American Gastroenterological Association Institute Guideline on the Medical
Management of Moderate to Severe Luminal and Fistulizing Crohn's Disease

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This document presents the official recommendations of the American Gastroenterological Association (AGA) on the medical management of moderate to severe luminal and fistulizing Crohn’s disease. The guideline was developed by the AGA’s Clinical Practice Guideline Committee and approved by the AGA Governing Board. Development of this guideline and its accompanying technical review was fully funded by the AGA Institute with no additional outside funding.

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INTRODUCTION

This document presents the official recommendations of the American Gastroenterological Association (AGA) on the medical management of moderate to severe luminal and fistulizing Crohn’s disease (CD) in adults. The guideline was developed by the AGA Institute’s Clinical Guidelines Committee and approved by the AGA Governing Board. It is accompanied by a technical review that provides a detailed synthesis of the evidence from which these recommendations were formulated.¹ Development of this guideline and the accompanying technical review was fully funded by the AGA Institute without additional outside funding. Jonathan Terdiman was the guideline panel chair and Joseph Feuerstein and Siddharth Singh were the methodologists. A patient representative was also included in the review process. The guideline was published online for public review and all comments were reviewed and addressed by the guideline committee. Guidelines are reviewed annually at the AGA clinical practice guideline committee meeting. The next complete guideline update is anticipated in three years from publication.

CD is a chronic inflammatory bowel disease with substantial morbidity when not adequately controlled.² Historically, approximately 20% of patients with CD were hospitalized every year, and the risk of surgery within one year of diagnosis was 24%, 36% by five years and 47% by 10 years.³ In recent years, outcomes have improved, likely because of earlier diagnosis, increasing use of biologics, escalation or alteration of therapy based on disease severity, and endoscopic management of colorectal cancer. CD includes multiple different phenotypes. The Montreal Classification categorizes CD as stricturing, penetrating, inflammatory (non-stricturing and non-penetrating) and perianal disease.⁴ ⁶ Each of these phenotypes can present with a range in severity from mild to severe disease.⁷

This guideline addresses the medical management of moderate to severe luminal and fistulizing CD. The International Organization for the Study of Inflammatory Bowel Disease
(IOIBD) characterizes severe disease as having a high risk for adverse disease-related complications including surgery, hospitalization, and disability based on a combination of structural damage, inflammatory burden and impact of quality of life. Contributors to severe disease include: large or deep mucosal lesions on endoscopy or imaging, presence of fistula and/or perianal abscess, presence of strictures, prior intestinal resections, particularly of segments >40cm, presence of a stoma, extensive disease (ileal involvement >40cm, or pancolitis), anemia, elevated C-reactive protein and low albumin. With respect to symptoms, patients with severe disease may have at least 10 loose stools/day, daily abdominal pain, presence of anorectal symptoms (anorectal pain, bowel urgency, incontinence, discharge, tenesmus), systemic corticosteroid use within the prior year, lack of symptomatic improvement despite prior exposure to biologics and/or immunosuppressive agents, or significant impact of the disease on activities of daily living. Moderate to severe disease can also be defined using the Crohn’s Disease Activity Index (CDAI). This standardized disease assessment score categorizes severity of disease as: remission < 150, mild to moderate as 150-220, moderate to severe as 220-450 and severe > 450. For this guideline, moderate to severe disease was considered a CDAI score of 220 or higher.

There are a number of different drug classes available for the management of moderate to severe CD, including tumor necrosis factor (TNF)-α antagonists (infliximab, adalimumab, certolizumab pegol), anti-integrin agents (natalizumab, vedolizumab), interleukin 12/23 antagonist (ustekinumab) and immunomodulators (thiopurines, methotrexate), corticosteroids (prednisone, budesonide). In general, most drugs, with the exception of corticosteroids, that are initiated for induction of remission are continued as maintenance therapy. Unless otherwise specified, we do not present separate recommendations for induction and maintenance of remission. The drugs are listed, in general, in order of Food and Drug Administration (FDA) approval. This guideline does not address surgical management of moderate to severe CD. Therapeutic drug monitoring
to guide the use of biologic therapy has been addressed in a separate AGA guidelines and is not included in this guideline.\textsuperscript{10}

In formulating this guideline, the predetermined critical outcomes were induction and maintenance of remission. The ability of the various drugs to achieve these outcomes are reported in the technical review with associated evidence profiles. For the questions regarding fistulizing disease, induction and maintenance of fistula remission was generally defined as complete cessation of fistula drainage. Important outcomes of interest were induction and maintenance of endoscopic remission, maintenance of corticosteroid-free remission, serious adverse events (including serious infections and malignancy), and treatment tolerability (drug discontinuation due to adverse events). These were considered in the evidence synthesis especially if inadequate or conflicting data were observed for critical outcomes. Safety considerations with these medications have been synthesized in the accompanying technical review. In the recommendations presented in this guideline, estimates of the effect of different medications are presented as the risk for failure to induce or maintain remission, i.e., a relative risk (RR) or odds ratio (OR) $<1$ suggests that the drug under consideration is more effective than the comparison drug or placebo for induction or maintenance of remission.

When considering the magnitude of benefit, for trials comparing interventions vs placebo, a minimal clinically important difference (MCID) was set at 10%. Failure to meet the MCID was considered to have no clinically meaningful impact over placebo. For additional details regarding the methodology please review the accompanying technical review.

This guideline and its accompanying technical review\textsuperscript{1} were developed using GRADE methodology\textsuperscript{11} and best practices as outlined by the Institute of Medicine.\textsuperscript{12} Optimal understanding of the guideline will be enhanced by reading the applicable portions of the technical review. The guideline panel and the authors of the technical review met virtually via a video conference call on two occasions August 14\textsuperscript{th} and August 28\textsuperscript{th} 2020 to discuss the findings from
the technical review and formulated the guideline recommendations using the GRADE evidence-to-decision framework. Although the quality of evidence (Table 1) was a key factor in determining the strength of the recommendations (Table 2), the panel also considered the balance between benefit and harm of interventions, patients' values and preferences, and overall resource utilization. The recommendations, quality of evidence, and strength of recommendations are summarized in Table 3.
PHARMACOLOGIC MANAGEMENT OF ADULT PATIENTS WITH MODERATE TO SEVERE LUMINAL CROHN’S DISEASE

1A. In adult outpatients with moderate to severe CD, the AGA recommends the use of anti-TNFα over no treatment for induction and maintenance of remission. (Strong recommendation, moderate quality evidence)

Comment: Though the evidence supporting infliximab and adalimumab was moderate quality, the evidence for certolizumab pegol was low quality.

1B. In adult outpatients with moderate to severe CD, the AGA suggests the use of vedolizumab over no treatment for the induction and maintenance of remission. (Conditional recommendation, low quality evidence for induction, moderate quality evidence for maintenance)

1C. In adult outpatients with moderate to severe CD, the AGA recommends the use of ustekinumab over no treatment for the induction and maintenance of remission. (Strong recommendation, moderate quality evidence)

1D. In adult outpatients with moderate to severe CD, the AGA suggests against the use of natalizumab over no treatment for the induction and maintenance of remission. (Conditional recommendation, moderate quality evidence)

Comment: Given evidence of harm in post marketing data from progressive multifocal leukoencephalopathy (PML) and the availability of other drugs, the AGA suggests against the use of natalizumab. Patients who are JC virus antibody negative who put a high value on the potential benefits and lower value on PML risk and who will adhere to ongoing monitoring for JC virus positivity, may consider using natalizumab.
The panel recommends treating adult outpatients with moderate to severe luminal CD with infliximab, adalimumab, certolizumab pegol, vedolizumab or ustekinumab over no treatment for the induction and maintenance of remission. In contrast, the panel recommended against the use of natalizumab for induction or maintenance of remission due to the potential harms associated with this medication. There were 13 randomized controlled trials (RCTs) comparing the TNFα antagonists, vedolizumab and ustekinumab to placebo for induction of remission and 9 RCTs informing on maintenance of remission. Induction of remission was assessed at 4-12 weeks and maintenance of remission was evaluated at 22-54 weeks. All active interventions were superior to placebo for induction of remission (infliximab: RR, 0.54; 95% CI, 0.39-0.75; adalimumab: RR, 0.82; 95% CI, 0.75-0.89; certolizumab pegol RR, 0.92 95% CI, 0.86-0.98; vedolizumab RR, 0.92; 95% CI, 0.87-0.97; ustekinumab RR, 0.90; 95% CI, 0.85-0.94). Likewise, all active interventions were superior to placebo for maintenance of remission (infliximab: RR, 0.77; 95% CI, 0.65-0.92; adalimumab: RR, 0.70; 95% CI, 0.62-0.79; certolizumab pegol RR, 0.88; 95% CI, 0.83-0.93; vedolizumab RR, 0.78; 95% CI, 0.67-0.91; ustekinumab RR, 0.75; 95% CI, 0.64-0.89). Though natalizumab did show benefit for induction (RR, 0.88; 95% CI, 0.82-0.96) and maintenance of remission (RR, 0.58; 95% CI, 0.48-0.70) compared to placebo, given the risk of progressive multifocal leukoencephalopathy (PML) and the availability of other drugs not associated with this devastating side effect, lead the guideline panel to recommend against its routine use in treating patients with moderate to severe luminal CD.

The overall quality of evidence for this recommendation was moderate for infliximab, adalimumab and ustekinumab rating down for imprecision secondary to the low number of events < 200 (low optimal information size, OIS). For certolizumab pegol and vedolizumab the quality of evidence was rated down to low quality for very serious imprecision since the summary risk estimates did not meet the MCID threshold of 10% over placebo. For maintenance of remission, the evidence was moderate quality, rated down for imprecision secondary to low OIS.
2A. In adult outpatients with moderate to severe CD who are naïve to biologic drugs, the AGA recommends the use of infliximab, adalimumab, or ustekinumab, over certolizumab pegol for the induction of remission (Strong recommendation, moderate quality evidence) and suggests the use of vedolizumab over certolizumab pegol for the induction of remission (Conditional recommendation, low quality evidence).

2B. In adult outpatients with moderate to severe CD who never responded to anti-TNFα (primary nonresponse), the AGA recommends the use of ustekinumab (Strong recommendation, moderate quality evidence) and suggests the use of vedolizumab over no treatment for the induction of remission. (Conditional recommendation, low quality evidence).

2C. In adult outpatients with moderate to severe CD who previously responded to infliximab (secondary nonresponse), the AGA recommends the use of adalimumab or ustekinumab (Strong recommendation, moderate quality evidence) and suggests the use of vedolizumab over no treatment for the induction of remission. (Conditional recommendation, low quality evidence).

Comment: if adalimumab was the first line drug utilized there is indirect evidence to suggest the option of using infliximab as a second line agent.

There were no head-to-head trials comparing the efficacy of different agents for induction and maintenance of remission. Therefore, indirect evidence was derived using network meta-analysis from drug trials with similar study designs and outcomes. Network meta-analysis can help assess comparative efficacy of several interventions and synthesize evidence across a network of RCTs, especially if there is weak (or absent) direct evidence. The analysis included 8 RCTs with a total of 1458 biologic-naïve patients with moderate-severe luminal CD. On network meta-analysis, infliximab was more effective than certolizumab pegol (OR, 4.33; 95% CI, 1.83-10.27) with moderate confidence in estimates (rated down for imprecision), and low confidence in estimates supporting its use over vedolizumab (OR, 2.20; 95% CI, 0.79-6.07) or ustekinumab (OR, 2.14; 95% CI, 0.89-5.15) rated down for imprecision. There was moderate confidence in estimates for the use of ustekinumab (OR, 2.02; 95% CI, 1.09-3.75) or adalimumab (OR, 2.97; 95% CI, 1.16-6.70) over certolizumab pegol with low confidence in estimates (rated down for very serious imprecision). There was low confidence in the estimates for the use of vedolizumab over...
certolizumab pegol (OR 1.97; 95% CI, 0.88-4.41). There was no significant difference in the efficacy of adalimumab, ustekinumab, or vedolizumab as a first-line agent (very low quality evidence).

The second part of the network meta-analysis compared drug efficacy after a prior failure of a TNFα antagonist. The failure of a TNFα antagonist can be categorized as primary or secondary non-response as defined in the prior AGA guideline and technical review on Therapeutic Drug Monitoring.¹⁰

In patients with prior TNFα antagonist exposure, 6 RCTs with 1606 patients were included in this part of the network meta-analysis. Three studies were performed exclusively in those with prior TNFα antagonist exposure (1 trial adalimumab and 2 trials of ustekinumab), two subgroup analyses of phase II trials (1 for adalimumab and 1 for vedolizumab), one trial of vedolizumab (GEMINI-II) in which 75% of patients had prior TNFα antagonist exposure, and one trial of adalimumab (GAIN) that only included patients with prior response or intolerance to infliximab. On network meta-analysis, ustekinumab was superior to placebo (OR, 2.58; 95% CI, 1.50-4.44) with moderate quality evidence rating down for imprecision. Using adalimumab in patients with prior intolerance or secondary non-response to infliximab (OR, 3.57; 95% CI, 1.66-7.65) was moderate quality evidence rating down for imprecision. Vedolizumab (OR, 1.53; 95% CI, 0.77-3.06) was supported by low quality evidence rating drown for very serious imprecision related to the very wide confidence intervals and crossing unity). Further indirect comparisons between the drugs were performed in the technical review but were not of high enough quality to formulate a recommendation. Of note, the studies included in the network meta-analysis did not consistently report what proportion of patients had exposure to more than one TNFα antagonist, exposure to multiple different classes of biologics, and reasons for failure of prior biologics (primary non-response vs. secondary loss of response vs. intolerance). In clinical practice, this information along with information from the results of therapeutic drug monitoring (See prior AGA guideline
on Therapeutic Drug Monitoring)\textsuperscript{10} may affect one's decision to select one biologic over another biologic.
3A. In adult outpatients with moderate to severe CD, the AGA suggests against the use of thiopurines monotherapy over no treatment for achieving remission. (Conditional recommendation, very low quality evidence)

3B. In adult outpatients with quiescent moderate to severe CD (or patients in corticosteroid-induced remission), the AGA suggests the use of thiopurines monotherapy over no treatment for the maintenance of remission. (Conditional recommendation, moderate quality evidence)

3C. In adult outpatients with moderate to severe CD, the AGA suggests the use of subcutaneous or intramuscular methotrexate monotherapy over no treatment for the induction and maintenance of remission. (Conditional recommendation, moderate quality evidence)

3D. In adult outpatients with moderate to severe CD, the AGA suggests against the use of oral methotrexate monotherapy over no treatment for the induction and maintenance of remission. (Conditional recommendation, low quality evidence)

In adult outpatients with moderate to severe luminal CD guideline panel suggests against using thiopurines over no treatment for achieving remission because 5 trials including 380 patients treated with thiopurines did not show increased efficacy compared to placebo in achieving corticosteroid-free remission in patients who were corticosteroid dependent. The quality of the evidence was very low quality due to serious bias, indirectness, and serious imprecision. However, 5 RCTs, did demonstrate that thiopurines were significantly more effective than placebo or no treatment (RR, 0.62; 95% CI, 0.47-0.81) for maintaining corticosteroid-free clinical
remission. The evidence was rated down for bias due to inadequate blinding and imprecision because of low OIS.

In evaluating methotrexate, the technical review panel and guideline panel opted to evaluate oral vs intramuscular/subcutaneous methotrexate separately due to underlying differences in efficacy related to route of administration and total dose. Subcutaneous methotrexate dosed at 25mg/week was evaluated in 1 trial of 141 patients and was effective for induction of remission (RR, 0.75; 95% CI, 0.61-0.93). For maintenance of remission, subcutaneous methotrexate dosed at 15mg/week was evaluated in one trial of 76 patients after they had achieved remission with 16-25 weeks of 25mg/week subcutaneous methotrexate. Subcutaneous methotrexate was more effective than placebo for maintaining corticosteroid-free remission (RR, 0.57; 95% CI, 0.34-0.94). The quality of evidence was moderate for induction and maintenance of remission, rating down for imprecision due to the small sample size.

In contrast to subcutaneous methotrexate, oral methotrexate was evaluated in a single RCT dosed at 12.5mg every week and was not effective for inducing remission (RR, 1.14; 95% CI, 0.72-1.82). In the maintenance arm of the study, 12.5mg/week was not more effective than placebo for maintaining remission (RR, 0.30; 95% CI, 0.04-2.27). The quality of evidence was very low due to indirectness from the lower dose of methotrexate and very serious imprecision due to the very wide 95% CI. The guideline panel noted that the single RCT evaluating oral methotrexate may have used a dose that is suboptimal. It is not clear if a higher dose of oral methotrexate would be more effective.
4. In adult outpatients with moderate to severe CD, the AGA recommends the use of biologic drug monotherapy over thiopurine monotherapy for the induction of remission. (Strong recommendation moderate quality of evidence)

The panel recommends the use of biologic drug monotherapy over thiopurine monotherapy for induction of remission. A separate recommendation for maintenance of remission was not provided since corticosteroid-sparing drugs that are started for induction of remission are typically continued for maintenance of remission. The SONIC study design was a three arm RCT including biologic and immunomodulator naïve patients comparing infliximab vs azathioprine vs infliximab + azathioprine. Infliximab was more effective than azathioprine for induction of clinical remission (RR, 0.79; 95% CI, 0.67-0.94) and endoscopic remission (65/93 vs. 91/109, p<0.01). The quality of evidence was moderate rating down for imprecision due to low OIS. Data on other biologics compared to thiopurines for induction of remission was lacking. However, given the overall efficacy of other biologics compared to placebo, and thiopurines failing to show efficacy compared to placebo for induction of remission, indirect evidence suggests that other biologics would also be more effective than thiopurines for induction of remission. Similarly, no RCTs compared biologic monotherapy to methotrexate monotherapy and data is therefore lacking.
5A. In adult outpatients with moderate to severe CD who are naïve to biologics and immunomodulators, the AGA suggests the use of infliximab in combination with thiopurines for the induction and maintenance of remission over infliximab monotherapy. (Conditional recommendation, moderate quality evidence)

Comment: Based on indirect evidence combination infliximab with methotrexate may be more effective over infliximab monotherapy.

5B. In adult outpatients with moderate to severe CD who are naïve to biologics and immunomodulators, the AGA suggests the use of adalimumab in combination with thiopurines for the induction and maintenance of remission over adalimumab monotherapy. (Conditional recommendation, very low quality evidence)

Comment: Based on indirect evidence combination adalimumab with methotrexate may be more effective over adalimumab monotherapy.

5C. In adult outpatients with moderate to severe CD, the AGA makes no recommendation regarding the use of ustekinumab or vedolizumab in combination with thiopurines or methotrexate over biologic drug monotherapy for the induction and maintenance of remission. (No recommendation, knowledge gap)

Two trials compared infliximab with a thiopurine to infliximab monotherapy. Combination therapy was more effective for induction of remission (RR, 0.77; 95% CI, 0.64-0.92). While there were no direct maintenance trials, both these studies included follow up of patients with active disease up to 50/52 weeks with combination therapy showing greater efficacy than infliximab monotherapy for maintenance of remission (RR, 0.74; 95% CI, 0.60-0.90). The quality of evidence for induction of remission was moderate, rating down for imprecision given the low OIS. Maintenance of remission evidence quality was low. This was rated down for indirectness.
Combination therapy using infliximab and methotrexate vs infliximab monotherapy was compared in one RCT with 126 patients. There was no difference in achieving corticosteroid-free remission at week 14 RR, 1.07; 95% CI, 0.57-2.03) and at week 50 there was no difference in failure to maintain corticosteroid-free clinical remission (RR, 1.18; 95% CI, 0.68-2.03). The quality of evidence for induction and maintenance of remission using infliximab with methotrexate was rated low due to very serious imprecision.

A single open-label RCT (DIAMOND study group) compared adalimumab and azathioprine to adalimumab monotherapy for 52 weeks. There was no difference between the two groups for induction of remission (RR, 1.31; 95% CI, 0.80-2.14) or maintenance of remission (RR, 1.13; 95% CI, 0.72-1.78). However, combination therapy was associated with higher rates of endoscopic remission at week 26 compared to adalimumab monotherapy (48/57 [84.2%] vs. 37/58 [63.2%], p=0.02). The quality of evidence was very low rating down for risk of bias (unblinded study with high rates of drug discontinuations due to treatment intolerance) indirectness of outcomes, and imprecision from the low OIS.

Importantly, use of combination therapy may be even more important in the subset of patients who have developed secondary non-response to TNFα antagonists. Roblin et al noted that combination therapy resulted in improved outcomes without clinical failure or unfavorable pharmacokinetics at 24 months with improvements of 77-78% for TNFα antagonists with a thiopurine compared to 22% with TNFα antagonists monotherapy (p<0.001). There were no RCTs to provide data on combination therapy using vedolizumab or ustekinumab with a thiopurine or methotrexate.
The mechanism by which combination therapy provides improved induction and maintenance of remission is unclear. Adding the thiopurine or methotrexate to infliximab may result in improved drug levels and lower risk of immunogenicity by preventing anti-drug antibody formation. It is possible that the benefits of combination therapy might be achieved by therapeutic drug monitoring, using the information obtained to adjust drug dose or dosing interval. This option may provide the same benefits of combination therapy without the risk and inconvenience of adding the thiopurine or methotrexate. Importantly, if the focus is on reduction of immunogenicity, the potential benefits of combination therapy with newer biologics like vedolizumab and ustekinumab may not be beneficial since these drugs are less immunogenic compared to infliximab.

Harms that must be considered when selecting combination therapy include the increased risk of infections and 2-3 fold higher risk of lymphoma compared to TNF-α antagonist monotherapy when adding a thiopurine.18

6. In adult outpatients with quiescent CD on combination therapy, the AGA makes no recommendation for withdrawal of either the immunomodulator or the biologic over ongoing combination therapy of a biologic and an immunomodulator. (No recommendation, knowledge gap)

There were 3 RCT that included 161 patients who were in maintenance of remission on combination therapy with TNFα antagonists and immunomodulators for at least 6 months (2 trials of infliximab-, 1 trial of adalimumab-based combination therapy). Overall, there were no significant differences in the risk of relapse over 12-24 months in patients who continued combination therapy vs. withdrew immunomodulators (RR, 1.02; 95% CI, 0.71-1.46). The quality of evidence was rated as very low due to risk of bias (unblinded trials) and very serious imprecision (wide 95%
CI and the inability to exclude significant benefit or harm with continuing or combination therapy). There were no RCTs comparing continued combination therapy to withdrawal of the biologic. There was a single prospective cohort study of 115 patients with CD who were on combination therapy and discontinued infliximab. The risks of relapse though was 44% at one year and 52% at 2 years.

While combination therapy is associated with a higher risk of complications compared to use of a single agent, it is possible that cessation of the immunomodulator may result in some patients losing response to the biologic. This risk, however, may be mitigated with use of therapeutic drug monitoring. Based on limited observational data, treatment strategies where the biologic drug is discontinued and the immune modulator is continued may lead to a high risk of relapse. Given the limited data to support a recommendation for or against this cessation of drug when used in combination, the panel opted to make no recommendation.

7. In adult outpatients with moderate to severe CD, the AGA suggests early introduction with a biologic with or without an immunomodulator rather than delaying their use until after failure of mesalamine and/or corticosteroids. (Conditional recommendation, low quality evidence)

The evidence informing this recommendation was based on several RCTs. D'haens et al randomized patients to early combination therapy with an immunosuppressant and infliximab compared to conventional step therapy in which patients were first given corticosteroids followed by azathioprine and infliximab. At 52 weeks 61.5% of patients in early combined immunosuppression group were in corticosteroid and surgery-free remission compared to 42.2% in the step-up therapy arm (RR for failure to achieve remission, 0.67; 95% CI, 0.46-0.97). A long-term extension arm of this trial to 8 years suggested lower rates of clinical relapse, and
corticosteroid use in the patients randomized to early combination therapy. The quality of the evidence was low due to risk of bias (open label trial) and imprecision (low OIS).

The REACT study was an open-label cluster randomized trial that compared an algorithmic approach of early combination therapy with an immunomodulator and biologic drug or conventional management of CD in 1982 patients.\textsuperscript{22} At 12 months, there was no significant difference in rates of corticosteroid-free remission (66\% early combination therapy vs 62\% in usual care). However, at 24-months, patients in the early combination therapy arm had lower rates of major adverse disease-related complications as compared to conventional management (hazard ratio, 0.73; 95\% CI, 0.62-0.86).

Data for early use of thiopurines alone was evaluated by Cosnes et al in an RCT of 122 patients in which patients were randomized to early azathioprine (within 6 months of CD diagnosis) vs conventional management in which azathioprine was only utilized in cases of corticosteroid dependency, in those not responding to corticosteroids, or those with perianal disease.\textsuperscript{23} Over a 3 year follow up, no significant differences were observed in the risk of corticosteroid-requiring flare (58/65 [89\%] vs. 61/67 [91\%], p=0.73), hospitalization (22/65 [34\%] vs. 26/67 [39\%], p=0.74) or CD-related surgery (5/65 [8\%] vs. 4/67 [6\%], p=0.68). Evidence was rated low due to risk of bias (open-label trial) and imprecision (very wide CI).

Data for 5-aminosalicylates indicate that these drugs are not effective for the management of moderate to severe CD (see question 9 below).

The guideline panel used these data to determine that delaying appropriate therapy by using a step-up policy may result in clinical harm from delaying appropriate disease treatment. The panel acknowledged that the treatment paradigm of earlier therapy with a combination of an immunomodulator and a biologic drug or biologic monotherapy may result in overtreating some patients and potentially exposing them to treatment related risks and costs with limited benefit. However, the step-up paradigm is associated with a potential risk of harm from disease progression related to inadequate disease therapy.
8A. In adult outpatients with moderate to severe CD, the AGA suggests the use of corticosteroids over no treatment for induction of remission. (Conditional recommendation, moderate quality of evidence)

8B. In adult outpatients with moderate to severe CD, the AGA recommends against the use of corticosteroids over no treatment for maintenance of remission. (Strong recommendation, moderate quality of evidence)

Systemic corticosteroids were evaluated in 2 RCTs with 267 patients. Corticosteroids at a prednisone dose equivalent up to 60mg/day was more effective than placebo for induction of remission (RR, 0.57; 95% CI, 0.45-0.73). Quality of evidence was low, rating down for bias (sequence generation and allocation concealment not reported) and imprecision given the low OIS. 3 RCTs with 367 patients compared controlled release budesonide vs placebo. Budesonide was more effective than placebo for induction of remission (RR, 0.74; 95% CI, 0.60-0.91) albeit two of the studies were in patients with mild to moderate CD. The quality of evidence was rated low due to indirectness (non-moderate to severe CD) and imprecision (low OIS).
Systemic corticosteroids as a maintenance drug were evaluated in 3 studies with 269 patients and were not more effective than placebo for maintenance of remission (RR, 1.02; 95% CI, 0.81-1.29). The quality of evidence was low due to risk of bias (unclear randomization) and imprecision (wide 95% CI that could not exclude significant benefit or harm).

The technical review performed an additional comparison between budesonide and systematic corticosteroids. 5 RCTs compared CIR budesonide to corticosteroids with budesonide being inferior to systematic corticosteroids for inducing remission (RR for failure to induce 1.20; 95% CI, 1.01-1.44). Nevertheless, in patients with CD involving the distal ileum and/or ascending colon who are more concerned about systemic corticosteroids and less concerning about the lower efficacy, they may reasonably chose budesonide over systematic corticosteroids.

The panel noted that while systemic corticosteroids play an integral role in the induction of remission in patients with moderate to severe luminal CD, the side effects in both the short and long-term with systematic corticosteroids are substantial (see technical review). Budesonide, however, due to a first pass metabolism in the liver is better tolerated with fewer side effects and no significant alterations on serum cortisol levels. Nevertheless, neither systemic corticosteroids nor budesonide have a role in long-term maintenance of remission in patients with moderate to severe luminal CD.

9. In adult outpatients with moderate to severe CD, the AGA recommends against the use of 5-ASA or sulfasalazine over no treatment for the induction or maintenance of remission. (Strong recommendation, moderate quality evidence)

Two RCTs compared mesalazine to placebo for induction of remission but the underlying severity of CD was not clear. There was no specific subgroup with moderate to
severe CD that could be extracted for our analysis. In these two studies, mesalamine did not reach the MCID of 10% over placebo (RR, 0.90; 95% CI, 0.81-1.00). Sulfasalazine was evaluated in 3 RCTs but the again the overall severity of CD was not clear. In these studies, sulfasalazine was more effective than placebo for induction of remission over 6-17 weeks (RR, 0.78; 95% CI, 0.65-0.93). However, it was unclear if these patients had moderate to severe luminal CD.

For maintenance of remission, 4 studies (415 patients) treated with sulfasalazine and 11 RCTs with 2014 patients treated with mesalamine did not find either drug to be more effective than placebo for maintenance of remission (sulfasalazine: RR, 0.98; 95% CI, 0.82-1.17, mesalamine: RR, 1.02; 95% CI, 0.92-1.16). The quality of evidence was very low for sulfasalazine. This was rated down for bias (sequence generation and allocation concealment), indirectness (wide variability in characteristics and outcome measures, and imprecision (very wide 95% CI). The quality of evidence for mesalamine was moderate, rating down for imprecision (modest benefit and harm could not be excluded).

The panel noted the robust safety profile of mesalamine but also noted that sulfasalazine is associated with many adverse events (see technical review). The main concern regarding the use of 5-ASAs was the lack of data on their use for induction of remission in moderate to severe luminal CD and the data showing their lack of efficacy for maintenance of remission. In general, the panel noted that most drugs started for induction of remission should be continued for maintenance of remission and that starting a drug that is ineffective can lead to delays in appropriate therapy and worsening disease. Given the lack of induction data in moderate to severe CD patients, and given the clear failure of 5-ASAs to maintain remission, the panel recommended against the use of mesalamine or sulfasalazine for induction or maintenance of remission for moderate to severe luminal CD.
PHARMACOLOGIC MANAGEMENT OF ADULT PATIENTS WITH FISTULIZING CROHN’S DISEASE

In Crohn’s disease fistula formation may occur from one loop of bowel to another or from bowel to other structures such as the bladder or vagina or from bowel to the skin. By far the most common form of fistula are perianal fistula. Data on drug therapy for types if fistula other than perianal fistula are almost totally lacking, so the technical review team and guideline panel limited their focus to the medical management of perianal fistula. Surgical management of fistulizing CD also was outside the scope of the technical review and guideline.

10A. In adult outpatients with CD and active perianal fistula, the AGA recommends the use of infliximab over no treatment for the induction and maintenance of fistula remission. (Strong recommendation, moderate quality evidence)

10B. In adult outpatients with CD and active perianal fistula, AGA suggests the use of adalimumab, ustekinumab, or vedolizumab over no treatment for the induction or maintenance of fistula remission. (Conditional recommendation, low quality evidence)

Comment: evidence suggests certolizumab pegol may not be effective for induction of fistula remission

10C. In adult outpatients with CD and active perianal fistula without perianal abscess, the AGA suggests against the use of antibiotics alone over no treatment for the induction of fistula remission. (Conditional recommendation, low quality evidence)

Infliximab was the only medication that had a dedicated RCT to assess the efficacy of the drug to induce fistula remission. Ninety four patients with symptomatic draining fistula were randomized to infliximab or placebo. Infliximab achieved a greater rate of induction of remission of fistula closure within 18 weeks (RR, 0.52; 95% CI, 0.34-0.78). The quality of evidence was moderate rating down only for imprecision due to the low OIS.
Adalimumab was evaluated in a subgroup analysis of 2 RCTs of 77 patients with symptomatic raining fistula. Adalimumab was not effective in complete fistula closure within 4 weeks compared to placebo (RR, 1.08; 95% CI, 0.93-1.27). However, indirect data indicates that adalimumab may be effective for induction of luminal CD and in the network meta-analysis adalimumab does appear effective for induction and maintenance of remission. Unfortunately, there are no dedicated randomized control trials using adalimumab for induction of remission or maintenance of remission for the primary outcome of fistula remission. Similarly, certolizumab pegol was also evaluated in a subgroup analysis of 2 RCTs including 165 patients and did not show a benefit compared to placebo for inducting fistula remission (RR, 1.01; 95% CI, 0.80-1.27). The ineffectiveness of certolizumab pegol was further supported by the indirect evidence of the failure of certozliumab pegol to induce remission in moderate to severe luminal CD. The evidence was very low quality for both drugs rating down for very serious imprecision (wide 95% CI which could not rule out significant risk of benefit or harm) and risk of bias (randomization was not stratified based on presence/abscess of fistula).

Vedolizumab was evaluated in a subgroup analysis of a single RCT with 165 patients who had a clinical response to luminal disease but had symptomatic draining fistula at baseline. Vedolizumab may be more effective than placebo for achieving complete fistula closure (RR, 0.81; 95% CI, 0.63-1.04) within 14 weeks. The quality of the evidence was very low rating down for risk of bias (randomization not stratified by presence/absence of fistula), indirectness (all patients received induction therapy with vedolizumab), and imprecision (95% CI crossing unity).

Ustekinumab was evaluated in a pooled analysis of 4 trials of induction therapy (238 patients) with active draining fistula. Ustekinumab was more effective than placebo in achieving fistula remission (RR, 0.85; 95% CI, 0.73-1.99). Quality of evidence was rated as low quality due to risk of bias (since randomization was not stratified by presence/absence of fistula), and imprecision (OIS not met).
Antibiotics were compared to placebo in a single 3 arm RCT of 25 patients with active draining perianal fistula. The 3 arms included: ciprofloxacin, metronidazole, and placebo. Antibiotics did not show more efficacy compared to placebo for induction of fistula remission (RR, 0.94; 95% CI, 0.67-1.33). Quality of evidence was low due to very serious imprecision (very wide 95% CI where significant benefit or harm with antibiotic monotherapy could not be excluded).

Data on maintenance of remission for the biologics was present for some but overall quite limited. In general, a drug that is started for induction of remission is typically continued for maintenance of remission. Similarly, data on thiopurines were also quite limited and the guideline panel did not find sufficient evidence to formulate a recommendation.

11. In adult outpatients with CD and active perianal fistula without perianal abscess, the AGA recommends the use of biologic agents in combination with an antibiotic over a biologic drug alone for the induction of fistula remission. (Strong recommendation, moderate quality evidence)

Two RCTs involving use of TNF-α antagonists (infliximab or adalimumab) in combination with ciprofloxacin for 12 weeks was significantly more effective than using the corresponding TNF-α antagonist alone in achieving fistula closure over 12-18 (RR, 0.42; 95% CI, 0.26-0.68). The quality of evidence was moderate, rating down for imprecision due to the low OIS.

SUMMARY

These practice recommendations for the medical management of moderate to severe luminal and fistulizing Crohn’s disease were developed using the GRADE framework and in adherence to the standards established by the Institute of Medicine for the development of trustworthy guidelines\textsuperscript{11,12}. The guideline recommendations incorporated data on the benefits and risks of treatment and non-treatment, along with patient values and preferences. The goal of this
guideline is to promote high quality and high value evidence-based care and to facilitate shared decision making with patients in the management of moderate to severe luminal and fistulizing CD.

Current evidence supports use of multiple drug classes, including: TNF-α antagonists, anti—integrins, anti-II12/23 inhibitors, methotrexate (subcutaneous/intramuscular) and corticosteroid for induction of remission and the use TNF-α antagonist, anti—integrins, anti-II12/23 inhibitors, thiopurines and methotrexate (subcutaneous/intramuscular) for the maintenance of remission. Thiopurines and methotrexate were also suggested for use as combination therapies with TNF-α antagonists for induction and maintenance of remission compared to TNF-α antagonist monotherapy. The panel made no recommendation for combination therapy with other biologics given a lack of data. Similarly, no recommendation could be made regarding withdrawal or either immunomodulators or a biologic agent over ongoing combination therapy in quiescent CD. The panel recommended against the use of natalizumab given the side effect profile and availability of other medications to manage moderate to severe CD. The panel also recommended against the use of thiopurines for induction of remission, corticosteroids for maintenance of remission and the use of mesalamine for induction or maintenance of remission due to overall lack of efficacy. Finally, the panel suggests the early introduction of a biologic with or without an immunomodulator rather than delaying their use until after failing mesalamine and/or corticosteroids. In patients who initially were treated with an TNFα antagonist with a primary nonresponse, the AGA recommends the use of ustekinumab and suggests the use of vedolizumab. However, in cases of those who previously responded to infliximab (secondary nonresponse), the AGA recommends the use of adalimumab or ustekinumab and suggests the use of vedolizumab. Of note, if adalimumab was the first drug failure with subsequent secondary nonresponse, indirect evidence suggests the consideration of infliximab as a second line agent.
In fistulizing disease, infliximab was noted to have the most robust evidence supporting its use than adalimumab or certolizumab pegol. Other effective agents for induction of fistula remission were vedolizumab and ustekinumab. In cases of perianal disease with an active fistula but no abscess, combining biologics with antibiotics were most effective in inducing fistula remission.

AREAS FOR FUTURE RESEARCH

The guideline panel identified multiple knowledge gaps and areas for future research in patients with moderate to severe luminal and fistulizing CD. The last two decades have witnessed many important advances in CD treatment with associated improved outcomes, but there continues to be a significant fraction of patients who fail to respond sufficiently to the available treatments. In addition to the ongoing development of new drugs and drug classes, there remain unanswered questions about the optimal application of the current therapies. Importantly, direct comparisons of the benefits and harms, especially over the long-term, of the available drugs and treatment strategies are mostly lacking. There remains an urgent need for improved patient specific predictors, clinical and biological, of response and harm to a particular drug or drug class to improve the rational choice of initial and second line therapeutic agents in a given patient. The need is especially great in special populations such as those with fistulizing disease or aggressive and recurrent fibrostenosing disease. Overall, the data on risk stratifying individual patients into low and high risk of disease complications and disability remains poor. These data would allow clinicians to better understand the optimal timing of initial therapies and the optimal duration of therapies, facilitating better-shared decision making with patients based on their values and preferences. Most all of our data on drug efficacy and safety is based on White patients from a narrow age range. We urgently need data on treatment outcomes in diverse populations including African Americans, Latinx and the elderly to name just the most glaring deficiencies. We urgently need better data on benefits and risks of combining drugs, not just biological drugs with immune
modulators, but also the combination of biologic drugs with one another, a strategy that might leverage the different mechanisms of actions of different drug classes to good effect. Fundamental questions, such as ideal target of therapy in CD also remain unanswered. Many of the studies referenced in this guideline regarding drug efficacy focused on clinical response and remission as defined by the CDAI and other mostly symptom based indices, but newer studies now include rates of endoscopic remission and in some cases histologic remission. Long-term patient outcomes appear to be better when we achieve these more objective and robust targets of response and remission, but there remains uncertainty in clinical practice about when to declare a drug successful or when to change treatment strategies looking for a better outcome. For patients that do respond well, like among those who achieve endoscopic or histologic remission, we need data to guide us in when or how to deescalate or discontinue therapy. In summary, though our ability to treat patients with moderate to severe Crohn’s has improved markedly over the past two decades, there remains much left to do to ensure that every patient has the best possible outcome.
Table 1. GRADE definitions of quality and certainty of the evidence

<table>
<thead>
<tr>
<th>Quality Grade</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>We are very confident that the true effect lies close to the estimate of the effect</td>
</tr>
<tr>
<td>Moderate</td>
<td>We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different.</td>
</tr>
<tr>
<td>Low</td>
<td>Our confidence in the estimate is limited. The true effect may be substantially different from the estimate of effect.</td>
</tr>
<tr>
<td>Very low</td>
<td>We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect</td>
</tr>
<tr>
<td>Evidence gap</td>
<td>Available evidence is insufficient to determine true effect</td>
</tr>
</tbody>
</table>
Table 2. GRADE definitions on strength of recommendation and guide to interpretation

<table>
<thead>
<tr>
<th>Strength of recommendation</th>
<th>Wording in the guideline</th>
<th>For the patient</th>
<th>For the clinician</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong</td>
<td>“The AGA recommends…”</td>
<td>Most individuals in this situation would want the recommended course and only a small proportion would not.</td>
<td>Most individuals should receive the recommended course of action. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.</td>
</tr>
<tr>
<td>Conditional</td>
<td>“The AGA suggests…”</td>
<td>The majority of individuals in this situation would want the suggested course, but many would not.</td>
<td>Different choices would be appropriate for different patients. Decision aids may be useful in helping individuals in making decisions consistent with their values and preferences. Clinicians should expect to spend more</td>
</tr>
<tr>
<td>No recommendation</td>
<td>“The AGA makes no recommendation…”</td>
<td>The confidence in the effect estimate is so low that any effect estimate is speculative at this time.</td>
<td>time with patients when working towards a decision.</td>
</tr>
</tbody>
</table>
Table 3. Summary of recommendations of the AGA Clinical Guidelines Committee for medical management of moderate to severe luminal and fistulizing Crohn’s disease

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Strength of recommendation</th>
<th>Quality of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1A. In adult outpatients with moderate to severe CD, the AGA recommends the use of anti-TNFα over no treatment for induction and maintenance of remission</strong></td>
<td>Strong</td>
<td>Moderate</td>
</tr>
<tr>
<td>Comment: Though the evidence supporting infliximab and adalimumab was moderate quality, the evidence for certolizumab pegol was low quality</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>1B. In adult outpatients with moderate to severe CD, the AGA suggests the use of vedolizumab over no treatment for the induction and maintenance of remission.</strong></td>
<td>Conditional</td>
<td>Low for induction</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Moderate for maintenance</td>
</tr>
<tr>
<td><strong>1C. In adult outpatients with moderate to severe CD, the AGA recommends the use of ustekinumab over no treatment for the induction and maintenance of remission</strong></td>
<td>Strong</td>
<td>Moderate</td>
</tr>
<tr>
<td><strong>1D. In adult outpatients with moderate to severe CD, the AGA suggests against the use of natalizumab over no treatment for the induction and maintenance of remission</strong></td>
<td>Conditional</td>
<td>Moderate</td>
</tr>
<tr>
<td>Comment: Given evidence of harm in post marketing data from progressive multifocal leucoencephalopathy (PML) and the availability of other drugs, the AGA suggests against the use of natalizumab. Patients who are JC virus antibody negative who put a high value on the potential benefits and lower value on PML risk and who will adhere to ongoing monitoring for JC virus positivity, may consider using natalizumab</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>2A. In adult outpatients with moderate to severe CD who are naïve to biologic drugs, the AGA recommends the use of infliximab, adalimumab, or ustekinumab, over certolizumab pegol for the induction of remission and suggests the use of vedolizumab over certolizumab pegol for the induction of remission</strong></td>
<td>Strong</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>Conditional</td>
<td>Low</td>
</tr>
<tr>
<td>2B. In adult outpatients with moderate to severe CD who never responded to anti-TNFα (primary nonresponse), the AGA recommends the use of ustekinumab and suggests the use of vedolizumab over no treatment for the induction of remission</td>
<td>Strong</td>
<td>Moderate</td>
</tr>
<tr>
<td>2C. In adult outpatients with moderate to severe CD who previously responded to infliximab (secondary nonresponse), the AGA recommends the use of adalimumab or ustekinumab and suggests the use of vedolizumab over no treatment for the induction of remission</td>
<td>Strong</td>
<td>Moderate</td>
</tr>
<tr>
<td>Comment: if adalimumab was the first line drug utilized there is indirect evidence to suggest the option of using infliximab as a second line agent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3A. In adult outpatients with moderate to severe CD, the AGA suggests against the use of thiopurines over no treatment for achieving remission</td>
<td>Conditional</td>
<td>Very low</td>
</tr>
<tr>
<td>3B. In adult outpatients with quiescent moderate to severe CD (or patients in corticosteroid-induced remission), the AGA suggests the use of thiopurines over no treatment for the maintenance of remission</td>
<td>Conditional</td>
<td>Moderate</td>
</tr>
<tr>
<td>3C. In adult outpatients with moderate to severe CD, the AGA suggests the use of subcutaneous or intramuscular methotrexate over no treatment for the induction and maintenance of remission</td>
<td>Conditional</td>
<td>Moderate</td>
</tr>
<tr>
<td>3D. In adult outpatients with moderate to severe CD, the AGA suggests against the use of oral methotrexate over no treatment for the induction and maintenance of remission</td>
<td>Conditional</td>
<td>Low</td>
</tr>
<tr>
<td>4. In adult outpatients with moderate to severe CD, the AGA recommends the use of biologic drug monotherapy over thiopurine monotherapy for the induction of remission</td>
<td>Strong</td>
<td>Moderate</td>
</tr>
<tr>
<td>5A. In adult outpatients with moderate to severe CD who are naïve to biologics and immunomodulators, the AGA suggests the use of infliximab in combination with thiopurines for the induction and maintenance of remission over infliximab monotherapy</td>
<td>Conditional</td>
<td>Moderate</td>
</tr>
<tr>
<td>Comment: Based on indirect evidence combination infliximab with methotrexate may be more effective over infliximab monotherapy</td>
<td></td>
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<tr>
<td>5B. In adult outpatients with moderate to severe CD who are naïve to biologics and immunomodulators, the AGA suggests the use of adalimumab in combination with thiopurines for the induction and maintenance of remission over adalimumab monotherapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conditional</td>
<td>Very low</td>
<td></td>
</tr>
<tr>
<td>Comment: Based on indirect evidence combination adalimumab with methotrexate may be more effective over adalimumab monotherapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5C. In adult outpatients with moderate to severe CD, the AGA makes no recommendation regarding the use of, ustekinumab or vedolizumab in combination with thiopurines or methotrexate over biologic drug monotherapy for the induction and maintenance of remission</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No recommendation</td>
<td>Knowledge gap</td>
<td></td>
</tr>
<tr>
<td>6. In adult outpatients with quiescent CD on combination therapy, the AGA makes no recommendation for withdrawal of either the immunomodulator or the biologic over ongoing combination therapy of a biologic and an immunomodulator</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No recommendation</td>
<td>Knowledge gap</td>
<td></td>
</tr>
<tr>
<td>7. In adult outpatients with moderate to severe CD, the AGA suggests early introduction with a biologic with or without an immunomodulator rather than delaying their use until after failure of mesalamine and/or corticosteroids</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conditional</td>
<td>Low</td>
<td></td>
</tr>
<tr>
<td>8A. In adult outpatients with moderate to severe CD, the AGA suggests the use of corticosteroids over no treatment for induction of remission</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conditional</td>
<td>Moderate</td>
<td></td>
</tr>
<tr>
<td>8B. In adult outpatients with moderate to severe CD, the AGA recommends against the use of corticosteroids over no treatment for maintenance of remission</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strong</td>
<td>Moderate</td>
<td></td>
</tr>
<tr>
<td>9. In adult outpatients with moderate to severe CD, the AGA recommends against the use of 5-ASA or sulfasalazine over no treatment for the induction or maintenance of remission</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strong</td>
<td>Moderate</td>
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</tbody>
</table>
10A. In adult outpatients with CD and active perianal fistula, AGA recommends the use of infliximab over no treatment for the induction and maintenance of fistula remission

<table>
<thead>
<tr>
<th>Recommendation</th>
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<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong</td>
<td>Moderate</td>
<td></td>
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</tbody>
</table>

10B. In adult outpatients with CD and active perianal fistula, AGA suggests the use of adalimumab, ustekinumab, or vedolizumab over no treatment for the induction or maintenance of fistula remission.

*Comment: evidence suggest certolizumab pegol may not be effective for induction of fistula remission*

<table>
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<tr>
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<td></td>
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</table>

10C. In adult outpatients with CD and active perianal fistula without perianal abscess, the AGA suggests against the use of antibiotics alone over no treatment for the induction of fistula remission

<table>
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<tr>
<th>Recommendation</th>
<th>Strength</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conditional</td>
<td>Low</td>
<td></td>
</tr>
</tbody>
</table>

11. In adult outpatients with CD and active perianal fistula without perianal abscess, the AGA recommends the use of biologic agents in combination with an antibiotic over a biologic drug alone for the induction of fistula remission

<table>
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<tr>
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<th>Strength</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong</td>
<td>Moderate</td>
<td></td>
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</tbody>
</table>

Abbreviations: 5-ASA 5-aminosalicylates, AGA American Gastroenterological Association, CD Crohn’s disease, TNF tumor necrosis factor.
REFERENCES


