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Strategies for the Care of Adults Hospitalized for Active Ulcerative Colitis

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Abstract

Ulcerative colitis is a chronic inflammatory disease of the colon; as many as 25% of patients with this disease require hospitalization. The goals of hospitalization are to assess disease severity, exclude infection, administer rapidly acting and highly effective medication regimens, and determine response. During the hospitalization, patients should be given venous thromboembolism prophylaxis and monitored for development of toxic megacolon. Patients who do not respond to intravenous corticosteroids should be considered for rescue therapy with infliximab or cyclosporine. Patients who are refractory to medical therapies or who develop toxic megacolon should be evaluated promptly for colectomy. Patients who do respond to medical therapies should be discharged on an appropriate maintenance regimen when they meet discharge criteria. We review practical evidence-based management principles and propose a day-by-day algorithm for managing patients hospitalized for ulcerative colitis.

Introduction

Ulcerative colitis (UC) is a chronic inflammatory disease of the colon that is usually manifest as diffuse, continuous, superficial inflammation of the colon. During periods of flare, some patients experience severe symptoms that require hospitalization. In severe cases, inflammation can become transmural, leading to deep ulcerations and risk of toxic

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megacolon. The estimated risk of a patient with UC requiring hospitalization for severe colitis ranges from 18% to 25% (1, 2). One study revealed that 9% of patients admitted with active UC undergo colectomy during that hospitalization (3). However, patients admitted with severe UC have a 27% rate of colectomy (4). The mortality of severe UC is 1% and the mortality of toxic colitis is much higher (1, 4). The total number of hospitalizations for UC in the United States increased by 52% from 1998 to 2007 (5). Although the treatment of severe colitis has recently been reviewed (6), specific detailed recommendations for management of individual patients are limited in the literature. We provide practical, evidence-based management principles for the care of patients hospitalized for UC.

Definitions

Severe Ulcerative Colitis

Several instruments can be used to define and quantify severe UC in clinical practice including the commonly used Truelove and Witts' Index. (Table 1)(7). The Lichtiger Index (please refer to web supplement) (8) has been used to assess disease activity in clinical trials but does not correlate with other measures of disease activity or clinical outcomes. Patients with severe disease, as defined by Truelove and Witts' Index, should be distinguished from outpatients with "moderate to severe disease unresponsive to conventional therapy" that were included in clinical trials of infliximab (9) and adalimumab (10).

Indications for Hospitalization

Indications for hospitalization of patients with UC can include: severe disease, toxic megacolon, failure of outpatient medical therapy, complications of the disease (i.e. arterial or venous thromboembolism), complications related to medical therapy (i.e. opportunistic infections), and severe extraintestinal manifestations.

Goals of Hospitalization

The primary goals during hospitalization are to comprehensively assess disease activity, monitor for complications, and apply medical treatments and/or surgery to improve the patient's symptoms. During the hospital admission, the medical team should determine the severity and anatomical extent of disease and assess for factors that might have led to disease exacerbation. Anatomic extent of disease is an important prognostic indicator: the presence of pancolitis is associated with more disease related complications, higher rates of failure of medical therapy, and a higher rate of colectomy (11–13). It is important to exclude concomitant infection with *Clostridium difficile* or cytomegalovirus (CMV). Rapidly acting and highly effective medication regimens such as intravenous steroids, infliximab, and cyclosporine should be administered while obtaining surgical consultation and following the patient closely to determine response to medical therapy and need for additional salvage medical therapy or colectomy.

Many of the treatments for severe colitis initially described in 1974 by Truelove and Jewell (14) remain the mainstay of treatment today, including intravenous fluids, electrolyte supplements, transfusion as needed, and intravenous steroids. The goal of medical therapy is to markedly improve symptoms such as urgency, pain, and frequent or bloody stools and to

transition the patient to an outpatient medication regimen. See *Discharge Criteria, Follow-up and Prevention of Re-Hospitalization* for proposed discharge criteria. Patients with massive hemorrhage, perforation, or toxic megacolon with impending perforation should not be considered for medical therapy, and should be immediately evaluated by a surgeon, ideally a colorectal surgeon or a general surgeon with experience in UC when available. When medical therapy is successful, patients should be expected to achieve or nearly achieve clinical remission before discharge. Some patients do not respond to medical therapy; for these cases, clinical judgment and clinical prediction rules should be used to assess prognosis (see Figure 1, which includes previously published clinical prediction rules within a proposed algorithm for the care of patients admitted with active UC). Lastly, attention should be paid to the prevention, diagnosis, and treatment of toxic megacolon; prevention of venous thromboembolism; and optimization of nutritional status.

History and Physical Examination

Information collected on patients' history should include a review of the initial diagnosis, anatomic extent of disease, current symptoms, presence or absence of extra-intestinal manifestations, medical treatment history, smoking history, and use of potentially exacerbating medications. Current symptoms should be characterized in terms of bowel movements (number, consistency, presence of nocturnal bowel movements, presence of blood, and urgency), abdominal pain, bloating, nausea and vomiting, fever, and weight loss. The patient's vital signs should be examined for evidence of hypovolemia or sepsis. The abdominal examination should include an assessment of the patient's bowel sounds, identification of abdominal distension, and determination of the degree and location of any abdominal tenderness, including the presence of guarding or rebound. In patients treated with high-dose corticosteroids and/or narcotic analgesics, as well as in elderly patients, the abdominal exam may be less reliable. Many of these symptoms and signs are non-specific, so one should consider other diagnoses that could present with symptoms and signs that are similar to that of a UC flare, such as other gastrointestinal diseases (appendicitis, diverticulitis, adhesion-related small-bowel obstruction, infectious colitis, and medication induced colitis) or non-gastrointestinal diseases. Some symptoms and signs that indicate non-gastrointestinal diseases include flank pain or tenderness (renal disease), or vaginal discharge (gynecologic disease).

Diagnostic Testing

Figure 1 presents a proposed algorithm for the care of patients admitted with active UC, along with a list of laboratory tests that should be performed at admission and throughout hospitalization. Initial laboratory tests should be performed to assess disease severity (complete blood count with differential, chemistry, erythrocyte sedimentation rate, and levels of albumin and C reactive protein) and identify co-infections (stool culture and testing for *C difficile*). Forty to fifty percent of patients hospitalized for severe UC fail intravenous steroid therapy, therefore tests required to initiate rescue therapy with infliximab and azathioprine or cyclosporine and azathioprine should be performed at admission. These tests include assays for thiopurine methyltransferase (TPMT) enzyme activity or genotype (in anticipation of azathioprine therapy); tests for latent *Mycobacterium tuberculosis* infection

(chest x-ray and purified protein derivative or Quantiferon), hepatitis B surface antigen, surface antibody and core antibody (in anticipation of infliximab); and assays for serum concentrations of cholesterol and magnesium (in anticipation of cyclosporine or tacrolimus).

Although not all patients require computed tomography (CT) scan, a plain film of the abdomen should be considered for all patients, to screen for a dilated colon or free air. Abdomino-pelvic CT scans should be considered for patients with severe abdominal pain or tenderness, nausea and vomiting, fever, distension, or increased white blood cell count.

Endoscopy

Patients hospitalized with severely active UC should be assessed by early flexible sigmoidoscopy, to assess disease extent and severity, to identify *C difficile* infection, and to collect biopsy samples for analysis of CMV infection. Endoscopic findings of deep ulcerations could indicate the presence of CMV, Crohn's disease, or severe UC. Deep ulcers and extensive disease are associated with failure of medical treatment and a higher rate of colectomy (12, 13, 15). Typically, flexible sigmoidoscopy should be performed early after admission (within the first 48 h), to assess disease severity and identify CMV infection.

The safety of colonoscopy during an acute flare of UC has been demonstrated (12, 16, 17), however, caution should be taken when a patient has a severely ulcerated or distended colon to avoid precipitating a perforation or toxic megacolon. Endoscopy is generally contraindicated in the presence of toxic megacolon. A large retrospective study revealed that there was a higher risk of perforation during colonoscopy of IBD inpatients, compared with healthy controls (1% vs 0.6%, respectively) (18). Such patients might have a higher risk for perforation, therefore terminal ileal intubation with biopsies should not be a priority.

Medical and Surgical Treatment of Severe UC

Medications

Mesalamine and Other 5-Aminosalicylate (5-ASA)-Based Medications—The value of continuing mesalamine therapy in patients hospitalized for severe UC is limited. Some experts advocate a trial of stopping mesalamine and other 5-ASAs because of the possibility of a paradoxical worsening of diarrhea either, from a hypersensitivity reaction or a drug-induced exacerbation of colitis that can be indistinguishable from a flare (19–22).

Corticosteroids—Patients should be considered for hospitalization and treatment with intravenous steroids when they have failed to respond to oral prednisone, 40–60 mg/day, or have severe UC. The recommended steroid dosing regimen for hospitalized patients with UC is methylprednisolone (40 mg to 1 mg/kg), administered once daily as an intravenous bolus. Once transitioned to oral steroids, the optimal dose of prednisone is 40 mg/day, which is more effective than 20 mg/day and similar in efficacy to 60 mg/day but with fewer side effects (23). A small randomized controlled trial of oral prednisolone comparing 40 mg, once daily to 10 mg, 4 times daily in patients with active proctocolitis revealed no difference in response rates or side effects between the groups (24). Although the optimal taper strategy is unknown, a commonly used taper is to give patients prednisone, 40 mg/day for 2–4

weeks, and then taper the dose by 5 mg per week, to a daily dose of 20 mg, and then by 2.5–5 mg per week, until prednisone is discontinued.

There have been no randomized controlled trials of intravenous corticosteroids for the treatment of severe UC. A systematic review of 32 cohort studies and controlled trials of intravenous steroids in UC from 1974 to 2006 showed that 581 of 1991 patients (27%) required colectomy and 22 patients (1%) died (4). Clinical remission generally occurs in steroid-sensitive cases within 5–7 days (25), however only ~60% of patients hospitalized for severe UC respond to intravenous corticosteroids (14, 26–28).

Thiopurine Immunosuppressives (Azathioprine and 6-Mercaptopurine)—The active metabolites for the thiopurine agents have a half-life of 3–5 days, requiring 2–4 weeks to reach steady state and up to 8–10 weeks to reach maximal clinical effect. They therefore have little utility as inductive agents in hospitalized patients with severe UC, but can be useful as an adjunctive agent for infliximab and as a maintenance agent following treatment with cyclosporine or tacrolimus. They are often initiated or continued in hospitalized patients with UC who previously received 1 of these treatment regimens. The activity or genotype of TPMT should be checked before initiating thiopurine immunosuppresive therapy; it will determine the suggested starting dose (29).

Cyclosporine—The calcineurin inhibitor cyclosporine is a rapidly acting immunosuppressive agent effective for severely active UC. Contraindications to using cyclosporine include hypocholesterolemia (risk of seizure), infection, and significant renal insufficiency. A small placebo-controlled trial demonstrated that intravenous cyclosporine was effective in hospitalized patients with severe steroid-refractory UC (82% in cyclosporine arm vs 0% in placebo arm) (30), however at 6 months, only 45% had avoided colectomy (31). Other studies have shown that monotherapy with intravenous cyclosporine (4 mg/kg) is comparable to treatment with intravenous steroids (32) or intravenous steroids in addition to cyclosporine (33). One recent efficacy trial demonstrated that intravenous cyclosporine was not superior to infliximab in patients that failed treatment with intravenous steroids (34). In a review of randomized controlled trials of cyclosporine for severe UC in the hospital setting, responses ranged from 64% to 84% (35); however, over a longer term (5–7 years of follow up), 38%–78% of patients still required colectomy (36–40). Relapse rates are higher among patients who previously failed maintenance therapy with azathioprine or 6-mercaptopurine (36, 39).

Cyclosporine is given as a continuous infusion of 2 mg/kg over 24 h, with a target whole-blood cyclosporine A concentration (HPLC or monoclonal radioimmunoassay) of ~200–250 ng/ml (41). Patients typically respond within 7 days; lack of response within that time frame should prompt a colectomy. If a patient responds to intravenous cyclosporine, they should eventually be discharged on oral cyclosporine (Sandimune or Neoral or Gengraf) at a dose that is approximately 2-fold the total daily dose that they received intravenously, with a target trough concentration of 200–250ng/ml. Oral cyclosporine therapy should overlap with either azathioprine or 6-mercaptopurine therapy for 2–3 months before it is tapered for maintenance of remission. Outpatients that do not respond to, or are intolerant of, thiopurines should not receive salvage cyclosporine therapy, because cyclosporine is given

with the ultimate goal of transitioning to a thiopurine therapy for long-term maintenance after induction of remission. There are no studies of oral cyclosporine for maintenance of remission in patients with UC.

Infliximab—Infliximab is an immunoglobulin (Ig)G1 monoclonal antibody to tumor necrosis factor (TNF); it is effective for treatment of outpatients with moderately to severely active UC (9). Two placebo-controlled trials demonstrated that infliximab is effective in hospitalized patients with severely active UC who fail intravenous steroids (42, 43). Contraindications to infliximab are listed in Figure 1. Two small controlled trials have indicated the similar efficacies of infliximab and intravenous steroids in hospitalized patients with severely active UC (44, 45). One recent efficacy trial demonstrated that intravenous cyclosporine was not superior to infliximab in patients who failed intravenous steroids (34).

The dosing regimen for induction therapy with infliximab is intravenous administration of 5 mg/kg at weeks 0, 2, and 6. Infliximab (5–10 mg/kg) can be administered subsequently every 8 weeks to maintain remission. A comparative effectiveness trial in outpatients with steroid-refractory UC demonstrated that combination therapy with infliximab and azathioprine was more effective than either agent alone (46), so combination therapy is preferred. No similar trials have been performed on inpatients. If one chooses to treat a patient with a thiopurine, they should be tested for TPMT at the time of admission, because of prolonged testing turn-around times. Although earlier data indicated an increased risk of post-operative complications in patients treated with infliximab (47–49), several more-recent studies found no increased post-operative outcomes after infliximab use (50–54).

A Note on Rescue Therapies—When a patient has no contraindications to either cyclosporine or infliximab and the center has adequate expertise with both, risks and benefits should be discussed with the patient. Cyclosporine therapy has 1%–2% mortality. A potential benefit of rescue therapy with infliximab, compared with cyclosporine, is that infliximab can be continued as maintenance therapy in patients who respond. Patients who receive rescue therapy with infliximab or cyclosporine should also start or continue taking azathioprine or 6-mercaptopurine. Patients who fail to respond to rescue therapy within 7–10 days should undergo colectomy rather than treatment with another rescue therapy. Switching from one rescue therapy to another has been reported to achieve remission in 30%–40% of patients but has been associated with serious adverse events and infections in 16%–20%, from excessive immunosuppression, and some patients have died (55, 56).

Clinical Prediction Rules

It is useful to attempt to predict which patients will and will not respond to intravenous steroid therapy. Several investigators have developed prediction rules to estimate the risk of colectomy (see Figure 1). One prospective study of 51 consecutive episodes of severe UC reported that more than 8 bowel movements/day after 3 days of treatment (or >2 bowel movements/day with a level of C-reactive protein >45mg/L, or of a score >4) had a 85% positive predictive value for colectomy. The study also estimated a 60% rate of colectomy if, at day 7 of treatment, patients have more than 3 bowel movements/day or if blood is still visible in the stool (15). This index has also been prospectively validated in a pediatric

cohort (57) and has been used in practice as well as in clinical trials. An alternative predictive index exists that uses the same parameters (58) (59). A newer prediction score known as the Ho Index gives points for colonic dilation, albumin, and stool frequency; a sum greater than 3 has an 80% positive predictive value for colectomy on day 3 of intravenous corticosteroid use (13). This score was based on a retrospective review of 167 patients with severe UC seen consecutively in 1 medical center and has not been prospectively validated. The Ho Index has also been used to predict avoidance of colectomy with use of cyclosporine therapy among patients that failed at least 5 days of corticosteroid use (60). It should be noted that clinical prediction calculations should not replace clinical judgment. Instead, these rules provide evidence-based percentages to assist the care team in setting expectations regarding the possibility of colectomy.

Surgery

Indications for surgery in hospitalized patients include longstanding disease refractory to medical therapy or emergent, severe disease or fulminant colitis that does not respond to medical therapy, toxic megacolon, perforation, and refractory hemorrhage (61). In patients with UC, perforation can occur in the absence of colonic dilation and can present without classic signs of peritonitis (62). Surgical consultation is highly recommended for patients admitted with severe colitis, because 27% will require colectomy. It is important to try to identify patients who are likely to require surgery because delay in surgery can worsen outcomes (63–65). There has been no demonstrable reduction in the colectomy rate during the last 30 years (4).

The standard of care in the non-urgent elective setting is total proctocolectomy, with or without a restorative procedure to preserve fecal continence, through creation of an ileoanal J pouch from the terminal ileum. This operation can be performed open, laparoscopically, or robotically. The ranges of morbidity and mortality for this surgery are 19%–27% and 0.2%–0.4%, respectively (62, 66). Total proctocolectomy with end ileostomy might be preferred for patients with significant medical comorbidities or distal rectal cancer, who are 60 years old or greater, or with pre-existing fecal incontinence (61).

Patients that require emergent surgery typically undergo restorative proctocolectomy in 3 stages. In the first stage, a total or subtotal abdominal colectomy with end ileostomy leaving a rectal or rectosigmoid stump as a Hartmann’s pouch is performed. Some surgeons bring the rectal stump up to the skin as a mucus fistula, and others advocate bringing the recto-sigmoid stump to the subcutaneous tissue at the lower end of wound, so that stump dehiscence results in wound infection rather than an intra-abdominal leak with abscess and peritonitis (61, 62). The goal in these cases is to expeditiously treat the emergent condition, allowing the patient to recover (systemically and nutritionally) and eventually undergo a restorative procedure or a completion proctectomy with end ileostomy. If the patient is a candidate for restorative proctectomy, the procedure is completed in 2 additional stages. In the second stage, the patient undergoes a completion proctocolectomy with ileoanal J pouch and a diverting loop ileostomy. In the third stage, the loop ileostomy is reversed. The goal of the 3-stage procedure is to reduce the risk of abdominal sepsis and leakage (62).

The potential risks of surgery include hemorrhage, infection, small-bowel obstruction, intra-abdominal or pelvic sepsis/abscess, anastomotic stricture, pouchitis, cuffitis, fistulas, reduced female fertility, erectile and sexual dysfunction, and need for surgical revision or excision of the pouch (61, 62).

C difficile

Patients with IBD are at increased risk of developing *C difficile* infection and incidence rates nearly doubled in patients with UC from 1998 to 2004 (67, 68). One study from Japan found that 40% of patients with symptoms of a UC flare were infected with *C difficile* (69). Hospitalized patients with UC who become infected with *C difficile* have a more aggressive disease course, longer and more costly hospital stays, and colectomy rates of approximately 20% (67, 70). Mortality is greater among patients hospitalized with IBD and *C difficile* infection than patients with IBD without *C difficile* infection (an adjusted odds ratio of 4.7) or patients with *C difficile* infection without IBD (an odds ratio of 2.2).

Although prior antibiotic use is a strong risk factor for patients with *C difficile* infection, 39% of patients with concomitant IBD did not have antibiotic exposure within 2 previous months, in 1 cohort (71). Patients with IBD and *C difficile* infection also tended to be older and have more comorbidities than patients with IBD without *C difficile* infection (70). *C difficile* infection often occurs in stable patients in remission on patient receiving combination or immunomodulator monotherapy before their clinical deterioration. In fact, maintenance use of immunomodulators, but not biologics, was independently associated with infection by *C difficile*, in one study (71). *C difficile* infection can mimic and exacerbate IBD (67). Because of the associated poor outcomes, it is important to diagnose and treat the infection promptly.

An ELISA of stool samples for *C difficile* toxins has a higher yield with repeated testing (71); newer and possibly more sensitive PCR-based assays need to be studied for patients with UC to assess whether a reduced frequency of testing has sufficient sensitivity to detect the infection in these patients (72). The endoscopic appearance of *C difficile* infection is different in patients with IBD, compared to controls (71). Pseudomembranes are seen in ~50% of all patients with *C difficile* infection (67). One cohort of patients with IBD and *C difficile* infection had no typical features on endoscopy or histology. The authors of this study advocated sending stool recovered during colonoscopy for *C difficile* testing in all patients with active colitis (71).

There are no guidelines for treatment of *C difficile* infection that are specific to patients with IBD. Not specific to patients with IBD, the Infectious Diseases Society of America suggests that patients with *C difficile* infection undergo treatment with metronidazole, as first-line therapy, unless the *C difficile* infection is severe, complicated, or is a second recurrence, in which case oral vancomycin should be given (72). No trials have studied oral vancomycin in patients with IBD, but because of increasing rates of metronidazole failure and arguably because of a higher likely severity of disease in this subgroup, some experts have recommended treating hospitalized patient with IBD with oral vancomycin as first-line therapy. One retrospective analysis of this practice associated lower rates of colectomy with

a change from metronidazole to oral vancomycin as the initial treatment regimen for patients with IBD and *C difficile* infection (from 45.5% to 3.5%, from 2004 to 2006) (73). One possible approach would be to initiate oral vancomycin either empirically (in patients where the infection is highly suspected) (67), or immediately after establishing that they are infected with *C difficile*.

Patients with IBD and concomitant *C difficile* infection often require added immunosuppression in the near future (74). A recent randomized trial revealed that treatment with fidaxomicin was noninferior to treatment with vancomycin and was superior to vancomycin for reducing the rate of recurrent infection with some strains of *C difficile*, although patients known to have UC or Crohn's disease were excluded from the study (75). Recurrence rates following treatment of *C difficile* infection are high; 1 study revealed a 59% recurrence rate within 1 month of treatment in patients with IBD in a small cohort, 26% of which required subsequent colectomy (67). Recurrent *C difficile* infection can be treated by repeating the initially prescribed regimen and if a second recurrence occurs, by a prolonged, high-dose, and/or tapering doses of oral vancomycin (72).

CMV

Patients admitted to the hospital with an acute flare of colitis should to be evaluated for the possibility of a concurrent infection with CMV—especially if they are receiving immunosuppressive medications that can reactivate latent infections (76). CMV infection (detection on objective tests, not necessarily with associated symptoms) is common in the general population and is not necessarily indicative of active disease. It is unclear whether CMV infection in the colon in patients with severe UC is pathogenic, a marker of more severe disease, or simply an innocent bystander. A review of the literature indicated that the presence of CMV antigens does not necessarily increase disease severity, and that CMV infection is reactivated in patients with severe UC but does not affect prognosis (77). The prevalence of CMV infection is difficult to estimate because of the heterogeneity of data and because most studies have been retrospective. Among specimens collected from colectomies, the CMV infection rate was as high as 22% (78). A higher prevalence of CMV was reported among steroid-refractory patients (33%–36%) (79, 80), but it is not clear whether these cases resulted from steroid-induced reactivation of CMV or the CMV was a marker of disease severity. Rates of colectomy among patients with CMV infection have been decreasing, according to recent studies. It is unusual to detect CMV infection in patients with mild to moderate UC (81, 82). Furthermore, cyclosporine, high-dose steroids, and tacrolimus can cause CMV to rapidly replicate and/or systemically disseminate (83).

CMV-induced colitis typically affects immunocompromised individuals, although it has been observed in patients that have not received steroids or immunosuppression, including patients with IBD (76). CMV reactivation has not been associated with the use of infliximab and, interestingly, TNF promotes replication of CMV; the absence of TNF has been associated with viral latency in vitro (77, 84). The relationship between CMV and UC is complex, however, in that there are occasional reported cases of colitis and documented cases of CMV infection that improved during treatment with corticosteroids and did not require antiviral agents (80, 85). Furthermore, CMV has been detected in histologic

specimens taken from patients without active colitis (78). Because of the high rate of colectomy and morbidity associated with CMV infection in patients with active UC, patients with biopsies that test positive for CMV are typically treated with antiviral agents, despite the uncertainty about how much of the colitis can be attributed to the CMV infection.

Tests for CMV infection include endoscopic, histologic, serologic, viral culture, antigen detection, and DNA analyses. Of note, fewer than 60% of IBD patients with CMV colitis have antigenemia (86). On the contrary, although DNA tests are sensitive, their specificity is questionable—cutoff values for determining whether or not a patient is infected with CMV have not been established or validated (76). Quantitative real-time PCR assays are more sensitive than antigenemia tests or histologic analysis in detecting CMV in samples from inflamed colon (86), but results do not always correlate with those from immunohistochemical analysis; real-time PCR might be so sensitive that it detects clinically insignificant reactivation of CMV.

When a patient is admitted with UC, it is reasonable to measure serum levels of CMV IgM and IgG, which together have a strong negative predictive value. Patients with active UC should be evaluated by endoscopy for CMV infection when they are admitted to the hospital, without waiting for the results of the serum antibody tests. Endoscopic features of CMV are non-specific but include deep ulcerations, patchy erythema, exudates, microerosions, diffuse edema, and even pseudotumors. Histologic examination reveals cytomegalic cells with large eosinophilic cowdry type A intranuclear inclusions, occasionally surrounded by a clear halo and smaller cytoplasmic inclusions. The detection of of CMV on H&E can be improved with use of immunohistochemical assays that use monoclonal antibodies against CMV immediate early antigen, which detect CMV infection with 93% sensitivity. CMV infection affects the right colon alone in 30% of cases (76). While awaiting pathology results, a negative result from a test for CMV antibodies (IgG) can be used to exclude CMV infection.

There have been no randomized clinical trials to investigate whether gancyclovir can be used to treat CMV infection in patients with severe or steroid-refractory UC. Guidelines from the American College of Gastroenterology do not make a specific recommendation regarding treatment, but instead state that “treatment with gancyclovir may lead to clinical improvement” (87). The European Crohn’s and Colitis Organization, however, recommends: “[i]n case of severe colitis with CMV detected in the mucosa during immunomodulator therapy, antiviral therapy should be initiated and discontinuation of immunomodulators considered until colitis symptoms improve. In case of systemic CMV infection immunomodulator therapy must be discontinued” (88).

Regardless, the low risk of antiviral therapy prompts most providers to treat CMV infections in patients with active colitis. One approach would be to consider reducing immunosuppression or tapering steroids and administering intravenous gancyclovir (5 mg/kg), twice daily for 14 days, followed by (oral) valgancyclovir (450 mg), twice daily for 28 days, although the efficacy of oral valgancyclovir treatment for CMV colitis is not well established. The most important adverse effect of gancyclovir is neutropenia. Colitis

remission rates after antiviral therapy for documented CMV infection in IBD patients ranged from 67% to 100% in a review of several small studies (76).

Toxic Megacolon

The most severe form of colitis is fulminant colitis (89). Toxic megacolon (Table 2), a potential complication of fulminant colitis, is a clinical diagnosis based on features of toxic colitis and colonic dilatation (61, 90). The traditional definition includes at least 3 of the following: temperature >38.6°C, heart rate >120 beats per minute, white blood cell counts $>10.5\times10^3/mm^3$, and anemia, plus at least 1 of the following: dehydration, altered mental status, electrolyte disturbances, and hypotension (91).

One percent to 2% of patients with severe UC progress to toxic colitis and/or megacolon. A prospective study found that 7.9% of patients admitted with UC to have toxic megacolon (92). Thirty percent of patients with toxic megacolon present within 3 months of diagnosis (93). It is important to test patients for *C difficile* infection. Although plain films are easy to repeat on a daily basis, they are less sensitive than CT for evaluating the extent and severity of colitis, determining the presence of colonic dilatation, and assessing for perforation (94).

Medical and surgical expertise are each required to manage patients with toxic megacolon. Barium enema, narcotic antidiarrheals, anticholinergics, loperamide, diphenoxylate, and narcotics should be avoided because they have been associated with the development of toxic megacolon. Frequent physical examinations, laboratory tests, and daily or twice daily abdominal X-rays are important if toxic colitis or megacolon is suspected. Patients should be transfused and receive intravenous fluids, electrolytes, and total parenteral nutrition, as indicated. Broad-spectrum antibiotics are often used in the management of toxic megacolon, due to the potential for microperforation. Nasogastric tube decompression is not helpful for colonic decompression (95). Patients with marked distension should be instructed to roll around in bed or lie in the knee-elbow position every 30 minutes, as these maneuvers have been shown to reduce colonic gas and bowel distension (96, 97). Although toxic megacolon is not necessarily an absolute indication for surgery, many advocate that surgery be performed immediately (98, 99). One reason for this recommendation is that many patients who initially respond to medical therapy will subsequently require colectomy.

Pain Management

The primary method of pain control in patients with severe UC is treatment of their underlying disease. Use of narcotics should be avoided in patients hospitalized for UC because they might precipitate megacolon, although 1 study found that 70.1% of hospitalized patients with IBD received narcotics (100). A retrospective review of patients with UC exposed to narcotics during hospitalization did not report higher rates of colectomy (101), although prospective studies are needed to confirm this finding. Narcotics are associated with increased infectious complications and mortality in patients with IBD (102).

Oral analgesics such as tramadol and acetaminophen can be used but may be insufficient to achieve a level of analgesia acceptable to the patient. Non-steroidal anti-inflammatory drugs should be avoided because of their association with disease exacerbation. Severe pain

related to UC could represent transmural inflammation and its persistence, despite medical therapy, often warrants surgery.

Nutrition

Most patients hospitalized with severe UC should continue to receive a normal diet. Two randomized controlled trials have demonstrated that bowel rest does not affect the outcome of severe UC in patients treated with intravenous prednisone (103, 104). Patients with toxic colitis or megacolon should be made nil-per-os because of the potential for imminent surgical intervention. Peripheral or central intravenous nutrition should be instituted if there is evidence of malnutrition, which has been associated with increased length of stay, total hospital charges, and in-hospital mortality in patients with IBD (105). The goal of intravenous nutrition is to replace nutritional deficits rather than for any primary therapeutic benefit. Hypoalbuminemia is associated with higher post-operative complications and is often a contraindication to surgery that requires anastomosis without a protective ileostomy (106).

Venous Thromboembolism Prophylaxis

Active UC with bloody bowel movements is not a contraindication to venous thromboembolism prophylaxis with low molecular weight heparin. IBD is recognized as a hypercoagulable state (107) and both venous and arterial clots, which can occur in usual or unusual sites and are at risk for embolization. IBD is associated with an approximate 3-fold increase in risk of venous thromboembolism, and the risks seems to be higher during a flare (a hazard ratio of 8.4) (108). Prophylaxis-dosed anti-coagulation is therefore recommended for patients hospitalized with IBD, although there has been no data from prospective studies to demonstrate that this intervention is effective (109, 110).

Discharge Criteria, Follow-Up, and Preventing Re-Hospitalization

There are no validated discharge criteria for patients hospitalized for active UC. It is reasonable to delay discharge until a patient has markedly improved (ideally defined as ≤1–2 non-bloody bowel movements/day, certainly not more than 3–4 bowel movements/day), has transitioned to an appropriate outpatient regimen of medications, and is able to tolerate oral hydration and nutrition. Clinical improvement cannot be assessed if the patient is not eating a normal or nearly normal diet.

Communication with the patient is paramount. It is critical to convey the plan for medical therapy, possible side effects, warning signs that should trigger a return to the hospital, contact information for the IBD treatment team, and the follow-up plan upon discharge.

Conclusions

UC is a chronic condition with a relapsing and remitting course that often results in hospitalization. Severity can be assessed and the extent of disease can be determined by conducting a thorough history and physical examination, laboratory tests, and endoscopy and imaging analyses when applicable. After exclusion of *C difficile* infection, the primary

treatment is administration of intravenous corticosteroids while preventing and monitoring for complications such as toxic megacolon and deep-vein thrombosis. Inadequate response to steroids should prompt the use of infliximab or cyclosporine, usually in combination with azathioprine. Patients who are not responding to medical therapy should be referred for colectomy. Patients can be considered for discharge once they have had a marked improvement in bowel habits with resolution of rectal bleeding and have a clear follow-up plan.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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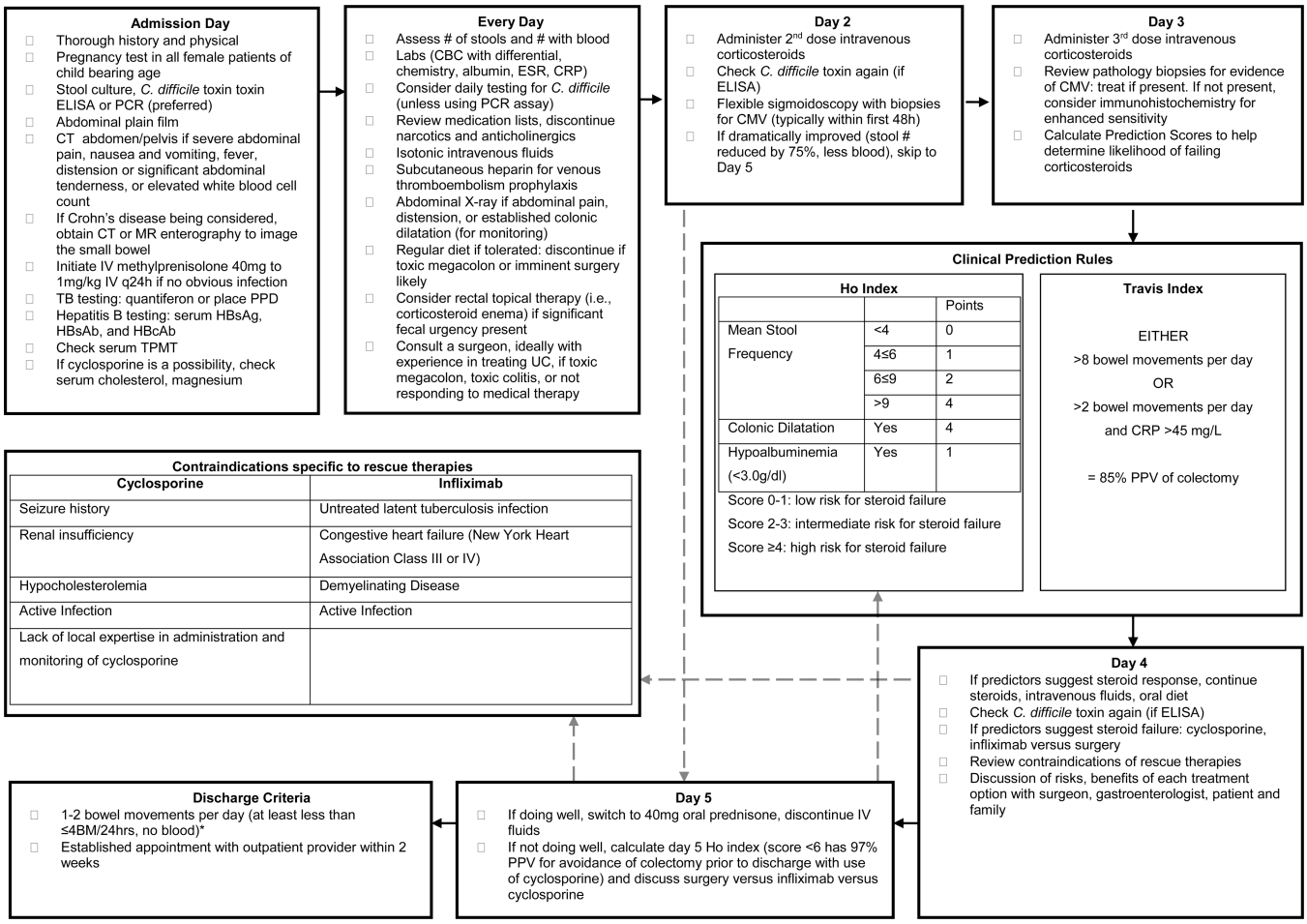

Figure 1. Proposed algorithm for managing ulcerative colitis in the hospital (13,15,63)

*Exact number of acceptable bowel movements varies patient to patient but needs to be while tolerating a full diet and manageable for that patient.

Table 1

Truelove and Witts Criteria for Evaluating the Severity of Ulcerative Colitis*

Variable	Mild Disease	Severe Disease	Fulminant Disease
Stools (number/d)	<4	>6	>10
Blood in stool	Intermittent	frequent	continuous
Temperature (°C)	Normal	>37.5	>37.5
Pulse (beats/min)	Normal	>90	>90
Hemoglobin	Normal	<75% of normal value	transfusion required
Erythrocyte sedimentation rate (mm/hr)	≤30	>30	>30
Colonic features on x-ray		air, edematous wall, thumbprinting	dilatation
Clinical signs		abdominal tenderness	abdominal distention and tenderness

* Moderate disease includes features of both mild and severe disease

(7)

Table 2

Summary of Toxic Megacolon

Definition	Clinical Diagnosis: Toxic colitis + Colonic dilatation
	Traditional Definition {{157 Jalan, K.N. 1969}} At least 3 of the following: □ Temperature >38.6°C □ Heart Rate >120 beats per minute □ WBC >$10.5\times10^3/mm^3$ □ Anemia □ **Plus** at least one of the following: □ Dehydration □ Altered mental status □ Electrolyte disturbances □ Hypotension
Predisposing Factors	*C. difficile* infection, barium enema, narcotic antidiarrheals, anticholinergics, loperamide, diphenoxylate, narcotics
Other Clinical Features	Abdominal distension and tenderness, decreased or absent bowel sounds. Dilated colon seen on radiographs.
Diagnostics	□ Frequent physical examinations □ Frequent laboratory tests (CBC, electrolytes) □ Testing for *C. difficile* infection □ CT scan of abdomen/pelvis initially and daily or twice daily abdominal X-rays to monitor
Management	*Surgical* □ Immediate surgical consultation □ Consideration of emergent colectomy *Medical* □ Treatment of underlying UC (IV corticosteroids for example) □ Treatment of infections when found □ Correction of electrolyte abnormalities □ Broad spectrum antibiotics □ Transfusion of packed red blood cells if needed □ Intravenous fluid administration □ Total parenteral nutrition as indicated □ Ask patient to roll around in bed or lie in knee-elbow position q 30 minutes

(92–101)