CME

Treatment of Hospitalized Adult Patients With Severe Ulcerative Colitis: Toronto Consensus Statements

REVIEW

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OBJECTIVES: **The objective of this study was to provide updated explicit and relevant consensus statements for clinicians to refer to when managing hospitalized adult patients with acute severe ulcerative colitis (UC).**

METHODS: **The Canadian Association of Gastroenterology consensus group of 23 voting participants developed a series of recommendation statements that addressed pertinent clinical questions. An iterative voting and feedback process was used to do this in conjunction with systematic literature reviews. These statements were brought to a formal consensus meeting held in Toronto, Ontario (March 2010), when each statement was discussed, reformulated, voted upon, and subsequently revised until group consensus (at least 80% agreement) was obtained. The modified GRADE (Grading of Recommendations Assessment, Development, and Evaluation) criteria were used to rate the strength of recommendations and the quality of evidence.**

RESULTS: **As a result of the iterative process, consensus was reached on 21 statements addressing four themes (General considerations and nutritional issues, Steroid use and predictors of steroid failure, Cyclosporine and infliximab, and Surgical issues).**

CONCLUSIONS: **Key recommendations for the treatment of hospitalized patients with severe UC include early escalation to second-line medical therapy with either infliximab or cyclosporine in individuals in whom parenteral steroids have failed after 72 h. These agents should be used in experienced centers where appropriate support is available. Sequential therapy with cyclosporine and infliximab is not recommended. Surgery is an option when first-line steroid therapy fails, and is indicated when second-line medical therapy fails and/or when complications arise during the hospitalization.**

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INTRODUCTION

In North America, annual incidence rates of ulcerative colitis (UC) range from 8.8 to 19.2 cases per 100,000 person years (1,2). Based on UC cohorts that have been studied, between 18 and 25% of UC patients will experience an episode of acute severe disease and require hospitalization (3,4). Severe disease can be defined as the passage of six or more bloody stools per day, tachycardia, anemia, and elevated erythrocyte sedimentation rate with or without systemic toxicity (5–7). In all, 20–30% of patients will undergo colectomy (urgent or elective) after an acute episode of severe UC (8–10). In patients who have been hospitalized with UC, 3-year all-cause crude mortality rates have approximated 3.7–5.6% after elective colectomy, 9–13.2% after emergency colectomy, and 9.8–16% without colectomy (11,12). In a meta-analysis of studies of patients receiving medical therapy for severe UC, it was calculated that short-term mortality has averaged 1% since the 1970s (13).

Guidelines for the treatment of acute severe UC have been published in Europe (7) and the United States (14). However, no such guidelines have been formulated in Canada. A needs assessment survey by the Canadian gastroenterologists identified the development of guidelines for the management of severe UC in hospital as a priority (15,16). This, along with the rapidly shifting approach to treatment with an emphasis on earlier escalation of medical therapy, has prompted the development of these formal guidelines by the Canadian Association of Gastroenterology (CAG). The current report aims to provide the most explicit and relevant guidance possible to clinicians involved in the treatment of hospitalized patients with severe UC. Where possible, guideline decisions were made

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using an evidence-based approach and consensus expert opinion was used where evidence was limited.

REVIEW

METHODS

Initial stages and identification of the consensus group

The guideline development process is summarized in **Figure 1**. The co-chairs of the consensus group (A.B. and R.P.) selected a steering committee (D.B., R.E., B.F., J.J., J.M., and S.W.) in consultation with the CAG Executive Committee. Following an initial meeting of the steering committee, voting participants who were experts in the treatment of severe UC were invited to participate in the consensus group. The voting participants were primarily gastroenterologists who treated adults, but two pediatric gastroenterologists and three colorectal surgeons were also included (see **Appendix**). In addition, two international experts (E.L. and S.T.) and a non-voting moderator (A.Ba.) were selected.

Systematic literature searches

Systematic literature searches of PubMed and Embase were performed using the following search terms: severe, serious, refractory, UC, treatment, therapy, pharmacotherapy, safety, complication, death, infection, cytomegalovirus (CMV), response, outcome, nutrition, parenteral, surgery, surgical, narcotics, antidiarrheals, antibiotics, tobramycin, vancomycin, gentamicin, and metronidazole. Searches were not limited by date or language, and focused on prospective studies and randomized controlled trials (RCTs). Reviews were excluded from the main searches. Additional searches (using the same search terms) were conducted to identify reviews published since 2005 and abstracts from Digestive Disease Week 2009. Although the consensus was aimed at adults with UC, the literature search included studies in pediatric patients.

These searches identified 1,630 articles. Titles and abstracts (where available) were downloaded to a specifically designed website for review by members of the steering committee who reached a consensus on which references were most relevant and important. This process led to ~400 articles being retained. Additional references were identified by the steering committee from citation list searches.

Development of statements and the iterative voting process

The steering committee categorized the management of severe UC into four sections: General considerations and nutrition, Steroid use and predictors of steroid failure, Cyclosporine and infliximab, and Surgical issues. For each category, the steering committee formulated draft voting statements based on an initial review of clinical questions and suspected gaps in knowledge. All members of the consensus group voted on the statements on two occasions before the consensus meeting. Results were compiled by the CAG to ensure voter anonymity. At each voting round, consensus group members were encouraged to make comments on the wording and validity of the statements. Following each voting round, the steering committee made iterative changes to the statements to reflect the comments received from the voters.

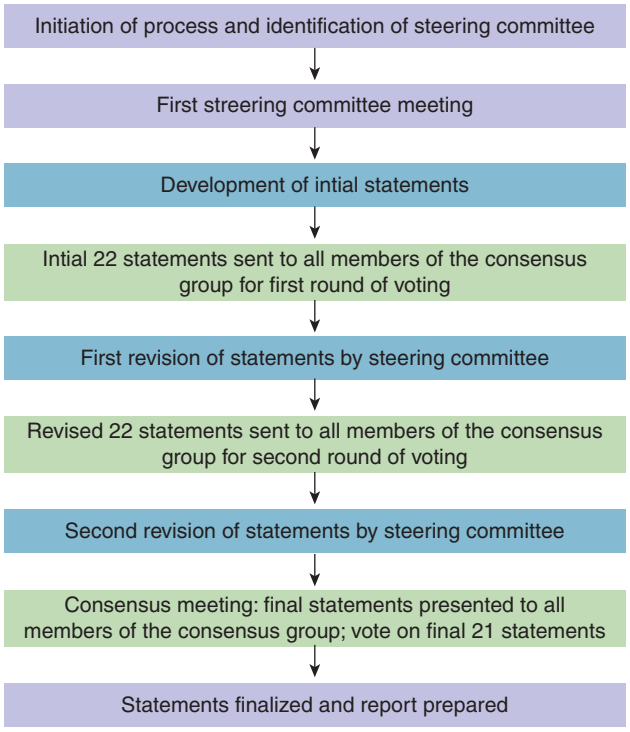

Figure 1. Guideline development process.

Consensus meeting and final voting

A 2-day consensus meeting was held in March 2010 in Toronto, Canada. Each of the four categories was introduced by an expert member of the consensus group who summarized the relevant literature and key issues. Each statement within each section was then discussed by the consensus group with the direction of the non-voting moderator (A.Ba.). An additional statement on antibiotic therapy in severe UC (Statement 9) was added at the final consensus meeting.

All voting members of the consensus group voted on each statement using anonymous electronic keypads. There were six voting options (**Table 1**). Consensus was defined *a priori* as 80% agreement. If consensus was not reached on the first round of voting, modifications were made based on group discussion before a second round of voting was carried out. Delegates discussed grading the level of evidence supporting each statement at the meeting. After the meeting, three members of the steering committee (J.M., J.J., and D.B.) graded the level of evidence and strength of recommendations for each statement using a modified GRADE (Grading of Recommendation Assessment, Development, and Evaluation) process (**Table 1**) (17). The grading was subsequently reviewed and agreed upon by the other members of the consensus group.

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Table 1. Summary of categories used in the voting and evidence grading processes

Voting options: level of agreement
Agree strongly (A+)
Agree with minor reservation (A)
Agree with major reservation (A−)
Disagree with minor reservation (D)
Disagree with major reservation (D−)
Disagree strongly (D+)
Grade of recommendation[a]
1A: Strong recommendation, high-quality evidence
1B: Strong recommendation, moderate-quality evidence
1C: Strong recommendation, low-quality or very low-quality evidence
2A: Weak recommendation, high-quality evidence
2B: Weak recommendation, moderate-quality evidence
2C: Weak recommendation, low-quality or very low-quality evidence

[a]Adapted from Guyatt *et al.* (17).

(Ville Saint-Laurent, Canada), UCB Pharma Canada (Oakville, Canada), and Warner Chilcott (Toronto, Canada). Conflict of interest statements were obtained for all members of the consensus group before the meeting. Honoraria were provided to the international and surgical experts who attended the meeting.

CONSENSUS STATEMENTS

Section 1: General considerations and nutritional issues

Statement 1: Patients should have stool samples assayed for *Clostridium difficile* cytotoxin (both A and B) and cultured for bacterial pathogens.
Vote: A+ = 90%, A = 10%; Grade of recommendation: 1B

Discussion. *C. difficile* infection is more common in patients with inflammatory bowel disease (IBD) than in those without this condition, and the incidence of infection in individuals with IBD is increasing. A single-center study in the United States found an increase in the incidence of *C. difficile* infection in hospitalized patients with UC from 18.4 per 1,000 in 1998 to 57.6 per 1,000 in 2004 (18). This finding was supported by the results of a larger study using the US Nationwide Inpatient Sample database, which showed that the proportion of hospitalizations for UC complicated by *C. difficile* infection increased significantly from 24 per 1,000 in 1998 to 39 per 1,000 in 2005 ($P<0.05$) (19). Of great concern is the finding in this study that patients with IBD who were infected with *C. difficile* had greater mortality and longer hospitalizations than those with IBD alone (odds ratio (OR): 4.7; 95% confidence interval (CI): 2.9–7.9 and OR: 3.0; 95% CI: 2.3–3.7 days, respectively) (19). Furthermore, patients with IBD and *C. difficile* infection had a 6.6-fold increase in the risk of colectomy compared with those with *C. difficile* infection but no IBD (19).

Bacterial infections such as *C. difficile* have also been reported to trigger IBD flares. A retrospective analysis of 237 IBD relapses found that pathogenic bacteria were present in the stool in 10.5% of relapses and that *C. difficile* was the most prevalent infection (20). This finding was supported by the results of a prospective study in which 11 of 64 patients with IBD had infecting bacteria in stool and intestinal biopsy specimens at relapse, with *C. difficile* again being the most common pathogen (21). However, in a recent prospective study in which bacterial infections were found in 10% of patients admitted to hospital with active IBD, *Campylobacter jejuni* was the most commonly isolated pathogen (22).

C. *difficile* infection presents in a wide variety of ways, including toxic megacolon, fulminant colitis, and sepsis (23). Risk factors for *C. difficile* infection are generally the same in individuals with IBD as they are in the general population (e.g., hospitalization, antibiotic use, immunosuppression, older age, and the presence of comorbidities). However, patients with IBD and no obvious risk factors may also become infected with C. *difficile*, and IBD may itself be a risk factor (23). A recent retrospective study evaluated the impact of immunosuppression on hospitalized IBD patients with *C. difficile* infection. Concomitant use of immunomodulators and antibiotics was associated with the primary outcome (death, colectomy within 3 months of admission, in-hospital megacolon, bowel perforation, hemodynamic shock, or respiratory failure), whereas antibiotic use alone was not. This association was greater if treatment consisted of two or three immunomodulators (OR: 17; 95% CI: 3.2–91; $P<0.01$) (24).

Commentary. Data supporting the increased incidence of *C. difficile* infection in patients with IBD, along with the more severe disease course associated with concomitant infection, led the delegates to recommend routine screening for this pathogen in hospitalized individuals with severe UC. There was also discussion as to whether stool samples should be collected for parasites. Several small studies conducted in countries where parasitic infections with, for example, *Entamoeba histolytica* and *Blastocystis hominis* are endemic (e.g., Turkey, Mexico, India, and Israel) have found a higher prevalence of these micro-organisms among patients with IBD compared with individuals without IBD (25–29). However, a North American study evaluating stool samples systematically for parasitic pathogens in 54 individuals with IBD found no positive parasitic cultures (30). It was therefore decided that parasites should not be routinely assayed for unless the patient had lived in or recently traveled to an endemic area.

Statement 2: Patients should have baseline abdominal radiographs.
Vote: A+ = 57%, A = 38%, A− = 5%; Grade of recommendation: 1C

Discussion. Plain abdominal radiographs should be obtained at baseline as part of the initial assessment of patients with severe UC. Changes that can be identified on radiographs include megacolon, thumbprinting, pneumatosis intestinalis, and perforation. Abdominal radiographs can also provide information on the extent of disease based on bowel wall edema. Certain findings

can also serve as indicators of disease severity and poor outcome. Colonic dilatation is associated with a high rate of colectomy, and the presence of mucosal islands (which represent mucosa surrounded by ulceration or denuded mucosa) reflects severe disease (31). The presence of an ileus was associated with a colectomy rate of 50% in a prospective study (32).

An abdominal radiograph at the beginning of hospitalization serves as an important comparator for subsequent radiographs that may be needed when the patient's clinical status changes. However, it should be noted that not all instances of perforation will be visible on a radiograph and it should not serve as a substitute for sound clinical judgment (33).

Commentary. Delegates discussed the potential use of CT (computed tomography) instead of plain radiographs at baseline. CT scanning increases exposure to radiation, which is a particular concern with pediatric patients. Plain radiographs are therefore to be recommended at baseline in preference to CT scans. However, in situations where perforation, or abdominal sepsis is suspected, a CT scan would be the imaging modality of choice.

Statement 3: Patients should have an early flexible sigmoidoscopy with biopsies to assess endoscopic severity, *C. difficile* infection or CMV colitis.
Vote: A + = 67%, A = 33%; Grade of recommendation: 1C

Discussion. A flexible sigmoidoscopy with biopsies should be performed as soon as possible after the patient is admitted to the hospital. The flexible sigmoidoscopy should be used to evaluate endoscopic severity and to identify *C. difficile* and CMV infection. The degree of endoscopic activity may help to predict the severity of the disease course. The presence of deep and extensive ulceration has been associated with an increased risk of colectomy in retrospective studies (34–36).

C. difficile infection may appear as pseudomembranes on endoscopy, although this finding has very low sensitivity and specificity. A recent study found that only 13% of 93 patients with *C. difficile* infection hospitalized with IBD had pseudomembranes (37). The histology of pseudomembranes reveals the classic 'volcano lesion' that demonstrates focal ulceration with eruption of necrotic debris and inflammatory cell infiltrate. However, this finding is not specific to *C. difficile* infection, so differentiating it from active IBD by endoscopy and histology may be difficult (23,38,39).

The pathogenic role of CMV infection in UC is unclear, particularly regarding whether the presence of the virus in colonic tissue worsens the outcome of patients with severe UC. Gastrointestinal CMV infection has been reported to be associated with UC exacerbations, medically resistant severe UC, and a worsening of disease course (40–44).

Clinically significant gastrointestinal CMV infection usually occurs in immunocompromised patients, such as those with severe UC who may be malnourished and taking immunosuppressants including systemic corticosteroids, thiopurines, or cyclosporine (42,43). The prevalence of CMV in patients with UC varies from 5 to 81%, depending on the population studied and the laboratory methods used to detect it (40). Prospective case series have provided CMV prevalence estimates of 16–36% in patients with IBD (41,45–47). Prevalence estimates of CMV infection in resected colonic specimens from patients with UC range from 0 to 22% (40,48).

Several diagnostic tests are available for the detection of CMV infection. The 'gold standard' for colonic disease is histopathology and immunohistochemistry on tissue specimens obtained from biopsy, with the immunohistochemistry leading to an increase in sensitivity (46). Other options such as serology, CMV culture, CMV antigen testing, and CMV DNA detection have lower sensitivity and/or specificity.

The treatment of choice for CMV infection is ganciclovir. This is generally recommended if CMV is diagnosed in hospitalized severe UC patients who are on immunosuppressants and may be malnourished. A systematic review of case series and case studies concluded that some patients who have IBD complicated by CMV infection may benefit from eradication with antiviral therapy (40). However, not all patients will benefit and some will still require surgery after antiviral treatment. The largest prospective series in patients with severe refractory IBD included 55 patients with UC and 7 with Crohn's disease (41). CMV was detected in histological specimens and buffy coat of 7 of 19 patients with steroid-refractory IBD (five with UC and two with Crohn's disease). Four patients received ganciclovir and two received foscarnet (due to bone marrow suppression). Five of six patients (83%) responded to antiviral therapy and were in clinical remission at week 3 and had completely ceased steroids. The authors of this study did not break down the results of antiviral treatment by diagnosis nor report the duration of therapy.

Commentary. There was discussion among delegates as to what constituted 'early' sigmoidoscopy during hospitalization. To assess endoscopic severity as a potential predictor of the disease course, sigmoidoscopy immediately on admission to hospital was thought to be appropriate. However, as data suggest that CMV is uncommon before the initiation of treatment with systemic steroids, flexible sigmoidoscopy may be more appropriate when the response to steroids is being measured—that is, on day 3 of hospitalization (43,49). A second look sigmoidoscopy can be considered in patients who had a sigmoidoscopy at admission and then failed steroids to assess for CMV infection or to re-evaluate disease activity before final surgical decision. Flexible sigmoidoscopy with minimal air insufflation was preferred to colonoscopy by delegates because of the theoretically greater risk of perforation with the latter.

Statement 4: Patients should be assessed for risk of tuberculosis (TB) including a careful history, chest X-ray, and TB testing at onset of hospitalization in preparation for possible infliximab therapy.
Vote: A + = 62%; A = 33%; A– = 5%; Grade of recommendation: 1B

Discussion. Currently, infliximab is the only anti-tumor necrosis factor-α (TNF-α) agent that has been evaluated in the treatment

of the hospitalized patient with severe UC. Treatment with anti-TNF agents have been reported to lead to reactivation of latent TB in patients with IBD (50). Screening programs for TB before anti-TNF therapy have been effective in reducing the incidence of TB reactivation. Patients admitted to hospital for severe UC may become candidates for infliximab therapy and should therefore be evaluated for their TB risk. This risk should be evaluated at onset of hospitalization in order to avoid delays that would result from TB testing should a decision be made subsequently to treat with infliximab. Recommendations for testing include a chest X-ray and tuberculin skin test (51). An interferon-γ releasing assay (e.g., QuantiFERON TB Gold (Cellestis, Valencia, CA)), which is not affected by bacillus of Calmette-Guérin vaccination, may also serve as a screening test for TB but is not readily available in many centers (52–54). If latent or active TB is found, treatment with infliximab should be postponed until appropriate therapy has been instituted.

Commentary. Delegates noted that false-negative TB test results may occur in patients with severe UC who have impaired immune function while receiving immunosuppressants such as high-dose corticosteroids or thiopurines. A careful epidemiologic and clinical history, physical examination, and chest radiograph should form part of a TB risk assessment. It was also noted that other anti-TNF agents may become available for the treatment of severe UC, and that assessment for TB risk is indicated for all anti-TNF agents.

Statement 5: Patients should be offered a normal diet or enteral nutrition unless such a diet is not tolerated.
Vote: A+ = 76%, A = 24%; Grade of recommendation: 1C

Discussion. There is no evidence that keeping patients on complete bowel rest improves the course of severe UC. The results of one small prospective clinical trial ($N = 27$) showed no difference in clinical outcomes between patients who underwent bowel rest with total parenteral nutrition (TPN) compared with those given an oral diet (55). Total enteric nutrition with polymeric formula was also found to be safe and well tolerated in a small prospective cohort of patients with severe UC (56). In pediatric patients, enteral administration of formulated food as the sole source of nutrition is employed as primary therapy for intestinal inflammation in active Crohn's disease; however, this is not the case in UC, where such therapeutic benefit is lacking.

There is no evidence that elimination diets affect the outcome of severe UC in either adult or pediatric patients. Lactose restriction may be beneficial in individuals with lactose intolerance but is not recommended routinely (57).

Commentary. Delegates agreed that maintaining adequate caloric intake was essential and that a normal diet or enteral feeding was recommended. If the patient's symptoms became worse (e.g., increased abdominal pain and bloody diarrhea), it was agreed that oral intake should be withheld and an alternative nutritional source, such as TPN, should be instituted (please see Statement 6).

Statement 6: TPN is not effective as primary therapy. TPN should be considered only in malnourished patients who cannot tolerate oral intake or enteral nutrition.
Vote: A+ = 95%, A = 5%; Grade of recommendation: 1B

Discussion. There is no evidence that TPN is of benefit as primary therapy in hospitalized patients with severe UC. Three prospective RCTs have evaluated TPN with bowel rest compared with either a standard oral diet or enteral nutrition as adjunctive therapy to corticosteroids in severe UC (55,58,59). No difference was found in these studies in the need for colectomy between patients administered TPN compared with those who did not receive TPN. All three studies, however, involved small numbers of patients ($n = 22$–42) and were potentially underpowered to detect any significant difference between the different nutritional strategies.

Commentary. Delegates agreed that TPN was of no benefit as primary therapy in severe UC. However, there was consensus that TPN was indicated as nutritional support in malnourished patients unable to tolerate oral feeds or who are to undergo colectomy.

Statement 7: Patients should receive prophylaxis for thromboembolic complications.
Vote: A+ = 71%, A = 24%, A− = 5%; Grade of recommendation: 1B

Discussion. There is strong evidence to support the use of unfractionated or low molecular weight heparins as prophylaxis for venous thromboembolic complications in medical inpatients (60,61). No specific studies of venous thromboembolic prophylaxis have been conducted in patients with UC; however, guidelines recommend the use of heparin for medical patients (such as those with IBD) who have risk factors for venous thromboembolism (62). As well as the risks associated with hospitalization, patients with IBD have an added risk of venous thromobembolic events inherent to their illness (63–65). These risks seem to be associated with greater disease extent and severity in patients with UC (66).

Concern about increasing the risk of rectal bleeding with heparin has prompted caution when considering venous thromboembolic prophylaxis. A meta-analysis of eight RCTs assessing the efficacy and safety of fractionated and unfractionated heparin in the treatment of active UC revealed no significant increase in bleeding in patients treated with heparin in addition to conventional therapy (aminosalicylates, steroids, and/or azathioprine) compared with patients receiving conventional therapy and no heparin (67). However, it also showed no added therapeutic benefit of heparin over conventional therapy.

Statement 8: Narcotics are best avoided.
Vote: A+ = 67%, A = 19%, A− = 10%, D− = 5%; Grade of recommendation: 1C

Discussion. Drugs that slow colonic motility, such as narcotics, have been linked to the possible development of toxic megacolon (68) and are best avoided. Similarly, anti-diarrheals

have no role in the treatment of severe UC and should not be used in this patient population.

Commentary. The delegates discussed the minority of patients with severe UC in whom pain management is a major clinical issue. In these individuals, the judicious use of narcotics may be necessary for pain relief while monitoring for signs of megacolon. One small case series describes the use of ketamine, an *N*-methyl-d-aspartate receptor antagonist, in the pain management of children with acute severe UC (69), but pain in most pediatric patients is managed with relaxation techniques and/or oral acetaminophen.

Statement 9: Routine use of antibiotics is not recommended.
Vote: A + = 67%, A = 33%; Grade of recommendation: 1B

Discussion. Several trials have shown that the use of antibiotics in addition to corticosteroids does not lead to additional benefits over corticosteroid treatment alone. A trial of hospitalized patients with severe UC who were randomized to receive metronidazole 500 mg every 8 h intravenous (IV) ($n = 19$) or placebo ($n = 20$) in addition to corticosteroids found no differences in outcome between the two groups (70). A second study of patients hospitalized with severe UC who were randomized to receive metronidazole 500 mg three times a day and tobramycin 4 mg/kg in divided doses every 8 h ($n = 19$) or placebo ($n = 20$) in addition to corticosteroids found no difference in response between the two groups (71). A third study investigated randomized patients who received ciprofloxacin 400 mg twice daily IV ($n = 29$) or placebo ($n = 27$) for 10 days in addition to corticosteroids (72). There were no differences in treatment response between the two groups. However, it is possible that these studies were underpowered to detect an effect. It should be noted that antibiotics are indicated in patients who develop signs of sepsis. Similarly, antibiotics, either metronidazole or vancomycin are indicated in patients with concurrent *C. difficile* infection.

Section 2: Steroid use and predictors of steroid failure

Statement 10: First-line medical therapy for patients should be intravenous corticosteroids.
Vote: A + = 86%, A = 14%; Grade of recommendation: 1A

Discussion. Intravenous corticosteroids have been established as the most effective first-line treatment for acute severe UC since the first trial of this treatment regimen was published in 1974 by Truelove and Jewell (73). In this study, 36 of 49 patients (73.5%) with severe UC were found to be in remission 5 days after commencing intensive intravenous treatment with prednisolone 60 mg/day (in divided doses). The introduction of intravenous corticosteroid treatment has led to a substantial decrease in the morbidity and mortality associated with acute severe UC (13,74).

A number of parenteral corticosteroids, including hydrocortisone, prednisolone, methylprednisolone, bethamethasone, and adrenocorticotropic hormone, have been tested in the treatment of severe UC (13). A systematic review found no obvious differences in treatment response between the various steroids used in the studies included (13). However, there have been no direct comparisons of the different treatment regimens. Similarly, no dose-ranging studies of the various intravenous corticosteroids have been carried out. The systematic review of response to corticosteroid treatment included a meta-regression controlled for disease severity at baseline; no correlation was found between corticosteroid dose and colectomy rate (13). The authors of the review concluded that there was no evidence to support increasing the corticosteroid dose beyond 60 mg/day of methylprednisolone or equivalent.

Bolus administration in a single or divided daily regimen is standard practice for treatment with corticosteroids. No published studies have shown other administration methods to be superior or safer to bolus dosing. In a one clinical trial, patients ($n = 66$) were randomized to receive up to 60 mg/day of methylprednisolone by either bolus (b.i.d. regimen) or continuous infusion (75). No significant differences in treatment response or adverse effects were found: one-half of the patients in each group were in clinical remission at day 7, and 35% of those in the continuous infusion group had undergone elective colectomy at 1 year compared with 28% in the bolus group. Two prospective studies have shown that pulsed therapy can be effective in the treatment of UC (76,77). However, both of these studies used unusually high steroid doses and neither had a comparator group, which limits the conclusions that can be drawn from these results.

Based on the very limited data that show no obvious differences in terms of efficacy or safety, the selection of a parenteral steroid and the dosing regimen in the hospitalized UC patient will most often be based on physician and center experience. A dose of methlyprednisolone of 60 mg/day or its equivalent should not be exceeded (13).

Statement 11: Patients who fail to improve on intravenous corticosteroids within 72 h, as determined by clinical, radiological, and laboratory parameters, have poor outcomes and should be considered for either surgery or second-line medical therapy.
Vote: A + = 81%, A = 19%; Grade of recommendation: 1B

Discussion. It is important to make an early decision concerning subsequent treatment options for patients who do not respond to intravenous corticosteroids. This is necessary to avoid delays in surgery or in obtaining second-line medical treatment, which may in turn lead to worsening patient outcomes (78). The critical issue is, therefore, to determine how and when to assess response to steroid therapy and consider initiating second-line therapy.

Response or lack of response to therapy needs to be assessed in a simple and objective manner. Various indices have been proposed with which to define UC disease activity levels objectively and that may be used to assess response to therapy (32,79–83). These indices use different criteria to define response, but tend to include at least one objective criterion such as stool frequency or CRP (C-reactive protein) level. The Oxford criteria define non-response as a CRP level above 45 mg/l and a stool frequency of 3–8 stools/day, or a stool frequency over 8 stools/day on day 3

(32,84). These criteria correlate well with the need for colectomy on the same admission (32). The PUCAI (Pediatric UC Activity Index) is the only validated index of UC severity and was assessed in a prospective study of 128 hospitalized pediatric patients (83). To maximize sensitivity in the recognition of steroid non-responders, the authors recommended that a day 3 PUCAI score of >45 should signal the need to prepare for second-line therapy. To maximize specificity, a day 5 PUCAI of >70 mandates implementation of the chosen rescue therapy.

A variety of predictors of steroid failure have been reported, but the paucity of prospective data and the lack of validation limits their use in clinical practice. As discussed above, stool frequency and elevated CRP levels seem to be the simplest and most reliable indicators of steroid failure (32,83). In addition, two studies have shown endoscopic severity to be a predictor of steroid failure and the need for colectomy (35,85). However, full colonoscopy cannot be advocated given the potentially increased risk of perforation associated with its use. Other factors evaluated on day 1 or 3 of hospitalization that have been reported to predict steroid failure include erythrocyte sedimentation rate, albumin, and fecal calprotectin levels, and abdominal radiographs showing mucosal islands (31,86). However, these factors are of limited use until they have been validated.

Section 3: Cyclosporine and infliximab

Statement 12: Either intravenous cyclosporine or infliximab is an appropriate choice for selected patients who have failed intravenous corticosteroid therapy.
Vote: A+ = 48%, A = 48%, A− = 4%; Grade of recommendation: 1A

Discussion. Therapeutic options in patients who do not respond to intravenous corticosteroids include medical therapy with either cyclosporine or infliximab, or colectomy. The choice of treatment depends on the balance between the risks and benefits of the options, physician experience with these agents, and the concerns and preferences of the patient.

Cyclosporine, a calcineurin inhibitor, given intravenously was the first agent to be used successfully as second-line therapy in severe steroid-refractory UC. In a small randomized, blinded, placebo-controlled trial ($n = 20$) of cyclosporine (4 mg/kg/day IV) in patients with severe UC in whom intravenous steroids given for at least 7 days had failed, 82% (9/11) of those treated with cyclosporine responded to treatment within a mean of 7 days compared with none of those given placebo ($P < 0.001$) (87). Response was defined as a score of <10 in the clinical activity index on 2 consecutive days (6). Five patients in the placebo group whose treatment was later switched to cyclosporine responded. In a controlled study comparing cyclosporine monotherapy 4 mg/kg/day IV with intravenous methylprednisolone, there was no difference in therapeutic efficacy between the treatment groups (88). After 8 days, 64% (9/14) of patients in the cyclosporine group had a therapeutic response compared with 53% (8/15) in the steroid group. The mean time to response was 5.2 (±0.9) days in the cyclosporine group compared with 4.3 (±0.7) days in the steroid group.

Studies exploring a lower induction dose of cyclosporine of 2 mg/kg/day have been performed in order to reduce the potential adverse events associated with higher doses (89–92). One RCT of patients with steroid-refractory UC ($n = 73$) found that cyclosporine 4 mg/kg/day IV offered no added benefit over 2 mg/kg/day in terms of clinical response at day 8 (90). Mean blood concentrations of cyclosporine were 237 and 332 ng/ml for the 2 and 4 mg/kg/day doses, respectively. In addition, there was a trend toward more frequent hypertension in patients receiving the higher dose. This study supports the initiation of cyclosporine therapy at the lower dose of 2 mg/kg/day IV followed by dose adjustment according to whole blood levels.

A Cochrane review identified only two high-quality RCTs that compared cyclosporine with either placebo or no intervention in patients with severe UC (87,88,93). These two studies showed that failure to respond to therapy was less likely in the cyclosporine group than the placebo group (relative risk (RR): 0.18; 95% CI: 0.05–0.64 and RR: 0.71; 95% CI: 0.29–1.75) (87,88). However, sample sizes were small and there was limited follow-up. This led the authors of the Cochrane review to note that, while the limited available evidence supports the short-term efficacy of cyclosporine for UC, further studies were needed to assess overall quality of life, costs, and long-term results. There were no statistically significant differences in the frequency of adverse effects between the cyclosporine and non-cyclosporine groups. Adverse events observed in the cyclosporine groups were mild, and included hypertension, vomiting, paresthesias, hypokalemia, and hypomagnesemia. There was one episode of grand mal seizure in a patient receiving cyclosporine who had hypocholesterolemia. In these short-term studies, there was no increase in nephrotoxicity or infectious complications.

In controlled trials, initial response rates with cyclosporine range from 64 to 90% when defined as the avoidance of colectomy; however, the results of long-term observational studies are less encouraging (94–96). Subsequent colectomy rates in initial responders to cyclosporine range from 20% at 1 year to 69% at 5 years (95,96).

Infliximab is an anti-TNF-α agent that is effective in the treatment of Crohn's disease and UC (97,98). Several studies have assessed infliximab for the treatment of both ambulatory patients with moderate-to-severe UC and hospitalized patients with severe UC (99–101). The Acute Ulcerative Colitis Trials (ACTs) 1 and 2 were placebo-controlled trials evaluating a total of 728 outpatients with moderate-to-severe UC (99). These two studies were included in a meta-analysis of seven RCTs assessing infliximab efficacy in inducing remission in either outpatients with moderate-to-severe UC or hospitalized patients with severe corticosteroid-refractory UC (97). In this meta-analysis, at 8 weeks, the infliximab induction regimen (5 or 10 mg/kg at 0, 2, and 6 weeks) was significantly superior to placebo in terms of inducing clinical remission (RR: 3.22; 95% CI: 2.18–4.76; NNT (number needed to treat) = 5), endoscopic remission (RR: 1.88; 95% CI: 1.54–2.28; NNT = 4), and clinical response (RR: 1.99; 95% CI: 1.65–2.41; NNT = 4). There appeared to be no difference in efficacy between the 5 and 10 mg/kg doses.

Specifically relating to the current guidelines, three of the seven controlled studies in the meta-analysis were performed in hospitalized patients with severe UC refractory to intravenous corticosteroids (100–102). In the largest of these trials, patients were enrolled who had severe or moderately severe UC according to the Seo index (103) and treatment with a single infusion of infliximab 5 mg/kg (mean dose: 4–5 mg/kg; $n=24$) was compared with placebo ($n=21$) (100). Patients were randomized on day 4 of steroid treatment if they had a fulminant colitis index of at least ≥8 on day 3 (80) or on days 6–8 of steroid treatment if their Seo index indicated severe or moderately severe UC on days 5–7. The primary end point was colectomy or death at 3 months. Significantly more patients in the placebo group than the infliximab group underwent colectomy in the 90 days after randomization (OR: 4.9; 95% CI: 1.4–17.0). However, at 3 months, there was no significant difference in terms of clinical remission (RR: 2.63; 95% CI: 0.59–11.64) or endoscopic remission (RR: 2.63; 95% CI: 0.59–11.64) between the two groups (97). A very small ($n=11$) study of patients with severe UC reported that 50% of those who received infliximab (single intravenous infusion of 5, 10, or 20 mg/kg) were considered to be treatment successes at 2 weeks compared with none of those who received placebo (101).

The potential benefits of infliximab need to be weighed against the potential adverse events associated with its use, which include anaphylactic reactions, infection, immunogenicity, autoimmunity, demyelinating disorders, and possible malignancy, including lymphoproliferative disorders. Adverse events associated with infliximab have previously been discussed in the CAG's consensus guidelines for biologic therapy in Crohn's disease (104). The meta-analysis of infliximab use in patients with UC found that none of the studies with a follow-up period of 8–13 weeks showed serious adverse events or infusion reactions with this agent (97). In ACT 1 and ACT 2, which included a total of 728 patients, the proportion of individuals with severe adverse events was similar in the infliximab and placebo groups (99).

There are currently no published controlled trials comparing cyclosporine with infliximab as a second-line therapy in patients with severe steroid-refractory UC. The choice of agent is often based on factors such as physician and hospital experience and patient preference. Comparing response rates in these agents is difficult because of varying study designs that use different disease activity indices, dosing regimens, and primary end points. Short-term response rates to cyclosporine in four RCTs range from 64 to 93% (87,88,90,105). Short-term response rates to infliximab are more difficult to quantify than those to cyclosporine because of the paucity of data in this hospitalized patient population. In one small study, 50% (4/8) of patients responded to infliximab with significant improvement by day 7 (101). In a larger clinical trial ($n=45$), there were no significant differences in 3-month colectomy rates between patients randomized to receive infliximab or placebo (47 vs. 69%; $P=0.276$) at day 3 based on a fulminant colitis index of ≥8 (100). However, patients with severe or moderately severe UC activity (according to the Seo index) on days 5–7 had significantly better outcomes at 3 months when randomized to the infliximab group compared with the placebo group (colectomy rate: 0 vs. 62.5%; $P=0.009$). This suggests that infliximab may be beneficial in patients with severe or moderately severe UC, but not in those with fulminant colitis (i.e., fulminant colitis index ≥8).

Previous use of thiopurines may be another factor to take into account when considering second-line treatment for patients with steroid-refractory severe UC. Prior use of azathioprine may predict failure of intravenous cyclosporine (96). Also, responders to intravenous cyclosporine who have previously been exposed to azathioprine have a greater risk of colectomy during maintenance treatment than patients who are azathioprine naive (96). Infliximab is a proven maintenance agent in UC and therefore may be a better choice for patients with severe UC in whom azathioprine therapy had previously failed.

Two clinical trials have been undertaken to compare the efficacy and safety of cyclosporine and infliximab in patients with severe steroid-refractory UC. Preliminary results of CySIF (comparing CycloSporine to InFliximab in severe UC) were recently presented (106). The study evaluated therapeutic response in 111 patients (55 cyclosporine and 56 infliximab) with severe UC who were refractory to treatment with at least 5 days of IV steroid treatment. The patients were randomized to receive IV cyclosporine 2 mg/kg/day for 7 days followed by oral cyclosporine for 3 months or infliximab 5 mg/kg at 0, 2, and 6 weeks. Azathioprine at a dose of 2.5 mg/kg/day was initiated and steroids were tapered. The primary end point was the rate of treatment failure as defined based on response and adverse effects criteria. Rates of treatment failure were 60% with cyclosporine and 54% with infliximab ($P=0.49$). Response rates at day 7 were similar (85.4% in the cyclosporine group vs. 85.7 in the infliximab group; $P=0.97$) as were the day 98 colectomy rates (18% in the cyclosporine group vs. 21% in the infliximab group; $P=0.66$). The second study (CONSTRUCT; COmparison of iNfliximab and ciclosporin in STeroid Resistant Ulcerative Colitis: http://www.controlled-trials.com/ISRCTN22663589) is currently underway and is comparing clinical effectiveness and cost effectiveness of these two medical strategies in patients with steroid-refractory UC.

Other anti-TNF agents available for the treatment of Crohn's disease may offer future therapeutic options in UC. However, there are currently no controlled data on the efficacy of these agents in the treatment of hospitalized patients with severe UC. In ambulatory patients with moderately to severe active UC, adalimumab was found to be superior to placebo in achieving the primary clinical end point of clinical remission at week 8 (107).

Oral tacrolimus, another calcineurin inhibitor, may also have a role in the treatment of steroid-refractory severe UC and its use in this clinical context has been reported, particularly in pediatric patients (108,109). The only controlled trial of tacrolimus that has been published to date is a small randomized, placebo-controlled study in hospitalized adults with refractory UC (110). In this study, patients were randomized to receive either tacrolimus, adjusted to achieve high ($n=22$) or low ($n=21$) serum trough levels, or placebo ($n=20$). At 2 weeks, clinical improvement was seen in 68.4% of patients in the high trough level group compared with 10% in the placebo group ($P<0.001$). A subsequent Cochrane Database review selected only this study and concluded that oral tacrolimus could be beneficial in the short-term treatment of refractory UC but that

the results should be interpreted with caution because of the small numbers of participants and other study limitations (111).

Vedolizumab also shows promise in UC although it has not been evaluated in the severe hospitalized UC patient. Vedolizumab is a humanized monoclonal antibody that interferes with the interaction between the α4 β7 integrin and its ligand on the endothelial cell surface and therefore blocks leukocyte trafficking into inflamed tissue. A controlled trial demonstrated its superior efficacy over placebo in achieving clinical and endoscopic remission in patients with active UC (112). Phase 3 clinical trials evaluating vedolizumab in ambulatory patients with active UC are currently being completed.

Statement 13: A decision regarding response to infliximab or cyclosporine should be made within 5–7 days after initiation of such therapy.
Vote: A+ = 81%, A = 19%; Grade of recommendation: 1C

Discussion. Once second-line medical therapy has been initiated, it is important to make appropriate and timely clinical decisions based on response to treatment to avoid delaying surgery in non-responders, because patient outcomes may worsen with prolonged medical therapy (12). For cyclosporine, the mean time to response in controlled trials ranges from 5 to 7 days (87,88), so this time frame seems an appropriate one in which to evaluate response. In a small placebo-controlled trial with the primary end point of treatment failure at 2 weeks, 4 of 8 patients with severe UC treated with infliximab who had a therapeutic response had improved significantly by day 7 (101). The key infliximab study did not specifically report the mean time to response, but it did report the mean time to colectomy (i.e., infliximab failure) as 8 days after the initiation of infliximab therapy (100). Corticosteroid therapy is maintained concurrently with second-line medical therapy.

Commentary. The delegates agreed that it was appropriate to wait 5–7 days before assessing the therapeutic response to infliximab or cyclosporine, and that waiting longer was not advisable because prolonging medical therapy would inappropriately delay surgery. Response can be defined based on the use of various clinical indices, including the Rachmilewitz index (colitis activity index) (113), Truelove and Witts criteria (6), Lichtiger index (87), Mayo score (114), Seo Index (59), and fulminant colitis index (80). Response should be clinical and defined as improvement or resolution of abdominal pain and rectal bleeding while being able to tolerate a regular oral diet.

Statement 14: Cyclosporine and infliximab should be utilized at centers with appropriate experience and support in their use.
Vote: A+ = 67%, A = 29%; A− = 4%; Grade of recommendation: 1C

Discussion. Cyclosporine and infliximab are second-line agents in refractory UC and must be used by experienced physicians who can gauge appropriate response or non-response while monitoring closely for adverse events. These drugs should be used in centers with appropriate laboratory, pharmacy, and consultant service support. Physicians must be aware of all side effects and be able to react appropriately should these arise.

Cyclosporine should be used in centers in which blood levels can be monitored. Physicians using these agents should be able to adjust the cyclosporine dose to achieve drug levels that will maximize therapeutic effect while minimizing potential toxicity. In addition, patients responding to cyclosporine will need to have their treatment switched to the oral formulation, and will therefore temporarily receive triple immunosuppressive therapy of cyclosporine, steroids, and thiopurines. It is therefore important to stress physician and center experience, as opportunistic infections such as *Pneumocystis jirovecii* pneumonia have been reported in the outpatient setting that can, on rare occasions, lead to death (96,115). Prophylaxis with sulfamethoxazole/trimethoprim should be considered in this patient population (96).

Physicians at centers in which infliximab is administered must also be prepared for infusion reactions including anaphylaxis, although this is very rare on first infusions. Patients who respond to infliximab are discharged on a tapering steroid regimen and infliximab. Again this stresses the importance of appropriate monitoring, in particular for the development of serious infections.

Commentary. It was emphasized that physicians at centers where experience and/or adequate support for second-line therapy are lacking should arrange for patients to be transferred appropriately early in their hospital course.

Statement 15: Patients who respond to intravenous cyclosporine should be switched to oral cyclosporine; subsequently azathioprine or 6-MP (6-mercaptopurine) should be initiated.
Vote: A+ = 67%, A = 33%; Grade of recommendation: 1C

Discussion. No RCTs have defined the best medical strategy once a patient with severe UC has responded to intravenous cyclosporine. The results of retrospective studies seem to point toward a beneficial effect of 6-MP/azathioprine compared with 5-aminosalicylates in terms of prolonging cyclosporine-induced remission and colectomy-free disease in patients with severe, steroid-refractory UC (116–119). A retrospective study found that 20% of patients with severe UC who responded to intravenous cyclosporine and were treated with azathioprine or 6-MP eventually required colectomy compared with 45% of those who received cyclosporine alone (119). Treatment strategies include a switch to oral cyclosporine, which acts as a bridge until thiopurines exert their therapeutic effect, or a direct change to thiopurines without oral cyclosporine (120). The former approach is most commonly used in clinical practice. Oral cyclosporine should not be continued for >6 months in order to avoid long-term adverse events, particularly nephrotoxicity.

Commentary. There was no clear consensus on when to initiate 6-MP or azathioprine therapy following cyclosporine-induced remission. Nonetheless, delegates favored the initiation of thiopurines any time between 2 and 8 weeks after hospital discharge. This was based on experience without firm data to di-

rect timing of thiopurine initiation. Some delegates argued for a delay of up to 8 weeks to allow a forced steroid taper. Thiopurine methyltransferase genotype identification or enzymatic activity testing should be performed before starting treatment to detect patients at risk of myelosuppression.

Statement 16: Patients who respond to a single infusion of infliximab should be given two additional induction doses at 2 and 6 weeks, followed by maintenance infliximab therapy.
Vote: A+ = 57%, A = 38%, A− = 0%, D− = 5%; Grade of recommendation: 1B

Discussion. Although the ACT 1 and ACT 2 trials were conducted in ambulatory patients with moderately severe UC, they demonstrated that this infliximab regimen is successful as both induction and maintenance treatment (99). More recently, the results of the UC SUCCESS trial have been reported (121). This study compared the efficacy of azathioprine alone to infliximab alone to the combination of azathioprine and infliximab in moderate-to-severe UC outpatients failing steroids. The trial demonstrated the superiority of combination therapy over either monotherapy. Although this study did not address severe hospitalized UC patients, it suggests that if infliximab is used as an induction treatment in UC, combination therapy may be more beneficial. There is no current evidence supporting the use of concomitant thiopurines with infliximab in maintaining remission in the hospitalized severe UC patient who has responded to infliximab induction therapy and has become an outpatient.

Statement 17: Sequential rescue therapy with cyclosporine and infliximab should be avoided.
Vote: A+ = 85%, A = 10%, A− = 5%; Grade of recommendation: 1B

Discussion. An initial study assessing sequential early rescue therapy (defined as receiving the alternative drug within 4 weeks of discontinuing the first drug) with cyclosporine following infliximab or vice versa has shown this approach to be associated with serious adverse events (122). In this study, only 37% (7/19) of patients receiving sequential therapy achieved short-term remission and 16% (3/19) of individuals had severe adverse events (including one death). A second retrospective study of 86 patients who received acute sequential therapy reported a probability of colectomy-free survival of 41% at one year (123). The rate of serious infections was 10% and one patient died from a pulmonary embolism. The authors recommended that the risk/benefit ratio of sequential therapy be considered individually. In a smaller study ($n = 16$) reviewing outcomes of patients treated with acute sequential therapy, a short-term colectomy rate of 37% and a low rate of adverse effects were reported (124). Varying short-term colectomy rates and few adverse events were reported in two other studies of individuals receiving delayed sequential therapy (125,126).

The potential for serious infectious adverse events may be a result of the cumulative immunosuppression caused by using both treatments in quick succession. Infliximab levels remain elevated in serum for up to 8 weeks (122,127). While cyclosporine is eliminated within 10–27 h (122), there may be added immunosuppression if infliximab is given within this time frame.

Commentary. Theoretically, there may be a lower risk of cumulative immunosuppression if cyclosporine is used first, given its relatively shorter half-life compared with infliximab. However, there was clear consensus among the delegates that despite the possibility of short-term salvage with sequential rescue therapy, the potential for serious adverse events outweighed the benefits. Delegates agreed that sequential therapy should not be advocated, particularly as the surgical option is potentially curative.

Section 4: Surgical issues

Statement 18: Urgent surgical consultation should be obtained for all patients with systemic toxicity or megacolon.
Vote: A+ = 100%; Grade of recommendation: 1B

Discussion. Toxic colitis can be defined as the presence of any three of the following signs: fever (>38.6°C), tachycardia (>100 b.p.m.), anemia (hemoglobin level <10 g/dl), leukocytosis (>10,500/mm^3), and decreased serum albumin level (<3.0 g/dl) (128). When colonic dilatation of the transverse colon exceeds 6 cm, the condition becomes toxic megacolon (129).

Urgent surgical consultation is warranted in individuals with toxic colitis with or without megacolon because of the increased risk of perforation, which ranges from 16 to 36% (128,130,131). Perforation, in early surgical series, is associated with high mortality rates ranging from 27 to 57% regardless of whether the perforation is contained or free and increases when time to surgery is protracted (130,132,133). More recent series have reported no post-operative mortality in their patients who developed toxic megacolon and/or perforation likely reflecting earlier timing of surgery, and improved intensive care (128,134).

Patients who undergo surgery before perforation have a significantly better outcome (131–133). Unfortunately, very few signs or symptoms reliably predict impending perforation. In immunosuppressed patients, perforation can occur without signs of overt peritonitis or colonic dilatation (132). In a recent study of 89 patients who underwent colectomy for toxic and fulminant colitis, 15 patients had a perforation identified at the time of operation, 13 of whom were on some form of immunosuppression (128). Four additional patients had an abscess discovered at surgery. Increasing colonic dilatation, pneumatosis coli, worsening local peritonitis, and the development of multisystem organ failure can be signs of impending or actual perforation (133,135,136). Localized peritonitis is not predictive of impending perforation because it may be associated with inflammation as well as with impending or localized perforation (133,135,136). The development of multisystem organ failure is an ominous complication. In one series of 180 patients with toxic colitis, there were 12 (6.7%) deaths, which included 8 of 11 patients who had developed multisystem organ failure (137).

Statement 19: Patients who have failed primary therapy and are being considered for infliximab or cyclosporine therapy should have a concomitant surgical consult.
Vote: A+ = 81%, A = 14%, A− = 5%; Grade of recommendation: 1C

Discussion. Patients who have failed primary corticosteroid therapy should receive a surgical consult when they are being considered for infliximab or cyclosporine therapy. Surgery should be seen as an equivalent option to second-line medical therapy. When considering the use of infliximab or cyclosporine therapy before surgery, the patient, the gastroenterologist and the surgeon must discuss all options to ensure that appropriate decisions are made for optimal patient care.

There has been concern that prolonging medical therapy may increase the complication rate in individuals who eventually require surgery. A recent study of 80 patients with severe UC found that duration of in-hospital medical treatment (corticosteroids and cyclosporine) was the only factor associated with a significant increase in post-operative complications (OR: 1.12; 95% CI: 1.00–1.24; $P = 0.044$) (78). Although corticosteroids alone have been associated with an increased risk of post-operative infectious complications, the effect of subsequently adding other immunosuppressants is unclear (138).

Cyclosporine use does not seem to increase the risk of post-colectomy complications (139–141). However, there are conflicting reports as to whether or not infectious or non-infectious post-surgical complications are increased in patients with severe UC who have received pre-operative infliximab treatment (138,142–144). The effect of infliximab is difficult to isolate as many patients are also on concomitant high-dose corticosteroids. Furthermore, the infliximab studies are not confined to the population of hospitalized patients with severe UC who receive the agent as salvage

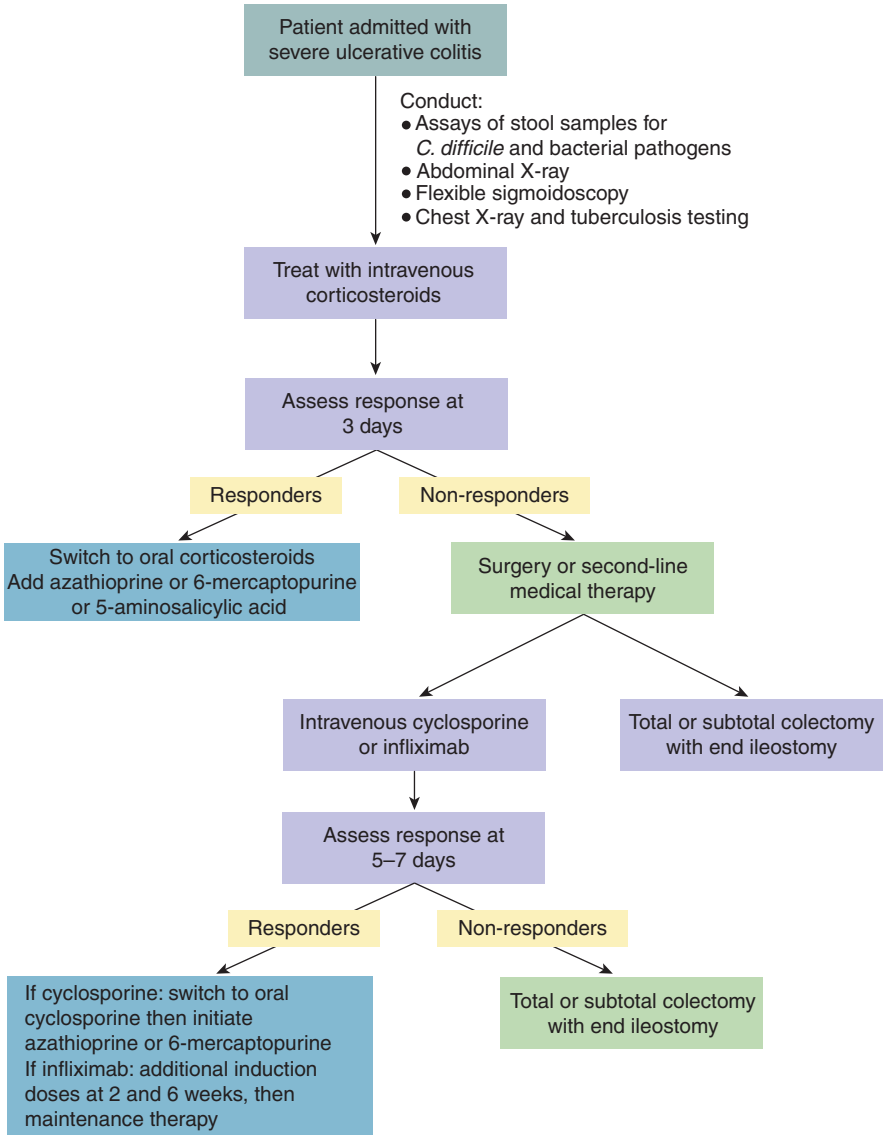

Figure 2. Consensus-guided approach to the treatment of hospitalized adult patients with severe ulcerative colitis.

therapy, but also include individuals administered infliximab as outpatient treatment for medically refractory UC. A recent meta-analysis of five published studies found that infliximab significantly increased the risk of short-term, post-operative complications in patients with UC (145). The study was not sufficiently powered to enable the risk of specific complications to be analyzed.

Commentary. There was consensus among delegates that a surgical consult was warranted in individuals in whom initial steroid therapy had failed. Some delegates stated that surgical consults should be sought early in the course of hospitalization before the patient developing a refractory response to steroids.

Statement 20: Patients who fail to respond to infliximab or cyclosporine within 5–7 days have a poor outcome and surgery is advisable.
Vote: A + = 81%, A = 19%; Grade of recommendation: 1B

Discussion. Patients who fail to improve after 3 days of high-dose intravenous corticosteroid treatment followed by 5–7 days of second-line therapy with cyclosporine or infliximab should undergo surgery. Therapeutic decisions for patients who partially respond to medical therapy are more difficult. While there is no literature to guide therapy for partial responders, a large proportion of these patients eventually go on to surgery despite continued intensive medical therapy. Thus, an early decision for surgery may be warranted.

Delayed surgery in hospitalized patients with severe UC is associated with poorer outcomes, including an increase in the incidence of post-operative complications and in-hospital mortality (146). In an analysis of the US Nationwide Inpatient Sample Database, patients who underwent colectomy within 3 days of admission for severe UC were less likely to die than those who had surgery after 6 days (OR: 2.12; 95% CI: 1.13–3.97) or 11 days (OR: 2.89; 95% CI: 1.41–5.91) (146).

Statement 21: When surgery is required, total or subtotal colectomy with end ileostomy is the procedure of choice.
Vote: A + = 95%, A = 5%; Grade of recommendation: 1B

Discussion. The absolute indications for surgery in acute severe UC include perforation and massive bleeding, both of which are uncommon. Toxic megacolon may also require surgery because over half of these patients fail to respond to intensive medical therapy. Failure to respond to medical therapy is by far the most common indication for acute surgery.

Regardless of the indication, total or subtotal colectomy with end ileostomy and rectal preservation is the procedure of choice for patients with acute severe UC (134,147). The procedure is effective and can be performed rapidly and safely. The majority of the diseased intestine is removed, allowing the patient to stabilize and recover. It also allows corticosteroid and immunosuppressant therapy to be tapered off. Furthermore, it avoids intestinal anastomosis and the potential for anastomotic leak, as well as pelvic dissection and its attending morbidity in an already compromised patient, while preserving future options for reconstruction.

The rectal stump may be managed by intraperitoneal closure or extrafascial placement. The latter may be associated with a lower rate of pelvic septic complications (148). Transanal drainage of the rectal stump may also reduce the risk of pelvic sepsis (149). An open mucous fistula may be necessary if the tissues are excessively friable and closure with suture or staples is not possible.

During the past decade, a laparoscopic approach has been advocated by some authors. However, there are no randomized trial data on this topic at the present time. Non-randomized data suggest a longer operative time but an earlier return of bowel function and thus a shorter hospital stay with laparoscopic surgery compared with open surgery (150–153). As expected, the early complication rates are similar to those found with open surgery. There are no data as yet on long-term complications such as incisional hernia or adhesive bowel obstruction. Thus, a laparoscopic approach is feasible but should only be attempted by surgeons with the appropriate ability and experience.

CONCLUSION

A number of therapeutic options are now available for hospitalized patients with severe UC. These clinical practice guidelines recommend a consensus-guided approach to the management of such individuals (**Figure 2**). Patients hospitalized with acute severe UC should receive first-line treatment with intravenous corticosteroids. These guidelines stress the importance of early escalation to second-line medical therapy with cyclosporine or infliximab in order to avoid the protracted medical treatment and hospitalization associated with poorer patient outcomes. Sequential medical therapy with cyclosporine and infliximab is not recommended. Surgery should be a therapeutic option for patients who are steroid refractory and is indicated when patients fail second-line cyclosporine or infliximab therapy or if complications arise.

Short- and long-term outcomes from studies comparing infliximab with cyclosporine in hospitalized patients with severe UC will soon emerge and may guide us in choosing the most appropriate agent for individuals in whom steroid treatment fails. Further studies are needed to clarify the potential benefits of other anti-TNF-α agents, tacrolimus, and newer monoclonal antibodies in the treatment of patients with steroid-refractory severe UC.

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CONFLICT OF INTEREST

Guarantor of the article: Alain Bitton, MD, FRCPC.
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at the consensus meeting in Toronto and contributed to the development of the consensus statements. All authors contributed to the preparation of the manuscripts including revisions and the final draft.

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APPENDIX

List of attendees

Co-chairs: Alain Bitton and Remo Panaccione; *Non-voting moderator*: Alan Barkun; *Steering committee*: Donald Buie, Robert Enns, Brian Feagan, Jennifer Jones, John Marshall, and Scott Whittaker; *Voting participants*: Paul Belliveau, Charles Bernstein, Brian Bressler, Zane Cohen, Richard Fedorak, Sylviane Forget, Anne Marie Griffiths, Edward Loftus, Donald MacIntosh, Earle Morgan, Pierre Paré, Robert Penner, Louis-Charles Rioux, Hillary Steinhart, and Simon Travis.