ACG Clinical Guideline: Ulcerative Colitis in Adults

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Ulcerative colitis (UC) is an idiopathic inflammatory disorder. These guidelines indicate the preferred approach to the management of adults with UC and represent the official practice recommendations of the American College of Gastroenterology. The scientific evidence for these guidelines was evaluated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) process. In instances where the evidence was not appropriate for GRADE, but there was consensus of significant clinical merit, "key concept" statements were developed using expert consensus. These guidelines are meant to be broadly applicable and should be viewed as the preferred, but not only, approach to clinical scenarios.

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INTRODUCTION

Ulcerative colitis (UC) is a chronic disease affecting the large intestine, with an increasing incidence worldwide. Nearly 1 million individuals each in the United States and Europe are affected by this condition and many more globally. Over the past decade, since the publication of the last guideline from the American College of Gastroenterology (ACG) on this topic, the management of disease has grown increasingly complex with availability of additional therapeutic classes. In addition, algorithms for initiating, optimizing, and monitoring response to existing therapies have undergone considerable evolution.

UC is a chronic immune-mediated inflammatory condition of the large intestine that is frequently associated with inflammation of the rectum but often extends proximally to involve additional areas of the colon. The absence of rectal involvement has been noted in fewer than 5% of adult patients with UC at diagnosis but may be seen in up to one-third of pediatric-onset colitis (1). The initial presentation of new UC is characterized by symptoms of an inflamed rectum, namely, bleeding, urgency, and tenesmus (a sense of pressure). The condition may present at any time and at all ages, but there is a predominant age distribution of onset that peaks between ages 15 and 30 years. The pattern of disease activity is most often described as relapsing and remitting, with symptoms of active disease alternating with periods of clinical quiescence, which is called remission. Some patients with UC have persistent disease activity despite diagnosis and medical therapy, and a small number of patients present with the rapid-onset progressive type of colitis known as fulminant disease (2,3).

UC causes significant morbidity and a described low incidence of mortality (4,5). Patients with active disease are more likely to have comorbid psychological conditions of anxiety and depression and are more likely to have impaired social interactions or career progression (6). Long-standing UC is also associated with a defined risk of dysplasia and colorectal cancer, which is believed to be related to long-standing unchecked inflammation (7–10).

Management of UC must involve a prompt and accurate diagnosis, assessment of the patient's risk of poor outcomes, and initiation of effective, safe, and tolerable medical therapies. The optimal goal of management is a sustained and durable period of steroid-free remission, accompanied by appropriate psychosocial support, normal health-related quality of life (QoL), prevention of morbidity including hospitalization and surgery, and prevention of cancer. An emerging goal in UC management is that of mucosal healing. To achieve these goals, understanding of the most effective diagnostic, treatment, and preventive strategies is necessary (11). As with any medical decision making, involvement of the patients' preferences forms an important component of care.

This clinical guideline addresses the diagnosis, treatment, and overall management of adult patients with UC, including an approach to the evaluation of the hospitalized patient and a separate section on colorectal cancer prevention. Additional recommendations regarding preventive care in inflammatory bowel disease (IBD) have been published by the ACG previously (12).

The guideline is structured in sections, each with recommendations, key concept statements, and summaries of the evidence. Each recommendation statement has an associated assessment of the quality of evidence and strength of recommendation based on the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) process. The GRADE system was used to evaluate the quality of supporting evidence (Table 1) (13). A "strong" recommendation is made when the benefits clearly outweigh the negatives and/or the result of no action. "Conditional" is used when some uncertainty remains about the balance of benefits and potential harms. The quality of the evidence is graded from high to low. "High"-quality evidence indicates that further research is unlikely to change the authors' confidence in the estimate of effect and that we are very confident that the true effect

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lies close to that of the estimate of the effect. "Moderate"-quality evidence is associated with moderate confidence in the effect estimate, although further research would be likely to have an impact on the confidence of the estimate, whereas "low"-quality evidence indicates that further study would likely have an important impact on the confidence in the estimate of the effect and would likely change the estimate. "Very low"–quality evidence indicates very little confidence in the effect estimate and that the true effect is likely to be substantially different than the estimate of effect.

Key concepts are statements that are not amenable to the GRADE process, either because of the structure of the statement or because of the available evidence. In some instances, key concepts are based on extrapolation of evidence and/or expert opinion.

Tables 2 and 3 summarize the GRADED recommendations and key concept statements in this guideline.

DIAGNOSIS, ASSESSMENT, AND PROGNOSIS OF ULCERATIVE COLITIS

Key concept statements

1. The diagnosis of UC should be suspected in patients with hematochezia and urgency.
2. Infectious etiologies should be excluded at the time of diagnosis.
3. Colonoscopy with intubation of the ileum and biopsies of affected and unaffected areas should be obtained to confirm the diagnosis of UC by a trained pathologist with expertise in gastrointestinal pathology when possible.
4. Categories of disease extent include (i) proctitis (within 18 cm of the anal verge, distal to the rectosigmoid junction), (ii) left-sided colitis (extending from the sigmoid to the splenic flexure), and (iii) extensive colitis (beyond the splenic flexure).
5. If the terminal ileum is normal, further evaluation of the stomach and small bowel by upper endoscopy and cross-sectional imaging is not needed unless there are other symptoms or findings to suggest proximal GI involvement or a diagnosis of Crohn's disease (CD) rather than UC.
6. Definitions of disease severity are needed to guide treatment decisions; definitions should be based on (i) patient-reported outcomes (PROs) (bleeding and normalization of bowel habits), (ii) inflammatory burden (endoscopic assessment including extent and severity and markers of inflammation), (iii) disease course (need for hospitalization, need for steroids, and failure to respond to medications), and (iv) disease impact (functionality and QoL).
7. Fecal calprotectin (FC) can be used in patients with UC as a noninvasive marker of disease activity and to assess response to therapy and relapse.

Recommendations

1. We recommend stool testing to rule out *Clostridioides difficile* (*C. diff*) in patients suspected of having UC (strong recommendation, very low quality of evidence).
2. We recommend against serologic antibody testing to establish or rule out a diagnosis of UC (strong recommendation, very low quality of evidence).
3. We recommend against serologic antibody testing to determine the prognosis of UC (strong recommendation, very low quality of evidence).

Summary of evidence Symptoms of bloody diarrhea, mucous, urgency, tenesmus, and abdominal cramping should trigger consideration of a UC diagnosis, particularly in the absence of an alternate cause. A full clinical history should include assessment

Table 1. Quality assessment criteria[a]

Study design	Quality of evidence	Lower if	Higher if
Randomized trial	High	Risk of bias	Large effect
		−1 serious	+1 large
		−2 very serious	+2 very large
	Moderate	Inconsistency	Dose-response
		−1 serious	+1 evidence of a gradient
		−2 very serious	
		Indirectness	All plausible confounding
		−1 serious	+1 would reduce a demonstrated effect or
		−2 very serious	+1 would suggest a spurious effect when results show no effect
Observational trial	Low	Imprecision	
		−1 serious	
		−2 very serious	
	Very low	Publication bias	
		−1 likely	
		−2 very likely	

[a]See Reference 13.

Table 2. Summary and strength of GRADED recommendations for the management of ulcerative colitis

Diagnosis, assessment, and prognosis of ulcerative colitis
1. We recommend stool testing to rule out *Clostridioides difficile* in patients suspected of having UC (strong recommendation, very low quality of evidence).
2. We recommend against serologic antibody testing to establish or rule out a diagnosis of UC (strong recommendation, very low quality of evidence).
3. We recommend against serologic antibody testing to determine the prognosis of UC (strong recommendation, very low quality of evidence).
Goals for managing patients with ulcerative colitis
4. We suggest treating patients with UC to achieve mucosal healing (defined as resolution of inflammatory changes (Mayo endoscopic subscore 0 or 1)) to increase the likelihood of sustained steroid-free remission and prevent hospitalizations and surgery (conditional recommendation, low quality of evidence).
5. We suggest FC as a surrogate for endoscopy when endoscopy is not feasible or available to assess for mucosal healing (conditional recommendation, very low quality of evidence).
Induction of remission in mildly active ulcerative colitis
6. In patients with mildly active ulcerative proctitis, we recommend rectal 5-ASA therapies at a dose of 1 g/d for induction of remission (strong recommendation, high quality evidence).
7. In patients with mildly active left-sided colitis, we recommend rectal 5-ASA enemas at a dose of at least 1 g/d preferred over rectal steroids for induction of remission (strong recommendation, moderate quality of evidence).
8. In patients with mildly active left-sided UC, we suggest rectal 5-ASA enemas at a dose of at least 1 g/d combined with oral 5-ASA at a dose of at least 2 g/d compared with oral 5-ASA therapy alone for induction of remission (conditional recommendation, low quality of evidence).
9. In patients with mildly active left-sided UC who are intolerant or nonresponsive to oral and rectal 5-ASA at appropriate doses (oral at least 2 g/d and rectal at least 1 g/d), we recommend oral budesonide MMX 9 mg/d for induction of remission (strong recommendation, moderate quality of evidence).
10. In patients with mildly active extensive colitis, oral 5-ASA at a dose of at least 2 g/d is recommended to induce remission (strong recommendation, moderate quality of evidence).
11. In patients with UC of any extent who fail to respond to 5-ASA therapy, we recommend oral systemic corticosteroids to induce remission (strong recommendation, low quality of evidence).
12. In patients with mildly active UC who fail to reach remission with appropriately dosed 5-ASA (at least 2 g/d oral 5-ASA and/or at least 1 g/d rectal 5-ASA), we suggest against changing to an alternate 5-ASA formulation to induce remission. Alternative therapeutic classes should be considered (conditional recommendation, low quality of evidence).
13. In patients with mildly active UC of any extent, we suggest using a low dose (2–2.4 g/d) of 5-ASA compared with a higher dose (4.8 g/d), as there is no difference in the remission rate (conditional recommendation, very low quality of evidence).
14. In patients with mildly to moderately active UC not responding to oral 5-ASA, we recommend the addition of budesonide MMX 9 mg/d to induce remission (strong recommendation, moderate quality of evidence).
15. In patients with mildly to moderately active UC of any extent using 5-ASA to induce remission, we recommend either once-daily or more frequently dosed oral 5-ASA based on patient preference to optimize adherence, as efficacy and safety are no different (strong recommendation, moderate quality evidence).
Maintenance of remission in patients with previously mildly active ulcerative colitis
16. In patients with mildly active ulcerative proctitis, we recommend rectal 5-ASA at a dose of 1 g/d to maintain remission (strong recommendation, moderate quality of evidence).
17. In patients with mildly active left-sided or extensive UC, we recommend oral 5-ASA therapy (at least 2 g/d) for maintenance of remission (strong recommendation, moderate quality of evidence).
18. We recommend against systemic corticosteroids for maintenance of remission in patients with UC (strong recommendation, moderate quality of evidence).
Induction of remission in moderately to severely active ulcerative colitis
19. In patients with moderately active UC, we recommend oral budesonide MMX for induction of remission (strong recommendation, moderate quality of evidence).
20. In patients with moderately to severely active UC of any extent, we recommend oral systemic corticosteroids to induce remission (strong recommendation, moderate quality of evidence).
21. In patients with moderately to severely active UC, we recommend against monotherapy with thiopurines or methotrexate for induction of remission (strong recommendation, low quality of evidence).
22. In patients with moderately to severely active UC, we recommend anti-TNF therapy using adalimumab, golimumab, or infliximab for induction of remission (strong recommendation, high quality of evidence).
23. In patients with moderately to severely active UC who have failed 5-ASA therapy and in whom anti-TNF therapy is used for induction of remission, we suggest against using 5-ASA for added clinical efficacy (conditional recommendation, low quality of evidence).
24. When infliximab is used as induction therapy for patients with moderately to severely active UC, we recommend combination therapy with a thiopurine (strong recommendation, moderate quality of evidence for azathioprine).

Table 2. (*continued*)

25. In patients with moderately to severely active UC, we recommend vedolizumab for induction of remission (strong recommendation, moderate quality of evidence).
26. In patients with moderately to severely active UC who have previously failed anti-TNF therapy, we recommend vedolizumab for induction of remission (strong recommendation, moderate quality of evidence).
27. In patients with moderately to severely active UC, we recommend tofacitinib 10 mg orally b.i.d. for 8 wk to induce remission (strong recommendation, moderate quality of evidence).
28. In patients with moderately to severely active UC who have previously failed anti-TNF therapy, we recommend tofacitinib for induction of remission (strong recommendation, moderate quality of evidence).
29. In patients with moderately to severely active UC who are responders to anti-TNF therapy and now losing response, we suggest measuring serum drug levels and antibodies (if there is not a therapeutic level) to assess the reason for loss of response (conditional recommendation, very low quality of evidence).
Maintenance of remission in patients with previously moderately to severely active ulcerative colitis
30. In patients with previously moderately to severely active UC who have achieved remission but previously failed 5-ASA therapy and are now on anti-TNF therapy, we recommend against using concomitant 5-ASA for efficacy of maintenance of remission (conditional recommendation, low quality of evidence).
31. We recommend against systemic corticosteroids for maintenance of remission in patients with UC (strong recommendation, moderate quality of evidence).
32. For patients with previously moderately to severely active UC now in remission due to corticosteroid induction, we suggest thiopurines for maintenance of remission compared with no treatment or corticosteroids (conditional recommendation, low quality of evidence).
33. In patients with previously moderately to severely active UC now in remission, we recommend against using methotrexate for maintenance of remission (conditional recommendation, low quality of evidence).
34. We recommend continuing anti-TNF therapy using adalimumab, golimumab, or infliximab to maintain remission after anti-TNF induction in patients with previously moderately to severely active UC (strong recommendation, moderate quality of evidence).
35. We recommend continuing vedolizumab to maintain remission in patients with previously moderately to severely active UC now in remission after vedolizumab induction (strong recommendation, moderate quality of evidence).
36. We recommend continuing tofacitinib for maintenance of remission in patients with previously moderately to severely active UC now in remission after induction with tofacitinib (strong recommendation, moderate quality of evidence).
Management of the hospitalized patient with acute severe ulcerative colitis
37. In patients with ASUC, we recommend DVT prophylaxis to prevent VTE (strong recommendation, low quality of evidence).
38. In patients with ASUC, we recommend testing for CDI (strong recommendation, moderate quality of evidence).
39. In patients with ASUC and concomitant CDI, we recommend treatment of CDI with vancomycin instead of metronidazole (strong recommendation, low quality of evidence).
40. We recommend against the routine use of broad-spectrum antibiotics in the management of ASUC (strong recommendation, low quality of evidence).
41. We suggest against total parenteral nutrition for the purpose of bowel rest in ASUC (conditional recommendation, very low quality of evidence).
42. In patients with ASUC, we recommend a total of 60 mg/d of methylprednisolone or hydrocortisone 100 mg 3 or 4 times per day to induce remission (strong recommendation, low quality of evidence).
43. In patients with ASUC failing to adequately respond to intravenous corticosteroids by 3–5 days we recommend medical rescue therapy with infliximab or cyclosporine (strong recommendation, moderate quality of evidence).
44. In patients with ASUC who achieve remission with infliximab treatment, we recommend maintenance of remission with the same agent (strong recommendation, moderate quality of evidence).
45. In patients with ASUC who achieve remission with cyclosporine treatment, we suggest maintenance of remission with thiopurines (conditional recommendation, low quality of evidence).
46. In patients with ASUC who achieve remission with cyclosporine treatment, we suggest maintenance of remission with vedolizumab (conditional recommendation, very low quality of evidence).
Colorectal cancer prevention in ulcerative colitis
47. We suggest colonoscopic screening and surveillance to identify neoplasia in patients with UC of any extent beyond the rectum (conditional recommendation, very low quality of evidence).
48. When using standard-definition colonoscopes in patients with UC undergoing surveillance, we recommend dye spray chromoendoscopy with methylene blue or indigo carmine to identify dysplasia (strong recommendation, low quality of evidence).
49. When using high-definition colonoscopes in patients with UC undergoing surveillance, we suggest white-light endoscopy with narrow-band imaging or dye spray chromoendoscopy with methylene blue or indigo carmine to identify dysplasia (conditional recommendation, low quality of evidence).

5-aminosalicylate, 5-ASA; ASUC, acute severe ulcerative colitis; CDI, *Clostridioides difficile* infection; FC, fecal calprotectin; MMX, multi-matrix; TNF, tumor necrosis factor; VTE, venous thromboembolism; UC, ulcerative colitis.

Table 3. Summary of key concept statements for the management of ulcerative colitis

Diagnosis, assessment, and prognosis of ulcerative colitis
1. The diagnosis of UC should be suspected in patients with hematochezia and urgency.
2. Infectious etiologies should be excluded at the time of diagnosis.
3. Colonoscopy with intubation of the ileum and biopsies of affected and unaffected areas should be obtained to confirm the diagnosis of UC by a trained pathologist with expertise in gastrointestinal pathology when possible.
4. Categories of disease extent include (i) proctitis (within 18 cm of the anal verge, distal to the rectosigmoid junction), (ii) left-sided colitis (extending from the sigmoid to the splenic flexure), and (iii) extensive colitis (beyond the splenic flexure).
5. If the terminal ileum is normal, further evaluation of the stomach and small bowel by upper endoscopy and cross-sectional imaging is not needed unless there are other symptoms or findings to suggest proximal gastrointestinal involvement or a diagnosis of CD rather than UC.
6. Definitions of disease severity are needed to guide treatment decisions; definitions should be based on (i) PROs (bleeding and normalization of bowel habits), (ii) inflammatory burden (endoscopic assessment including extent and severity and markers of inflammation), (iii) disease course (need for hospitalization, need for steroids, and failure to respond to medications), and (iv) disease impact (functionality and QoL).
7. FC can be used in patients with UC as a noninvasive marker of disease activity and to assess response to therapy and relapse.
Goals for managing patients with ulcerative colitis
8. UC is a chronic condition for which therapy is required to induce and maintain remission; therapeutic decisions should be categorized into those for (i) induction and (ii) maintenance, with a goal of obtaining and maintaining a steroid-free remission.
9. Strategies for management of UC should reflect the patient's and provider's goals and recognize the chronic nature of the disease.
10. Corticosteroid-free remission may be defined based on symptoms, endoscopic findings, or disease impact without ongoing corticosteroid use. Symptomatic remission relates to improvement in PROs, whereas endoscopic healing is defined as restoration of intact mucosa without friability. Deep remission is a combination of symptomatic remission and endoscopic healing and is a preferred goal of management.
11. Selection of induction and maintenance therapies for UC should be based on disease extent, severity, and prognosis.
12. Initial treatment of UC should focus on restoration of normal bowel frequency and control of the primary symptoms of bleeding and urgency. An endoscopically healed mucosa is associated with sustained remission and reduced risk of colectomy.
13. Histological healing is associated with some improved clinical outcomes but has not yet been validated prospectively as an end point of treatment.
14. Control of mucosal inflammation may reduce dysplasia risk.
15. Given the chronic nature of UC and the therapies for UC, monitoring for disease-related and drug-related complications is important. This should incorporate preventive strategies as outlined in a separate guideline from the ACG.
16. Routine visits to assess the state of UC are recommended to monitor for relapse and address health maintenance needs.
17. Patients with UC should be screened for coexistent anxiety and depressive disorders, and when identified, patients should be provided with resources to address these conditions.
Induction of remission in mildly active ulcerative colitis
18. Patients with mildly active UC and a number of prognostic factors associated with an increased risk of hospitalization or surgery should be treated with therapies for moderately to severely active disease (Table 8). Each prognostic factor carries a different weight and must be discussed in a shared decision-making fashion with the patient. For example, age alone is a weaker prognostic factor than severe endoscopic activity. However, young age combined with another factor may represent sufficient criteria to treat according to the moderately to severely active disease protocol.
19. Patients with mildly active UC should be reassessed to determine response to induction therapy within 6 weeks.
20. FMT requires more study and clarification of treatment before use as a therapy for UC.
21. Complementary therapies such as probiotics and curcumin require further study with adequate power and clarification of end points.
Induction of remission in moderately to severely active ulcerative colitis
22. Strategies for the management of the nonhospitalized patient with moderately to severely active UC are similar with the exception of a few considerations in which the data exist specifically for a patient with moderately active UC:
a. 5-ASA therapy could be used as monotherapy for induction of moderately but not severely active UC.
b. In patients with moderately active UC, consider nonsystemic corticosteroids such as budesonide MMX before the use of systemic therapy.
c. In patients with severely active UC, consider systemic corticosteroids rather than topical corticosteroids.
23. Robust data on combination anti-TNF and immunomodulator therapy in moderately to severely active UC exist only for infliximab and thiopurines.
24. Patients who are primary nonresponders to an anti-TNF (defined as lack of therapeutic benefit after induction despite adequate drug levels) should be evaluated and considered for alternative mechanisms of disease control (e.g., in a different class of therapy) rather than cycling to another drug within the anti-TNF class.

Table 3. (*continued*)

25. In patients with moderately to severely active UC who had an initial response but subsequently lost efficacy to one anti-TNF therapy, we recommend alternative anti-TNF therapy (but not the biosimilar to the original brand) compared with no treatment for induction of remission.
26. The patient with nonresponse or loss of response to therapy should be assessed with therapeutic drug monitoring to identify the reason for lack of response and whether to optimize the existing therapy or to select an alternate therapy.
27. Obtain consultation with a surgeon and consider colectomy in patients with moderately to severely active UC who are refractory or intolerant to medical therapy.
Maintenance of remission in patients with previously moderately to severely active ulcerative colitis
28. 5-ASA therapy for maintenance of remission is likely not as effective in previously severely active UC compared with previously moderately active UC.
29. Budesonide MMX has not been studied for maintenance of remission of previously moderately to severely active UC.
30. Most clinical trials and available data demonstrate a benefit of using the steroid-sparing therapy that induces remission to maintain that remission.
31. There is insufficient evidence supporting a benefit for proactive therapeutic drug monitoring in all unselected patients with UC in remission.
32. We suggest elective proctocolectomy in patients with UC failing maximal medical management.
Management of the hospitalized patient with acute severe ulcerative colitis
33. All patients admitted with ASUC should have stool testing to rule out CDI.
34. All patients with ASUC should undergo a flexible sigmoidoscopy within 72 hr, and preferably within 24 hr of admission. This should be used to assess endoscopic severity of inflammation and to obtain biopsies to evaluate for CMV colitis.
35. All patients with ASUC should be assessed for the presence of toxic megacolon on a regular basis during the hospital admission.
36. Response in patients with ASUC should be monitored using stool frequency, rectal bleeding, physical examination, vital signs, and serial CRP measurements.
37. NSAIDs, opioids, and medications with anticholinergic side effects should be avoided in ASUC.
38. In patients failing to adequately respond to medical therapy by 3–5 days or with suspected toxicity, surgical consultation should be obtained.
39. The choice between infliximab and cyclosporine should be based on provider experience with the agent, history of previous failure of immunomodulator or anti-TNF therapy, and serum albumin.
40. Toxic megacolon, colonic perforation, severe refractory hemorrhage, and refractoriness to medical therapy are indications for surgery in patients with ASUC.
41. Infliximab and cyclosporine do not increase postoperative complications of colectomy, and surgery should not be deferred based on this exposure.
Colorectal cancer prevention in ulcerative colitis
42. Screening and subsequent surveillance colonoscopy to assess for dysplasia in individuals with UC of extent greater than the rectum should start 8 years after diagnosis.
43. Patients with UC and PSC should undergo a screening colonoscopy at the time of diagnosis of UC and surveillance annually thereafter.
44. Surveillance colonoscopies in patients with UC should be performed at 1- to 3-year intervals based on the combined risk factors for CRC in UC and the findings on previous colonoscopy. Specific interval should be based on combined risk factors and findings from previous examinations.
45. During colonoscopic examination in patients with UC, the endoscopist should identify raised lesions and abnormal pit patterns and perform targeted biopsies. Endoscopically discrete lesions should be removed, clearly labeling and separating distinct lesions and segments of the colorectum.
46. Most neoplasia in UC is visible with standard- or high-definition white-light examinations.
47. It is unclear whether segmental random biopsies are still required during surveillance colonoscopy in UC.
48. Pathologic interpretation of UC-associated neoplasia should be performed by a pathologist experienced in gastrointestinal pathology, and neoplastic findings should be reviewed by a second experienced pathologist.
49. When dysplasia in UC of any grade is discrete and has been completely removed, proctocolectomy may not be necessary. If surgery is not performed, subsequent surveillance colonoscopy should initially be performed at shortened intervals.
50. When dysplasia in UC is not resectable or is multifocal, the patient should be referred for proctocolectomy.
51. Patients with UC who have extensive inflammatory polyps may not be able to have adequate surveillance and should be informed about this fact and that more frequent surveillance or surgery may be required.
52. No medical therapy has demonstrated sufficient prevention of dysplasia or CRC to avoid colonoscopic surveillance in UC.
53. Patients with UC-associated dysplasia who are undergoing ongoing active surveillance may benefit from the use of augmented visualization by dye spray chromoendoscopy in their first examination after UC-associated dysplasia was detected.
54. Fecal DNA testing and CT colonography are not recommended for screening or surveillance of UC-associated neoplasia because of insufficient evidence.

5-aminosalicylate, 5-ASA; ACG, American College of Gastroenterology; ASUC, acute severe ulcerative colitis; CD, Crohn's disease; CDI, *Clostridioides difficile* infection; CMV, cytomegalovirus; CRC, colorectal cancer; CRP, C-reactive protein; CT, computed tomography; DVT, deep venous thrombosis; FC, fecal calprotectin; FMT, fecal microbiota transplantation; MMX, multi-matrix; NSAID, nonsteroidal anti-inflammatory drug; PRO, patient-reported outcome; PSC, primary sclerosing cholangitis; QoL, quality of life; TNF, tumor necrosis factor; UC, Ulcerative colitis.

of severity of disease, triggers precipitating onset, and potential alternate etiologies. Symptoms assessed should include frequency of bowel movements, including number of nocturnal bowel movements. Assessment of bleeding should include the proportion of bowel movements that are mixed with blood. Other important symptoms to assess include urgency, abdominal pain, cramping, and weight loss, a marker of severity of disease. In addition, a thorough history should assess the presence of extraintestinal manifestations, including joint, skin, ocular, and oral manifestations, and symptoms suggesting hepatobiliary involvement. Potential precipitants of UC may include recent smoking cessation (14), nonsteroidal anti-inflammatory drug (NSAID) use (15,16), and enteric infections (17). *C. diff* infection (CDI) is increasingly recognized as complicating a significant proportion of patients with UC and is associated with an increased risk of hospitalizations, surgery, and even mortality (18,19). The prevalence of CDI among patients with newly diagnosed or relapsing IBD ranges from 5% to 47%. Concomitant CDI with UC has worse outcomes including higher mortality (20,21). Testing for *C. diff* is typically performed by polymerase chain reaction (PCR) or enzyme-linked immunosorbent assay (ELISA) and has been reviewed in recent guidelines (22). Other enteric infections that could mimic UC include infection with *Escherichia coli* (*E. coli* O157:H7), *Salmonella*, *Shigella*, *Yersinia*, and *Campylobacter* and parasitic infections such as amebiasis in the right clinical setting. Therefore, an infectious etiology should always be suspected and excluded at the time of diagnosis in the right clinical setting. Several institutions use comprehensive intestinal pathogen testing through PCR-based assays that include many bacterial and viral pathogens. The prevalence and impact of non–*C. diff* intestinal pathogens detected through such assays remain to be robustly established, with initial results suggesting *C. diff* to be the predominant infectious determinant of adverse outcomes in patients with IBD (23).

The diagnosis of UC requires a lower gastrointestinal endoscopic examination with histologic confirmation. For most patients, a complete colonoscopy including examination of the terminal ileum should be performed. This allows for assessment of the full extent of disease at diagnosis and can rule out distal ileal involvement, which can be seen with CD. Subsequent examinations can then assess response to therapy. However, in individuals with severe disease, a complete colonoscopy may be associated with a greater risk of perforation, and in this case, a sigmoidoscopy with biopsies is sufficient. Endoscopically, UC most often presents as a continuously inflamed segment involving the distal rectum and extending proximally. Endoscopic features of inflammation include loss of vascular markings, granularity and friability of the mucosa, erosions, and, in the setting of severe inflammation, deep ulcerations and spontaneous bleeding. The index colonoscopy should note involvement of the rectum and complete extent of inflammation. Proximal histologic extension may be seen even in endoscopically normal-appearing colon and may have implications for defining the extent of disease and subsequent surveillance intervals. Therefore, biopsies should be obtained from the proximal endoscopically normal-appearing colon even if the inflamed segment appears to be restricted to the distal colon. Similarly, even if the distal rectum appears endoscopically normal, separate biopsies from the rectum should be obtained because patchy histologic inflammation may be seen in 5%–30% of children with UC despite the absence of endoscopically visible inflammation (24).

Routine upper endoscopic evaluation is not required in adults with a new diagnosis of UC and should be restricted to those with symptoms of upper gastrointestinal disease. While in the pediatric population, up to 8% of children with UC may have their diagnosis modified to CD based on upper endoscopic findings (25), such occurrences are less frequent in adult-onset disease (26). Gastritis and erosions may be seen in up to one-third of patients with UC (27). Imaging the small bowel with computed tomography (CT) or magnetic resonance imaging is also not routinely required in all patients with normal appearance of the terminal ileum on colonoscopy. However, in those with abdominal symptoms not explained by endoscopically active disease, with suspicion of CD (such as predominantly watery diarrhea, weight loss, or abdominal pain), or where proximal extent of involvement cannot be evaluated because of severity of inflammation, CT, magnetic resonance imaging, or video capsule endoscopy may be useful.

Once a diagnosis of UC is made, determining the severity of disease becomes important. We have proposed new definitions of mildly, moderately, and severely active disease that incorporate both PROs and laboratory- and endoscopy-based values (Table 4 and Figure 1).

Active UC is frequently marked by an elevation in C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) (28,29). Although such markers are nonspecific and may be elevated with other causes of systemic inflammation, they often correlate with the endoscopic severity of disease (30). Such markers also have prognostic significance and have a role in predicting the risk of colectomy (31–33) and response to therapy (32–34). However, up to a quarter of patients with endoscopically active disease may have a normal CRP, and the frequency of elevation is lower in individuals with mild endoscopic activity. Measurement of hemoglobin and serum albumin levels at diagnosis can be helpful in assessing disease severity and prognosis.

Demonstration of fecal leukocytes alone is not sufficiently sensitive, nor is it specific for the diagnosis or assessment of the activity of UC. FC is a nonspecific neutrophilic marker of inflammation and is elevated in infectious and inflammatory colitis but not in noninflammatory causes of diarrhea such as irritable bowel syndrome. Several studies have confirmed its utility in differentiating IBD from irritable bowel syndrome using cutoffs that vary from 6 to 280 μg/g of stool (35). The pooled sensitivity and specificity of elevated FC for diagnosis of UC are 0.88 and 0.79, respectively, with a modest positive likelihood ratio of 4.2 and a more clinically meaningful negative likelihood ratio of 0.15. In a primary care population, FC in patients with suspected UC (diarrhea and rectal bleeding) can be used to prioritize patients for colonoscopic evaluation, particularly among children (36,37). The utility of FC as a marker of inflammation and treatment target is discussed in the management section.

Serologic markers such as perinuclear antineutrophil cytoplasmic antibodies (pANCAs) may be found in up to 70% of patients with UC, and combination of negative anti–*Saccharomyces cerevisiae* antibodies with elevated pANCA levels has been proposed to facilitate establishing a diagnosis of UC (38,39). However, the pooled sensitivity of antibody testing for diagnosis of UC is low, and such markers are not used for establishing or ruling out a diagnosis of UC (38). Although pANCA positivity has also been associated with treatment refractory UC, the evidence supporting this is limited, and there is

Table 4. Proposed American College of Gastroenterology Ulcerative Colitis Activity Index[a]

	Remission	Mild	Moderate-severe	Fulminant
Stools (no./d)	Formed stools	<4	>6	>10
Blood in stools	None	Intermittent	Frequent	Continuous
Urgency	None	Mild, occasional	Often	Continuous
Hemoglobin	Normal	Normal	<75% of normal	Transfusion required
ESR	<30	<30	>30	>30
CRP (mg/L)	Normal	Elevated	Elevated	Elevated
FC (μg/g)	<150–200	>150–200	>150–200	>150–200
Endoscopy (Mayo subscore)	0–1	1	2–3	3
UCEIS	0–1	2–4	5–8	7–8

[a]Modified from reference 44.
The above factors are general guides for disease activity. With the exception of remission, a patient does not need to have all the factors to be considered in a specific category.
CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; FC, fecal calprotectin; UCEIS, Ulcerative Colitis Endoscopic Index of Severity.

currently no role for such testing to determine the likelihood of disease evolution and prognosis (40,41).

Determination of the extent and severity of disease is important to select the appropriate treatment algorithm. Extent of the disease should be characterized according to the Montreal classification as proctitis (E1), left-sided colitis (E2), or extensive colitis (E3) (extension proximal to the splenic flexure) (42,43). Commonly, severity of UC has been classified according to the Truelove and Witts' (44) criteria published in 1955. Mild colitis is defined as fewer than 4 bowel movements daily, normal temperature, heart rate, hemoglobin (>11 g/dL), and ESR (<20 mm/hr). Severe disease is defined by bowel frequency greater than 6 times a day in conjunction with fever, tachycardia, anemia, or an elevation in ESR. Although simple to use and useful in defining the need for hospitalization, the index does not provide a quantitative or longitudinal measure of severity, excludes other important symptoms such as nocturnal symptoms and extraintestinal manifestations, and does not consider endoscopic severity. Several quantitative disease activity indexes are available (45), including the Mayo score (Table 5) (46), Seo Index (47), Rachmilewitz Index (48), Simple Clinical Colitis Activity Index (SCCAI) (Table 6) (49), PRO2 (50), and the Pediatric UC Activity

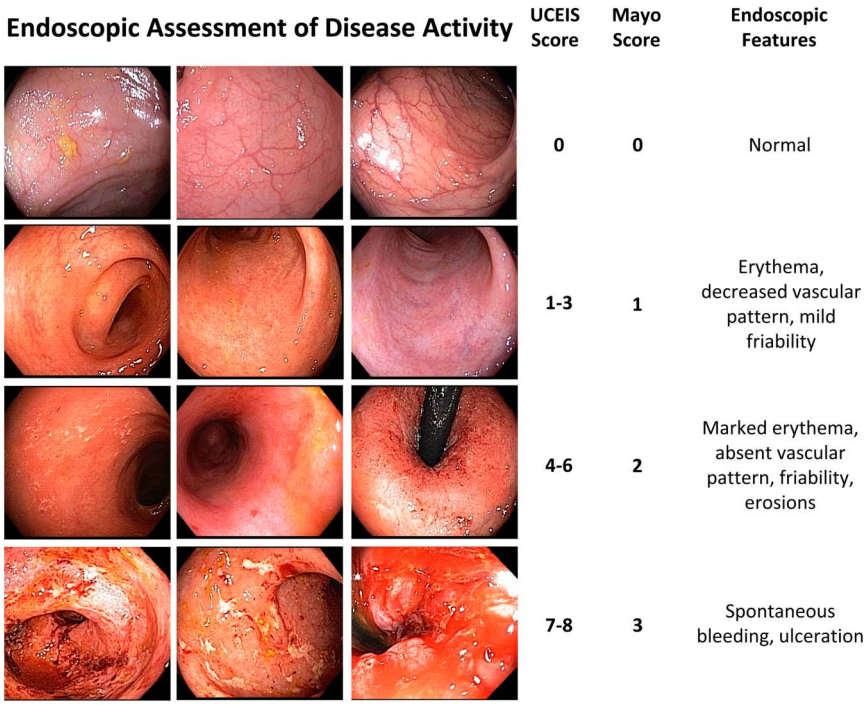

Figure 1. Sample endoscopic images of ulcerative colitis using the Mayo endoscopic subscore (49) and the Ulcerative Colitis Endoscopic Index of Severity (41). (Images courtesy of David T. Rubin, MD.)

Index (PUCAI) (51). Although disease extent broadly affects prognosis, it should not limit therapeutic options. Although most clinical activity indexes have not been rigorously validated, there is broad agreement between most of the indexes (52), and they generally correlate well with endoscopic disease activity. In a prospective comparison, the PUCAI, SCCAI, and partial Mayo score demonstrated the best validity and responsiveness (51,53,54). The PRO2 (derived from components of the Mayo score) has been shown to discriminate between active drug and placebo and yielded similar effect sizes for remission when applied to previously collected clinical trial data. This has been proposed as an interim outcome measure when combined with endoscopic data (50). Ongoing efforts also aim to develop and validate PROs that incorporate patients' perception of severity of disease; (55) preliminary work suggests that such PROs correlate well with established disease activity indexes and may improve the ability to predict patient-defined remission.

Previous definitions of disease severity have been used in clinical trials but not in clinical practice. Inclusion criteria for clinical trials of agents for moderately to severely active UC have required components such as (i) inability to taper off prednisone, (ii) previous failure of immunosuppressants, and (iii) moderately to severely active disease defined by the Mayo score (including the specific endoscopy subscore). In clinical trials, the definition of remission has been a Mayo endoscopic subscore of 0 or 1 and lack of rectal bleeding. In clinical practice, the previously used definitions of remission refer to clinical parameters of current relapse (number of bowel movements, bleeding, and evidence of toxicity

Table 5. Mayo score for ulcerative colitis activity[a]

Parameter	Subscore (0–3)
Stool frequency	0 = normal number of stools
	1 = 1–2 stools more than normal
	2 = 3–4 stools more than normal
	3 = 5 or more stools more than normal
Rectal bleeding	0 = no blood seen
	1 = streaks of blood with stool less than one-half of the time
	2 = obvious blood with stool most of the time
	3 = blood alone passed without stool
Findings on endoscopy	0 = normal or inactive disease
	1 = mild disease (erythema, decreased vascular pattern, and mild friability)
	2 = moderate disease (marked erythema, lack of vascular pattern, friability, and erosions)
	3 = severe disease (spontaneous bleeding and ulcerations)
Physician's global assessment	0 = normal
	1 = mild disease
	2 = moderate disease
	3 = severe disease

[a]See reference 42.

Table 6. Simple Clinical Colitis Activity Index[a]

Symptom	Score
Bowel frequency (d)	
1–3	0
4–6	1
7–9	2
9+	3
Bowel frequency (night)	
0	0
1–3	1
4–6	2
Urgency of defecation	
None	0
Hurry	1
Immediate	2
Incontinence	3
Blood in stool	
None	0
Trace	1
Occasionally frank	2
Usually frank	3
General well-being	
Very well	0
Slightly below par	1
Poor	2
Very poor	3
Terrible	4
Extracolonic features	1 per manifestation

[a]See reference 49.

such as vital signs or colonic dilation) but do not include objective parameters of increased disease activity other than CRP (which lacks sensitivity). These measures also do not place the current flare in the context of the previous disease course as this guideline now recommends. In addition, when using a newer disease activity definition that takes into account disease course, any patient with more than mildly active disease should be treated according to recommendations for moderately to severely active UC.

In the absence of endoscopy, other objective markers of inflammation can be considered such as normalization of CRP and FC. More recent measures of remission now include symptomatic remission (no rectal bleeding and no urgency) and endoscopic evidence of mucosal healing. Retrospective data have investigated histologic remission as a potential therapeutic target and have shown histologic quiescence and histologic normalization to be predictive of relapse-free survival (56). However, only a small percentage of patients seem to reach these end points. The available data do not yet support histologic healing or normalization as a goal of treatment for patients with UC.

With increasing recognition of endoscopic mucosal response and remission as treatment targets and their prognostic

Table 7: Ulcerative Colitis Endoscopic Index of Severity[a]

Descriptor	Likert scale anchor points	Definitions
Vascular pattern	0 = normal	Normal vascular pattern with arborizations of capillaries clearly defined
	1 = patchy obliteration	Patchy obliteration of vascular pattern
	2 = obliterated	Complete loss of vascular pattern
Bleeding	0 = none	No visible blood
	1 = mucosal	Spots or streaks of coagulated blood on the mucosa surface, which can be washed off
	2 = luminal mild	Some free liquid blood in the lumen
	3 = luminal moderate or severe	Frank blood in the lumen or visible oozing from the mucosa after washing or visible oozing from a hemorrhagic mucosa
Erosions and ulcers	0 = none	Normal mucosa, no visible ulcers or erosions
	1 = erosions	Small defects in the mucosa (≤5 mm), white or yellow, flat edge
	2 = superficial ulcer	Larger defects in the mucosa (>5 mm), discrete fibrin covered, remain superficial
	3 = deep ulcer	Deeper excavated defects in the mucosa, with a slightly raised edge

[a]See reference 35.

significance for future relapses, need for hospitalization, and surgery, it is essential to include endoscopic severity assessment in the diagnosis and management of UC (57,58). There are several tools to quantify endoscopic activity in UC, although few have been rigorously validated (59). The Mayo endoscopic score is frequently used in clinical trials and is simple to use in clinical practice, ranging from 0 for normal or inactive disease to 3 for severely active disease (46). Using a rigorous methodology for derivation and validation using regression models and central readings of recorded procedures, the UC Endoscopic Index of Severity (UCEIS) has recently been proposed (Table 7) (38). This score incorporates 3 items—vascular pattern, bleeding, and erosions and ulcers, quantifying each on a scale of 0–3 (0–2 for vascular pattern) for a total score ranging between 0 and 8. The UCEIS demonstrated excellent correlation with disease severity (60) and good intra- and inter-observer reliability (60,61). Preliminary data suggest that this score is also responsive to therapy, and improvement with treatment predicts medium- and long-term outcomes (62). Table 4 summarizes the different parameters used in this guideline for the purpose of defining mildly active and moderately to severely active UC (44,63). Figure 1 shows representative endoscopic photographs comparing the traditional Mayo endoscopic subscore and the UCEIS.

UC is also associated with psychosocial and economic disruption and disability. There are ongoing efforts to quantify such disability through validated indexes that correlate well with disease severity and QoL (63–65). There are insufficient data to recommend the routine use of such scores in clinical practice. However, it is important to include assessments of the impact of the disease on the patients' lives in the determination of overall severity and selection of the appropriate treatment algorithm.

Evaluation of UC during relapses should include assessment of severity of symptoms and potential triggers, including enteric infections (particularly *C. diff*), NSAID use, and recent smoking cessation. Nonadherence to therapy is common in patients with UC and is associated with an increased risk of relapse and cost of care (66,67). UC is an evolving disease, and the risk of disease extension should be kept in mind in individuals with initially localized disease, particularly with nonresponse to topical treatment. Up to 46% of patients with proctitis and 70% with left-sided colitis may develop extensive colitis on follow-up (68). It is important to recognize that endoscopic evaluation in individuals with loss of response may reveal patchiness of endoscopic and histologic activity including an appearance of relative rectal sparing with the use of topical treatments.

A comprehensive assessment of severity of UC should include predictors of an aggressive disease course, need for colectomy, and response to therapies. Several prospective cohorts have examined the role of clinical parameters, genetics, and serologic markers in predicting the need for colectomy in UC (69,70). Extensive colitis, need for systemic steroids, young age at diagnosis, and elevated CRP or ESR are associated with higher rates of colectomy (69,71). Patients with a previous hospitalization for their UC are also at a higher risk of subsequent colectomy (72). The yield of genetic or serologic markers in predicting severity and course of UC has been modest at best, and their use cannot be recommended in routine clinical practice based on available data (40,41). Table 8 summarizes the factors associated with an increased risk of colectomy and a poor prognosis (3).

Table 8. Poor prognostic factors in ulcerative colitis disease severity

Poor prognostic factors
Age <40 yr at diagnosis
Extensive colitis
Severe endoscopic disease (Mayo endoscopic subscore 3, UCEIS ≥ 7)
Hospitalization for colitis
Elevated CRP
Low serum albumin

The greater the number of poor prognostic factors, the worse the prognosis as measured by the likelihood of colectomy (4).
CRP, C-reactive protein; UCEIS, Ulcerative Colitis Endoscopic Index of Severity.

GOALS FOR MANAGING PATIENTS WITH ULCERATIVE COLITIS

Key concept statements

8. UC is a chronic condition for which therapy is required to induce and maintain remission; therapeutic decisions should be categorized into those for (i) induction and (ii) maintenance, with a goal of obtaining and maintaining a steroid-free remission.
9. Strategies for management of UC should reflect the patient's and provider's goals and recognize the chronic nature of the disease.
10. Corticosteroid-free remission may be defined based on symptoms, endoscopic findings, or disease impact without ongoing corticosteroid use. Symptomatic remission relates to improvement in PROs, whereas endoscopic healing is defined as restoration of intact mucosa without friability. Deep remission is a combination of symptomatic remission and endoscopic healing and is a preferred goal of management.
11. Selection of induction and maintenance therapies for UC should be based on disease extent, severity, and prognosis.
12. Initial treatment of UC should focus on restoration of normal bowel frequency and control of the primary symptoms of bleeding and urgency. An endoscopically healed mucosa is associated with sustained remission and reduced risk of colectomy.
13. Histologic remission is associated with some improved clinical outcomes but has not yet been validated prospectively as an end point of treatment.
14. Control of mucosal inflammation may reduce dysplasia risk.
15. Given the chronic nature of UC and the therapies for UC, monitoring for disease-related and drug-related complications is important. This should incorporate preventive strategies as outlined here and in a separate guideline from the ACG (12).
16. Routine visits are recommended to monitor for relapse and address health maintenance needs.
17. Patients with UC should be screened for coexistent anxiety and depressive disorders, and when identified, patients should be provided with resources to address these conditions.

Recommendations

4. We suggest treating patients with UC to achieve mucosal healing (defined as resolution of inflammatory changes (Mayo endoscopic subscore 0 or 1)) to increase the likelihood of sustained steroid-free remission and prevent hospitalizations and surgery (conditional recommendation, low quality of evidence).
5. We suggest FC as a surrogate for endoscopy when endoscopy is not feasible or available to assess for mucosal healing (conditional recommendation, very low quality of evidence).

Summary of evidence Patients' and providers' goals may not always align. Studies have identified disparities between QoL measures as perceived by patients and their providers (73). Symptoms alone should not be used as the only measure of remission, and patients need to be educated about these concepts, as symptomatic remission can lag behind healing (74). In addition, a large portion of patients with UC have been shown to have mucosal inflammation without clinical symptoms (75). Therefore, it is important to rely on objective clinical targets and use validated scores and instruments (including endoscopy) in confirming remission (60,76). According to Food and Drug Administration guidance, a PRO involves the generation of items from qualitative patient interviews and testing for reliability and responsiveness to changes in clinical health (77). An optimized PRO derived from the Mayo score and the SCCAI has been validated (55). Resolution of rectal bleeding and urgency, normalization of bowel habits, and improvement in general well-being should be the goal for patient-reported symptoms.

Disease activity indexes used in clinical trials can be used to define steroid-free remission. These include the Mayo score (46), Rachmeliwitz Index (48), SCCAI (49), and PUCAI (54). Targets have been defined for the treatment of UC, and goals of therapy should be directed at these targets. A treat-to-target approach uses regular assessment of disease activity by using objective and clinical biological outcome measures and the subsequent adjustment of treatments (78).

Therapeutic targets have been recommended for UC, as part of the Selecting Therapeutic Targets in Inflammatory Bowel Diseases (STRIDE) consensus statement, which was based on a systematic literature review and expert opinion of 28 IBD specialists. The targets for UC were composite end points that include resolution of rectal bleeding, normalization of bowel habits, and a Mayo endoscopic subscore of 0 or 1. STRIDE proposed that these end points should be assessed at a minimum every 3 months during the active phase of disease (79). The STRIDE recommendations to set endoscopic remission as a primary target were based on evidence that supports that the degree of mucosal healing is correlated with clinical outcomes, including avoiding colectomy (57,58,80). It is acknowledged that endoscopic improvement (Mayo endoscopic subscore of 0 or 1) rather than complete healing (Mayo endoscopic subscore of 0) may be sufficient and associated with similar outcomes (58).

At the time of the 2015 STRIDE statement, histology was not identified as a target for treatment, but the research and understanding of this biomarker has evolved. Recent studies and critical reviews of histology as a marker of disease activity and potential end point of therapy demonstrate that the presence of active microscopic inflammation (defined by the presence of mucosal neutrophils) is predictive of clinical relapse, hospitalization, and steroid use (81). In addition, there are several significant studies, which demonstrate that the increased degree of histological inflammation is associated with dysplasia and colorectal cancer (also discussed below) (8–10). Although a specific index for clinical use has not been clarified, it is anticipated that further work will clarify the value of this end point as a separate target for management and prognosis. However, at this time, based on the lack of clinical trial data and current levels of evidence, histologic healing is not a recommended management end point.

There is a need for less invasive markers of inflammation. Such markers can be used to assess for subclinical detection of disease relapse, response to therapy, and distinction between inflammatory and noninflammatory causes of symptoms. There are studies exploring fecal lactoferrin, FC, and, more recently, fecal immunohistochemical tests of hemoglobin (82). In general, these fecal markers are better tools in UC than in CD, and the attractiveness of them is that they offer less invasive and less resource-intense ways to serially assess disease activity. The most data exist for FC.

Calprotectin is an antimicrobial manganese sequestration protein complex, which comprises 60% of the soluble proteins in the cytosol of neutrophils (83). It is secreted by an unknown mechanism during inflammation, is a stable protein in stool, and quantification of it is possible with commercially available laboratory assays. FC levels correlate with degrees of

endoscopic and histologic inflammation in UC and therefore have been proposed as a marker of disease activity to guide treatment (83,84). FC levels are more sensitive and specific than serum inflammatory markers and obviously also less invasive than endoscopy or mucosal biopsies, so this assessment has become routine for many clinicians who are managing patients with UC (35,85). FC therefore has been proposed as a monitoring tool to assess response to therapy or subclinical relapse (86,87). Higher levels of FC correlate with more endoscopically severe disease, but absolute levels may not correlate with the colonic extent of inflammation. The cutoffs for defining clinical or endoscopic remission and as the optimal therapeutic target have not been studied prospectively and are thus not amenable to the GRADE process. Relevant cutoffs will differ based on whether studies of FC are assessing (i) mucosal healing (by endoscopy or histology) or (ii) clinical relapse and are limited by intrapatient variability (88–90). In separate studies, FC $<$ 60 mg/g and $<$187 mg/g predicted deep remission (88) and mucosal healing (89), respectively, whereas an FC $>$ 321 mg/g in clinical remission predicted the risk of relapse at 6 and 12 months (91). As with other inflammatory markers, the degree of elevation of FC correlates with burden of inflammation, and values may be normal or borderline in mild disease and may need to be repeated over time. A recent meta-analysis of 25 eligible studies revealed that FC had a pooled sensitivity for endoscopic inflammation in UC of 87.3%, with a specificity of 77.1% and area under the curve of 0.91 (92). This analysis described that the optimum cutoff varied widely by studies, but that the best sensitivity of 90% (87.9–92.9) was achieved at a cutoff level of 50 μg/g, whereas the best specificity of 78.2% (75.7–80.6) was achieved for cutoff levels greater than 100 μg/g (92). In an individual patient, serial FC can be useful as a predictor of response to therapy or relapse. This principle was demonstrated in a phase 3 trial of tofacitinib for moderately to severely active UC, in which serial FC levels were obtained. An FC cutoff value of 150 mg/kg achieved the highest summation of sensitivity and specificity for clinical remission (0.68 and 0.79, respectively; κ coefficient, 0.44) and endoscopic remission (0.79 and 0.75, respectively; κ coefficient, 0.38). More recently, FC levels have been correlated with histologic disease activity as well (93). Further research into optimal cutoffs of FC will guide clinical practice, but the available data support it as an appropriate surrogate to sigmoidoscopy or colonoscopy for assessment and monitoring of mucosal inflammation.

MANAGEMENT OF ULCERATIVE COLITIS

Therapeutic management in UC should be guided by the specific diagnosis (i.e., Montreal classification), an assessment of disease activity (i.e., mild, moderate, or severe), and disease prognosis. A distinction made in this updated guideline is that treatment selection should be based not only on inflammatory activity but also on disease prognosis. For example, a patient who satisfies the criteria for mildly active disease but who has steroid dependence and a previous hospitalization should be evaluated for treatments typically recommended for patients with moderately to severely active disease because their steroid dependence and previous hospitalization have a significant impact on their disease prognosis.

Induction of remission in mildly active UC

Key concept statements

18. Patients with mildly active UC and a number of prognostic factors associated with an increased risk of hospitalization or surgery should be treated with therapies for moderately to severely active disease (Table 8). Each prognostic factor carries a different weight and must be discussed in a shared decision-making fashion with the patient. For example, age alone is a weaker prognostic factor than severe endoscopic activity. However, young age combined with another factor may represent sufficient criteria to treat according to the moderately to severely active disease protocol.
19. Patients with mildly active UC should be reassessed to determine response to induction therapy within 6 weeks.
20. Fecal microbiota transplantation (FMT) requires more study and clarification of treatment before use as a therapy for UC.
21. Complementary therapies such as probiotics and curcumin require further study with adequate power and clarification of end points.

Recommendations

6. In patients with mildly active ulcerative proctitis, we recommend rectal 5-aminosalicylate therapies at a dose of 1 g/d for induction of remission (strong recommendation, high-quality evidence).
7. In patients with mildly active left-sided UC, we recommend rectal 5-aminosalicylate enemas at a dose of at least 1 g/d preferred over rectal steroids for induction of remission (strong recommendation, moderate quality of evidence).
8. In patients with mildly active left-sided UC, we suggest rectal 5-aminosalicylate enemas at a dose of at least 1 g/d combined with oral 5-aminosalicylate at a dose of at least 2 g/d compared with oral 5-aminosalicylate therapy alone for induction of remission (conditional recommendation, low quality of evidence).
9. In patients with mildly active left-sided UC who are intolerant or nonresponsive to oral and rectal 5-aminosalicylate (5-ASA) at appropriate doses (oral at least 2 g/d and rectal at least 1 g/d), we recommend oral budesonide multi-matrix (MMX) 9 mg/d for induction of remission (strong recommendation, moderate quality of evidence).
10. In patients with mildly active extensive UC, oral 5-ASA at a dose of at least 2 g/d is recommended to induce remission (strong recommendation, moderate quality of evidence).
11. In patients with UC of any extent who fail to respond to 5-ASA therapy, we recommend oral systemic corticosteroids to induce remission (strong recommendation, low quality of evidence).
12. In patients with mildly active UC who fail to reach remission with appropriately dosed 5-ASA (at least 2 g/d oral 5-ASA and/or at least 1 g/d rectal 5-ASA), we suggest against changing to an alternate 5-ASA formulation to induce remission. Alternative therapeutic classes should be considered (conditional recommendation, low quality of evidence).
13. In patients with mildly active UC of any extent, we suggest using a low dose (2–2.4 g/d) of 5-ASA compared with a higher dose (4.8 g/d), as there is no difference in the remission rate (conditional recommendation, very low quality of evidence).
14. In patients with mildly to moderately active UC not responding to oral 5-ASA, we recommend the addition of budesonide MMX 9 mg/d to induce remission (strong recommendation, moderate quality of evidence).
15. In patients with mildly to moderately active UC of any extent using 5-ASA to induce remission, we recommend either once-daily or more frequently dosed oral 5-ASA based on patient preference to optimize adherence, as efficacy and safety are no different (strong recommendation, moderate quality evidence).

Summary of evidence A meta-analysis of 11 randomized controlled trials (RCTs) of patients with UC treated with 5-ASA for induction or maintenance demonstrated superiority of 5-ASAs in inducing remission compared with placebo (94). In this analysis, patients receiving 5-ASA were more likely to achieve remission. Only 60.3% of patients treated with 5-ASAs failed to reach remission compared with 80.2% of patients treated with placebo (risk ratio (RR), 0.79; confidence interval (CI), 0.73–85; $P = 0.009$; number needed to treat = 6). Efficacy of 5-ASAs in inducing remission was similar whether remission was defined clinically or endoscopically. Another meta-analysis of 38 studies in patients with mildly to moderately active proctitis or left-sided UC found that rectal 5-ASA was superior to placebo, with a pooled odds ratio (OR) of 8.30 (95% CI, 4.28–16.12; $P < 0.00001$) for symptomatic remission and 5.31 for endoscopic remission (95% CI, 3.15–8.92; $P < 0.00001$). There were no significant differences due to dose (1 or 4 g/d) or formulation (liquid, gel, foam, or suppository) (95). Rectal 5-ASA was also found to be superior to rectal corticosteroids for inducing symptomatic remission (OR, 1.65; 95% CI, 1.1–2.5) (95). Despite the superiority of rectal 5-ASA over rectal steroids, steroids remain an important option for patients with mildly active left-sided UC who cannot retain rectal 5-ASA, have hypersensitivity to 5-ASA, or who are not responding to 5-ASA (95).

In left-sided UC, a meta-analysis of 4 RCTs using combination treatment with rectal 5-ASA enemas (1 g/d) combined with oral 5-aminosalicylate (at least 2 g/d) was more effective than oral 5-ASA alone for induction of remission (relative risk induction failure RR, 0.65; 95% CI, 0.47–0.91) (96). Another meta-analysis comparing the 2 regimens showed an RR of 0.86 for induction failure when using the combination therapy (95% CI, 0.81–0.91) (97). However, in patients with mildly active extensive colitis, oral 5-ASA at a dose of at least 2 g/d is preferred to induce remission (97,98). In a recent meta-analysis, a low dose of 2–2.4 g of 5-ASA was found to be just as effective as a higher dose (4.8 g/d) (RR, 0.91; 95% CI, 0.85–0.98) (97). A subgroup analysis indicated that patients with more active (moderate) disease may benefit from the higher dose of 4.8 g/d (99). Once-daily dosing of oral 5-ASA was demonstrated to be as effective as multiple doses daily and may facilitate compliance (99).

In patients with mildly active UC who fail to reach remission with appropriately dosed 5-ASA, switching to an alternate 5-ASA formulation is not recommended because meta-analyses have not demonstrated a therapeutic difference between different formulations (100,101). However, no formal switch studies have been published. In patients with UC who fail to respond to oral 5-ASA therapy, oral corticosteroids can be used to induce remission. A meta-analysis showed that corticosteroids are more effective than placebo in induction of remission (RR, 0.65; 95% CI, 0.45–0.93) (102). The typical starting doses of oral prednisone are 40–60 mg/d, usually in a single dose, and clinical response is expected within 5–7 days of treatment. There were no observed differences, however, when starting at doses higher than 60 mg/d (103). The duration of systemic corticosteroids should be as short as possible with early initiation of steroid-sparing therapy. The speed of the taper should be guided by clinical symptoms, cumulative steroid exposure, and onset of action of alternate therapies.

Budesonide is a locally acting corticosteroid with high first-pass metabolism and minimal systemic side effects. In patients with UC who fail to respond to 5-ASA, budesonide MMX 9 mg for 8 weeks was found to be superior in achieving a combined end point of clinical and endoscopic remission compared with continuing 5-ASA and placebo ($P = 0.049$) (104). The use of corticosteroid preparations with high first-pass metabolism and low systemic effects may be preferred over systemically active glucocorticoids. Oral budesonide MMX is also safe and more effective than placebo in inducing remission in patients with mildly active UC. In a prospective RCT, patients given 9 or 6 mg budesonide MMX or 5-ASA achieved clinical remission 17.9%, 13.2%, and 12.1% of the time, respectively, compared with 7.4% in the placebo group ($P = 0.0143$, $P = 0.1393$, and $P = 0.2200$, respectively) (98).

Adherence to medication is a factor in relapse in patients with mildly active UC. A meta-analysis of 3 trials found no significant differences in efficacy or adherence between once-daily and conventionally dosed 5-ASA for induction of remission in patients with UC (nonremission RR, 0.95; 95% CI, 0.82–1.10) (97,105). However, clinical trial populations are known to have higher adherence rates than clinical practice settings. The prevalence of nonadherence in the community is high (40%), reaching up to 68% in patients on more than 4 prescription medications (106). An RCT found that patients with proctosigmoiditis preferred once-daily 5-ASA dosing over 3-times-daily dosing. Patients also had a significantly higher rate of clinical remission in the once-daily dose group (86%; n = 97) vs the t.i.d. group (73%; n = 100; $P = 0.0298$) (107). Therefore, reinforcement of compliance is an important aspect of management of UC, and any means to optimize adherence should be used, including discussing once-daily dosing options with patients, given these data on similar efficacy and safety.

In patients with mildly to moderately active UC, on appropriately dosed 5-ASA, probiotic VSL#3® at a daily dose of 3.6×10^{12} CFU/d has been studied as an adjunct to 5-ASA therapy to improve symptoms compared with no treatment. In a meta-analysis from 2017 including 22 studies of probiotics in the treatment of IBD, there was no benefit of probiotics in general for induction of remission. However, when only studies of VSL#3® were included (n = 3), there did seem to be a benefit (RR, 0.74; 95% CI, 0.63–0.87) in these small studies. All these studies were at risk of bias, and the quality of the evidence was too low to make a recommendation for or against the use of VSL#3® in UC (108). In 1 clinical trial using VSL#3® as add-on therapy to 5-ASA, endoscopic improvement was not achieved (109). A meta-analysis of 3 studies found that treatment with *E. coli* Nissle 1917 was comparable to 5-ASA therapy in patients with inactive UC (RR_{pooled}, 1.08; 95% CI, 0.86–1.37) (110). Similar methodological concerns for these studies exist, including small sample size, risk of bias, and high degree of heterogeneity, limiting the level of evidence supporting this intervention. The control population included placebo or 5-ASA. However, the comparison doses of 5-ASA were often ≤1,500 mg (less than a recommended maintenance dose). In 1 clinical trial, patients with UC randomized to *E. coli* Nissle were less likely than those on placebo to reach remission (111). Therefore, there is not sufficient evidence to recommend for or against *E. coli* Nissle for induction of remission of UC.

Similarly, FMT has showed some promising data in the treatment of UC and has been studied in 3 RCTs (112–114). These trials of FMT in UC have different designs, delivery mechanisms, donor types, and inclusion criteria. The RCTs for FMT have had variable benefits but not significant steroid-sparing effects. The variability in fecal donors, delivery systems,

duration of treatment, and end points makes interpretation of these results difficult, and this is not currently a recommended treatment option for UC (115).

Maintenance of remission in patients with previously mildly active UC

Recommendations

16. In patients with mildly active ulcerative proctitis, we recommend rectal 5-ASA at a dose of 1 g/d for maintenance of remission (strong recommendation, moderate quality of evidence).
17. In patients with mildly active left-sided or extensive UC, we recommend oral 5-ASA therapy (at least 2 g/d) for maintenance of remission (strong recommendation, moderate quality of evidence).
18. We recommend against systemic corticosteroids for maintenance of remission in patients with UC (strong recommendation, moderate quality of evidence).

Summary of evidence A meta-analysis of 11 trials demonstrated the efficacy of oral 5-ASA agents (mesalamine, olsalazine, and sulfasalazine) compared with placebo in patients with quiescent UC (distal, left-sided, or extensive colitis) in maintenance of remission (94). The overall RR of relapse was 0.65 (95% CI, 0.55–0.76). Fewer patients on the high-to-standard dose of 5-ASA (≥2 g/d) experienced relapse of their quiescent disease compared with those on low dose (<2 g/d) (RR of relapse, 0.79; 95% CI, 0.64–0.97). The type of 5-ASA agent was not found to predict rates of relapse in these patients with controlled UC. In a recent Cochrane meta-analysis, oral 5-ASA compared with sulfasalazine was associated with a higher rate of failure to maintain clinical or endoscopic remission (RR, 1.14; 95% CI, 1.03–1.27) and a higher rate of failure to maintain remission in general (RR, 1.08; 95% CI, 0.92–1.26). (101) However, sulfasalazine is often limited by intolerance (headache and nausea), allergy to the sulfa moiety, and need for multiple daily doses. A meta-analysis of 7 trials assessed the efficacy of topical 5-ASA in preventing relapse in controlled UC (116). Only 1 of the included placebo-controlled trials assessed patients with extensive UC, whereas the remaining trials recruited patients with proctitis, proctosigmoiditis, or left-sided colitis. Among the trials that reported disease duration, the mean duration was 5–7 years. Compared with patients receiving placebo, patients receiving topical 5-ASA had an RR of 0.60 (95% CI, 0.49–0.73) for relapse. Two trials evaluated time to relapse in patients with rectal disease, and both found that patients receiving topical 5-ASA experienced relapse at a later time compared with those receiving placebo. Corticosteroids are ineffective in maintaining remission and are limited by their side effects and possible complications. Therefore, corticosteroids are not used for maintenance of remission (117–120).

MANAGEMENT OF MODERATELY TO SEVERELY ACTIVE ULCERATIVE COLITIS

Induction of remission

Key concept statements

22. Strategies for the management of the nonhospitalized patient with moderately to severely active UC are similar with the exception of a few considerations in which the data exist specifically for a patient with moderately active UC:
    a. 5-ASA therapy could be used as monotherapy for induction of moderately but not severely active UC.
    b. In patients with moderately active UC, consider nonsystemic corticosteroids such as budesonide MMX before the use of systemic therapy.
    c. In patients with severely active UC, consider systemic corticosteroids rather than topical corticosteroids.
23. Robust data on combination anti-tumor necrosis factor (TNF) and immunomodulator therapy in moderately to severely active UC exist only for infliximab and thiopurines.
24. Patients who are primary nonresponders to an anti-TNF (defined as lack of therapeutic benefit after induction despite adequate drug levels) should be evaluated and considered for alternative mechanisms of disease control (e.g., in a different class of therapy) rather than cycling to another drug within the anti-TNF class.
25. In patients with moderately to severely active UC who had an initial response but subsequently lost efficacy to one anti-TNF therapy, we recommend alternative anti-TNF therapy (but not the biosimilar to the original brand) compared with no treatment for induction of remission.
26. The patient with nonresponse or loss of response to therapy should be assessed with therapeutic drug monitoring to identify the reason for lack of response and whether to optimize the existing therapy or to select an alternate therapy.
27. Obtain consultation with a surgeon and consider colectomy in patients with moderately to severely active UC who are refractory or intolerant to medical therapy.

Recommendations

19. In patients with moderately active UC, we recommend oral budesonide MMX for induction of remission (strong recommendation, moderate quality of evidence).
20. In patients with moderately to severely active UC of any extent, we recommend oral systemic corticosteroids to induce remission (strong recommendation, moderate quality of evidence).
21. In patients with moderately to severely active UC, we recommend against monotherapy with thiopurines or methotrexate for induction of remission (strong recommendation, low quality of evidence).
22. In patients with moderately to severely active UC, we recommend anti-TNF therapy using adalimumab, golimumab, or infliximab for induction of remission (strong recommendation, high quality of evidence).
23. In patients with moderately to severely active UC who have failed 5-ASA therapy and in whom anti-TNF therapy is used for induction of remission, we suggest against using 5-ASA for added clinical efficacy (conditional recommendation, low quality of evidence).
24. When infliximab is used as induction therapy for patients with moderately to severely active UC, we recommend combination therapy with a thiopurine (strong recommendation, moderate quality of evidence for azathioprine).
25. In patients with moderately to severely active UC, we recommend vedolizumab for induction of remission (strong recommendation, moderate quality of evidence).
26. In patients with moderately to severely active UC who have previously failed anti-TNF therapy, we recommend vedolizumab for induction of remission (strong recommendation, moderate quality of evidence).
27. In patients with moderately to severely active UC, we recommend tofacitinib 10 mg orally b.i.d. for 8 weeks to induce remission (strong recommendation, moderate quality of evidence).

28. In patients with moderately to severely active UC who have previously failed anti-TNF therapy, we recommend tofacitinib for induction of remission (strong recommendation, moderate quality of evidence).
29. In patients with moderately to severely active UC who are responders to anti-TNF therapy and now losing response, we suggest measuring serum drug levels and antibodies (if there is not a therapeutic level) to assess the reason for loss of response (conditional recommendation, very low quality of evidence).

Summary of evidence Treatment with 5-ASA therapy has been shown to be efficacious and safe as monotherapy for induction of moderately but not severely active UC. One meta-analysis showed that patients with moderately active disease benefited from treatment with 2.4 g/d, whereas corticosteroid therapy remained more effective for patients with severe disease (97).

Systemic corticosteroids are an acknowledged induction strategy for moderately to severely active UC, with several small controlled studies demonstrating benefit to this strategy (98,102,121). In a meta-analysis of trials in patients with active UC, the use of systemic glucocorticoids compared with placebo demonstrated a benefit favoring steroids (RR of failure to achieve remission, 0.65; 95% CI, 0.45–0.93) (102,122). A colonic delivery system of budesonide offers more directed therapy and fewer systemic side effects, given the high first-pass hepatic metabolism of budesonide. In a dose-finding RCT in mildly to moderately active UC, patients receiving oral 9 mg budesonide MMX were more likely than patients receiving placebo to achieve induction of combined clinical and endoscopic remission at week 8 (OR, 2.71; 95% CI, 1.19–6.16) (98). A multicenter phase 3 RCT showed similar results, with significantly more patients treated with budesonide MMX 9 mg (but not 6 mg/d) achieving combined clinical and endoscopic remission at week 8 compared with placebo (OR, 4.49; 95% CI, 1.47–13.72; $P = 0.0047$) (121). Patients receiving budesonide had a similar rate of adverse events compared with patients receiving placebo (121).

Thiopurines are slow acting and do not induce remission in moderately to severely active UC (122–124). Similarly, methotrexate is not an effective induction agent in moderately to severely active UC. Previous studies of oral methotrexate have not demonstrated benefit, and 2 recent meta-analyses of methotrexate 25 mg intramuscularly are negative (123,125). In the recent European multicenter study of methotrexate for induction of remission of moderately to severely active UC, a higher proportion of patients receiving parenteral methotrexate (25 mg/wk) achieved steroid-free remission at week 16, but this result did not achieve statistical significance (126).

Infliximab, adalimumab, and golimumab are effective for the induction of remission of moderately to severely active UC. All 3 anti-TNF agents have demonstrated superiority over placebo in achieving the primary end points of response and remission, but there have been no head-to-head trials comparing the agents to one another (127–129). In the ULTRA 2 trial, 494 patients with moderately to severely active UC were randomized to receive adalimumab or placebo (130). The primary end point, induction of remission at week 8, was reported based on anti-TNF exposure. In patients who were previously exposed to anti-TNF agents, patients receiving adalimumab were more likely than patients receiving placebo to achieve remission at week 8 (9.2% vs 6.9%, $P = 0.559$) (130). Two meta-analyses compared the efficacy of infliximab with the other anti-TNF agents using a network meta-analysis methodology (128,129). Although some of the comparisons did not reach statistical significance, there was a trend of higher remission rates in the patients with UC receiving infliximab compared with those receiving adalimumab or golimumab. In patients with moderately to severely active UC who were naive to anti-TNF agents and immunomodulators and who had normal thiopurine methyltransferase activity, combination therapy with infliximab 5 mg/kg (loading 0, 2, and 6 weeks) and azathioprine (2.5 mg/kg orally) was superior to monotherapy with either agent alone in inducing corticosteroid-free clinical remission at 16 weeks (131). Unlike a larger, similar study in CD (132), monotherapy with infliximab was not superior to monotherapy with azathioprine in this study of patients with UC. Observational studies have compared the efficacy of infliximab and adalimumab in biologic-naive patients with UC. In a Danish study of 1,719 adults with UC, adalimumab was associated with a higher rate of all-cause and UC-related hospitalizations but not abdominal surgery (133). A second study suggested lower corticosteroid usage in infliximab-treated patients with UC compared with those using adalimumab (134). There are limited data on the role of methotrexate in combination with an anti-TNF agent in UC. Extrapolating data from patients with CD, it is possible that methotrexate may offer the same benefit in terms of reducing immunogenicity and improving drug concentrations when used in combination with an anti-TNF agent and may be the preferred immunomodulator for combination therapy in those at a higher risk of adverse effects of thiopurines such as young men or those with multiple skin cancers.

The anti-integrin drug vedolizumab is an effective therapy for induction of remission of moderately to severely active UC. The mechanism of this therapy (inhibition of alpha-4 beta-7 integrins) targets the mucosal immune system of the gut, and therefore, the therapy has had a favorable safety profile with a lower risk of infections when compared with more systemic immunosuppression. In the GEMINI 1 induction trial, 374 patients were randomized in a comparison cohort to receive vedolizumab or placebo at weeks 0 and 2, whereas 521 patients were enrolled in the open-label vedolizumab cohort (135). Approximately 40% of these patients had failed or were intolerant to anti-TNF agents before enrollment in this study. In the comparison cohort, 16.9% and 40.9% of patients receiving vedolizumab achieved clinical remission and mucosal healing at week 6, respectively, compared with 5.4% and 24.8% of patients receiving placebo ($P = 0.001$ for both comparisons). Patients in the open-label cohort achieved comparable remission rates as those receiving vedolizumab in the comparison cohort. A *post hoc* analysis of the GEMINI 1 study also demonstrated a greater efficacy for vedolizumab compared with placebo at inducing remission in patients who had previously failed treatment with anti-TNF agents (136). Three subsequent systematic reviews demonstrated the superiority of vedolizumab over placebo for induction of remission in UC (128,137,138).

Tofacitinib is an orally administered small molecule that is a nonselective inhibitor of the Janus kinase enzyme. Tofacitinib was approved by the Food and Drug Administration for the treatment of moderate to severe UC in June 2018. The OCTAVE 1 (n = 598) and OCTAVE 2 (n = 541) induction trials were conducted to assess the efficacy of tofacitinib 10 mg orally b.i.d. compared with placebo (139). Patients enrolled had moderately to severely active UC and had failed conventional therapies (half of them had previously failed anti-TNF agents). The primary end point was remission (total Mayo score of ≤ 2, no subscore of >1,

and rectal bleeding subscore of 0) at 8 weeks. In both trials, clinical remission at week 8 occurred in a significantly higher proportion of patients treated with tofacitinib 10 mg b.i.d. (18.5% and 16.6%, respectively) compared with those receiving placebo (8.2% and 3.6%, respectively). At 52 weeks, in the maintenance trial, 40.6% of patients treated with tofacitinib 10 mg b.i.d. and 34.3% of patients treated with 5 mg b.i.d. achieved remission compared with 11.1% of those treated with placebo. Infectious complications were slightly more frequent with tofacitinib compared with placebo in both the induction and maintenance trials. In particular, herpes zoster occurred in 5.1% of patients treated with tofacitinib 10 mg b.i.d. compared with 0.5% of patients receiving placebo (139).

Up to one-fifth of patients receiving anti-TNF agents may not respond initially, and an additional 10%–15% may lose response every year despite an initial benefit (140,141). There are multiple factors that may contribute to primary nonresponse or secondary loss of response, including concurrent intestinal infection, overlapping functional bowel symptoms, and, importantly, inadequate therapeutic drug concentrations. There are several reasons for low serum levels of drug, including increased clearance due to increased inflammatory burden, protein loss from a permeable inflamed mucosa, the development of neutralizing antidrug antibodies, or other patient-related factors such as increased body mass index or male sex (142,143). Therefore, the approach to a patient with inadequate primary response or secondary loss of response should include careful clinical evaluation, confirmation of inflammation using objective measures (endoscopy or surrogates such as CRP or FC), exclusion of enteric infections, and assessment of serum drug concentration to address the specific contributing factors and make a decision regarding treatment options, pharmacokinetic manipulation, or cycling/swapping therapies or mechanisms (144,145). In patients who have nonresponse or loss of response to an anti-TNF therapy, and in whom there is an adequate serum level of anti-TNF, cycling within the class to another anti-TNF therapy is not likely to be of benefit. In these situations, swapping to a different mechanism of inflammatory control may be preferred (144,145).

An emerging strategy in the treatment of UC is the use of less systemic treatments before the use of systemic therapy. However, the lack of head-to-head trials of this strategy limits the strength of these considerations. Further data on comparative efficacy with endoscopic and clinical outcomes could dramatically influence our order of therapeutic agent selection in UC. Nonetheless, the general principle of balancing efficacy and safety in choosing therapies could support an approach of starting with organ-selective treatments before the use of systemic therapies. Relevant examples could be the use of topical rectal therapy before systemic therapy in distal colitis or the use of budesonide formulations before the use of systemic corticosteroids. Similarly, in some patient populations, it is reasonable to consider the use of the gut-selective anti-integrin therapy vedolizumab before the use of systemically acting anti-TNF therapies or small molecules such as Janus kinase inhibitors. For patients who have pronounced extra-intestinal manifestations such as skin or joint problems, more systemic or combination approaches may be preferred. There are some reasonable considerations for preferential use of organ-selective therapy, such as the older patient in whom there may be concern for a higher risk of opportunistic infections with systemic therapy or the patient with the paradoxical UC in the setting of organ transplantation and concomitant immune suppression (146,147).

Maintenance of remission in patients with previously moderately to severely active UC

Key concept statements

28. 5-ASA therapy for maintenance of remission is likely not as effective in previously severely active UC compared with previously moderately active UC.
29. Budesonide MMX has not been studied for maintenance of remission of previously moderately to severely active UC.
30. Most clinical trials and available data demonstrate a benefit of using the steroid-sparing therapy that induces remission to maintain that remission.
31. There is insufficient evidence supporting a benefit for proactive therapeutic drug monitoring in all unselected patients with UC in remission.
32. We suggest elective proctocolectomy in patients with UC failing maximal medical management.

Recommendations

30. In patients with previously moderately to severely active UC who have achieved remission but previously failed 5-ASA therapy and are now on anti-TNF therapy, we recommend against using concomitant 5-ASA for efficacy of maintenance of remission (conditional recommendation, low quality of evidence).
31. We recommend against systemic corticosteroids for maintenance of remission in patients with UC (strong recommendation, moderate quality of evidence).
32. For patients with previously moderately to severely active UC now in remission due to corticosteroid induction, we suggest thiopurines for maintenance of remission compared with no treatment or corticosteroids (conditional recommendation, low quality of evidence).
33. In patients with previously moderately to severely active UC now in remission, we recommend against using methotrexate for maintenance of remission (conditional recommendation, low quality of evidence).
34. We recommend continuing anti-TNF therapy using adalimumab, golimumab, or infliximab for maintenance of remission after anti-TNF induction in patients with previously moderately to severely active UC (strong recommendation, moderate quality of evidence).
35. We recommend continuing vedolizumab to maintain remission in patients with previously moderately to severely active UC now in remission after vedolizumab induction (strong recommendation, moderate quality of evidence).
36. We recommend continuing tofacitinib for maintenance of remission in patients with previously moderately to severely active UC now in remission after induction with tofacitinib (strong recommendation, moderate quality of evidence).

Summary of evidence Although corticosteroids are efficacious in inducing remission in patients with active UC, they should not be used for maintenance of remission and should be tapered instead (118–120). Although the optimal tapering regimen has not been determined, the dose is usually reduced over 8–12 weeks (117). In 2 RCTs, thiopurines have not been shown to provide significant maintenance benefit in patients with UC who have had induction of remission with corticosteroids (RR, 0.85; 95% CI, 0.71–1.01) (123). In an additional 3 RCTs, azathioprine

prevented relapse in 127 patients (RR, 0.6; 95% CI, 0.37–0.95) (123). Another systematic review encompassing 1,632 patients with UC in 30 studies showed that azathioprine and mercaptopurine had a 76% mean efficacy in maintenance of remission. Compared with placebo, treatment with thiopurines resulted in an absolute risk reduction of 23% and a number needed to treat of 5 to prevent recurrence (OR, 2.59; 95% CI, 1.26–5.3) (148). Thiopurine therapy also provided clinical benefit when treating patients who had failed or could not tolerate mesalamine or sulfasalazine (149). However, in a prospective RCT, methotrexate was not found to be superior for maintenance of remission when compared with placebo (150). The US-based Methotrexate Response in Treatment of Ulcerative Colitis (MERIT-UC) trial demonstrated that parenteral methotrexate (25 mg/wk) was not superior to placebo in maintaining remission after steroid induction (151). In this study, 29/44 (66%) patients receiving methotrexate experienced relapse compared with 25/40 (63%) patients receiving placebo (151).

In patients with moderately to severely active UC who have responded to anti-TNF therapy during induction dosing, anti-TNF agents are superior to placebo in maintaining remission (127). A systemic meta-analysis including 6 placebo-controlled, double-blind studies demonstrated that adalimumab, golimumab, and infliximab were all more efficacious than placebo in maintaining clinical remission in patients with UC (128). A meta-analysis, however, showed no difference in the superiority of a single agent over the other anti-TNF agents (129). Similarly, vedolizumab was effective in maintaining remission in patients with UC compared with no treatment (128,146). One systematic review and meta-analysis encompassing 4 studies with a total of 606 patients indicated that vedolizumab was superior to placebo in the maintenance of remission, with no statistical difference in adverse events or serious adverse events between the groups (137,138). In a pivotal trial of vedolizumab as maintenance therapy, patients responding to induction were randomized at week 6 to maintenance therapy with vedolizumab (300 mg i.v. every 8 weeks) or to placebo. A total of 40% of patients receiving vedolizumab maintained remission at week 52 compared with 16% of patients who received placebo (135). A *post hoc* analysis demonstrated that patients who were anti-TNF naive were more likely than those who had received anti-TNF therapy previously to respond to vedolizumab (136).

Tofacitinib also has efficacy in maintenance of moderately to severely active UC. The maintenance trial of tofacitinib compared remission rates of tofacitinib (5 or 10 mg) b.i.d. with placebo at week 52, with remission rates of 34.3% in the 5-mg group, 40.6% in the 10-mg group, and 11% in the placebo group ($P < 0.001$ for both 5- and 10-mg arms compared with placebo) (139). In subgroup analyses, patients with previous anti-TNF failure seemed to benefit from the higher maintenance dose (152). The rates of serious adverse events were comparable across the 3 groups, with the exception of a higher rate of herpes zoster infection in the tofacitinib group (139).

MANAGEMENT OF THE HOSPITALIZED PATIENT WITH ACUTE SEVERE ULCERATIVE COLITIS

Key concept statements

33. All patients admitted with acute severe ulcerative colitis (ASUC) should have stool testing to rule out CDI.
34. All patients with ASUC should undergo a flexible sigmoidoscopy within 72 hours, and preferably within 24 hours of admission. This should be used to assess endoscopic severity of inflammation and to obtain biopsies to evaluate for cytomegalovirus (CMV) colitis.
35. All patients with ASUC should be assessed for the presence of toxic megacolon on a regular basis during the hospital admission.
36. Response in patients with ASUC should be monitored using stool frequency, rectal bleeding, physical examination, vital signs, and serial CRP measurements.
37. NSAIDs, opioids, and medications with anticholinergic side effects should be avoided in ASUC.
38. In patients failing to adequately respond to medical therapy by 3–5 days or with suspected toxicity, surgical consultation should be obtained.
39. The choice between infliximab and cyclosporine should be based on provider experience with the agent, history of previous failure of immunomodulator or anti-TNF therapy, and serum albumin.
40. Toxic megacolon, colonic perforation, severe refractory hemorrhage, and refractoriness to medical therapy are indications for surgery in patients with ASUC.
41. Infliximab and cyclosporine do not increase postoperative complications of colectomy, and surgery should not be deferred based on this exposure.

Recommendations

37. In patients with ASUC, we recommend DVT prophylaxis to prevent venous thromboembolism (VTE) (strong recommendation, low quality of evidence).
38. In patients with ASUC, we recommend testing for CDI (strong recommendation, moderate quality of evidence).
39. In patients with ASUC and concomitant CDI, we recommend treatment of CDI with vancomycin instead of metronidazole (strong recommendation, low quality of evidence).
40. We recommend against the routine use of broad-spectrum antibiotics in the management of ASUC (strong recommendation, low quality of evidence).
41. We suggest against total parenteral nutrition for the purpose of bowel rest in ASUC (conditional recommendation, very low quality of evidence).
42. In patients with ASUC, we recommend methylprednisolone 60 mg/d or hydrocortisone 100 mg 3 or 4 times per day to induce remission (strong recommendation, low quality of evidence).
43. In patients with ASUC failing to adequately respond to intravenous corticosteroids (IVCS) by 3–5 days, we recommend medical rescue therapy with infliximab or cyclosporine (strong recommendation, moderate quality of evidence).
44. In patients with ASUC who achieve remission with infliximab treatment, we recommend maintenance of remission with the same agent (strong recommendation, moderate quality of evidence).
45. In patients with ASUC who achieve remission with cyclosporine treatment, we suggest maintenance of remission with thiopurines (conditional recommendation, low quality of evidence).
46. In patients with ASUC who achieve remission with cyclosporine treatment, we suggest maintenance of remission with vedolizumab (conditional recommendation, very low quality of evidence).

Summary of evidence Acute severe ulcerative colitis (ASUC) is defined as the presence of 6 or more bowel movements daily accompanied by at least 1 systemic sign of toxicity including tachycardia, fever, anemia (hemoglobin < 10.5 g/dL), or elevated inflammatory markers (ESR $>$ 30 mm/hr) (44). In children,

a PUCAI ≥ 65 is used to define ASUC (54). Patients with ASUC should be admitted to the hospital for inpatient management, IVCS therapy initiation in addition to supportive care with fluids and electrolytes. Up to one-quarter of patients with UC may develop ASUC requiring hospitalization (153,154), resulting in colectomy in 40% of patients (154). Even if the index hospitalization does not result in colectomy, patients requiring hospitalization represent a subgroup at a high risk of subsequent adverse outcomes including need for colectomy (155). Thresholds for hospitalization vary across institutions, and patients with UC who do not meet these criteria may require hospitalization for inpatient management. In addition, although most patients with severe colitis should be admitted to the hospital, in select cases, outpatient management with close follow-up may be appropriate.

We recommend initial *C. diff* testing in patients with ASUC. In a retrospective observational study at a tertiary referral center, it was found that in 2004–2005, more than half of the *C. diff*–infected patients with IBD required hospitalization, and 20% required colectomy (156). Various tests are available for the diagnosis of CDI in this setting, the most common ones being ELISA against *C. diff* toxins A + B and nucleic acid amplification tests such as PCR (22). The latter tests are more sensitive, but emerging evidence suggests that they may result in false-positive results, particularly in patients without documented diarrhea (22). Repeat stool testing is frequently not required but has been demonstrated to improve yield in some settings and should be performed on a case-by-case basis (156). In 1 series, up to 47% of hospitalizations for UC were associated with CDI (157). Although other cohorts have reported a lower frequency, patients with UC and CDI have a 4-fold increase in mortality, longer hospital stays, and higher rate of colectomy, emergency department visits, therapy escalation, and hospitalizations up to 1 year after the index episode (18,157–159). Patients with IBD who develop CDI also frequently lack the traditional risk factors associated with *C. diff*, such as previous hospitalization or antibiotic use (160). Consequently, a high index of suspicion must be maintained. More extensive disease, more severe disease, and immunosuppression (in particular corticosteroid use) may be associated with a higher risk of CDI (156,160,161). Although controlled trial data are limited, emerging evidence suggests a higher failure rate with metronidazole, suggesting that oral vancomycin should be the first-line agent for treatment of CDI in the hospitalized patient with ASUC (22,162).

There are several goals of endoscopic evaluation in patients with ASUC, namely, to establish the severity of inflammation, to confirm the diagnosis (in the setting of diagnostic uncertainty), and to obtain biopsies to diagnose CMV colitis. As a complete colonoscopy in patients with severe inflammation may be associated with higher rates of colonic dilation and perforation, a carefully performed flexible sigmoidoscopy with minimal insufflation by an experienced operator is sufficient for most patients. Although there are no standardized endoscopic activity scores specific to ASUC, endoscopic findings of deep ulcerations correlate with failure of corticosteroid therapy and need for rescue therapy or colectomy. In a cohort of 89 patients hospitalized with ASUC, the UCEIS was higher in patients requiring rescue therapy or colectomy (median 6) than in those who did not (median 5, $P < 0.005$). A UCEIS score of 5 or greater was associated with a 50% likelihood of rescue therapy and 33% rate of colectomy compared with 27% and 9%, respectively, in those with a score of ≤4 (163). In a prospective French study of 85 consecutive patients with ASUC, the presence of extensive deep colonic ulcerations was associated with nonresponse to corticosteroid therapy and need for colectomy (80). A recent retrospective review of 92 patients with ASUC showed that the UCEIS score correlated with both the Mayo endoscopic score (Spearman's rho, 0.762; $P < 0.001$) and the need for colectomy (adjusted OR, 3.25; 95% CI, 1.77–5.97; $P < 0.001$) (164). A UCEIS score of ≥7 had a higher positive predictive value of need for colectomy when compared with a Mayo endoscopic score of 3 (receiver-operator characteristic area 0.85 vs 0.65, respectively).

CMV colitis may affect up to one-third of patients with ASUC refractory to corticosteroid therapy (165,166). Risk factors for CMV include medically refractory disease, treatment with corticosteroids (less consistently immunomodulators and biologics), and presence of endoscopic ulceration (167). Endoscopically, CMV has a predisposition for actively inflamed tissues; biopsies from the base of the ulcer have the greatest yield. Histologic evidence of viral cytopathic effect on hematoxylin-eosin has poor sensitivity in identifying CMV disease (168). Immunohistochemistry staining, rapid viral culture methods, and PCR-based assays are the preferred modalities to diagnose CMV disease (165,166). Although there is debate about whether CMV colitis represents a true pathogenic effect or a "bystander effect," evidence suggests a higher rate of treatment refractoriness and need for colectomy in patients with demonstrable CMV colitis. Consequently, identification of this disease should prompt treatment with antiviral therapy in the setting of refractoriness to steroids or biologic therapy. In patients who are responding to standard treatment of UC such as intravenous steroids, studies have not demonstrated that there is an added benefit to antiviral treatment. When treating CMV colitis, the most commonly studied agent is ganciclovir, administered initially intravenously and subsequently orally for a 14-day course (165,166), with a response rate around 70%. Oral therapy with valganciclovir may also be appropriate in selected patients. Given the uncertainty about the pathogenic role of CMV in this setting, colectomy should not be deferred until the completion of the full course of treatment in nonresponders.

Features suggestive of severe colitis on plain abdominal films include a thickened colonic wall, loss of haustrations, and mucosal islands (edematous mucosa surrounded by ulcerations). In 1 study, the presence of 3 or more dilated, gas-filled small bowel loops indicated a high likelihood of nonresponse to medical therapy and need for colectomy (169). In addition, plain abdominal radiographs may be useful in identifying colonic dilation (transverse colon diameter > 5.5 cm), which predicts a worse outcome. Abdominal imaging should be in conjunction with a careful physical examination eliciting abdominal tenderness, rebound, guarding, tympany, and ileus. Cross-sectional imaging with CT should be restricted to patients with a suspected extraluminal complication, perforation, and in those newly diagnosed where the distinction between CD and UC may not be apparent on sigmoidoscopy.

Close monitoring of patients with ASUC is essential to identify early nonresponders to IVCS therapy who may require medical or surgical rescue therapy. Day-to-day monitoring should include assessment of vital signs, physical examination to evaluate for abdominal distension or tenderness, and assessment of frequency of bowel movements, presence of visible blood, abdominal pain, and systemic symptoms. Several indexes have been proposed to identify nonresponders to therapy. The most widely recognized is

the Oxford index where more than 8 bowel movements on day 3 of IVCS treatment or 3–8 bowel movements along with a CRP > 45 mg/L predicted colectomy in 85% of patients meeting the above criteria (32). By contrast, the rate of colectomy in those with partial and complete response was 40% and 5%, respectively. In children, a PUCAI score of greater than 45 at day 3 or greater than 70 at day 5 predicted failure of IVCS therapy and need for salvage (170). Other parameters predicting failure of steroid therapy include hypoalbuminemia and colonic dilation (integrated into the Ho index in conjunction with number of bowel movements) (171), elevation in ESR > 75 mm/hr, and body temperature > 38 °C (172).

NSAIDs have been associated with IBD-related hospitalizations and disease relapses in up to one-third of patients (15). Consequently, they should be avoided in ASUC. Opioids and agents with anticholinergic side effects may precipitate colonic dilation and toxicity and have been associated with poor outcomes including risk of infections and mortality and should be avoided. With the above restrictions, management of pain in patients with ASUC is challenging and should be multimodal, relying on pharmacologic and nonpharmacologic measures. A combination approach with nonpharmacologic measures (such as heating pads), acetaminophen, in conjunction with anxiolytics and sedatives may be helpful to allay pain in a significant proportion of patients. Suspicion for paradoxical hypersensitivity to aminosalicylate therapy should be entertained in patients who have recently initiated therapy with oral or topical 5-ASA agents, and such medications should be stopped at hospitalization.

All patients hospitalized with ASUC should be closely followed by a multidisciplinary team. Surgical consultation should be obtained for patients who are failing IVCS and are initiating rescue therapy. In addition to medically refractory disease, urgent surgery is indicated for patients who develop toxic megacolon (fewer than 5% of patients with ASUC), perforation, or massive hemorrhage. Delayed surgery in ASUC is associated with poor outcomes and must be avoided. The preferred surgical treatment of choice is a subtotal or a total colectomy with end ileostomy. Medical rescue therapy with infliximab or cyclosporine has not been shown to increase rates of postoperative complications, and necessary surgery should not be deferred based on this exposure (173).

Inflammatory bowel disease is associated with an increased risk of VTE (174–178). This risk is particularly apparent in hospitalized patients and is proportional to severity of inflammation (177). Other factors contributing to VTE risk in these patients include loss of antithrombotic proteins, use of corticosteroids, reduced mobility, and abdominal surgery (176,179). As many patients with IBD who develop VTE do not seem to have an underlying genetic predisposition or other risk factors (178), thromboprophylaxis with low-molecular-weight heparin should be given to all hospitalized patients with acute colitis. Subcutaneous low-molecular-weight heparin seems to be safe even in patients with active bleeding from their UC and is not associated with worsening hemorrhage (180). Administration of pharmacologic prophylaxis may additionally be associated with reduced rates of VTE after hospitalization, although this benefit has not been robustly demonstrated (181,182).

Four clinical trials have examined the role of adjuvant antibiotics in hospitalized patients with ASUC. The antibiotics studied included metronidazole (183), tobramycin (184), ciprofloxacin (185), and vancomycin (186). In each of the studies, there was no difference in the proportion of patients responding to medical therapy or needing surgery. In addition, given the known association between antibiotics and risk of CDI in this population, the use of antibiotics should be restricted to those with suspected extraluminal complications or systemic signs of toxicity.

The role of complete bowel rest and parenteral nutrition has been examined in RCTs where there was no benefit over placebo (187,188). In a trial comprising 36 patients, 6/17 patients in the control group and 9/19 patients with total bowel rest and TPN required surgery for treatment of their colitis (P = not significant) (188).

Systemic IVCS are the main stay of treatment of ASUC. Their efficacy was first established in an open-label series, in which 49 patients hospitalized with severe colitis were administered prednisolone 60 mg/d in divided doses along with topical hydrocortisone enemas. At 5 days, 73% of patients were in remission, and only 18% reported no improvement or worsening of symptoms. On long-term follow-up, 47% of patients achieving remission were able to maintain their clinical status, and only 18% required subsequent surgery (189). In a systematic review of 32 studies that included 1,948 adults receiving IVCS therapy, the mean response rate was 67% (103). Just under one-third of patients (27%) underwent colectomy during the index hospitalization. Meta-regression revealed no benefit to a dose higher than 60 mg of methylprednisolone. IVCS can be administered as a single dose, divided doses, or a continuous drip with no difference in efficacy (190). Topical corticosteroid therapy may additionally help patients with symptoms of distal involvement. Response to IVCS is usually apparent within 3–5 days of initiation, and additional response after 7 days is unlikely. Thus, prolonged IVCS therapy beyond this duration without initiation of rescue therapy cannot be recommended. In the setting of suspected CDI or CMV infection, it may be necessary to continue IVCS therapy, as the effect of infection may not be separable from that of the underlying colitis. The efficacy of cyclosporine in acute steroid-refractory colitis was first established in a landmark controlled trial. Twenty patients with severely active UC without response to 7 days of IVCS therapy were randomized to receive cyclosporine 4 mg/kg or placebo (191). Nine of 11 patients who were administered cyclosporine demonstrated a clinical response at a mean of 7 days compared with none of the patients who received placebo. Similar short-term efficacy has been demonstrated at other centers (192,193). However, on long-term follow-up, up to 80% of patients may eventually require colectomy (193,194). Patients who are thiopurine naive at the time of initiation of cyclosporine and receive thiopurine maintenance therapy have a lower risk of colectomy than patients who were either not initiated on thiopurines or had previously failed this therapy (194–196). One study demonstrated comparable clinical response and colectomy rates with 2 mg/kg of cyclosporine compared with 4 mg/kg, suggesting that the lower dose should be preferred, given similar response and lower frequency of adverse events (197). Therefore, 2 mg/kg is the targeted cyclosporine dose for treatment of ASUC, with additional studies describing drug levels in the range of 200–400 for efficacy (198,199). Although cyclosporine has similar efficacy to IVCS (200), its use should be restricted to those failing IVCS therapy except in patients who have contraindications or intolerance to corticosteroids.

The efficacy of infliximab in the treatment of patients with ASUC has been demonstrated in small clinical trials and several observational case series. In 1 pilot study, 4 of 8 patients who

received infliximab had clinical response by 2 weeks compared with none of the patients who were administered placebo (201). Infliximab was also associated with biochemical response with improvement in circulating inflammatory markers. In a pivotal RCT, 45 patients not responding to 4 days of corticosteroid therapy were randomized to a single infusion of infliximab 5 mg/kg or placebo. Among 24 patients who received infliximab, only 7 patients required a colectomy by 3 months compared with 14/21 patients receiving placebo ($P = 0.017$) (202). Long-term follow-up of this trial revealed continued benefit at 3 years (203). Prospective observational series confirmed the short-term efficacy of infliximab therapy in ASUC (204,205). In a long-term follow-up study of 211 patients from Sweden, the colectomy-free survival rates after infliximab rescue therapy at 3, 12, 36, and 60 months were 71%, 64%, 59%, and 53%, respectively, with over half the patients achieving steroid-free remission by 12 months (206). There is growing interest in the optimization of infliximab dosing in ASUC, recognizing that fecal drug loss may result in subtherapeutic serum and tissue concentrations, resulting in a suboptimal response rate (207). A retrospective study of 50 patients receiving accelerated infliximab induction, defined as 3 induction doses within a median period of 24 days, demonstrated a lower rate of colectomy with the accelerated regimen (7%) compared with standard dosing (40%); however, the rates of colectomy at 3 months were similar between the 2 groups, suggesting that the short-term benefit may not translate into improved long-term outcomes (208). Thus, although accelerated or high-dose induction regimens may be appropriate for a subgroup of patients with severe UC, their routine use cannot be recommended with the existing evidence. There are no data on the use of adalimumab, golimumab, vedolizumab, or tofactinib as rescue therapy in ASUC, and their use cannot currently be recommended in this setting. Routine use of medical salvage therapy in patients failing infliximab or cyclosporine therapy cannot be recommended and may be associated with a significant risk of adverse outcomes.

Tacrolimus is a calcineurin inhibitor that has been examined in the treatment of steroid-refractory UC both in children and adults. In a double-blind placebo-controlled trial of 62 patients, the clinical response rate at week 2 was 50% with tacrolimus compared with 13% with placebo ($P = 0.003$) (209). Rates of mucosal healing were also superior with tacrolimus compared with placebo (44% vs 13%), and side effects were few. The optimal target serum trough levels for tacrolimus seem to be 10–15 ng/mL (210), and efficacy seems to be similar in children (211). However, there are limited data on long-term outcomes and colectomy rates (211).

In a RCT comparing cyclosporine with infliximab in patients with acute severe UC not responding to IVCS (Study Comparing Cyclosporine With Infliximab in Steroid-Refractory Severe Attacks of Ulcerative Colitis), 115 patients across 27 institutions were randomized to receive cyclosporine (2 mg/kg for 1 week, followed by oral cyclosporine) or infliximab (5 mg/kg at weeks 0, 2, and 6) (212). Responders in both groups received treatment with azathioprine from day 7 and were followed through 98 days. At the end of the follow-up, treatment failure defined as absence of day 7 clinical response, relapse between day 7 and day 98, or absence of steroid-free remission at day 98 was similar with cyclosporine (60%) and infliximab (54%). The median change in the Lichtiger score was greater at days 3 and 4 with infliximab compared with cyclosporine, but the median time to response was similar between both groups (5 days with cyclosporine and 4 days with infliximab) (213). There was no difference in the rates of mucosal healing or need for colectomy. In long-term follow-up from this trial, there was no difference in colectomy-free survival based on treatment arm. Infliximab patients were maintained with infliximab, and the cyclosporine patients had various maintenance strategies that did not include cyclosporine. Colectomy-free survival rates after 1 and 5 years of follow-up were, respectively, 70.9% (95% CI, 59.2%–82.6%) and 61.5% (95% CI, 48.7%–74.2%) in patients who received cyclosporine and 69.1% (95% CI, 56.9%–81.3%) and 65.1% (95% CI, 52.4%–77.8%) in those who received infliximab ($P = 0.97$) (214). A second clinical trial, COmparison of iNfliximab and cyclosporine in STeroid Resistant Ulcerative ColiTis (CONSTRUCT), additionally compared differences in QoL and health care costs between the 2 treatments. There were no differences between the 2 groups (each group consisting of 135 patients allocated to either treatment) in terms of quality-adjusted survival, frequency of colectomy, time to colectomy, or adverse events (including mortality) (215). Another multicenter study, using data from the ENEIDA registry, with a total of 740 patients treated with cyclosporine, infliximab, or sequential rescue therapy showed a similar efficacy between the 2 treatments, including similar colectomy and mortality rates, but highlighted a lower rate of adverse effects in the cyclosporine group (216).

The choice between cyclosporine and infliximab should be made based on provider experience with each drug. Infliximab is commonly used in the outpatient management of both CD and UC, and consequently, there is greater provider familiarity with dosing and monitoring for adverse events. By contrast, as cyclosporine is used less frequently and only at select centers, its use in steroid-refractory colitis should be restricted to providers who are familiar with dosing, monitoring trough concentrations, and managing adverse effects. As the rates of treatment failure and colectomy are significantly higher in patients receiving cyclosporine who have previously failed immunomodulator therapy, infliximab may be a preferred agent in such patients. *Post hoc* stratified analysis of the Study Comparing Cyclosporine With Infliximab in Steroid-Refractory Severe Attacks of Ulcerative Colitis trial additionally revealed treatment effects favoring infliximab in patients with albumin <23 g/L (212). In addition, patients with lower serum cholesterol or magnesium are at a greater risk of neurological adverse events from cyclosporine therapy and should be considered for treatment with infliximab.

There is considerable interest in the use of cyclosporine or infliximab as salvage therapy after failure of either agent. However, data supporting long-term efficacy are scarce. In a retrospective review of patients who either received infliximab after failing cyclosporine ($n = 10$) or cyclosporine after failing infliximab ($n = 9$), the rates of remission ranged from 30% to 40% in both groups. However, severe adverse outcomes were noted in 16%, including 1 death from sepsis and 1 case each of herpetic esophagitis and acute pancreatitis with bacteremia. Other observational series similarly suggest that 60% of patients require colectomy by 12 months with either cyclosporine or infliximab salvage (217,218). However, the rate of severe adverse outcomes, including infectious complications, seems to be high. This suggests that the select patients who are receiving salvage therapy should be closely monitored for such outcomes.

Patients with ASUC who have previously failed infliximab or other anti-TNF biologic therapy are a growing subgroup. Previously, if such patients had also failed immunomodulator

therapy, they were not considered candidates for calcineurin therapy induction in the absence of an effective maintenance agent. Several recent reports suggest that vedolizumab may serve as a maintenance therapy for such patients when combined with a calcineurin agent (cyclosporine or tacrolimus) for a more rapid induction of remission. Eleven patients with UC received combination therapy with a calcineurin inhibitor and vedolizumab as a bridge to vedolizumab monotherapy, of which 55% of these achieved steroid-free clinical remission by week 14. At 1 year, 45% of these patients with UC were in steroid-free clinical remission. Two patients received salvage therapy with a calcineurin inhibitor after primary nonresponse to vedolizumab; 1 patient was off the calcineurin inhibitor and achieved steroid-free remission at week 52 (199).

Indications for colectomy in UC include (i) ASUC or (ii) chronic refractory UC not responding to traditional medical therapy or (iii) development of dysplasia and/or carcinoma in chronic UC. We focus on the first 2 indications for the purpose of this guideline. The absolute indications for surgery in ASUC include toxic megacolon, perforation, uncontrolled severe hematochezia, and multiorgan dysfunction (219). Colectomy should also be considered in any patient who fails to progress after 3–5 days of corticosteroids. Delays in surgery can be associated with an increased risk of postoperative complications (220). Delayed surgery for ASUC is associated with an increased risk of postoperative complications (221). The definition of chronic refractory UC can include either (i) individuals who are refractory to induction of remission with biologics, corticosteroids, or small molecule therapies or (ii) individuals who are corticosteroid dependent. Patients who meet these criteria should be considered for surgery and offered early referral and consultation with a surgeon.

A recent systematic review demonstrated that early complications of colectomy (≤30 days postoperatively) occurred in 9%–65% of patients with UC, whereas late complications (>30 days postoperatively) occurred in 17%–55% of patients. Overall postoperative mortality associated with colectomy for UC was 1% (222). Of the various therapies for UC, prolonged corticosteroids in particular are associated with an increased risk of postoperative infectious complications in observational studies after surgery (223). In a meta-analysis of observational studies of anti-TNF use before surgery in IBD, the pooled prevalence of any postoperative complication in UC was 35%. Preoperative anti-TNF was associated with an increased risk of postoperative infectious complications in CD but not in UC (224). In a single-center retrospective cohort, a detectable level of anti-TNF (compared with no level) was not associated with increased surgical complications in patients with UC (225). A retrospective series describing perioperative use of vedolizumab and postoperative infectious complications in patients with UC undergoing colectomy demonstrated no increased risk, although overall numbers were small (226). There are no current data on small molecules and subsequent colectomy in patients with UC.

Another factor heavily influencing surgical outcomes is nutritional status/malnourishment. Optimization of nutritional status should be considered in the period before colectomy if possible. Poor nutritional status is associated with increased in-hospital mortality, increased length of stay and costs, and increased infection rates. Definitions of malnourishment include weight loss >10%–15% in the previous 6 months, body mass index <18.5 kg/m^2, and serum albumin <30 g/L (227,228). Enteral and/or parenteral options should be considered in malnourished patients with UC based on individual clinical scenarios.

Restorative proctocolectomy with ileal pouch–anal anastomosis (IPAA) is currently the surgical procedure of choice for the management of refractory UC. Construction of the pouch is not performed in the first stage of the procedure for the refractory patient on medical therapies such as corticosteroids. This staged approach minimizes complications and initial operation time. Delaying the reconstruction allows for improvement in nutritional status and the ability to minimize the potential for infectious complications of UC therapies. Therefore, a multiple-staged approach should be considered in patients with UC undergoing colectomy for ASUC or chronic refractory UC not responding to medical therapy.

COLORECTAL CANCER PREVENTION IN ULCERATIVE COLITIS

Key concept statements

42. Screening and subsequent surveillance colonoscopy to assess for dysplasia in individuals with UC of extent greater than the rectum should start 8 years after diagnosis.
43. Patients with UC and primary sclerosing cholangitis (PSC) should undergo a screening colonoscopy at the time of diagnosis of UC and surveillance annually thereafter.
44. Surveillance colonoscopies in patients with UC should be performed at 1- to 3-year intervals based on the combined risk factors for colorectal cancer (CRC) in UC and the findings on previous colonoscopy. Specific interval should be based on combined risk factors and findings from previous examinations.
45. During colonoscopic examination in patients with UC, the endoscopist should identify raised lesions and abnormal pit patterns and perform targeted biopsies. Endoscopically discrete lesions should be removed, clearly labeling and separating distinct lesions and segments of the colorectum.
46. Most neoplasia in UC is visible with standard- or high-definition white-light examinations.
47. It is unclear whether segmental random biopsies are still required during surveillance colonoscopy in UC.
48. Pathologic interpretation of UC-associated neoplasia should be performed by a pathologist experienced in gastrointestinal pathology, and neoplastic findings should be reviewed by a second experienced pathologist.
49. When dysplasia in UC of any grade is discrete and has been completely removed, proctocolectomy may not be necessary. If surgery is not performed, subsequent surveillance colonoscopy should initially be performed at shortened intervals.
50. When dysplasia in UC is not resectable or is multifocal, the patient should be referred for proctocolectomy.
51. Patients with UC who have extensive inflammatory polyps may not be able to have adequate surveillance and should be informed about this fact and that more frequent surveillance or surgery may be required.
52. No medical therapy has demonstrated sufficient prevention of dysplasia or CRC to avoid colonoscopic surveillance in UC.
53. Patients with UC-associated dysplasia who are undergoing ongoing active surveillance may benefit from the use of augmented visualization by dye spray chromoendoscopy in their first examination after UC-associated dysplasia was detected.
54. Fecal DNA testing and CT colonography are not recommended for screening or surveillance of UC-associated neoplasia because of insufficient evidence.

Recommendations

47. We suggest colonoscopic screening and surveillance to identify neoplasia in patients with UC of any extent beyond the rectum (conditional recommendation, very low quality of evidence).
48. When using standard-definition colonoscopes in patients with UC undergoing surveillance, we recommend dye spray chromoendoscopy with methylene blue or indigo carmine to identify dysplasia (strong recommendation, low quality of evidence).
49. When using high-definition colonoscopes in patients with UC undergoing surveillance, we suggest white-light endoscopy with narrow-band imaging or dye spray chromoendoscopy with methylene blue or indigo carmine to identify dysplasia (conditional recommendation, low quality of evidence).

Summary of evidence CRC is a well-described complication of chronic UC, and the risk factors include longer duration of disease, increased inflammatory activity, younger age of diagnosis, greater extent of colonic inflammation, coexisting PSC, and a family history of a first-degree relative with CRC (229). The longest maintained UC surveillance program at St. Mark's Hospital in the United Kingdom reports that the incidence rate of CRC in patients with UC is 4.7 per 1,000 patient-years (208). A meta-analysis of studies of risk factors and time trends identified that over time, the risk of CRC in UC has been decreasing, with the rates of advanced CRC and interval CRC steadily decreased over the past 4 decades. In this analysis, the cumulative risks of CRC in UC were estimated to be 1%, 2%, and 5% after 10, 20, and >20 years of disease duration, respectively (230). Although previously described as a risk factor, newer data suggest that inflammatory pseudopolyps may not be a risk factor for CRC (231).

CRC in UC is believed to arise from dysplasia, which is the unequivocal neoplastic transformation of the colonic epithelium. The classical description of dysplasia in UC includes flat, spreading lesions rather than sessile or pedunculated polyps. When flat dysplasia in UC is confirmed, historically, this has been associated with a high rate of synchronous or metachronous cancer. By contrast, discrete, polypoid, "adenoma-like" lesions are likely associated with a low risk of CRC (232).

Identification of the risks of CRC in patients with UC has led to strategies aimed at prevention, and the predominant approach has been secondary prevention via colonoscopic screening and surveillance. However, although this approach seems reasonable and is postulated to be one of the reasons for the decreased incidence of CRC in UC, there are a number of limitations in the existing studies of CRC risk in UC. There are no prospective studies of CRC prevention in UC that demonstrate reduction of CRC incidence or death from CRC associated with surveillance colonoscopy. In a retrospective study, the incidence of CRC was significantly higher (2.7%) in patients with UC without a recent colonoscopy compared with 1.6% in those with a colonoscopy within 3–36 months before diagnosis of CRC (233). A Cochrane analysis of 3 small studies of UC-related cancer prevention did not identify a significant mortality benefit (234). Nonetheless, because of observations that the presence of classical dysplasia is associated with concurrent or subsequent CRC, detection of dysplasia has been used as the marker of successful screening/surveillance and was accompanied by recommendations to perform proctocolectomy. This may in fact be a flawed strategy because it is also possible that cancer rates are decreasing due to better control of inflammation (reducing the primary risk of neoplastic transformation) or access to surgery for medically resistant disease (removing at-risk patients from these cohorts earlier). Therefore, conclusions and recommendations about cancer prevention in UC that are based on dysplasia detection must be considered in the context of these limitations.

The timing of the first screening examination and subsequent surveillance intervals have not been prospectively determined. Previous guidelines have suggested starting screening and surveillance after 8–10 years of disease, but such models of screening and risk assessment did not adequately adjust for degree of inflammation or other confounding variables. More recent data suggest that CRC may be occurring earlier in some patients, so these guidelines have suggested starting screening after 8 years of disease (235). The exception in all published guidelines has been patients with concomitant PSC with UC, in which the increased risk of CRC is so high that surveillance examinations should start at the time of diagnosis of the UC and continue annually. This is both to address the risk and because one of the theories for the increased risk of CRC in UC/PSC is that the inflammatory activity in UC is less severe, and patients may have had disease longer than was previously known (236). More recently, increased histologic activity of inflammation was described in the proximal colon in such patients, providing some additional insights into these observations and the importance of colonoscopic examination to better monitor and survey (237).

For patients with UC without PSC, it is difficult to better define intervals required for colonoscopic surveillance because of the lack of prospective studies. The intervals for surveillance examinations should be chosen based on the natural history of cancer in the at-risk individuals, the sensitivity of screening and surveillance technology for the detection of precancerous findings, and the risk factors for development of new neoplasia. A rational approach to this challenge is to combine risk factors and adjust the intervals based on the combination of risk factors, including the degree of inflammation on the previous examination. Shorter intervals are recommended for patients who have a greater number of risk factors, and longer intervals between examinations may be offered to patients with fewer risk factors and in whom the (histologic) inflammation is under excellent control. In these guidelines, a range of intervals between 1 and 3 years is suggested. Recent analyses that quantify risk over time from the St. Mark's surveillance program support this general approach (238), but there are clearly insufficient data to make more informed recommendations at this time.

The approach to dysplasia detection has evolved along with improvements in technology, and therefore, recommendations for the detection of dysplasia are also updated (239). Historically, because dysplasia in UC was not easily visible with fiber optic colonoscope technology, recommendations were to perform nontargeted ("random") biopsies in a systematic and segmental method to sample the mucosa. The belief was that when colitis-associated neoplasia occurred, it was in the setting of a "field effect" of at-risk mucosa, and segmental biopsies would identify neoplastic change to allow for surgical intervention. Subsequently, it was reported in retrospective studies of standard-definition colonoscopes that most neoplasia was visible in the majority of patients (240,241). With additional endoscopic improvements and clinical studies, endoscopists now have the ability to visualize mucosal abnormalities even at the level of pit patterns of dysplastic crypts. In addition, utilization of dye spray with either methylene blue or indigo carmine further improved

dysplasia detection. Multiple studies demonstrated that the use of dye spray chromoendoscopy compared with standard-definition colonoscopy detected a greater number of dysplastic lesions (242). This led to publication of an international consensus statement recommending dye spray chromoendoscopy over white-light colonoscopy for surveillance in UC (229). This was a strong recommendation compared with standard-definition white-light colonoscopes and a conditional recommendation compared with high-definition white-light colonoscopes (243). Adoption of this recommendation was limited because of challenges in incorporation of the techniques, perception of increased time and expense of examinations, and lack of training or experience by many gastroenterologists (244). Multiple studies have demonstrated a low yield of the systematic nontargeted biopsies and poor compliance with this approach, and a recent prospective randomized trial in patients with UC found that targeted and random biopsies detected similar proportions of neoplasia, but the examination times in the targeted biopsy group were shorter (41.7 vs 26.6 minutes, $P < 0.001$) (245). A single prospective multicenter study in France of high-definition colonoscopies with dye spray chromoendoscopy in combination with additional random biopsies demonstrated a low yield of additional dysplasia with the random biopsies (7 patients) that was separate from those that were visible during chromoendoscopy and 12 patients in whom no lesions were seen by chromoendoscopy but dysplasia was found by random biopsies (246). No cancers were missed, and no benefit in cancer mortality was measured, so, in sum, the evolution of enhanced visualization techniques suggests that dysplasia detection by direct visualization and targeted biopsies is safe and efficient.

More recently, the widespread availability of higher-resolution colonoscopes and monitors has resulted in what is believed to be greater visibility of neoplasia, and the utility of dye spray chromoendoscopy has been questioned in this setting. A retrospective cohort study found similar numbers of dysplastic lesions in patients who underwent white-light or dye spray chromoendoscopy examinations (247). Although previous studies of narrow-band imaging with standard-definition and high-definition colonoscopies did not demonstrate superior detection of dysplasia compared with white light (248–250), a more recent prospective randomized study using high-definition colonoscopes demonstrated similar dysplasia detection between high-definition colonoscopes using narrow-band imaging and high-definition colonoscopes with dye spray chromoendoscopy (251), supporting an approach that does not seem to require dye spray examinations in patients with UC. However, once dysplasia is found, these patients are at a higher risk of subsequent neoplasia and may benefit from enhanced visualization in their follow-up examination (252,253). Alternately, if there is no evidence of dysplasia on consecutive examinations or with dye spray chromoendoscopy, there is a very low risk of advanced colorectal neoplasia on follow-up (254–256). In these individuals, after consecutive negative examinations, longer surveillance intervals in this selected population may be safe.

A critical component to a cancer prevention strategy focused on dysplasia detection is accurate histopathologic diagnosis, and several analyses have emphasized the importance of pathologists with expertise reviewing suspected UC-associated neoplasia (257). In particular, low-grade dysplasia and indefinite dysplasia have some diagnostic errors associated with them (258). Distinction between colitis-associated neoplasia and sporadic/age-related neoplasia is not clear, especially when isolated dysplastic lesions are found, but flat dysplasia or "invisible" (defined as found on nontargeted biopsies) neoplasia is thought to be colitis associated. The colitis-associated lesions are also more likely to be flat or spreading lesions rather than morphologically sessile or pedunculated. Because of improvements in visualization, the term "DALM" (dysplasia-associated lesion or mass) should no longer be used to describe neoplasia. Instead, descriptive terminology should be incorporated that characterizes the size, shape, and pit patterns of the mucosa.

Patients with UC that has healed may develop inflammatory polyps. Inflammatory polyps, sometimes called "pseudopolyps," are not precancerous, but distinction between inflammatory polyps and dysplastic polyps can be difficult. Some patients may develop extensive pseudopolyposis, in which visualization of the intervening mucosa can be difficult or not possible. Because of this fact, an approach to surveillance has not been clarified. Therefore, patients with pseudopolyposis should be informed that their surveillance may not be adequate. More frequent surveillance examinations or surgical resection of the affected area may be required (259).

The general approach to a confirmed neoplastic lesion in a patient with UC has been surgical resection of the colorectum with ileostomy or continent reservoir creation. The most common approach to this surgery is a 2- or 3-stage creation of continent reservoir IPAA. A stapled anastomosis provides better functional outcomes than mucosectomy with a handsewn anastomosis, so mucosectomy may be reserved for those patients with neoplasia that involves the rectum and who have a higher risk of recurrence in this region (260,261).

The evolution of technology and the ability to see neoplasia has moved us away from recommending proctocolectomy for all patients with any form of dysplasia. When discrete polypoid lesions are discovered in patients with UC, if these can be completely resected, patients can be followed with ongoing surveillance rather than surgery (262). One of the challenges in UC-associated dysplasia detection is the patient with extensive inflammatory polyps, in whom assessment or removal of the large number of polyps is technically impossible and adequate inspection of the lesions and underlying mucosa for neoplasia is hindered. In this situation, it may be prudent to advise the patient of the technical difficulty and consider a surgical resection due to inability to perform adequate surveillance (263).

Previous technical reviews suggested that after polypoid lesions are resected in UC, biopsies of the flat mucosa surrounding the area should be obtained to confirm that no residual neoplasia is left *in situ*. With the newer enhanced visualization techniques and technologies, this approach may not be necessary in many patients (264–266). We now consider bowel-sparing segmental or subtotal resections in select patients (those in deep remission, those who are not good candidates for IPAA, and in those where dysplasia is proximal and not involving the rectum) (267).

Because the primary driver of cancer risk in UC seems to be inflammation, there may be a role for primary prevention (chemoprevention) of CRC by medical treatment of UC. Data from various case-control and cohort studies have demonstrated a protective effect of medical therapies for development of dysplasia in UC, including 5-ASA therapies (268) and azathioprine (269). However, these results have been inconsistent across studies, and effect sizes are less when adjustments for all confounders including degree of inflammation are included in the

analyses (9). Therefore, optimized medical therapy alone is not an appropriate prevention method for CRC in patients with UC and does not supplant colonoscopy. Using appropriate secondary prevention (screening and surveillance) is necessary at this time to prevent CRC in patients with long-standing UC.

CONCLUSIONS

UC is an idiopathic chronic inflammatory condition of the rectum and colon, which presents with variable degrees of clinical activity and severity and is associated with significant morbidity. The appropriate management of patients with UC involves successful induction of both clinical and endoscopic remission, followed by the use of a steroid-free maintenance strategy. Choice of therapy for UC is based on activity, severity, extent of inflammation, and prognostic factors and may include oral, topical (rectal), or systemic therapies, as well as surgery. When possible and appropriate based on individual clinical factors, organ-specific treatments can be used before systemic therapies. In general, the induction therapy selected directs the choice of maintenance therapy. Patients with UC are at an increased risk of CRC and should undergo surveillance colonoscopy focused on identifying and removing precancerous dysplasia. The evolution of technology has resulted in more directly visualized approaches, removal of endoscopically discrete lesions, and in select patients, active surveillance rather than proctocolectomy.

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CONFLICTS OF INTEREST

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