients[73]. Methotrexate might thus be considered as the alternative agent to azathioprine/6-mercaptopurine.

Antibiotics: A small uncontrolled study reported a clinical response to metronidazole in 20 out of 21 patients and complete healing after maintenance treatment in 10 out of 18 patients. A follow-up study demonstrated that dosage reduction was associated with exacerbation of fistulae in all patients and healing was again achieved if the drug was reintroduced[74]. Ciprofloxacin alone showed an improvement in 7 out of 10 patients treated with up to 1.5 g over three months[75]. Although controlled clinical trials are lacking, the combination of metronidazole and ciprofloxacin is often initiated.

Infliximab: Infliximab offers robust data from randomized, placebo-controlled trials in the treatment of enterocutaneous fistulae. In the first trial by Present and colleagues, three infusions of infliximab at 0, 2, and 6 wk resulted in complete healing of enterocutaneous fistulae in 55% of patients compared to 13% in the placebo group[76]. Data from the ACCENT 2 trial showed that infliximab maintained healing of enterocutaneous fistulae in 36% patients who responded to the initial three infliximab infusions[77]. However, it was shown that healing of fistulae needed repeated infusions, which is similar to the experiences observed in a clinical routine. In summary, data from controlled clinical trials suggest that infliximab might be the most potent drug in the treatment of CD fistulae. Three infusions with a dose of 5 mg/kg at wk 0, 2, and 6 are recommended as standard for the treatment of fistulizing CD.

Cyclosporin A: Cyclopsorin A offers an effective alternative treatment for CD fistulae. There are numerous uncontrolled trials that describe a mean initial response in 83% of patients with discontinuation of treatment leading to frequent relapses (reviewed in ref. [78]). However, cyclosporin A toxicity can be dramatic, including renal failure, and thus application should be performed only in centers with expertise. Continuous infusions of 4 mg/kg per day is required and concentrations of 300-400 ng/mL should be maintained[78]. Dosing can be switched to oral if patients respond to intravenous cyclosporin.

Tacrolimus: A recent placebo-controlled trial showed that tacrolimus at a dose of 0.2 mg/kg was more effective than placebo in improvement of fistulae (defined as closure of >/= 50% of draining fistulas). However, no difference was observed with respect to fistula remission as defined by closure of all fistulas and maintenance of that closure for at least 4 wk. In addition, adverse events such as headache, increased serum creatinine levels, and insomnia were found significantly more often in the tacrolimus group[79].

Summary: Treatment of fistulizing CD

No standardized treatment algorithm exists in the medical treatment of fistulizing CD. Importantly, effective management requires good collaboration between the gastroenterologist and the surgeon in both simple and complex fistulae. Azathioprine/6-mercaptopurine are the basis of fistulae treatment. Antibiotic combination therapy, preferable with metronidazole and ciprofloxacin, can be considered over a period of 2-3 mo especially if an abscess might be suspected to occur. In patients with complex fistulae including underlying rectal inflammation not improving from above mentioned strategies, a three dose therapy regimen with infliximab should be applied. If patients respond, therapy with azathioprine and infliximab might be necessary to maintain fistula healing. In refractory cases, therapy

with cyclosporine and tacrolimus should be considered.

Chronic active disease

Various definitions of chronic active disease exist and thus results from clinical trials in this complicated group of patients are rather difficult to interpret. The German consensus conference on the treatment of CD describes chronic active disease as the persisting or recurrent occurrence of symptoms over more than 6 mo despite standardized therapy[65]. Patients with chronic active disease should thus be treated first with azathioprine/6-mercaptopurine or alternatively with methotrexate. If patients do not respond or are intolerant to these approaches, infliximab should be given. Due to severe long-term side effects, systemic corticosteroids should be avoided. 5-ASA is not effective in chronically active CD.

Steroid-dependent disease

Steroid-dependency is a frequently observed phenomenon in CD and it is defined as the need for corticosteroids to maintain a patient in stable remission after two unsuccessful attempts to withdraw steroids within the last six months. About 28%-44% of patients will become steroid-dependent after an initial course of corticosteroids[80,81]. Long term use of corticosteroids should be avoided due to severe side effects such as osteoporosis, diabetes and hypertension. Prophylaxis of osteoporosis with calcium and vitamin D should be applied. Similar to patients with chronic active disease, azathioprine/6-mercaptopurine is the treatment of choice and methotrexate is the alternative agent to avoid long term steroid therapy. Two meta-analyses reported a steroid-sparing effect for azathioprine[20,43] and the same properties were observed for methotrexate[26]. In addition, infliximab has also been shown to have steroid-sparing properties and thus should also be considered as an alternative[52].

Steroid-refractory disease

Patients with persisting clinical activity under continuing therapy with corticosteroids at a dose greater than 1 mg/kg per day are described as steroid-refractory. This clinical situation occurs in about 20%-30% of patients treated with corticosteroids[8,9,80]. Only a few drugs have been tested in this situation: azathioprine/6-mercaptopurine and methotrexate have shown to be effective in steroid-refractory patients[20,26,43]. In addition, infliximab offers a therapeutic alternative[52]. However, if medical therapy fails in severe cases, surgical interventions such as colectomy might be necessary.

Gastroduodenal CD

Sympotmatic involvement of stomach and duodenum is a rare phenomenon observed in about 4%-5.5% of patients[82,83]. Endoscopic and histologic involvement might be found in up to 40% of patients[84-86]. Due to the low frequency of patients with symptomatic gastroduodenal involvement, however, randomized, placebo-controlled trials are not available. Combination therapy with high dose acid suppression (proton pump inhibitors) and standard therapy of CD are usually used. Corticosteroids[87], azathioprine[88,89], and infliximab[90] have been reported to be effective in selected patients. However, many patients with obstructive symptoms caused by strictures will have to undergo surgical interventions such as gastroduodenal or gastrojejunal bypass, even performed laparoscopically. Gastroduodenal bypass has been reported to result in a good outcome in up to 87% of patients[91].

Fibrostenotic disease behaviour

CD is often complicated by fibrostenotic strictures that can be located within the whole gastrointestinal tract. Strictures can remain clinically asymptomatic over years until the intraluminal caliber causes obstruction. However, it is often difficult to differentiate between an inflammatory or fibrostenotic stricture. Ultrasound and MRI with the possibility to visualize mucosal blood flow are helpful in differential diagnosis. Before initiating surgical interventions, many clinicians try at least one attempt of medical treatment for strictures suggested to have an inflammatory component. Corticosteroids are most commonly used in this clinical situation. Fibrostenotic strictures will not respond to medical therapy. Endoscopic ballon dilatations, stricturoplasty or resections are required in most cases.

ROLE OF NUTRITION IN CD

Prevention and treatment of malnutrition

During an acute flare of CD, undernutrition with weight loss, protein deficiency and specific deficiencies in vitamins, minerals and trace elements are commonly found. Malnutrition is mainly caused by anorexia, increased intestinal losses and systemic inflammation. In children and adolescents a decrease in growth velocity may occur, secondary to inadequate nutrition and steroid therapy. The relevance and extent of these deficiencies vary according to the site and extent of the diseased intestine as well as disease activity. In active CD, an improvement in nutritional status cannot be achieved by nutritional counselling alone but oral nutritional supplements or tube feeding leads to improvement of the nutritional status[92,93]. Both malnutrition and growth retardation require enteral nutrition (EN).

The use of oral nutritional supplements or tube feeding should also be taken into account in the perioperative setting. An increased frequency of postoperative complications has been shown in undernourished patients with CD[94], with undernutrition being defined as weight loss and/or plasma albumin levels below 35 g/L. Although specific data concerning the effect of perioperative nutrition in CD are lacking, there is a considerable body of evidence on the effect of perioperative nutrition in general gastrointestinal surgery and preoperative nutritional support is therefore recommended in malnourished patients[95]. A prospective study showed that a preoperative oral supplementation with a formula enriched with arginine, omega-3 fatty acids, and RNA was associated with reduced postoperative infections and shorter lengths of hospital stay[96]. Supplementation of specific deficiencies may be crucial. Iron deficiency is most common and should be treated with oral or i.v. iron supplements. Vitamin D and calcium should be supplemented in patients

on steroid therapy and patients treated with sulfasalazine are at risk to develop Vitamin B12 deficits.

Treatment of active disease

EN is also effective in the treatment of an acute flare in CD with approximately 60% of all patients reaching remission. In children, active disease frequently leads to growth retardation and enteral nutrition is therefore the treatment of choice. In adults, however, treatment with corticosteroids is more effective as shown by a recent meta-analysis[97]. Enteral nutrition as sole therapy for acute CD is indicated mainly when treatment with corticosteroids is not feasible; e.g. due to intolerance or refusal. Combined therapy (enteral nutrition and drugs) is indicated in undernourished patients as well as in those with inflammatory stenosis of the intestine. If active CD is treated with systemic corticosteroids in combination with EN and supplementary EN is continued after the active phase, it prolongs the relapse free interval[98].

Total parenteral nutrition is no better than enteral nutrition in the therapy of active CD and should therefore be restricted to patients with a contraindication to or intolerance of enteral nutrition[99]. EN in subileus and high grade stenosis does require special caution. A documented stenosis however is not a contraindication to EN *per se*[100].

EXTRAINTESTINAL MANIFESTATIONS

CD is much more than a bowel disease since it can affect almost every other organ of the body. We will describe only briefly the most common extraintestinal manifestations (EIMs) and the recommended therapeutic approaches. The treatment of most extraintestinal manifestations has not arisen from randomized clinical trials but more from experiences and case reports and thus remains often nonempirical. With respect to all EIMs, a collaboration with rheumatologists, dermatologists and especially ophthalmologists should be part of the therapeutic regimen. The basis of treatment of EIMs is to obtain remission since it will positively affect the course of the particular extraintestinal manifestation, especially if symptoms occur parallel to exacerbation of the disease.

Arthritis

Joint involvement is the most frequently found extraintestinal manifestation in CD, which can be separated into axial and peripheral involvement. Peripheral involvement can be subdivided into a pauciarticular, large joint arthropathy, and a bilateral symmetrical polyarthropathy[101]. Axial involvement can result in sacroiliitis or ankylosing spondylitis. Placebo-controlled trials have shown that sulfasalazine is effective in the treatment of ankylosing spondylitis[102,103]. Furthermore physiotherapy is important. A low dose of corticosteroids (usually no more than 10 mg/d) can be a therapeutic option. Nonsteroidal anti-inflammatory drugs (NSAIDs) and COX-II-inhibitors might lead to pain relief but should be avoided since they might exacerbate CD. Many patients need analgetics to control symptoms. The use of tramadol or metamizol is preferable. Due to the experiences with rheumatoid arhritis, methotrexate might be offered as an alternative. In the same respect, infliximab has shown to be very effective[104,105].

Erythema nodosum, pyoderma gangrenosum, ocular involvement, PSC

Erythema nodosum is the most common skin manifestation in conjunction with active CD and usually responds to therapy with corticosteroids. Severe or refractory cases have been shown to respond to infliximab[106]. In pyoderma gangrenosum, corticosteroids are the treatment of choice, even applied by the intravenous route in refractory cases. Topical therapy should be considered as an adjuvant to systemic therapy. However, a recent study reported healing of pyoderma gangrenosum after infliximab treatment in all 13 patients[107]. These results suggest that infliximab might be considered as the treatment of choice for pyoderma gangrenosum, especially in refractory cases. An ocular manifestation such as iridocyclitis or anterior uveitis should be treated with topical steroids and cycloplegics. A case with improvement of uveitis after infliximab treatment was recently reported[108]. Considering primary sclerosing cholangitis (PSC), although more frequently seen in ulcerative colitis, an earlier study showed that ursodeoxycholic acid (UDCA) at a dose of 10-15 mg/d can result in significant liver enzyme improvement[109]. However, a recent 5-year, placebo-controlled trial of high-dose UDCA (17-23 mg/d) failed to show benefit for UDCA on survival or the prevention of cholangiocarcinoma in PSC[110]. Taking all published studies into consideration, Olsson and colleagues conclude that there is, if at all, only a very limited effect of UDCA in PSC. PSC is associated with the occurrence of cholangiocarcinoma where liver transplantation seems to be the only curative approach.

CONCLUSION

Based on the currently available data from randomized, placebo-controlled trials, including meta-analyses, we describe the conventional treatment of Crohn's disease. This coventional approach suggests a step-up approach usually in the order of 5-ASA, corticosteroids, immunosuppressants and usually infliximab in refractory or severe cases including fistulizing disease behaviour. In contrast, a more aggressive form of treatment (bottom-down) has been recently proposed. This regimen starts out early at diagnosis of CD with the combination of biologicals (infliximab) in combination with immunosuppressants (azathioprine). Studies are warranted to elucidate the role of this new therapeutic approach in comparison to the standard therapy algorithms. Furthermore the value of mucosal healing and its effect on the course of CD, including its potential to reduce complications, surgical interventions and hospitalisation rates, should be evaluated in upcoming studies.

The past years have resulted in enormous new insights into the pathophysiology of CD with respect to molecular genetics, mucosal bacteria and immunology. Now it is time to translate these findings into newer therapeutic concepts. Numerous agents, especially biologicals, have been tested but most of them have not been introduced

into the market due to low efficacy or severe side effects. Apart from infliximab, other TNFα-antagonists, such as adalimumab or CDP870, might offer a potent alternative in the future. However, apart from evidence-based medicine, CD therapy will always be an individualized therapy. In addition, many patients construct their own therapeutic regimen, especially after long term disease. Such approaches might be effective in individual situations, although they do often not stand the criteria of evidence-based medicine. Moreover, many clinical situations are complex and might never have been studied in randomized, placebo-controlled trials. Therefore, the treatment of CD frequently requires individual decisions and creativity despite a very good basis of evidence-based therapies.

REFERENCES

1 **Podolsky DK**. Inflammatory bowel disease. *N Engl J Med* 2002; **347**: 417-429
2 **Timmer A**, Sutherland LR, Martin F. Oral contraceptive use and smoking are risk factors for relapse in Crohn's disease. The Canadian Mesalamine for Remission of Crohn's Disease Study Group. *Gastroenterology* 1998; **114**: 1143-1150
3 **Cosnes J**, Carbonnel F, Beaugerie L, Le Quintrec Y, Gendre JP. Effects of cigarette smoking on the long-term course of Crohn' s disease. *Gastroenterology* 1996; **110**: 424-431
4 **Cosnes J**, Beaugerie L, Carbonnel F, Gendre JP. Smoking cessation and the course of Crohn's disease: an intervention study. *Gastroenterology* 2001; **120**: 1093-1099
5 **Sandborn WJ**, Feagan BG, Hanauer SB, Lochs H, Löfberg R, Modigliani R, Present DH, Rutgeerts P, Schölmerich J, Stange EF, Sutherland LR. A review of activity indices and efficacy endpoints for clinical trials of medical therapy in adults with Crohn's disease. *Gastroenterology* 2002; **122**: 512-530
6 **Best WR**, Becktel JM, Singleton JW, Kern F. Development of a Crohn's disease activity index. National Cooperative Crohn's Disease Study. *Gastroenterology* 1976; **70**: 439-444
7 **Hanauer SB**, Sandborn W. Management of Crohn's disease in adults. *Am J Gastroenterol* 2001; **96**: 635-643
8 **Summers RW**, Switz DM, Sessions JT, Becktel JM, Best WR, Kern F, Singleton JW. National Cooperative Crohn's Disease Study: results of drug treatment. *Gastroenterology* 1979; **77**: 847-869
9 **Malchow H**, Ewe K, Brandes JW, Goebell H, Ehms H, Sommer H, Jesdinsky H. European Cooperative Crohn's Disease Study (ECCDS): results of drug treatment. *Gastroenterology* 1984; **86**: 249-266
10 **Van Hees PA**, Van Lier HJ, Van Elteren PH, Driessen M, Van Hogezand RA, Ten Velde GP, Bakker JH, Van Tongeren JH. Effect of sulphasalazine in patients with active Crohn's disease: a controlled double-blind study. *Gut* 1981; **22**: 404-409
11 **Singleton JW**, Summers RW, Kern F, Becktel JM, Best WR, Hansen RN, Winship DH. A trial of sulfasalazine as adjunctive therapy in Crohn's disease. *Gastroenterology* 1979; **77**: 887-897
12 **Rasmussen SN**, Lauritsen K, Tage-Jensen U, Nielsen OH, Bytzer P, Jacobsen O, Ladefoged K, Vilien M, Binder V, Rask-Madsen J. 5-Aminosalicylic acid in the treatment of Crohn' s disease. A 16-week double-blind, placebo-controlled, multicentre study with Pentasa. *Scand J Gastroenterol* 1987; **22**: 877-883
13 **Mahida YR**, Jewell DP. Slow-release 5-amino-salicylic acid (Pentasa) for the treatment of active Crohn's disease. *Digestion* 1990; **45**: 88-92
14 **Tremaine WJ**, Schroeder KW, Harrison JM, Zinsmeister AR. A randomized, double-blind, placebo-controlled trial of the oral mesalamine (5-ASA) preparation, Asacol, in the treatment of symptomatic Crohn's colitis and ileocolitis. *J Clin Gastroenterol* 1994; **19**: 278-282
15 **Hanauer SB**, Strömberg U. Oral Pentasa in the treatment of active Crohn's disease: A meta-analysis of double-blind, placebo-controlled trials. *Clin Gastroenterol Hepatol* 2004; **2**: 379-388
16 **Kane SV**, Schoenfeld P, Sandborn WJ, Tremaine W, Hofer T, Feagan BG. The effectiveness of budesonide therapy for Crohn's disease. *Aliment Pharmacol Ther* 2002; **16**: 1509-1517
17 **Present DH**, Korelitz BI, Wisch N, Glass JL, Sachar DB, Pasternack BS. Treatment of Crohn's disease with 6-mercaptopurine. A long-term, randomized, double-blind study. *N Engl J Med* 1980; **302**: 981-987
18 **Candy S**, Wright J, Gerber M, Adams G, Gerig M, Goodman R. A controlled double blind study of azathioprine in the management of Crohn's disease. *Gut* 1995; **37**: 674-678
19 **Pearson DC**, May GR, Fick GH, Büschenfelde LR. Azathioprine and 6-mercaptopurine in Crohn disease. A meta-analysis. *Ann Intern Med* 1995; **123**: 132-142
20 **Sandborn W**, Sutherland L, Pearson D, May G, Modigliani R, Prantera C. Azathioprine or 6-mercaptopurine for inducing remission of Crohn's disease. *Cochrane Database Syst Rev* 2000; **2**: CD000545
21 **Ewe K**, Press AG, Singe CC, Stufler M, Ueberschaer B, Hommel G, Meyer zum Buschenfelde KH. Azathioprine combined with prednisolone or monotherapy with prednisolone in active Crohn's disease. *Gastroenterology* 1993; **105**: 367-372
22 **Feagan BG**, Rochon J, Fedorak RN, Irvine EJ, Wild G, Sutherland L, Steinhart AH, Greenberg GR, Gillies R, Hopkins M. Methotrexate for the treatment of Crohn's disease. The North American Crohn's Study Group Investigators. *N Engl J Med* 1995; **332**: 292-297
23 **Oren R**, Moshkowitz M, Odes S, Becker S, Keter D, Pomeranz I, Shirin C, Reisfeld I, Broide E, Lavy A, Fich A, Eliakim R, Patz J, Villa Y, Arber N, Gilat T. Methotrexate in chronic active Crohn 's disease: a double-blind, randomized, Israeli multicenter trial. *Am J Gastroenterol* 1997; **92**: 2203-2209
24 **Arora S**, Katkov W, Cooley J, Kemp JA, Johnston DE, Schapiro RH, Podolsky D. Methotrexate in Crohn's disease: results of a randomized, double-blind, placebo-controlled trial. *Hepatogastroenterology* 1999; **46**: 1724-1729
25 **Ardizzone S**, Bollani S, Manzionna G, Imbesi V, Colombo E, Bianchi Porro G. Comparison between methotrexate and azathioprine in the treatment of chronic active Crohn's disease: a randomised, investigator-blind study. *Dig Liver Dis* 2003; **35**: 619-627
26 **Feagan BG**, Fedorak RN, Irvine EJ, Wild G, Sutherland L, Steinhart AH, Greenberg GR, Koval J, Wong CJ, Hopkins M, Hanauer SB, McDonald JW. A comparison of methotrexate with placebo for the maintenance of remission in Crohn's disease. North American Crohn's Study Group Investigators. *N Engl J Med* 2000; **342**: 1627-1632
27 **Swidsinski A**, Ladhoff A, Pernthaler A, Swidsinski S, Loening-Baucke V, Ortner M, Weber J, Hoffmann U, Schreiber S, Dietel M, Lochs H. Mucosal flora in inflammatory bowel disease. *Gastroenterology* 2002; **122**: 44-54
28 **Sutherland L**, Singleton J, Sessions J, Hanauer S, Krawitt E, Rankin G, Summers R, Mekhjian H, Greenberger N, Kelly M. Double blind, placebo controlled trial of metronidazole in Crohn's disease. *Gut* 1991; **32**: 1071-1075
29 **Blichfeldt P**, Blomhoff JP, Myhre E, Gjone E. Metronidazole in Crohn's disease. A double blind cross-over clinical trial. *Scand J Gastroenterol* 1978; **13**: 123-127
30 **Ambrose NS**, Allan RN, Keighley MR, Burdon DW, Youngs D, Barnes P, Lennard-Jones JE. Antibiotic therapy for treatment in relapse of intestinal Crohn's disease. A prospective randomized study. *Dis Colon Rectum* 1985; **28**: 81-85
31 **Rosén A**, Ursing B, Alm T, Bárány F, Bergelin I, Ganrot-Norlin K, Hoevels J, Huitfeldt B, Järnerot G, Krause U, Krook A, Lindström B, Nordle O. A comparative study of metronidazole and sulfasalazine for active Crohn's disease: the cooperative Crohn's disease study in Sweden. I. Design and methodologic considerations. *Gastroenterology* 1982; **83**: 541-549
32 **Ursing B**, Alm T, Bárány F, Bergelin I, Ganrot-Norlin K, Hoevels J, Huitfeldt B, Järnerot G, Krause U, Krook A,

Lindström B, Nordle O, Rosén A. A comparative study of metronidazole and sulfasalazine for active Crohn's disease: the cooperative Crohn's disease study in Sweden. II. Result. *Gastroenterology* 1982; **83**: 550-562

33 **Arnold GL**, Beaves MR, Pryjdun VO, Mook WJ. Preliminary study of ciprofloxacin in active Crohn's disease. *Inflamm Bowel Dis* 2002; **8**: 10-15

34 **Colombel JF**, Lémann M, Cassagnou M, Bouhnik Y, Duclos B, Dupas JL, Notteghem B, Mary JY. A controlled trial comparing ciprofloxacin with mesalazine for the treatment of active Crohn's disease. Groupe d'Etudes Thérapeutiques des Affections Inflammatoires Digestives (GETAID). *Am J Gastroenterol* 1999; **94**: 674-678

35 **Prantera C**, Zannoni F, Scribano ML, Berto E, Andreoli A, Kohn A, Luzi C. An antibiotic regimen for the treatment of active Crohn's disease: a randomized, controlled clinical trial of metronidazole plus ciprofloxacin. *Am J Gastroenterol* 1996; **91**: 328-332

36 **Steinhart AH**, Feagan BG, Wong CJ, Vandervoort M, Mikolainis S, Croitoru K, Seidman E, Leddin DJ, Bitton A, Drouin E, Cohen A, Greenberg GR. Combined budesonide and antibiotic therapy for active Crohn's disease: a randomized controlled trial. *Gastroenterology* 2002; **123**: 33-40

37 **Lügering A**, Schmidt M, Lügering N, Pauels HG, Domschke W, Kucharzik T. Infliximab induces apoptosis in monocytes from patients with chronic active Crohn's disease by using a caspase-dependent pathway. *Gastroenterology* 2001; **121**: 1145-1157

38 **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

39 **Silverstein MD**, Loftus EV, Sandborn WJ, Tremaine WJ, Feagan BG, Nietert PJ, Harmsen WS, Zinsmeister AR. Clinical course and costs of care for Crohn's disease: Markov model analysis of a population-based cohort. *Gastroenterology* 1999; **117**: 49-57

40 **Cottone M**, Rosselli M, Orlando A, Oliva L, Puleo A, Cappello M, Traina M, Tonelli F, Pagliaro L. Smoking habits and recurrence in Crohn's disease. *Gastroenterology* 1994; **106**: 643-648

41 **Cammà C**, Giunta M, Rosselli M, Cottone M. Mesalamine in the maintenance treatment of Crohn's disease: a meta-analysis adjusted for confounding variables. *Gastroenterology* 1997; **113**: 1465-1473

42 **Akobeng AK**, Gardener E. Oral 5-aminosalicylic acid for maintenance of medically-induced remission in Crohn's Disease. *Cochrane Database Syst Rev* 2005; **1**: CD003715

43 **Pearson DC**, May GR, Fick G, Sutherland LR. Azathioprine for maintaining remission of Crohn's disease. *Cochrane Database Syst Rev* 2000; **2**: CD000067

44 **Bouhnik Y**, Lémann M, Mary JY, Scemama G, Taï R, Matuchansky C, Modigliani R, Rambaud JC. Long-term follow-up of patients with Crohn's disease treated with azathioprine or 6-mercaptopurine. *Lancet* 1996; **347**: 215-219

45 **Lémann M**, Mary JY, Colombel JF, Duclos B, Soule JC, Lerebours E, Modigliani R, Bouhnik Y. A randomized, double-blind, controlled withdrawal trial in Crohn's disease patients in long-term remission on azathioprine. *Gastroenterology* 2005; **128**: 1812-1818

46 **Korelitz BI**, Mirsky FJ, Fleisher MR, Warman JI, Wisch N, Gleim GW. Malignant neoplasms subsequent to treatment of inflammatory bowel disease with 6-mercaptopurine. *Am J Gastroenterol* 1999; **94**: 3248-3253

47 **Farrell RJ**, Ang Y, Kileen P, O'Briain DS, Kelleher D, Keeling PW, Weir DG. Increased incidence of non-Hodgkin's lymphoma in inflammatory bowel disease patients on immunosuppressive therapy but overall risk is low. *Gut* 2000; **47**: 514-519

48 **Papi C**, Luchetti R, Gili L, Montanti S, Koch M, Capurso L. Budesonide in the treatment of Crohn's disease: a meta-analysis. *Aliment Pharmacol Ther* 2000; **14**: 1419-1428

49 **Hanauer S**, Sandborn WJ, Persson A, Persson T. Budesonide as maintenance treatment in Crohn's disease: a placebo-controlled trial. *Aliment Pharmacol Ther* 2005; **21**: 363-371

50 **Sandborn WJ**, Löfberg R, Feagan BG, Hanauer SB, Campieri M, Greenberg GR. Budesonide for maintenance of remission in patients with Crohn's disease in medically induced remission: a predetermined pooled analysis of four randomized, double-blind, placebo-controlled trials. *Am J Gastroenterol* 2005; **100**: 1780-1787

51 **Rutgeerts P**, D'Haens G, Targan S, Vasiliauskas E, Hanauer SB, Present DH, Mayer L, Van Hogezand RA, Braakman T, DeWoody KL, Schaible TF, Van Deventer SJ. Efficacy and safety of retreatment with anti-tumor necrosis factor antibody (infliximab) to maintain remission in Crohn's disease. *Gastroenterology* 1999; **117**: 761-769

52 **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

53 **Rutgeerts P**, Feagan BG, Lichtenstein GR, Mayer LF, Schreiber S, Colombel JF, Rachmilewitz D, Wolf DC, Olson A, Bao W, Hanauer SB. Comparison of scheduled and episodic treatment strategies of infliximab in Crohn's disease. *Gastroenterology* 2004; **126**: 402-413

54 **Baert F**, Noman M, Vermeire S, Van Assche G, D' Haens G, Carbonez A, Rutgeerts P. Influence of immunogenicity on the long-term efficacy of infliximab in Crohn's disease. *N Engl J Med* 2003; **348**: 601-608

55 **Mekhjian HS**, Switz DM, Watts HD, Deren JJ, Katon RM, Beman FM. National Cooperative Crohn's Disease Study: factors determining recurrence of Crohn's disease after surgery. *Gastroenterology* 1979; **77**: 907-913

56 **Becker JM**. Surgical therapy for ulcerative colitis and Crohn's disease. *Gastroenterol Clin North Am* 1999; **28**: 371-390, viii-ix

57 **Rutgeerts P**, Geboes K, Vantrappen G, Beyls J, Kerremans R, Hiele M. Predictability of the postoperative course of Crohn's disease. *Gastroenterology* 1990; **99**: 956-963

58 **Bergman L**, Krause U. Postoperative treatment with corticosteroids and salazosulphapyridine (Salazopyrin) after radical resection for Crohn's disease. *Scand J Gastroenterol* 1976; **11**: 651-656

59 **Smith RC**, Rhodes J, Heatley RV, Hughes LE, Crosby DL, Rees BI, Jones H, Evans KT, Lawrie BW. Low dose steroids and clinical relapse in Crohn's disease: a controlled trial. *Gut* 1978; **19**: 606-610

60 **Hellers G**, Cortot A, Jewell D, Leijonmarck CE, Löfberg R, Malchow H, Nilsson LG, Pallone F, Pena S, Persson T, Prantera C, Rutgeerts P. Oral budesonide for prevention of postsurgical recurrence in Crohn's disease. The IOIBD Budesonide Study Group. *Gastroenterology* 1999; **116**: 294-300

61 **Ewe K**, Böttger T, Buhr HJ, Ecker KW, Otto HF. Low-dose budesonide treatment for prevention of postoperative recurrence of Crohn's disease: a multicentre randomized placebo-controlled trial. German Budesonide Study Group. *Eur J Gastroenterol Hepatol* 1999; **11**: 277-282

62 **Sutherland LR**, Ramcharan S, Bryant H, Fick G. Effect of cigarette smoking on recurrence of Crohn's disease. *Gastroenterology* 1990; **98**: 1123-1128

63 **Büning C**, Genschel J, Bühner S, Krüger S, Kling K, Dignass A, Baier P, Bochow B, Ockenga J, Schmidt HH, Lochs H. Mutations in the NOD2/CARD15 gene in Crohn's disease are associated with ileocecal resection and are a risk factor for reoperation. *Aliment Pharmacol Ther* 2004; **19**: 1073-1078

64 **Lochs H**, Mayer M, Fleig WE, Mortensen PB, Bauer P, Genser D, Petritsch W, Raithel M, Hoffmann R, Gross V, Plauth M, Staun M, Nesje LB. Prophylaxis of postoperative relapse in Crohn's disease with mesalamine: European Cooperative Crohn's Disease Study VI. *Gastroenterology* 2000; **118**: 264-273

65 **Stange EF**, Schreiber S, Fölsch UR, von Herbay A, Schölmerich J, Hoffmann J, Zeitz M, Fleig WE, Buhr HJ, Kroesen AJ, Moser G, Matthes H, Adler G, Reinshagen M, Stein J. Diagnostics and treatment of Crohn's disease -- results of an evidence-based consensus conference of the German Society for Digestive and

Metabolic Diseases. *Z Gastroenterol* 2003; **41**: 19-20
66 **Hanauer SB**, Korelitz BI, Rutgeerts P, Peppercorn MA, Thisted RA, Cohen RD, Present DH. Postoperative maintenance of Crohn's disease remission with 6-mercaptopurine, mesalamine, or placebo: a 2-year trial. *Gastroenterology* 2004; **127**: 723-729
67 **Ardizzone S**, Maconi G, Sampietro GM, Russo A, Radice E, Colombo E, Imbesi V, Molteni M, Danelli PG, Taschieri AM, Bianchi Porro G. Azathioprine and mesalamine for prevention of relapse after conservative surgery for Crohn's disease. *Gastroenterology* 2004; **127**: 730-740
68 **Rutgeerts P**, Hiele M, Geboes K, Peeters M, Penninckx F, Aerts R, Kerremans R. Controlled trial of metronidazole treatment for prevention of Crohn's recurrence after ileal resection. *Gastroenterology* 1995; **108**: 1617-1621
69 **Gionchetti P**, Rizzello F, Morselli C, Romagnoli R, Campieri M. Management of inflammatory bowel disease: does rifaximin offer any promise? *Chemotherapy* 2005; **51** Suppl 1: 96-102
70 **Rutgeerts P**, Van Assche G, Vermeire S, D'Haens G, Baert F, Noman M, Aerden I, De Hertogh G, Geboes K, Hiele M, D'Hoore A, Penninckx F. Ornidazole for prophylaxis of postoperative Crohn's disease recurrence: a randomized, double-blind, placebo-controlled trial. *Gastroenterology* 2005; **128**: 856-861
71 **D'Haens G**. Prevention of postoperative recurrence in Crohn' s disease. *Curr Gastroenterol Rep* 1999; **1**: 476-481
72 **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
73 **Mahadevan U**, Marion JF, Present DH. Fistula response to methotrexate in Crohn's disease: a case series. *Aliment Pharmacol Ther* 2003; **18**: 1003-1008
74 **Bernstein LH**, Frank MS, Brandt LJ, Boley SJ. Healing of perineal Crohn's disease with metronidazole. *Gastroenterology* 1980; **79**: 357-365
75 **Turunen U**. Long-term outcome of ciprofloxacin treatment in severe perianal and fistulous Crohn's disease. *Gastroenterology* 1993; **104**: A793
76 **Present DH**, Rutgeerts P, Targan S, Hanauer SB, Mayer L, van Hogezand 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
77 **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
78 **Present DH**. Crohn's fistula: current concepts in management. *Gastroenterology* 2003; **124**: 1629-1635
79 **Sandborn WJ**, Present DH, Isaacs KL, Wolf DC, Greenberg E, Hanauer SB, Feagan BG, Mayer L, Johnson T, Galanko J, Martin C, Sandler RS. Tacrolimus for the treatment of fistulas in patients with Crohn's disease: a randomized, placebo-controlled trial. *Gastroenterology* 2003; **125**: 380-388
80 **Munkholm P**, Langholz E, Davidsen M, Binder V. Frequency of glucocorticoid resistance and dependency in Crohn's disease. *Gut* 1994; **35**: 360-362
81 **Faubion WA**, Loftus EV, Harmsen WS, Zinsmeister AR, Sandborn WJ. The natural history of corticosteroid therapy for inflammatory bowel disease: a population-based study. *Gastroenterology* 2001; **121**: 255-260
82 **Fielding JF**, Toye DK, Beton DC, Cooke WT. Crohn's disease of the stomach and duodenum. *Gut* 1970; **11**: 1001-1006
83 **Wagtmans MJ**, Verspaget HW, Lamers CB, van Hogezand RA. Clinical aspects of Crohn's disease of the upper gastrointestinal tract: a comparison with distal Crohn's disease. *Am J Gastroenterol* 1997; **92**: 1467-1471
84 **Alcántara M**, Rodriguez R, Potenciano JL, Carrobles JL, Muñoz C, Gomez R. Endoscopic and bioptic findings in the upper gastrointestinal tract in patients with Crohn's disease. *Endoscopy* 1993; **25**: 282-286
85 **Oberhuber G**, Püspök A, Oesterreicher C, Novacek G, Zauner C, Burghuber M, Vogelsang H, Pötzi R, Stolte M, Wrba F. Focally enhanced gastritis: a frequent type of gastritis in patients with Crohn's disease. *Gastroenterology* 1997; **112**: 698-706
86 **Oberhuber G**, Hirsch M, Stolte M. High incidence of upper gastrointestinal tract involvement in Crohn's disease. *Virchows Arch* 1998; **432**: 49-52
87 **Griffiths AM**, Alemayehu E, Sherman P. Clinical features of gastroduodenal Crohn's disease in adolescents. *J Pediatr Gastroenterol Nutr* 1989; **8**: 166-171
88 **Korelitz BI**, Adler DJ, Mendelsohn RA, Sacknoff AL. Long-term experience with 6-mercaptopurine in the treatment of Crohn's disease. *Am J Gastroenterol* 1993; **88**: 1198-1205
89 **Miehsler W**, Püspök A, Oberhuber T, Vogelsang H. Impact of different therapeutic regimens on the outcome of patients with Crohn's disease of the upper gastrointestinal tract. *Inflamm Bowel Dis* 2001; **7**: 99-105
90 **Grübel P**, Choi Y, Schneider D, Knox TA, Cave DR. Severe isolated Crohn's-like disease of the gastroduodenal tract. *Dig Dis Sci* 2003; **48**: 1360-1365
91 **Nugent FW**, Roy MA. Duodenal Crohn's disease: an analysis of 89 cases. *Am J Gastroenterol* 1989; **84**: 249-254
92 **Belli DC**, Seidman E, Bouthillier L, Weber AM, Roy CC, Pletincx M, Beaulieu M, Morin CL. Chronic intermittent elemental diet improves growth failure in children with Crohn 's disease. *Gastroenterology* 1988; **94**: 603-610
93 **Aiges H**, Markowitz J, Rosa J, Daum F. Home nocturnal supplemental nasogastric feedings in growth-retarded adolescents with Crohn's disease. *Gastroenterology* 1989; **97**: 905-910
94 **Lindor KD**, Fleming CR, Ilstrup DM. Preoperative nutritional status and other factors that influence surgical outcome in patients with Crohn's disease. *Mayo Clin Proc* 1985; **60**: 393-396
95 **Lochs H**, Dejong C, Hammarqvist F, Hebuterne X, Leon-Sanz M, Schütz T, van Gemert W, van Gossum A, Valentini L, Lübke H, Bischoff S, Engelmann N, Thul P. ESPEN Guidelines on Enteral Nutrition: Gastroenterology. *Clin Nutr* 2006; **25**: 260-274
96 **Zachos M**, Tondeur M, Griffiths AM. Enteral nutritional therapy for inducing remission of Crohn's disease. *Cochrane Database Syst Rev* 2001; **3**: CD000542
97 **Gianotti L**, Braga M, Nespoli L, Radaelli G, Beneduce A, Di Carlo V. A randomized controlled trial of preoperative oral supplementation with a specialized diet in patients with gastrointestinal cancer. *Gastroenterology* 2002; **122**: 1763-1770
98 **Wilschanski M**, Sherman P, Pencharz P, Davis L, Corey M, Griffiths A. Supplementary enteral nutrition maintains remission in paediatric Crohn's disease. *Gut* 1996; **38**: 543-548
99 **Wright RA**, Adler EC. Peripheral parenteral nutrition is no better than enteral nutrition in acute exacerbation of Crohn' s disease: a prospective trial. *J Clin Gastroenterol* 1990; **12**: 396-399
100 **Schwab D**, Raithel M, Hahn EG. Enteral nutrition in acute Crohn disease. *Z Gastroenterol* 1998; **36**: 983-995
101 **Orchard TR**, Wordsworth BP, Jewell DP. Peripheral arthropathies in inflammatory bowel disease: their articular distribution and natural history. *Gut* 1998; **42**: 387-391
102 **Dougados M**, Boumier P, Amor B. Sulphasalazine in ankylosing spondylitis: a double blind controlled study in 60 patients. *Br Med J* (Clin Res Ed) 1986; **293**: 911-914
103 **Dougados M**, vam der Linden S, Leirisalo-Repo M, Huitfeldt B, Juhlin R, Veys E, Zeidler H, Kvien TK, Olivieri I, Dijkmans B. Sulfasalazine in the treatment of spondylarthropathy. A randomized, multicenter, double-blind, placebo-controlled study. Arthritis Rheum 1995; **38**: 618-627
104 **Van den Bosch F**, Kruithof E, De Vos M, De Keyser F, Mielants H. Crohn's disease associated with spondyloarthropathy: effect of TNF-alpha blockade with infliximab on articular symptoms. *Lancet* 2000; **356**: 1821-1822
105 **Braun J**, Brandt J, Listing J, Zink A, Alten R, Golder W, Gromnica-Ihle E, Kellner H, Krause A, Schneider M,

Sörensen H, Zeidler H, Thriene W, Sieper J. Treatment of active ankylosing spondylitis with infliximab: a randomised controlled multicentre trial. *Lancet* 2002; **359**: 1187-1193

106 **Viscido A**, Habib FI, Kohn A, Papi C, Marcheggiano A, Pimpo MT, Vernia P, Cadau G, Caprilli R. Infliximab in refractory pouchitis complicated by fistulae following ileo-anal pouch for ulcerative colitis. *Aliment Pharmacol Ther* 2003; **17**: 1263-1271

107 **Regueiro M**, Valentine J, Plevy S, Fleisher MR, Lichtenstein GR. Infliximab for treatment of pyoderma gangrenosum associated with inflammatory bowel disease. *Am J Gastroenterol* 2003; **98**: 1821-1826

108 **Fries W**, Giofré MR, Catanoso M, Lo Gullo R. Treatment of acute uveitis associated with Crohn's disease and sacroileitis with infliximab. *Am J Gastroenterol* 2002; **97**: 499-500

109 **Lindor KD**. Ursodiol for primary sclerosing cholangitis. Mayo Primary Sclerosing Cholangitis-Ursodeoxycholic Acid Study Group. *N Engl J Med* 1997; **336**: 691-695

110 **Olsson R**, Boberg KM, de Muckadell OS, Lindgren S, Hultcrantz R, Folvik G, Bell H, Gangsøy-Kristiansen M, Matre J, Rydning A, Wikman O, Danielsson A, Sandberg-Gertzén H, Ung KA, Eriksson A, Lööf L, Prytz H, Marschall HU, Broomé U. High-dose ursodeoxycholic acid in primary sclerosing cholangitis: a 5-year multicenter, randomized, controlled study. *Gastroenterology* 2005; **129**: 1464-1472

S- Editor Pan BR **L- Editor** Lutze M **E- Editor** Liu WF