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Management of the hospitalized adult patient with severe ulcerative colitis

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INTRODUCTION

Ulcerative colitis (UC) is a chronic inflammatory condition of the large intestine that is limited to the mucosal layer of the colon. It almost always involves the rectum, and may extend in a proximal and continuous fashion to involve other portions of the colon. The pattern of disease activity is characterized by periods of active inflammation alternating with periods of remission.

Acute severe UC is a potentially life-threatening condition, and patients are at risk for progressing to bowel perforation or toxic megacolon. In addition, the short- and long-term risk for colectomy is high.

This topic will review the management of hospitalized patients with acute severe ulcerative colitis. The management of ambulatory, low-risk patients with mild to moderate colitis and the management of ambulatory, high-risk patients with moderate to severe ulcerative colitis are discussed separately. (See "Medical management of low-risk adult patients with mild to moderate ulcerative colitis" and "Management of moderate to severe ulcerative colitis in adults".)

Surgical management of ulcerative colitis is discussed separately. (See "Surgical management of ulcerative colitis".)

The diagnosis and management of toxic megacolon is discussed separately. (See "Toxic megacolon".)

DEFINING DISEASE SEVERITY

Clinical trials of UC often use formal grading systems to describe disease activity. The severity of UC is generally classified as mild, moderate, or severe disease; however, the definition of severe disease activity may vary in the literature depending on the specific index or score being used (eg, Truelove and Witts severity index [1], Mayo Clinic score [2], Montreal classification [3]). (See "Medical management of low-risk adult patients with mild to moderate ulcerative colitis", section on 'Disease activity, severity, and risk'.)

In clinical practice, the following definition of acute severe UC may be more useful [1]:

- Bloody stool frequency ≥6 per day
- PLUS at least one of the following characteristics (ie, evidence of systemic toxicity):
    - Fever (temperature ≥37.8 degrees C)
    - Tachycardia (heart rate ≥90 beats/minute)
    - Anemia (hemoglobin <10.5 g/dL [105 g/L])
    - Elevated inflammatory marker (eg, C-reactive protein, erythrocyte sedimentation rate)

In addition, a small subgroup of patients may present with (or progress to) fulminant UC, which is characterized by bloody stool frequency ≥10 per day with fecal urgency, often accompanied by abdominal pain and abdominal distension, in addition to the criteria for acute severe UC [4]. (See 'Complications' below.)

PRETREATMENT EVALUATION

When a patient presents with clinical features of acute severe UC, the pretreatment evaluation (ie, laboratory studies, lower endoscopy, imaging) serves to exclude alternative or co-existing conditions and to determine the severity and extent of disease.

Our approach to diagnostic testing for hospitalized patients with acute severe UC includes the following:

- **Laboratory studies -** We initially obtain complete blood count, liver biochemical tests, blood urea nitrogen, creatinine, albumin, total cholesterol, and C-reactive protein (CRP). While CRP as a serologic marker of inflammation has largely replaced erythrocyte sedimentation rate (ESR), both may be sent in combination, and in rare circumstances, clinicians may only have access to ESR [5-7].

For patients with fever (temperature ≥37.8 degrees C) or with leukocytosis in the absence of glucocorticoids, we also obtain blood cultures.

- **Stool studies** – We typically obtain stool testing for infection (ie, *Clostridiodes* [formerly *Clostridium*] *difficile*, routine stool cultures [*Salmonella*, *Shigella*, *Campylobacter*, *Yersinia*], and specific testing for *E. coli* O157:H7). For patients with risk factors for parasitic infection (eg, recent travel to a region where parasitic infections are endemic), stool microscopy for ova and parasites (three specimens) and a *Giardia* stool antigen test are also checked. If feasible, we also favor evaluation for amebiasis with stool antigen testing or stool PCR. Stool analysis for the detection of pathogens is discussed in more detail separately:

  - (See "*Clostridioides difficile* infection in adults: Clinical manifestations and diagnosis", section on 'Diagnosis'.)
  - (See "Approach to the adult with acute diarrhea in resource-abundant settings".)
  - (See "Giardiasis: Epidemiology, clinical manifestations, and diagnosis".)
  - (See "Approach to stool microscopy".)
  - (See "Intestinal Entamoeba histolytica amebiasis".)

  Clostridiodes (formerly *Clostridium*) *difficile infection* (CDI) is common in patients with UC who are acutely ill, and CDI is associated with increased risk of colectomy and mortality [8-10]. In an observational study of 45 patients with UC and CDI, the colectomy rate at one year was higher in patients with CDI compared with age- and sex-matched controls (36 versus 10 percent) [9]. Management of CDI is discussed separately. (See "*Clostridioides difficile* infection in adults: Treatment and prevention".)

- **Limited endoscopic evaluation –** For hospitalized patients with acute severe UC, we usually perform a limited lower endoscopy (eg, flexible sigmoidoscopy) without a bowel preparation to assess the severity of mucosal disease, and we obtain biopsies to exclude infection (eg, cytomegalovirus). (See "Approach to the diagnosis of cytomegalovirus infection", section on 'Gastrointestinal disease'.)

  Endoscopic features of severe UC include marked mucosal erythema, absent vascular pattern, friability, and erosions [11,12]. The colonic mucosa may also bleed spontaneously and exhibit frank ulceration. The endoscopic appearance of UC is discussed in more detail separately. (See "Endoscopic diagnosis of inflammatory bowel disease in adults", section on 'Differentiating ulcerative colitis from Crohn disease'.)

  Complete colonoscopy (ie, endoscopic examination to the cecum) is avoided in hospitalized patients with severe colitis because of the increased risk of colonic dilation and perforation [13].

- **Imaging** – Patients with acute severe UC should undergo plain abdominal radiography at presentation to determine if there is colonic dilation (diameter ≥5.5 cm) or toxic megacolon (colon diameter ≥6 cm and evidence of systemic toxicity). In addition, imaging features suggestive of severe colitis include thickened colonic wall and loss of haustral pattern. We also repeat plain abdominal imaging if the patient's clinical status deteriorates (eg, worsening abdominal distension). The management of toxic megacolon is discussed separately. (See "Toxic megacolon".)

  We obtain cross sectional imaging (computed tomography scan) for patients with a suspected complication (eg, diffuse peritonitis resulting from colonic perforation), and the clinical manifestations and diagnosis of intestinal perforation are discussed separately. (See "Overview of gastrointestinal tract perforation".)

INPATIENT MANAGEMENT

Goals of therapy — The short-term treatment goal for patients with acute severe UC is to achieve hemodynamic stability and symptomatic improvement (fewer stools, less or no bleeding), while the long-term goals are to achieve clinical remission (ie, resolution of diarrhea and bleeding) and endoscopic remission by demonstrating complete mucosal healing [4]. Response to therapy in the acute setting can be determined by assessing symptoms and hemodynamic status, performing serial physical examinations (eg, less abdominal tenderness and/or distension), and obtaining laboratory testing (eg, C-reactive protein [CRP]).

General supportive care — Patients with acute severe UC are treated in an inpatient setting, and some patients may require critical care support if they are hemodynamically unstable upon presentation. Patients are given fluid and electrolyte replacement, and some may also require blood products. Initial management consists of medical therapy, although some patients may not respond and will need surgery during the index hospitalization. (See 'Surgery' below.)

Patients with acute severe UC require a multidisciplinary approach involving specialists in gastroenterology, surgery, and for some patients, critical care medicine [14,15].

- **Monitoring** – Inpatient care includes monitoring vital signs, performing physical examination (ie, assess for abdominal distension and tenderness), and tracking stool output (frequency, consistency, and presence of visible blood).

- **Fluids and electrolytes** – Intravenous fluid and electrolyte replacement are necessary to correct and prevent dehydration or electrolyte imbalance. The approach to fluid resuscitation in hospitalized patients is discussed in detail elsewhere. (See "Evaluation of

and initial approach to the adult patient with undifferentiated hypotension and shock", section on 'Hemodynamic support' and "Maintenance and replacement fluid therapy in adults".)

- **Preventing venous thromboembolism** – Pharmacologic venous thromboembolism prophylaxis should be administered to reduce the risk of thromboembolism in patients hospitalized with severe UC [16-18]. Studies have demonstrated an increased risk of venous thromboembolism and pulmonary embolism in patients with inflammatory bowel disease in both population-based and hospital-based cohorts [19-21]. (See "Prevention of venous thromboembolic disease in acutely ill hospitalized medical adults", section on 'Our approach' and "Pulmonary complications of inflammatory bowel disease", section on 'Prophylaxis for venous thromboembolism'.)

- **Nutrition** – If patients with acute severe UC can tolerate oral intake, continuation of regular diet is appropriate; bowel rest tends to reduce stool volume but does not affect disease activity [22,23]. (See "Nutrition and dietary management for adults with inflammatory bowel disease".)

  However, if patients have moderate to severe pain when they eat or if they cannot take in adequate calories, parenteral nutrition may be required until clinical improvement allows for enteral feeding or until the patient goes to surgery. Enteral nutrition should also be stopped if a complication such as toxic megacolon is suspected (systemic toxicity and radiographic evidence of colonic dilation), and this is discussed separately. (See "Toxic megacolon".)

- **Blood products** – Transfusion of packed red blood cells is typically needed if the hemoglobin is <9 g/dL (90 g/L) for high-risk patients (eg, hemodynamically unstable) and if it is <7 to 8 g/dL (70 to 80 g/L) in low-risk patients (eg, hemodynamically stable, no cardiovascular disease). Indications for red blood cell transfusions and risk assessment are discussed in more detail separately. (See "Indications and hemoglobin thresholds for RBC transfusion in adults".)

- **Antibiotics –** We do not routinely use broad-spectrum intravenous antibiotics for patients with acute severe UC; however, we do initiate antibiotic therapy for patients who have peritoneal signs, fever (temperature ≥37.8 degrees C), or who meet the criteria for either fulminant colitis or toxic megacolon. (See 'Defining disease severity' above and "Toxic megacolon".)

  For these selected patients, broad-spectrum antibiotics (eg, ciprofloxacin and metronidazole) are given to reduce septic complications and in anticipation of peritonitis

resulting from perforation. (See "Antimicrobial approach to intra-abdominal infections in adults", section on 'Approach to empiric antibiotic selection'.)

Routine use of antibiotics does not increase the likelihood of responding to medical therapy or lower the colectomy rate [24-27].

- **Medications to avoid** – The following medications are avoided in patients with acute severe UC:
  - All antimotility agents, opioids, and anticholinergic medications are avoided due to the risk of worsening ileus and precipitating toxic megacolon.
  - Oral 5-aminosalicylate (5-ASA) preparations are discontinued at the time of hospital admission because 5-ASA preparations are usually ineffective for inducing remission in patients with acute severe UC [28].
  - Nonsteroidal anti-inflammatory medications are avoided because they have been associated with disease flares and inflammatory bowel disease (IBD)-related hospitalizations [29].

Initial therapy — Initial therapy for most patients with acute severe UC includes systemic and topical glucocorticoids; however, an anti-tumor necrosis factor (TNF) agent (infliximab) is an alternative initial treatment for some patients (eg, those who do not tolerate glucocorticoids). (See 'Infliximab' below.)

Systemic glucocorticoids — We begin intravenous glucocorticoid therapy as initial treatment for acute severe UC [30]. Regimens for intravenous glucocorticoid include methylprednisolone (16 to 20 mg intravenously [IV] every eight hours) or hydrocortisone (100 mg IV every eight hours). Methylprednisolone is preferred because that formulation is associated with less sodium-retention and potassium-wasting than hydrocortisone. Continuous infusions of intravenous glucocorticoids are not safer or more effective than bolus doses in achieving clinical remission in patients with severe UC [31].

Most patients who respond to intravenous glucocorticoids will have symptomatic improvement (ie, fewer stools and less bleeding) within three to five days after starting therapy. However, patients who have no clinical improvement within five to seven days of starting systemic glucocorticoids are unlikely to respond [32,33]. For patients who do not respond within five days, we initiate second-line therapy with either an anti-TNF agent or cyclosporine. (See 'Failure to respond' below.)

Treatment with intravenous glucocorticoids results in clinical improvement for some patients with severe UC. In a systematic review of 26 trials and cohort studies including 1429 adult patients who were hospitalized with severe UC and treated with intravenous glucocorticoids, 67 percent (95% CI 65-69) of patients achieved a clinical response [34]. In addition, data from randomized trials suggested that oral glucocorticoids were effective for inducing remission in patients with UC. In a meta-analysis of five trials including 445 patients with active UC, oral glucocorticoid therapy resulted in higher rates of achieving remission compared with placebo (46 versus 19 percent) [35].

Topical glucocorticoids — In addition to intravenous glucocorticoids, we also use topical glucocorticoid therapy (eg, suppository, foam, or enema daily or twice daily) for patients with acute severe UC involving the distal colon because topical treatment may help provide symptomatic relief (eg, reduced fecal urgency, tenesmus) (table 1) [4]. However, no randomized trials have examined the benefit of topical glucocorticoid therapy in this setting. (See "Medical management of low-risk adult patients with mild to moderate ulcerative colitis", section on 'Ulcerative proctitis or proctosigmoiditis'.)

Failure to respond — Patients with acute severe UC who fail to improve within three to five days of intravenous glucocorticoids are given either infliximab or cyclosporine as second-line medical therapy, or they undergo colectomy.

Escalating medical therapy — Medical therapy is escalated to either infliximab or cyclosporine for patients who do not respond to intravenous glucocorticoids after three to five days [30]. The decision to choose infliximab versus cyclosporine in hospitalized patients with acute, glucocorticoid-refractory UC depends upon several factors: patient characteristics and comorbidities (eg, hypertension, renal disease); hypersensitivity or allergy to infliximab, cyclosporine, and/or thiopurines; and patient and clinician preferences. Infliximab is commonly used in the management of both UC and Crohn disease, and clinicians may be more familiar with the dosing, monitoring, and adverse effects of anti-TNF agents compared with cyclosporine, which is used less frequently. The efficacy and safety are not significantly different between infliximab and cyclosporine for patients with acute severe UC refractory to intravenous glucocorticoids [36-40].

Use of tofacitinib, an oral small molecule, for patients with acute severe UC has been reported in case series, although further studies are needed to establish its safety and dosing regimen in this setting [41,42]. (See "Management of moderate to severe ulcerative colitis in adults", section on 'Small molecules'.)

Infliximab — We typically use infliximab for most patients with glucocorticoid-refractory acute severe UC, and we initially use standard induction dosing of infliximab (5 mg/kg at 0, 2, and 6 weeks). Patients typically demonstrate a clinical response (eg, hemodynamic stability, fewer stools, no bleeding) to infliximab within three to five days; the goal is induction of clinical remission. Specifically, patients should have <6 formed stools, without associated blood, and should be able to resume oral intake without diarrhea or abdominal pain.

Patients who fail to respond to the initial infliximab infusion within five days are usually given a second infliximab infusion at a dose of 10 mg/kg [43]. For patients who respond to the second infliximab infusion, we give the third induction infusion of infliximab in four weeks following the second induction dose. We generally reduce the infliximab dose to standard dosing (5 mg/kg) after clinical remission has been achieved, and we use infliximab for maintenance therapy. (See 'Infliximab-responders' below.)

Patients who do not respond to the second infliximab infusion within five days are evaluated for colectomy. (See 'Surgery' below.)

Some of the patients who initially respond to infliximab will eventually require surgery after the index hospitalization. Thus, it is important to discuss surgery as an option and to consult a colorectal surgeon to participate in both the initial and the long-term care of the patient [44-46]. (See "Surgical management of ulcerative colitis".)

Pretreatment screening, dosing, monitoring, and adverse effects associated with anti-TNF agents are discussed separately:

- (See "Overview of dosing and monitoring of biologic agents and small molecules for treating ulcerative colitis in adults".)
- (See "Tumor necrosis factor-alpha inhibitors: An overview of adverse effects".)

Contraindications to the use of anti-TNF therapies (briefly summarized) include the following (see "Treatment of axial spondyloarthritis (ankylosing spondylitis and nonradiographic axial spondyloarthritis) in adults", section on 'Use of TNF inhibitors'):

- Active uncontrolled infection
- Latent (untreated) tuberculosis
- Demyelinating disease (eg, multiple sclerosis, optic neuritis)
- Heart failure
- Malignancy

We initially continue intravenous and topical glucocorticoids with the intent of eventually tapering all glucocorticoids. The approach to tapering glucocorticoids and providing maintenance therapy is discussed below. (See 'Tapering glucocorticoids' below and 'Infliximab-responders' below.)

Small trials and observational studies have demonstrated short- and long-term efficacy of infliximab in patients with acute severe UC [46-49]. In a trial including 45 patients with acute severe UC, patients given infliximab had lower colectomy rates at three months compared with patients given placebo (30 versus 67 percent; odds ratio for colectomy in placebo group 4.9; 95% CI 1.4-17) [47]. In an observational study of 211 patients who were given infliximab for acute severe UC, the colectomy-free survival rates at 12 and 60 months were 64 and 53 percent, respectively [49].

Additional studies are needed to identify the optimal dosing regimen for infliximab in acute severe UC. A retrospective study of 50 hospitalized patients with steroid-refractory, acute severe UC compared colectomy rates in patients who received standard infliximab dosing (at 0, 2, and 6 weeks) with an accelerated dosing regimen consisting of three induction doses of infliximab within a median period of 24 days [50]. Although colectomy rates during induction therapy were lower with the accelerated regimen compared with the standard regimen (7 versus 40 percent), there were no significant differences in colectomy rates between the two groups in the two-year follow-up period.

Cyclosporine — We use intravenous cyclosporine for selected patients who are refractory to intravenous glucocorticoids as a short-term bridge to therapy with a slower onset, longer-acting medication (azathioprine or 6-mercaptopurine). (See 'Cyclosporine-responders' below.)

However, we do **not** use cyclosporine in patients with any of the following conditions:

- Hypertension (blood pressure >140/90 mmHg).
- Renal disease (serum creatinine >1.4 mg/dL [124 microm/L]).
- History of seizure disorders.
- Low serum total cholesterol (<120 mg/dL [3.11 mmol/L]).
- Low serum magnesium level.
- Low serum albumin (<2.3 g/dL [23 g/L]) [36].
- Prior intolerance or failure of immunomodulator therapy (eg, azathioprine).
- Prior failure of biologic agent (eg, infliximab) [51].
- Inability to comply with dosing and monitoring requirements while on cyclosporine.

For patients with no contraindications to cyclosporine, we typically initiate a dose of 2 mg/kg intravenously daily (in two divided doses) because this dose is effective and is associated with

less toxicity compared with a higher dose (4 mg/kg) [52,53]. Side effects and drug interactions with cyclosporine are common, and some may be life-threatening. Thus, patients receiving therapy must be carefully monitored for electrolyte abnormalities, nephrotoxicity, hypertension, neurotoxicity, and infections. Prophylaxis against *Pneumocystis* pneumonia during therapy is required. The side effects of cyclosporine, drug interactions, and strategies to minimize toxicity are discussed in detail separately. (See "Pharmacology of cyclosporine and tacrolimus" and "Treatment and prevention of Pneumocystis pneumonia in patients without HIV", section on 'Prophylaxis'.)

To achieve target cyclosporine concentrations in patients with UC, blood levels of cyclosporine should be checked every one to two days after initiating therapy and after each dosing change, and then every two to three days when on stable doses. Clinical practice varies with regard to monitoring of cyclosporine levels; some experts have suggested aiming for trough levels <300 ng/mL [54]. The dose can be increased in 0.5 mg/kg per day increments as tolerated to a maximum of 4 mg/kg per day. Doses can be rounded to the nearest 25 mg, to aid in subsequent conversion to oral cyclosporine.

Patients who respond to cyclosporine typically have symptomatic improvement within two to three days, while the goal is resolution of symptoms. Specifically, patients should have <6 formed stools, without associated blood, no abdominal pain, and should be able to eat, prior to converting intravenous formulation to oral cyclosporine microemulsion. Patients who fail to improve within three days are evaluated for colectomy [33,55].

For patients who respond to intravenous cyclosporine, conversion to oral modified cyclosporine (a microemulsion formulation) is calculated by doubling the intravenous dose that had led to adequate levels, administered in divided doses 12 hours apart. For example, patients who had a good response at levels of 4 mg/kg per day of intravenous cyclosporine would be converted to 8 mg/kg per day of oral modified cyclosporine, delivered as 4 mg/kg every 12 hours. Steady state is achieved after the third dose; trough levels are checked immediately prior to fourth dose, with a goal level of 200 ng/mL to 300 ng/mL. Cyclosporine levels <200 ng/mL have been associated with loss of response [54].

We initially continue intravenous and topical glucocorticoids with the intent of eventually tapering all glucocorticoids. The approach to tapering cyclosporine and glucocorticoids and initiating long-term maintenance therapy is discussed below. (See 'Cyclosporine-responders' below and 'Tapering glucocorticoids' below.)

Short-term efficacy of cyclosporine has been demonstrated in small trials [56-58]. In a trial including 20 patients with glucocorticoid-refractory severe colitis, clinical response occurred in 9

of 11 patients given cyclosporine compared with none of the patients given placebo [56]. However, long-term follow-up studies suggest that the long-term risk of colectomy (despite initial clinical remission) ranges from 35 to 58 percent [56,59].

Surgery — For patients with acute severe UC who fail to respond to intravenous glucocorticoids and either anti-TNF therapy or cyclosporine, surgery (eg, total abdominal colectomy with end ileostomy) is indicated. In addition, patients who develop one or more life-threatening complications (eg, colonic perforation, toxic megacolon, severe hematochezia with hemodynamic instability) require urgent surgery. The indications for surgery and specific surgical options for patients with UC are discussed in more detail separately. (See "Surgical management of ulcerative colitis".)

Complications

Fulminant ulcerative colitis — Patients with acute severe UC may progress to fulminant UC (or patients may present initially with fulminant colitis). The management of patients with fulminant UC is similar to treatment of patients with acute severe UC with the following additions (see 'Defining disease severity' above and 'Inpatient management' above):

- Patients with fulminant colitis are typically monitored in a critical care setting and followed closely with vital signs and physical examination every four to six hours to evaluate for signs of peritonitis. A complete blood count, serum electrolytes, serum albumin, liver biochemical tests, and CRP are checked every 12 to 24 hours.

- Initial management of patients with fulminant UC includes bowel rest, intravenous fluids, broad-spectrum antibiotics, in addition to intravenous and topical glucocorticoids. (See 'Initial therapy' above.)

- Patients who do not respond to initial treatment with glucocorticoids within three days are treated with either infliximab or cyclosporine. If the patient does not respond to second-line medical therapy within three days, colectomy is typically performed. (See 'Failure to respond' above.)

Toxic megacolon — Toxic megacolon is a potentially lethal complication of IBD, especially UC, that is characterized by nonobstructive colonic dilatation plus systemic toxicity. The diagnosis and management of toxic megacolon is discussed separately. (See "Toxic megacolon".)

Colonic perforation — Patients with UC who develop colonic perforation require colectomy, although this complication is rare. Colonic perforation and surgical management of UC are

discussed separately. (See "Overview of gastrointestinal tract perforation" and "Surgical management of ulcerative colitis".)

TRANSITION TO OUTPATIENT CARE

Criteria for discharge — Most patients with severe UC have symptomatic improvement after receiving either first- or second-line medical therapy (eg, intravenous glucocorticoids with or without a second-line agent [eg, infliximab]). Hospitalized patients are reassessed daily to determine if they are eligible to be discharged. While achieving clinical remission is not a requirement, patients must meet all criteria listed below before they can be discharged from the hospital:

- Normalization of vital signs (ie, resolution of fever, tachycardia, or hypotension)
- <6 stools per day with no or small amounts of blood with each bowel movement
- Resolution of severe abdominal pain
- Tolerance of oral diet

Tapering glucocorticoids — We discontinue intravenous glucocorticoids and begin an oral formulation (prednisone 60 mg by mouth daily) prior to hospital discharge. Oral glucocorticoids are not used for long-term maintenance, and a medication taper is usually started two weeks after symptoms improve (ie, <6 stools daily, no or minimal blood, no abdominal pain). We typically taper prednisone by decreasing the dose by 5 to 10 mg every week until a daily dose of 20 mg is reached, and then by 2.5 mg every week until it is discontinued [60]. Topical glucocorticoids are also gradually tapered, and this is discussed separately. (See "Medical management of low-risk adult patients with mild to moderate ulcerative colitis", section on 'Alternative therapy'.)

While glucocorticoids induce remission for some patients with severe UC, they are not used for maintenance therapy because of the adverse effects associated with long-term use [61]. (See "Major adverse effects of systemic glucocorticoids".)

MAINTAINING REMISSION

Goals of therapy — The goal of management for patients in remission is to maintain glucocorticoid-free remission and prevent clinical and endoscopic relapse. After achieving clinical remission (ie, resolution of diarrhea and bleeding), colonoscopy is typically performed in 6 to 12 months to assess for mucosal healing. Additional monitoring (eg, laboratory studies) for

patients with UC in remission is discussed separately. (See "Management of moderate to severe ulcerative colitis in adults", section on 'Monitoring'.)

Selecting a therapy — For patients who respond to medical therapy, the choice of maintenance therapy depends primarily on response to induction therapy, but it also may depend on patient preferences, clinician preferences, and insurance coverage/cost.

Glucocorticoid-responders — Options for maintenance therapy for patients who responded to systemic glucocorticoids include:

- **Anti-tumor necrosis factor (TNF) agent** – An anti-TNF agent (eg, infliximab) with or without a thiopurine is used as maintenance therapy for most patients who achieve clinical remission with intravenous glucocorticoids [62,63]. (See 'Infliximab-responders' below.)

- **Thiopurine monotherapy** – Thiopurine monotherapy (ie, azathioprine [AZA] or 6-mercaptopurine [6-MP]) may be used as an alternative to an anti-TNF-based regimen for maintaining remission [64]. The pretreatment screening, dosing, safety, and monitoring of AZA and 6-MP are discussed in detail separately. (See "Overview of azathioprine and mercaptopurine use in inflammatory bowel disease" and "Thiopurines: Pretreatment testing and approach to therapeutic drug monitoring for adults with inflammatory bowel disease".)

  The efficacy of thiopurine monotherapy for maintaining remission for patients with UC is discussed separately. (See "Management of moderate to severe ulcerative colitis in adults", section on 'Maintenance of remission'.)

Infliximab-responders — Patients who achieve clinical remission with infliximab are generally continued on infliximab for maintenance therapy, and for most patients, a thiopurine (ie, AZA) is added to the drug regimen upon hospital discharge [62,63]. The thiopurine is generally given for six months after clinical remission has been achieved, and then the thiopurine is stopped, while continuing anti-TNF agent monotherapy for long-term maintenance.

However, for young, male patients (age <30 years), we use anti-TNF agent monotherapy for maintaining remission. We avoid combination therapy that includes a thiopurine because of the risk of hepatosplenic T-cell lymphoma in such patients, and this is discussed separately. (See "Medical management of moderate to severe Crohn disease in adults", section on 'Hepatosplenic T-cell lymphoma'.)

The pretreatment screening, maintenance dosing, monitoring, and safety of anti-TNF agents and thiopurines are discussed separately. (See "Overview of dosing and monitoring of biologic

agents and small molecules for treating ulcerative colitis in adults" and "Overview of azathioprine and mercaptopurine use in inflammatory bowel disease".)

The efficacy of anti-TNF agents as maintenance monotherapy is established, but the data supporting combination therapy (ie, infliximab plus a thiopurine) are more limited [46,63,65-67]:

- **Anti-TNF monotherapy** – For patients with active UC who responded to anti-TNF induction therapy, anti-TNF agents are effective for maintaining remission [46,65,66]. In a meta-analysis of three trials including 1070 patients with UC, patients on anti-TNF therapy were more likely to maintain remission compared with placebo (relative risk 2.00; 95% CI 1.52-2.62) [66].

- **Anti-TNF agent plus thiopurine** – In a trial of 239 patients with moderate to severe UC, patients treated with infliximab plus azathioprine had higher rates of glucocorticoid-free clinical remission at 16 weeks compared with patients treated with infliximab monotherapy or azathioprine monotherapy (40 versus 24 and 22 percent, respectively) [63]. However, the rates of mucosal healing (defined as a Mayo endoscopy subscore of 0 or 1) were not significantly different for patients on combination therapy compared with patients on infliximab alone. (See "Endoscopic diagnosis of inflammatory bowel disease in adults", section on 'Differentiating ulcerative colitis from Crohn disease'.)

Cyclosporine-responders — Patients who respond to intravenous cyclosporine are transitioned to oral modified cyclosporine (a microemulsion formulation), and the outpatient regimen also includes *Pneumocystis* pneumonia prophylaxis, a thiopurine, and glucocorticoid taper, followed by cyclosporine taper:

- (See 'Cyclosporine' above.)
- (See 'Tapering glucocorticoids' above.)
- (See "Treatment and prevention of Pneumocystis pneumonia in patients without HIV", section on 'Prophylaxis'.)

For long-term maintenance therapy, azathioprine (or 6-mercaptopurine) is started. The pretreatment screening, administration, safety, and monitoring of thiopurines are discussed separately. (See "Overview of azathioprine and mercaptopurine use in inflammatory bowel disease" and "Thiopurines: Pretreatment testing and approach to therapeutic drug monitoring for adults with inflammatory bowel disease".)

The efficacy of thiopurine monotherapy for maintaining remission for patients with UC is discussed separately. (See "Management of moderate to severe ulcerative colitis in adults", section on 'Maintenance of remission'.)

After the glucocorticoid taper has been completed, oral cyclosporine is tapered to discontinuation by reducing the dose once per week in four (approximately) equal increments. Patients who achieve remission with cyclosporine but who cannot maintain remission on thiopurine monotherapy in the absence of glucocorticoids and cyclosporine are evaluated for surgery. (See "Surgical management of ulcerative colitis".)

NUTRITION

The use of nutrition and dietary therapy in patients with inflammatory bowel disease is discussed separately. (See "Nutrition and dietary management for adults with inflammatory bowel disease".)

HEALTH MAINTENANCE

It is important to address routine health maintenance, including screening and prevention of other diseases as well as monitoring for side effects of therapy in patients with inflammatory bowel disease (IBD). Patients with longstanding IBD affecting the colon also require endoscopic surveillance for dysplasia. These issues are discussed in detail separately. (See "Medical management of low-risk adult patients with mild to moderate ulcerative colitis", section on 'Health maintenance' and "Surveillance and management of dysplasia in patients with inflammatory bowel disease".)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Ulcerative colitis in adults".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading

level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Ulcerative colitis in adults (The Basics)")
- Beyond the Basics topics (see "Patient education: Ulcerative colitis (Beyond the Basics)" and "Patient education: Sulfasalazine and the 5-aminosalicylates (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- **Pretreatment evaluation** – Therapy for UC is guided by pretreatment evaluation (ie, laboratory studies, lower endoscopy, imaging), and the goals are to exclude alternative or co-existing conditions and determine the extent and severity of disease. (See 'Pretreatment evaluation' above.)
- **Defining disease severity** – In clinical practice, acute severe UC can be defined by the following. (See 'Defining disease severity' above.):
  - Bloody stool frequency ≥6 per day
  - PLUS at least one of the following (ie, evidence of systemic toxicity):
    - Fever (temperature ≥37.8°C)
    - Tachycardia (heart rate [HR] ≥90 beats/minute)
    - Anemia (hemoglobin <10.5 g/dL [105 g/L])
    - Elevated inflammatory marker (eg, C-reactive protein)
- **Inpatient management** – Patients with acute severe UC are managed with inpatient hospitalization, monitoring, fluid and electrolyte replacement, and they may require blood products. (See 'General supportive care' above.)

  Patients are initially managed with medical therapy, although some patients will need surgery during the index hospitalization:

  - **Initial therapy** – For patients with acute severe UC, we recommend intravenous glucocorticoid therapy as initial treatment to induce remission (algorithm 1) (**Grade**

1B). We also use topical glucocorticoid therapy because topical treatment may provide symptomatic relief (eg, reduced fecal urgency, tenesmus). (See 'Initial therapy' above.)

- **Escalating medical therapy** – For patients with acute severe UC who fail to respond to intravenous glucocorticoid therapy in five days, we initiate second-line therapy with either infliximab or cyclosporine. Selecting a second-line agent depends on patient characteristics, patient preferences, and clinician preference. (See 'Escalating medical therapy' above.)

- **Transition to outpatient care** – For patients with acute severe UC who have symptomatic improvement with medical therapy, the following criteria should be met prior to hospital discharge. (See 'Transition to outpatient care' above.):

  - Normalization of vital signs (ie, resolution of fever, tachycardia, or hypotension)
  - <6 stools per day with no or small amounts of blood with each bowel movement
  - Resolution of severe abdominal pain
  - Tolerance of oral diet

- **Maintaining remission** – For patients with acute severe UC who achieve clinical remission with medical therapy, we suggest long-term medical therapy for maintaining remission. The choice of maintenance therapy depends primarily on the specific agent used to achieve remission, and it also depends on patient preferences, clinician preferences, and insurance coverage/cost. Commonly used maintenance therapy regimens include an anti-tumor necrosis factor (TNF) agent with a thiopurine, anti-TNF agent monotherapy, or thiopurine monotherapy. (See 'Maintaining remission' above.)

- **Complications** – The management of fulminant UC is similar to the management of acute severe UC with the following additional measures: bowel rest (nothing by mouth), empiric, intravenous broad-spectrum antibiotics, and lower threshold for surgical intervention (ie, no clinical improvement after three days of glucocorticoid therapy and three days of second-line therapy). (See 'Complications' above.)

  Toxic megacolon is a potentially lethal complication of severe UC that is characterized by nonobstructive colonic dilation plus systemic toxicity. The diagnosis and management of toxic megacolon is discussed separately. (See "Toxic megacolon".)

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Topic 4068 Version 37.0

GRAPHICS

Medical therapy for mild to moderate ulcerative colitis

Role	Medication	Brand name (United States or as noted)	Usual dose
Induction of remission	**Topical (rectal) mesalamine**[*]		
	Suppository	Canasa, Mezera[¶], Pentasa[¶], Salofalk[¶]	1 gram (one suppository) once daily at bedtime
	Retention enema	Pentasa[¶], Rowasa, Salofalk[¶]	4 grams once daily at bedtime or twice daily[Δ]
	Rectal foam (United States: Not available)	Mezera[¶]	2 grams (two actuations) once daily at bedtime
	Topical (rectal) glucocorticoids		
	Hydrocortisone suppository	Anucort-HC, Anusol-HC, Hemmorex-HC, Proctocort	One suppository (25 or 30 mg) once or twice daily
	Hydrocortisone aerosol foam 10%	Cortifoam	90 mg (one applicatorful) once or twice daily
	Hydrocortisone enema	Cortenema, Colocort	100 mg (one 60 mL unit) once or twice daily
	Budesonide aerosol foam	Uceris	2 mg (one metered dose) once or twice daily
	Budesonide enema (reconstituted dispersible tablets)	Entocort[¶]	2 mg (one enema) once daily prior to bedtime
	Oral 5-aminosalycylic acid (5-ASA) derivatives		
	Sulfasalazine tablet	Azulfidine, Salazopyrin[¶]	4 grams per day in four divided doses
	Mesalamine[*◇]		
	▪ Delayed release enteric coated tablet	Asacol[¶], Asacol HD	2.4 to 4.8 grams daily in three divided doses
		Mezera[¶]	3 grams daily in three divided doses
		Octasa[¶]	4.8 grams daily or in divided doses

		Salofalk[¶]	3 to 4 grams daily in three to four divided doses
	▪ Capsule containing delayed release enteric coated tablet	Delzicol	2.4 grams daily in three divided doses
	▪ Delayed and extended release tablet, multimatrix (MMX)	Lialda, Mezavant[¶]	2.4 to 4.8 grams daily once daily
	▪ Capsule containing delayed release enteric coated granules	Apriso	1.5 to 4.5 grams once each morning
	▪ Controlled release capsule	Pentasa	4 grams daily in four divided doses
	▪ Mesalamine granules (United States and Canada: Not available)	Salofalk sachet[¶]	1.5 to 3 grams daily in one to three divided doses
		Pentasa sachet[¶]	2 to 4 grams daily in two to four divided doses
	Olsalazine capsule	Dipentum	2 to 3 grams daily in two to four divided doses
	Balsalazide capsule	Colazal	6.75 grams daily in three divided doses
	Oral glucocorticoids		
	Budesonide delayed and extended release tablet, multimatrix (MMX)	Uceris	9 mg once daily in the morning for eight weeks
	Prednisone or prednisolone		40 to 60 mg once daily in the morning or in two divided doses
Maintenance of remission	**Topical (rectal) mesalamine[*]**		
	Suppository	Canasa, Mezera[¶], Pentasa[¶], Salofalk[¶]	1 gram (one suppository) once daily at bedtime
	Enema	Pentasa[¶], Rowasa, Salofalk[¶]	1 to 4 grams once daily at bedtime[Δ]
	Oral 5-aminosalycylic acid (5-ASA) derivatives		

	Sulfasalazine tablet	Azulfidine, Salazopyrin[¶]	2 to 4 grams daily in three or four divided doses
	Mesalamine[*◇]		
	▪ Delayed release enteric coated tablet	Asacol[¶], Asacol HD	1.6 to 2.4 grams daily in one to three divided doses
	▪ Capsule containing delayed release enteric coated tablet	Delzicol	1.6 to 2.4 grams daily in one to three divided doses
	▪ Delayed and extended release tablet, multimatrix (MMX)	Lialda, Mezavant[¶]	2.4 to 3.6 grams once daily
	▪ Capsule containing delayed release enteric coated granules	Apriso	1.5 to 3 grams once each morning
	▪ Controlled release capsule	Pentasa	1.5 to 4 grams daily in thre to four divided doses
	▪ Mesalamine granules (United States and Canada: Not available)	Salofalk sachet[¶]	1.5 to 4 grams daily in one to three divided doses
		Pentasa sachet[¶]	2 to 4 grams once daily
	Olsalazine capsule	Dipentum	1 gram daily in two divided doses
	Balsalazide capsule	Colazal	2.25 to 6.75 grams daily in three divided doses

Choice of medication is based on factors including disease location, patient preference and tolerance, and medication availability; refer to UpToDate topic. Approved uses vary by drug, formulation, and country. Refer to product-specific labeling for more detail. Generic (nonproprietary) products may also be available.

5-ASA: 5-aminosalicylate.

* Mesalamine is a United States generic name. Mesalazine is an international generic (nonproprietary) name.

¶ Not available in the United States; however, is available in other areas (eg, Canada, United Kingdom, Europe).

Δ In the United States, mesalamine enema is available as 4 g/60 mL. Other concentrations and dosages are available elsewhere. Refer to product-specific information.

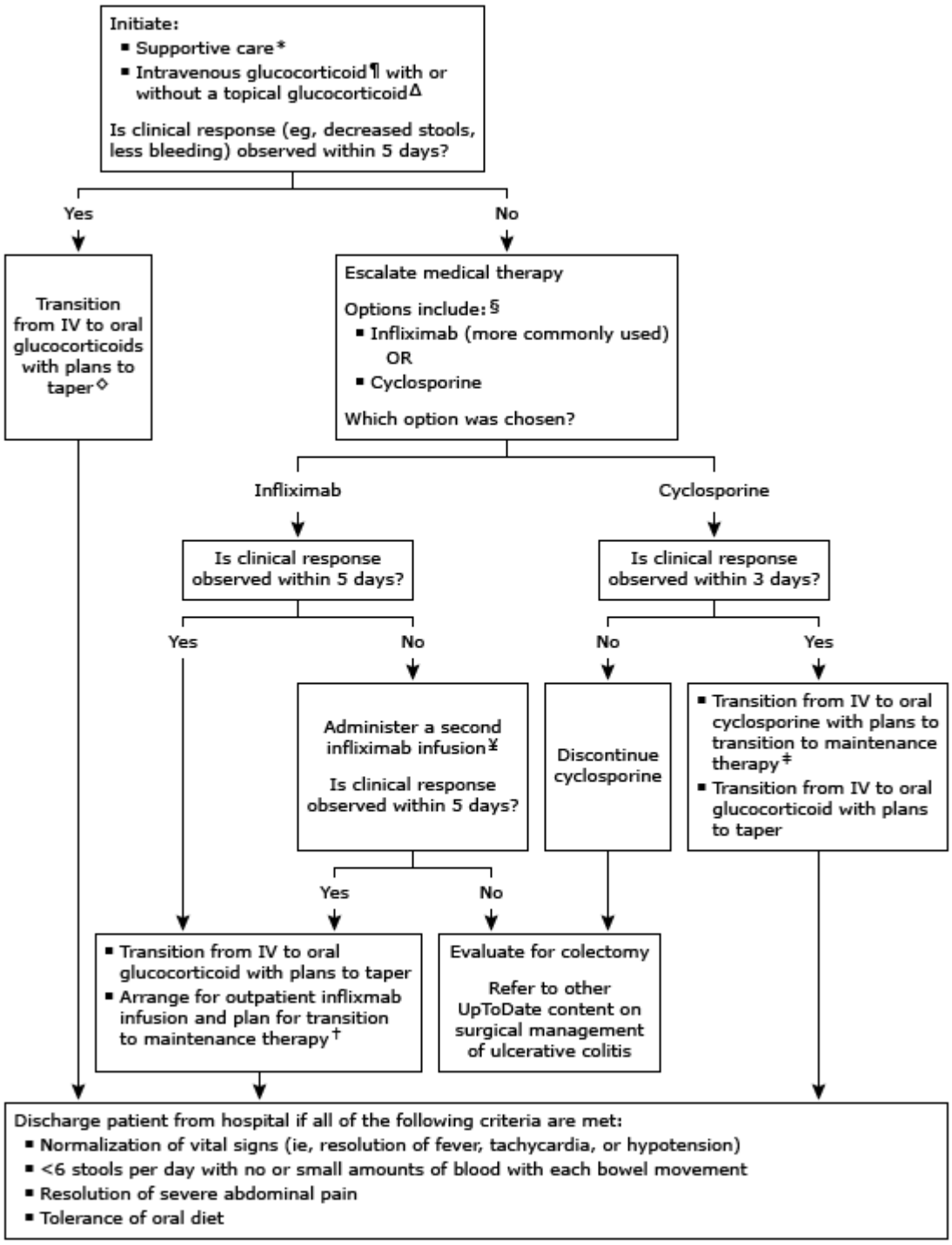
◇ Oral mesalamine may be dosed once daily instead of multiple times daily; there is no significant difference in efficacy and safety.[1,2]

Data courtesy of authors with additional data from:

1. *Ko CW, Singh S, Feuerstein JD, et al. American Gastroenterological Association Institute Clinical Guidelines Committee. AGA clinical practice guidelines on the management of mild-to-moderate ulcerative colitis. Gastroenterology 2019; 156:748.*
2. *Rubin DT, Ananthakrishnan AN, Siegel CA, Sauer BG, Long MD. ACG clinical guideline: Ulcerative colitis in adults. Am J Gastroenterol 2019; 114:384.*
3. *UpToDate Lexidrug. More information available at https://online.lexi.com/.*

Graphic 86774 Version 19.0

Inpatient management for adult patients with severe ulcerative colitis



The short-term treatment goal of hospital management is to achieve clinical response (fewer stools, less or no bleeding), while the long-term goals are to achieve clinical remission (ie, resolution of diarrhea and bleeding) and endoscopic remission by demonstrating complete mucosal healing. Hospitalized patients with severe UC require a multidisciplinary approach including surgery consultation. Patients who do not improve with medical therapy or who have worsening symptoms may require colectomy during hospitalization. In addition, patients who develop a life-threatening complication (eg, colonic perforation) require urgent surgery. This algorithm represents the approach of the UpToDate contributors and does not substitute for the clinical judgment of the treating specialist. Refer to UpToDate content on the

diagnosis and management of hospitalized adult patients with severe ulcerative colitis for additional details.

IV: intravenous.

* Supportive care includes monitoring vital signs and stool output, intravenous fluid and electrolyte replacement, and venous thromboembolism prophylaxis.

¶ Options for IV glucocorticoids include methylprednisolone and hydrocortisone. We prefer methylprednisolone and administer IV glucocorticoids as intermittent, bolus doses rather than a continuous infusion.

Δ We use topical glucocorticoid therapy for severe disease involving the distal colon to help provide symptomatic relief (eg, reduced fecal urgency).

◇ Glucocorticoids are not used for long-term maintenance therapy. Options for maintenance therapy include an anti-tumor necrosis factor agent (eg infliximab) with or without a thiopurine or thiopurine monotherapy.

§ The efficacy and safety of infliximab and cyclosporine appear comparable in this setting. We use infliximab for most hospitalized patients with glucocorticoid-refractory severe ulcerative colitis, but cyclosporine is an acceptable option depending on patient comorbidities and clinician preference. We avoid cyclosporine in patients with certain comorbidities, including hypertension, renal disease, and history of seizure disorder.

¥ For patients who do not respond to the initial infliximab infusion, the second infliximab dose is typically 10 mg/kg.

‡ Cyclosporine is used as a short-term bridge to maintenance therapy with a thiopurine. Prophylaxis against Pneumocystis jirovecii pneumonia should be given during cyclosporine therapy.

† For patients who respond to the first infliximab infusion, the next infusion is given in two weeks. For patients who respond to second infliximab infusion, the next infusion is given in four weeks. For most patients who respond to infliximab, a thiopurine is added to the drug regimen upon hospital discharge.

Graphic 123047 Version 1.0

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