Treatment Algorithms in IBD (1)

Digestive Diseases

Dig Dis 2009;27:542–549
DOI: 10.1159/000233295

Medical Management of Ulcerative Colitis

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Key Words
Ulcerative colitis · Topical therapy · Medical management · Aminosalicylates · Inflammatory bowel disease · Systemic therapy

Abstract
Ulcerative colitis (UC) is a chronic and relapsing inflammation limited to the colonic mucosa and always involving the rectum with variable extension towards the cecum. The aim of medical treatment is to induce and maintain clinical remission. In contrast to Crohn's disease for which a 'top-down' or 'early aggressive' therapy is discussed, in UC the concept of a step-up treatment is still valid. This step-up approach includes local or systemic administration of 5-aminosalicylic acid as first-line therapy followed by topical or systemic steroid administration as well as azathioprine, 6-mercaptopurine, cyclosporine, and more recently anti-tumor necrosis factor monoclonal antibodies as options in refractory or chronic active disease. Colectomy may be necessary if medical treatments are unsuccessful or if complications develop. The decision about the individual therapy of UC is dependent on both disease activity and on disease location. Different therapy strategies are applied in ulcerative proctitis, left-sided colitis, pancolitis and fulminant colitis as well as in chronic active disease and maintenance of remission. This overview presents important concepts in the treatment of UC based on the published guidelines.

Introduction

Ulcerative colitis (UC) besides Crohn's disease is the most important chronic inflammatory bowel disease. Its incidence in Europe is estimated to be 5–25 new patients per 100,000 inhabitants per year [1–5]. As its course and extent vary considerably, an individualized diagnostic approach and therapy are mandatory.

Clearly the therapeutic management of UC is focused on the induction and maintenance of remission. However, presently we face a discussion of whether clinical or endoscopical remission should be the final treatment goal. During relapses or flares of UC, pharmacological or surgical interventions are needed to re-establish remission. For the re-establishment of remission and achievement of long-term remission, strategies have to be employed that minimize steroid use and therapy-related side effects.

Treatment decisions are based on disease severity, i.e. mild, moderate or severe. The degree of inflammation is a crucial factor for the choice of the therapeutic procedures. In addition, the duration of the symptoms, preceding therapy/therapies, disease history as well as individual symptoms influence the therapy decision. The extent of the disease (pancolitis, left-sided colitis, rectosigmoiditis or proctitis) will clearly be of impact on the decision for a specific therapy. Symptoms indicating the severity of the disease flare – such as vomiting, signs of bowel obstruction, number of bowel movements, presence of blood, weight loss, high fever and abdominal tenderness

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and pain during defecation – are useful practical criteria of severity in everyday medical practice. Frequently, the efficacy of a topical local therapy is underestimated, or is not addressed, because of the rectal application.

The valid guidelines represent the basis on which the optimal therapy must be determined for the individual patient.

Medical Management of Acute Flares of Ulcerative Colitis

An acute flare of UC is usually characterized by typical clinical complaints, such as frequent bowel movements, bloody diarrhea and abdominal pain. It is frequently recommended to exclude an infectious colitis before starting any treatment. The impact and efficacy of such 'routine diagnostics', however, has never been really evaluated. A recent development is an increase in the incidence of *Clostridium difficile* colitis and CMV colitis among UC patients, especially under immunosuppressive conditions. This has to be kept in mind in patients that seem to have steroid-refractory UC.

The choice of therapy for acute flares or relapses of UC is based on the clinical presentation. The value of laboratory markers for the therapy decision is limited. As a minimum requirement, hemoglobin levels, leukocyte counts as well as general inflammation parameters such as thrombocyte counts, ESR or CRP should be determined [6]. 'Control colonoscopies' without therapeutic or prognostic consequences are not indicated and should not be performed during an acute flare of UC. Changes in the extension of the disease can also be proven by ultrasound in the hands of an experienced doctor.

In general, a step-up approach is recommended in all guidelines for the treatment of UC (fig. 1). An abundance of evidence exists that supports the use of aminosalicylates (5-ASA) in mild to moderate UC for the induction of remission. Corticosteroids are used in patients not responding to 5-ASA or in patients with more severe disease. Azathioprine (AZA) and 6-mercaptopurine (6-MP) have been shown to be useful in steroid-refractory patients.

Left-Sided Colitis, Rectosigmoiditis, Proctitis

Distal or left-sided UC with mild to moderate activity should be initially treated topically [7]. The rectal application of steroids (as enema or foam) is superior to placebo; however, 5-aminosalicylic acid (5-ASA) is superior to steroids in topical application [8, 9]. Consecutively,

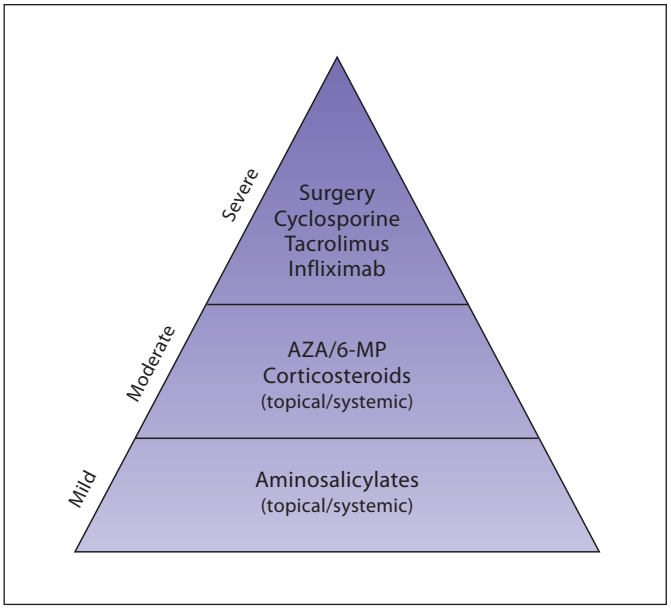

Fig. 1. Step-up therapy approach in UC.

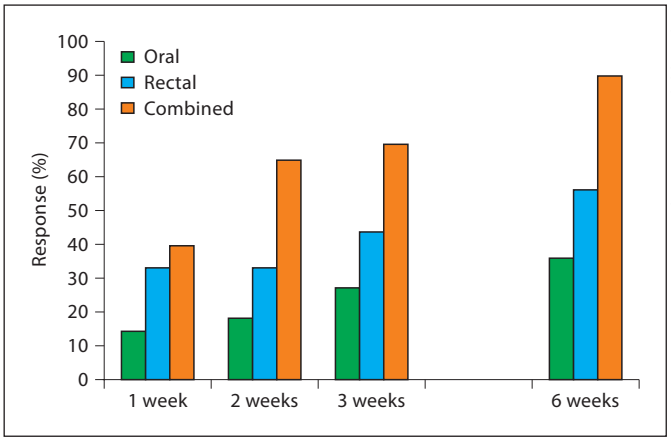

Fig. 2. Advantage of combination therapy of oral and rectal 5-ASA therapy over monotherapy (according to Safdi et al. [12]).

treatment of first choice in mild to moderate left-sided colitis or rectosigmoiditis are foams or enemas with 5-ASA (mesalamine) [7, 10]. During an acute flare of colitis, application of enemas is frequently uncomfortable due to the at times large volume (up to 100 ml), making them less well tolerated by the patients [11]. In patients with UC, the rectum is usually the side of the most severe inflammation. It contains the highest number of sensory nerves in the bowel. Therefore, it is easily conceivable that

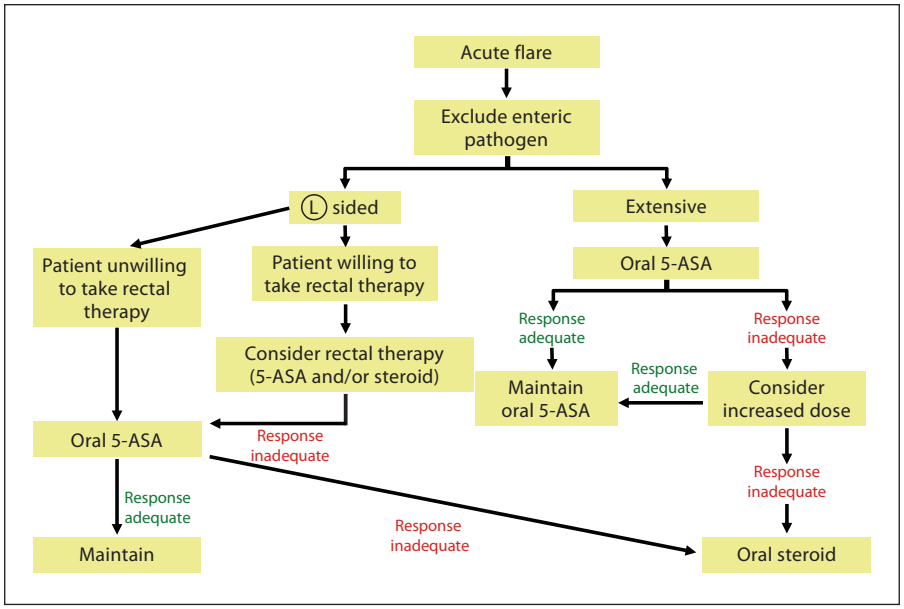

Fig. 3. Treatment algorithm for mild to moderate UC.

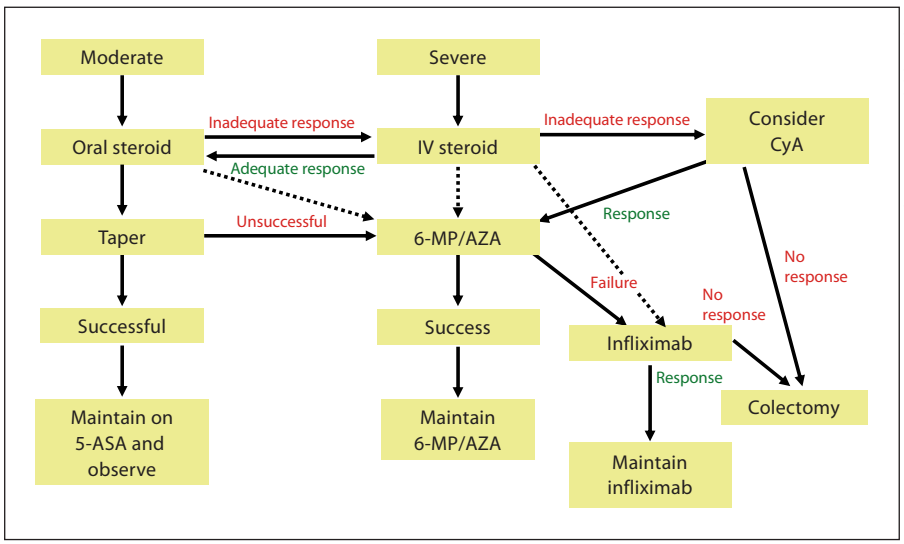

Fig. 4. Treatment algorithm for moderate to severe UC.

such a large volume of fluid will cause complaints. Foams are better accepted by the patients in general (potentially also due to the smaller volume). In ulcerative proctitis, 5-ASA suppositories should be used [11].

If the disease extends to the left colonic flexure, it appears to be recommendable to combine topical therapy with an oral 5-ASA preparation [12–14]. The recommended duration of treatment is at least 4 weeks [10, 15]. The minimal, but sufficient topical dose for the achievement of a remission is 1 g 5-ASA per day [14]. Higher doses up to 4 g/day have not been proven to be more effective [10, 15, 16]. If a topical therapy with 5-ASA over several weeks is ineffective, topical steroids should be added for at least 4 weeks [17, 18]. If the topical therapy finally fails, systemic steroids should be used [13, 19]. A severe flare of a distal colitis should primarily be treated orally with systemic steroids, if possible in combination with topical use of 5-ASA [13, 20] (fig. 2).

In different studies, initial steroid doses between 40 and 60 mg/day did not seem to exhibit remarkable differences in therapeutic efficacy [21].

Pancolitis

A mild to moderate flare of a pancolitis should initially be treated with oral 5-ASA [16, 22, 23] (fig. 3). 4 g 5-ASA per day are superior to 2 g. Usually it has been rec-

ommended that 5-ASA should be taken in three doses over the day. Newer studies from the last years indicate that the total daily dose can be taken at one time (e.g. in the morning) – or even should be taken at one time, as in some studies there was even increased efficacy under these conditions [24–26]. The possibility to take the whole dose at one time is also likely to increase patient compliance and adherence to therapy. From several studies we know that the main drawback of 5-ASA therapy (and probably the most important reason for therapy failure) is a reduced adherence due to the mode of intake and the number of tablets or capsules (up to 8 per day). With respect to this, new formulations as 'granules' or 'sachets' may also be of clear advantage.

During severe pancolitis or lack of response to a therapy with 5-ASA, systemic glucocorticoids should be used orally or intravenously (initially a 60-mg prednisone equivalent per day) [27, 28] (fig. 4). In patients requiring steroid therapy, the immediate outcomes are favorable, but the long-term outcome at 1 year is somewhat disappointing. About half of the patients with UC initially treated with steroids will require additional therapy after 1 year. A population-based study has shown that a year after the initial course of corticosteroid treatment, a prolonged steroid response is seen in only 49% of patients with UC. However, sometimes a second course of steroid therapy will induce remission again. In addition, numbers may change with sufficient and well-adhered maintenance therapy. Steroid dependence has been reported to develop in 22% of UC patients, with surgery being required in 29% of those patients. In general, a state of steroid dependence should clearly be avoided. Therefore, it is questionable whether this really can be a measure in clinical studies. Whether the steroids for pancolitis are given orally or intravenously should be decided with respect to the clinical presentation of the patient.

Usually steroids are combined with oral aminosalicylates, although the efficacy or advantage of such a combination has never been documented by appropriate clinical studies. The tapering of steroids has long been performed very schematically. Tapering regimes differing from country to country have been established. In the meantime it is accepted that tapering of steroids should be planned individually according to the patient's clinical symptoms. If no response can be achieved by the oral administration of steroids, a change to one course of intravenous administration is usually recommended. This could be justified with the assumption that during severe colitis there is increased peristalsis also of the small bowel and resorption of oral steroids could be reduced. Studies on the change of an oral steroid administration to an intravenous one do not exist; however, in the experience of most clinicians this approach has clinically worked for a number of patients. An intravenous therapy duration of 10 days is generally sufficient. If no improvement is observed within a period of 10 days, therapy has to be reconsidered and changed. Before the infliximab era, cyclosporine at a dose of 4 mg/kg·day i.v. was primarily recommended [28]. The Leuven group has shown that cyclosporine 2 mg/kg·day i.v. is equivalently effective [29]. Serum levels can be measured at any time during therapy, since by the continuous infusion steady-state levels are reached early. The ACT-1 and ACT-2 studies among others showed that the anti-tumor necrosis factor antibody infliximab (5 mg/kg in weeks 0, 2 and 8 and then every 8 weeks) is effective in severe UC [30–32]. The discussion at which time point in the step-up approach of severe UC treatment infliximab should be used is still ongoing [33]. New data also exist for a successful therapy with tacrolimus in this situation [34, 35]. Tacrolimus can be used in individual cases as an alternative to cyclosporine.

Medical Management of Severe Acute Colitis/Toxic Megacolon

A severe flare is characterized by the respective clinical symptoms which include systemic signs such as fever, tachycardia and anemia as well as increased inflammation parameters. Crucial symptoms are frequent bloody diarrhea, fever >38.5°C and weight loss. An abdominal X-ray should be performed to search for a dilation of the colon (toxic megacolon) [36].

A megacolon is present if the diameter of the colon transversum is >5.5 cm. Ultrasound can be a useful diagnostic supplement in this situation [36]. A sigmoidoscopy may be useful to exclude *C. difficile* colitis and CMV colitis. Since a fulminant colitis or a toxic megacolon can also occur on the basis of an intestinal infection, investigations on *C. difficile* toxin as well as an adequate CMV diagnostic (e.g. immunohistochemistry for pp65) should be performed [37–39]. For the treatment of a fulminant flare of UC, the patient should be hospitalized. An interdisciplinary approach between gastroenterologists and visceral surgeons is mandatory. A conservative therapy should only be performed if no contraindications exist [40].

Treatment can be started with a course of intravenous steroids, e.g. 4 × 100 mg hydrocortisone per day [41]. In

addition to fluid and electrolyte substitution, parenteral nutrition may be indicated. If steroid therapy fails (no sufficient treatment response within 3–5 days) and a clear indication for surgery is not given, a therapy with intravenous cyclosporine (2 or 4 mg/kg·day as continuous infusion) may be applied [28, 42, 43]. As mentioned, infliximab has been proven to be an alternative in this situation in several studies [31, 44–46].

If intravenous cyclosporine is successful after 7–10 days, it is usually switched to oral therapy for maintenance of remission and combined with other immunosuppressants such as AZA (2.5 mg/kg·day) [43]. Oral cyclosporine cannot be expected to maintain remission for longer periods. Approximately 60–80% of the patients benefit on a long-term basis and for 40% of the patients colectomy can be avoided [43]. As an alternative to cyclosporine, tacrolimus has also been successfully used [34, 47]. This therapy should be reserved to centers with appropriate experience.

If the need for a rapid surgical intervention is possible, further corticosteroids should be avoided as steroids increase the risk of post-surgical (infectious) complications [48]. Parenteral nutrition should applied for fluid and electrolyte substitution. In controlled studies, however, this was not superior to enteral nutrition. Clearly, enteral nutrition cannot be used under subileus/ileus conditions. Controlled studies do not show an advantage of an additional administration of antibiotics; therefore, this should only be done if signs of infection/superinfection or peritonitis are present.

After achieving remission, AZA (2–2.5 mg/kg) can be used for maintenance therapy [49, 50]. A *Pneumocystis carinei/jiroveci* prophylaxis is recommended during the triple immunosuppression (cyclosporine, AZA and systemic steroids). The efficacy of such prophylaxis has not been proven so far [51]. If therapy fails, early colectomy should be performed. The clinical value of leukocyte apheresis is still a matter of discussion.

Medical Management of Chronic Active Ulcerative Colitis

A chronic active disease is characterized by the persistence of clinical symptoms (diarrhea, blood loss, pain) despite an adequate medical therapy. Also, a disease course that has shown some improvement upon therapy which is however not complete and permanent (<2 relapses/year) is termed a *chronic active disease*. A colonoscopy with biopsies and subsequent histology may be helpful in individual cases, e.g. for the exclusion of CMV colitis. In cases of severe, chronically active UC, the option of a colectomy should always be discussed with the patient.

If no colectomy is performed for the moment, an immunosuppression with AZA/6-MP may be useful [52, 53]. Newer studies indicate that infliximab can also be given if a fast therapy response is desired or necessary [32]. In individual cases the discrimination of a chronically active colitis and irritable bowel syndrome can be difficult. Particularly in therapy-refractory disease under immunosuppression, an appropriate diagnostic procedure must be undertaken to exclude CMV colitis. Oral systemic steroids should not be used as continuous therapy due to their side effects. In chronically active distal colitis, however, the long-term rectal administration of steroid enemas or foams may be acceptable due to their low systemic bioavailability.

A therapy failure on AZA therapy can at the earliest be diagnosed after 6 months of continuous administration. Maintenance therapy with AZA or 6-MP should be applied for 3–5 years [54, 55]. According to all available data, the administration of AZA during pregnancy is regarded as being safe. Upon administration of AZA/6-MP the leukocyte count and the transaminases must be controlled regularly if abdominal pain occurs. Additionally, serum lipase levels should be determined. After start of the immunosuppressive therapy, leukocyte counts and GPT values should be controlled after 1, 2, 4, 8 and 12 weeks, thereafter at least every 12 weeks. Upon AZA therapy, bone marrow suppression may occur, which must be discovered in time. With leukocyte numbers <2,500, AZA therapy should be terminated. After normalization of the values a therapy may be restarted with lower doses (e.g. 50 mg/day) under close supervision. Pancreatitis may occur usually in the first weeks of treatment and require immediate termination therapy. Minor increases in serum lipase or amylase without clinical symptoms are frequently observed in inflammatory bowel disease patients; their relevance remains obscure, an observing attitude is acceptable. A subsequent rise of serum liver enzymes under therapy is also a reason for termination of AZA/6-MP therapy.

The use of infliximab represents an important therapy alternative [32]. It is regarded to be safe and well tolerated, however, a tuberculosis skin test or lymphocyte stimulation test (such as QuantiFERON®) as well as a lung X-ray need to be performed prior to starting the therapy. It needs to be kept in mind that tuberculosis screening can be false-negative due to immunosuppres-

sion. Only 22% of patients will be in remission without the need of additional steroids according to the ACT-1 and ACT-2 data. On the other hand, treatment success is usually rapid and an improvement of the patients can be observed sometimes already on the day after the administration.

The administration of methotrexate can be considered in individual cases in adult patients but also in children [56]. The initial dose is 20–25 mg parenterally (oral, i.m., s.c.) every week (children: 15 mg/m^2 body surface). After achieving remission, a dose reduction to 10–15 mg/week is usually recommended. Regular blood cell counts must also take place under a therapy with methotrexate. For the monitoring of the potential hepatotoxicity, regular measurements of liver enzymes should be performed. Preexisting chronic liver disease or chronic lung disease represent contraindications for the therapy. The oral administration of tacrolimus (0.1–0.2 mg/kg b.w.) and the use of a leukocyte apheresis can be considered in individual cases.

Maintenance of Remission in Ulcerative Colitis

The definition of remission is based on clinical features. Criteria for remission are absence of diarrhea (>3 bowel movements/day), no visible blood in stools as well as no UC-associated intestinal or extraintestinal complaints. For maintenance of remission in patients with UC, first-line therapy is 5-ASA administered orally or rectally [57–59]. The combination of oral and rectal/topical therapy is superior to oral monotherapy (fig. 2). In the case of distal UC, evidence for the superiority of the rectal application exists [59].

The compliance or adherence on maintenance therapy is crucial for its success [60]. If more than two-thirds of the recommended dose is taken, the risk of a flare or relapse in the first year is only approximately 10–20% [61]. With respect to this, it is certainly favorable that newer studies point to the fact that the entire 5-ASA dosage can be taken at one time (e.g. either the morning or evening), i.e., the distribution into three doses is no longer necessary.

The effectiveness of the following minimal dosages has been demonstrated in clinical studies: (1) *oral administration:* SASP 2 g/day; 5-ASA 1.5 g/day; olsalazine 1.0 g/day, (2) *rectal administration:* left-sided colitis: 5-ASA enemas either 1 g/day or 4 g each third day or 4 g/day on the first 7 days of the month; proctitis: 5-ASA suppositories 2 × 500 mg/day or 1 g/day three times weekly.

Since individual patients prefer mesalazine foams as compared to enemas, this form of application can probably be given at a similar dosage, even if studies are not available for maintenance of remission with foam preparations. Maintenance therapy should be administrated for at least 2 years.

Upon incompatibility of 5-ASA, a probiotic pathogen preparation, e.g. *Escherichia coli* Nissle, can be used successfully for the maintenance of remission with a similar clinical efficacy [62, 63]. As alternatives for complicated UC, AZA/6-MP [53] and infliximab can be used for the maintenance of remission [32]. Systemic steroids should not be used for maintenance therapy. The increased efficacy of a combination of oral and rectal therapy with 5-ASA is well documented by clinical studies; however, most patients prefer monotherapy.

Disclosure Statement

The author has received research funding from Abbott, Essex, Falk, UCB, Ardeypharm and Lifor. The author is member of advisory boards for Abbott, Essex, Novartis and UCB.

References

1 Rao SS, Holdsworth CD, Read NW: Symptoms and stool patterns in patients with ulcerative colitis. Gut 1988;29:342–345.
2 Jones HW, Grogono J, Hoare AM: Surveillance in ulcerative colitis: burdens and benefit. Gut 1988;29:325–331.
3 Armitage EL, Aldhous MC, Anderson N, Drummond HE, Riemersma RA, Ghosh S, Satsangi J: Incidence of juvenile-onset Crohn's disease in Scotland: association with northern latitude and affluence. Gastroenterology 2004;127:1051–1057.
4 Turunen P, Kolho KL, Auvinen A, Iltanen S, Huhtala H, Ashorn M: Incidence of inflammatory bowel disease in Finnish children, 1987–2003. Inflamm Bowel Dis 2006;12:677–683.
5 Vind I, Riis L, Jess T, Knudsen E, Pedersen N, Elkjaer M, Bak Andersen I, Wewer V, Nørregaard P, Moesgaard F, Bendtsen F, Munkholm P: Increasing incidences of inflammatory bowel disease and decreasing surgery rates in Copenhagen City and County, 2003–2005: a population-based study from the Danish Crohn colitis database. Am J Gastroenterol 2006;101:1274–1282.

6 Descos L, Andre F, Andre C, Gillon J, Landais P, Fermanian J: Assessment of appropriate laboratory measurements to reflect the degree of activity of ulcerative colitis. Digestion 1983;28:148–152.
7 Gionchetti P, Amadini C, Rizzello F, Venturi A, Campieri M: Treatment of mild to moderate ulcerative colitis and pouchitis. Aliment Pharmacol Ther 2002;16(suppl 4):13–19.
8 Marshall JK, Irvine EJ: Rectal corticosteroids versus alternative treatments in ulcerative colitis: a meta-analysis. Gut 1997;40:775–781.
9 Campieri M, Gionchetti P, Belluzzi A, Brignola C, Migaldi M, Tabanelli GM, Bazzocchi G, Miglioli M, Barbara L: Efficacy of 5-aminosalicylic acid enemas versus hydrocortisone enemas in ulcerative colitis. Dig Dis Sci 1987;32:67S–70S.
10 Marshall JK, Irvine EJ: Rectal aminosalicylate therapy for distal ulcerative colitis: a meta-analysis. Aliment Pharmacol Ther 1995;9:293–300.
11 Campieri M, Gionchetti P, Belluzzi A, Brignola C, Tabanelli GM, Miglioli M, Barbara L: 5-Aminosalicylic acid as enemas or suppositories in distal ulcerative colitis? J Clin Gastroenterol 1988;10:406–409.
12 Safdi M, DeMicco M, Sninsky C, Banks P, Wruble L, Deren J, Koval G, Nichols T, Targan S, Fleishman C, Wiita B: A double-blind comparison of oral versus rectal mesalamine versus combination therapy in the treatment of distal ulcerative colitis. Am J Gastroenterol 1997;92:1867–1871.
13 Regueiro M, Loftus EV Jr, Steinhart AH, Cohen RD: Medical management of left-sided ulcerative colitis and ulcerative proctitis: critical evaluation of therapeutic trials. Inflamm Bowel Dis 2006;12:979–994.
14 Marshall JK, Irvine EJ: Putting rectal 5-aminosalicylic acid in its place: the role in distal ulcerative colitis. Am J Gastroenterol 2000;95:1628–1636.
15 Sutherland L, MacDonald JK: Oral 5-aminosalicylic acid for induction of remission in ulcerative colitis. Cochrane Database Syst Rev 2003:CD000543.
16 Sutherland L, Macdonald JK: Oral 5-aminosalicylic acid for induction of remission in ulcerative colitis. Cochrane Database Syst Rev 2006:CD000543.
17 Mulder CJ, Tytgat GN, Wiltink EH, Houthoff HJ: Comparison of 5-aminosalicylic acid (3 g) and prednisolone phosphate sodium enemas (30 mg) in the treatment of distal ulcerative colitis. A prospective, randomized, double-blind trial. Scand J Gastroenterol 1988;23:1005–1008.
18 Mulder CJ, Fockens P, Meijer JW, van der Heide H, Wiltink EH, Tytgat GN: Beclomethasone dipropionate (3 mg) versus 5-aminosalicylic acid (2 g) versus the combination of both (3 mg/2 g) as retention enemas in active ulcerative proctitis. Eur J Gastroenterol Hepatol 1996;8:549–553.
19 Lofberg R, Danielsson A, Suhr O, Nilsson A, Schioler R, Nyberg A, Hultcrantz R, Kollberg B, Gillberg R, Willen R, Persson T, Salde L: Oral budesonide versus prednisolone in patients with active extensive and left-sided ulcerative colitis. Gastroenterology 1996;110:1713–1718.
20 Katz JA: Medical and surgical management of severe colitis. Semin Gastrointest Dis 2000;11:18–32.
21 Baron JH, Connell AM, Kanaghinis TG, Lennard-Jones JE, Jones AF: Outpatient treatment of ulcerative colitis. Comparison between three doses of oral prednisone. Br Med J 1962;2:441–443.
22 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.
23 Schroeder KW, Tremaine WJ, Ilstrup DM: Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. N Engl J Med 1987;317:1625–1629.
24 Kruis W, Kiudelis G, Racz I, Gorelov IA, Pokrotnieks J, Horynski M, Batovsky M, Kykal J, Bohm SK, Greinwald R, Muller R: Once-daily versus three-times-daily mesalazine granules in active ulcerative colitis: a double-blind, double-dummy, randomised non-inferiority trial. Gut 2009;58:233–240.
25 Kamm MA, Sandborn WJ, Gassull M, Schreiber S, Jackowski L, Butler T, Lyne A, Stephenson D, Palmen M, Joseph RE: Once-daily, high-concentration MMX mesalamine in active ulcerative colitis. Gastroenterology 2007;132:66–75.
26 Dignass AU, Bokemeyer B, Adamek HE, Mross MR, Vinter-Jensen L, Boerner N, Silvennoinen J, Tan TG, Oudkerk-Pool M, Stijnen T, Dietel P, Klugmann T, Veerman H: Maintenance therapy with once-daily 2 g mesalazine (Pentasa) treatment improves remission rates in subjects with ulcerative colitis compared to twice daily 1 g mesalazine: data from a randomised controlled trial. Gastroenterology 2008;134:A494.
27 Truelove SC, Witts LJ: Cortisone in ulcerative colitis; final report on a therapeutic trial. Br Med J 1955;2:1041–1048.
28 D'Haens G, Lemmens L, Geboes K, Vandeputte L, Van Acker F, Mortelmans L, Peeters M, Vermeire S, Penninckx F, Nevens F, Hiele M, Rutgeerts P: Intravenous cyclosporine versus intravenous corticosteroids as single therapy for severe attacks of ulcerative colitis. Gastroenterology 2001;120:1323–1329.
29 Van Assche G, D'Haens G, Noman M, Vermeire S, Hiele M, Asnong K, Arts J, D'Hoore A, Penninckx F, Rutgeerts P: Randomized, double-blind comparison of 4 versus 2 mg/kg intravenous cyclosporine in severe ulcerative colitis. Gastroenterology 2003;125:1025–1031.
30 Feagan BG, Reinisch W, Rutgeerts P, Sandborn WJ, Yan S, Eisenberg D, Bala M, Johanns J, Olson A, Hanauer SB: The effects of infliximab therapy on health-related quality of life in ulcerative colitis patients. Am J Gastroenterol 2007;102:794–802.
31 Regueiro M, Curtis J, Plevy S: Infliximab for hospitalized patients with severe ulcerative colitis. J Clin Gastroenterol 2006;40:476–481.
32 Rutgeerts P, Sandborn WJ, Feagan BG, Reinisch W, Olson A, Johanns J, Travers S, Rachmilewitz D, Hanauer SB, Lichtenstein GR, de Villiers WJ, Present D, Sands BE, Colombel JF: Infliximab for induction and maintenance therapy for ulcerative colitis. N Engl J Med 2005;353:2462–2476.
33 Tsai HH, Punekar YS, Morris J, Fortun P: A model of the long-term cost effectiveness of scheduled maintenance treatment with infliximab for moderate-to-severe ulcerative colitis. Aliment Pharmacol Ther 2008;28:1230–1239.
34 Ogata H, Matsui T, Nakamura M, Iida M, Takazoe M, Suzuki Y, Hibi T: A randomised dose finding study of oral tacrolimus (FK-506) therapy in refractory ulcerative colitis. Gut 2006;55:1255–1262.
35 Yamamoto S, Nakase H, Mikami S, Inoue S, Yoshino T, Takeda Y, Kasahara K, Ueno S, Uza N, Kitamura H, Tamaki H, Matsuura M, Inui K, Chiba T: Long-term effect of tacrolimus therapy in patients with refractory ulcerative colitis. Aliment Pharmacol Ther 2008;28:589–597.
36 Hoffmann JC, Schwandner O, Bruch HP: Ulcerative colitis. Fulminant disease (in German). Z Gastroenterol 2004;42:1002–1006.
37 Minami M, Ohta M, Ohkura T, Ando T, Ohmiya N, Niwa Y, Goto H: Cytomegalovirus infection in severe ulcerative colitis patients undergoing continuous intravenous cyclosporine treatment in Japan. World J Gastroenterol 2007;13:754–760.
38 Kojima T, Watanabe T, Hata K, Shinozaki M, Yokoyama T, Nagawa H: Cytomegalovirus infection in ulcerative colitis. Scand J Gastroenterol 2006;41:706–711.
39 Kambham N, Vij R, Cartwright CA, Longacre T: Cytomegalovirus infection in steroid-refractory ulcerative colitis: a case-control study. Am J Surg Pathol 2004;28:365–373.
40 Cima RR, Pemberton JH: Surgical indications and procedures in ulcerative colitis. Curr Treat Options Gastroenterol 2004;7:181–190.

41 Meyers S, Lerer PK, Feuer EJ, Johnson JW, Janowitz HD: Predicting the outcome of corticoid therapy for acute ulcerative colitis. Results of a prospective, randomized, double-blind clinical trial. J Clin Gastroenterol 1987; 9:50–54.
42 Lichtiger S, Present DH, Kornbluth A, Gelernt I, Bauer J, Galler G, Michelassi F, Hanauer S: Cyclosporine in severe ulcerative colitis refractory to steroid therapy. N Engl J Med 1994;330:1841–1845.
43 Cohen RD, Stein R, Hanauer SB: Intravenous cyclosporin in ulcerative colitis: a five-year experience. Am J Gastroenterol 1999;94: 1587–1592.
44 Jarnerot G: Infliximab or cyclosporine for severe ulcerative colitis. Gastroenterology 2006;130:287.
45 Hanauer SB: Infliximab or cyclosporine for severe ulcerative colitis. Gastroenterology 2005;129:1358–1359.
46 Jarnerot G, Hertervig E, Friis-Liby I, Blomquist L, Karlen P, Granno C, Vilien M, Strom M, Danielsson A, Verbaan H, Hellstrom PM, Magnuson A, Curman B: Infliximab as rescue therapy in severe to moderately severe ulcerative colitis: a randomized, placebo-controlled study. Gastroenterology 2005;128:1805–1811.
47 Baumgart DC, Pintoffl JP, Sturm A, Wiedenmann B, Dignass AU: Tacrolimus is safe and effective in patients with severe steroid-refractory or steroid-dependent inflammatory bowel disease – a long-term follow-up. Am J Gastroenterol 2006;101:1048–1056.
48 Aberra FN, Lewis JD, Hass D, Rombeau JL, Osborne B, Lichtenstein GR: Corticosteroids and immunomodulators: postoperative infectious complication risk in inflammatory bowel disease patients. Gastroenterology 2003;125:320–327.
49 Fernandez-Banares F, Bertran X, Esteve-Comas M, Cabre E, Menacho M, Humbert P, Planas R, Gassull MA: Azathioprine is useful in maintaining long-term remission induced by intravenous cyclosporine in steroid-refractory severe ulcerative colitis. Am J Gastroenterol 1996;91:2498–2499.
50 Sood A, Kaushal V, Midha V, Bhatia KL, Sood N, Malhotra V: The beneficial effect of azathioprine on maintenance of remission in severe ulcerative colitis. J Gastroenterol 2002;37:270–274.
51 Higgins RM, Bloom SL, Hopkin JM, Morris PJ: The risks and benefits of low-dose cotrimoxazole prophylaxis for *Pneumocystis pneumonia* in renal transplantation. Transplantation 1989;47:558–560.
52 Sands BE: Immunosuppressive drugs in ulcerative colitis: twisting facts to suit theories? Gut 2006;55:437–441.
53 Timmer A, McDonald J, Macdonald J: Azathioprine and 6-mercaptopurine for maintenance of remission in ulcerative colitis. Cochrane Database Syst Rev 2007:CD000478.
54 Mantzaris GJ, Sfakianakis M, Archavlis E, Petraki K, Christidou A, Karagiannidis A, Triadaphyllou G: A prospective randomized observer-blind 2-year trial of azathioprine monotherapy versus azathioprine and olsalazine for the maintenance of remission of steroid-dependent ulcerative colitis. Am J Gastroenterol 2004;99:1122–1128.
55 Lopez-Sanroman A, Bermejo F, Carrera E, Garcia-Plaza A: Efficacy and safety of thiopurinic immunomodulators (azathioprine and mercaptopurine) in steroid-dependent ulcerative colitis. Aliment Pharmacol Ther 2004;20:161–166.
56 Egan LJ, Sandborn WJ, Tremaine WJ, Leighton JA, Mays DC, Pike MG, Zinsmeister AR, Lipsky JJ: A randomized dose-response and pharmacokinetic study of methotrexate for refractory inflammatory Crohn's disease and ulcerative colitis. Aliment Pharmacol Ther 1999;13:1597–1604.
57 Sutherland L, Macdonald JK: Oral 5-aminosalicylic acid for maintenance of remission in ulcerative colitis. Cochrane Database Syst Rev 2006:CD000544.
58 Orchard T, Probert CS, Keshav S: Review article: maintenance therapy in patients with ulcerative colitis. Aliment Pharmacol Ther 2006;24(suppl 1):17–22.
59 Gionchetti P, Rizzello F, Morselli C, Tambasco R, Campieri M: Aminosalicylates for distal colitis. Aliment Pharmacol Ther 2006; 24(suppl 3):41–44.
60 Bergman R, Parkes M: Systematic review: the use of mesalazine in inflammatory bowel disease. Aliment Pharmacol Ther 2006;23: 841–855.
61 Kane SV, Cohen RD, Aikens JE, Hanauer SB: Prevalence of nonadherence with maintenance mesalamine in quiescent ulcerative colitis. Am J Gastroenterol 2001;96:2929–2933.
62 Bohm SK, Kruis W: Probiotics: do they help to control intestinal inflammation? Ann NY Acad Sci 2006;1072:339–350.
63 Kruis W, Fric P, Pokrotnieks J, Lukas M, Fixa B, Kascak M, Kamm MA, Weismueller J, Beglinger C, Stolte M, Wolff C, Schulze J: Maintaining remission of ulcerative colitis with the probiotic *Escherichia coli* Nissle 1917 is as effective as with standard mesalazine. Gut 2004;53:1617–1623.