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***SYMPOSIUM REPORT***

# Improving IBD Care: A Personalized Approach to Management

## Proceedings of a Symposium
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## Target Audience

This CME monograph will target gastroenterologists, primary care physicians, nurse practitioners, physician assistants, and nurses.

## Learning Objectives

After completing this activity, participants should be better able to:

- Personalize treatment plans for patients based on risk of aggressive disease
- Incorporate therapeutic drug monitoring–based strategies into clinical practice
- Differentiate among various oral and IV iron formulations
- Incorporate current clinical pathways for managing iron deficiency anemia in IBD effectively into clinical practice

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## Source Material

This monograph is based on presentations by Maria T. Abreu, MD, Gary R. Lichtenstein, MD, and Edward V. Loftus Jr, MD, given at the 2017 Advances in Inflammatory Bowel Diseases Conference: Multidisciplinary Approaches to IBD Patient-Centered Care, "Improving IBD Care: A Personalized Approach to Management." Stephen B. Hanauer, MD, was the lead faculty and reviewed the monograph.

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# Improving IBD Care: A Personalized Approach to Management

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## A Case-Based Approach to Personalizing Care in IBD

A 24-year-old man presents with new-onset bloody diarrhea. He had been in his usual state of health until about 4 months ago, when he noted the gradual onset of bloody diarrhea. He is currently having about 5 bowel movements per day, all of which are bloody. He is experiencing significant urgency but no nocturnal awakenings to defecate or incontinence. He has complained of mild cramping with bowel movements, but denies having any extraintestinal manifestations. His family history is significant for his mother having been diagnosed with ulcerative colitis (UC) at age 37 years.

On physical examination, he is noted to be well-nourished with no oral ulcers or skin rashes. His abdomen is soft and nontender, and there is no hepatosplenomegaly nor masses.

Sigmoidoscopy shows continuous symmetric involvement from the anal verge to 50 centimeters, with a decrease in the vascular pattern, erosions, and adherent mucus (Mayo 2 endoscopic score). Biopsies demonstrate chronic active colitis without evidence of granulomas or viral inclusions.

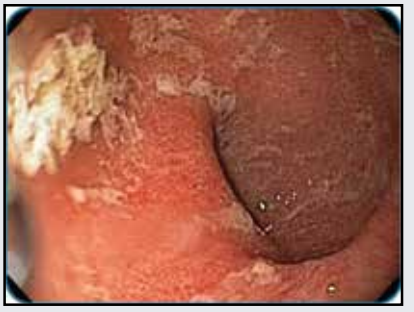
***How do you approach the management of this patient?***

According to the most recent American College of Gastroenterology (ACG) clinical practice guidelines on UC, disease activity can be characterized as mild, moderate, or severe based on the number of daily stools and presence of systemic toxicity.[1] Disease extent is assessed endoscopically and characterized as distal (disease confined below the descending colon) or extensive (extending proximal to the descending colon). However, recognizing the need to tailor therapy based on patient prognosis rather than symptoms alone, the American Gastroenterological Association (AGA) UC Care Clinical Pathway has identified several factors that can help predict a patient's disease prognosis and risk of colectomy. As Dr Gary R. Lichtenstein noted, "This is something that will dictate the current and future therapies that we use to not only get the patient to a better state of well-being, but also to prevent

**PATIENT CASE: Initial Presentation**

**Presentation**

- 24-year-old man
- Usual state of health until 4 months ago, when he noted gradual onset of bloody diarrhea
- Currently having 5 BMs per day, almost all of which are bloody
- Significant urgency but no nocturnal awakenings to defecate or incontinence
- Mild abdominal cramping with BMs
- Denies having extraintestinal manifestations



**Laboratory**

- ESR: 15 mm/hr
- CRP: 5.4 mg/dL
- Hb: 14.1 g/dL
- CMP: Normal

**Imaging**

Sigmoidoscopy shows continuous involvement from the anal verge to 50 cm with decreased vascular pattern, friability with contact, erosions, and adherent mucus (Mayo 2 endoscopic score). Biopsies demonstrate chronic active colitis without evidence of granulomas or viral inclusions. *Clostridium difficile* testing is negative.

BMs, bowel movements; CMP, complete metabolic panel; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; Hb, hemoglobin.

**Table 1.** Risk Stratification in Ulcerative Colitis[2]

| Low Colectomy Risk | High Colectomy Risk |
|---|---|
| • Limited anatomic extent<br>• Mild endoscopic disease | • Extensive colitis<br>• Deep ulcers<br>• Age <40 years<br>• High C-reactive protein and erythrocyte sedimentation rate<br>• Corticosteroid-requiring disease<br>• History of hospitalization<br>• *Clostridium difficile* infection<br>• Cytomegalovirus infection |

hospitalizations and surgery." Patients with limited anatomic involvement and milder endoscopic disease have a lower risk of colectomy compared with patients with extensive colitis, deep ulcers, previous requirement for corticosteroids, and other key risk factors (Table 1).[2] These factors, Dr Lichtenstein continued, "indicate that a patient has a high risk of colectomy and aggressive therapeutic intervention is needed at the onset." This patient's presentation with limited, superficial disease suggests that he is at low risk for colectomy.

The choice of therapy is guided by the level of clinical activity and extent of disease as well as the risk of colectomy (Figure 1).[1-3] 5-aminosalicylates (5-ASAs) are the cornerstone of therapy for induction and maintenance of remission in patients with mild disease who are at low risk of colectomy.[1] Rectal 5-ASAs are considered first-line in distal disease, as these agents are superior to rectal corticosteroids or oral 5-ASA agents in this setting and typically have a more rapid onset of action than oral therapies.[1,2,4] However, oral therapies are needed when disease extends proximal to the descending colon (ie, outside of the reach of rectal therapy).[1] Oral 5-ASA agents have demonstrated efficacy in achieving and maintaining remission in patients with mild to moderately active disease, with expected remission rates of around 50%.[1,3] Because patients with extensive disease may also have distal disease and proctitis symptoms, combinations of oral and rectal therapies are often used. Indeed, the combination of rectal and oral 5-ASAs has been shown to achieve

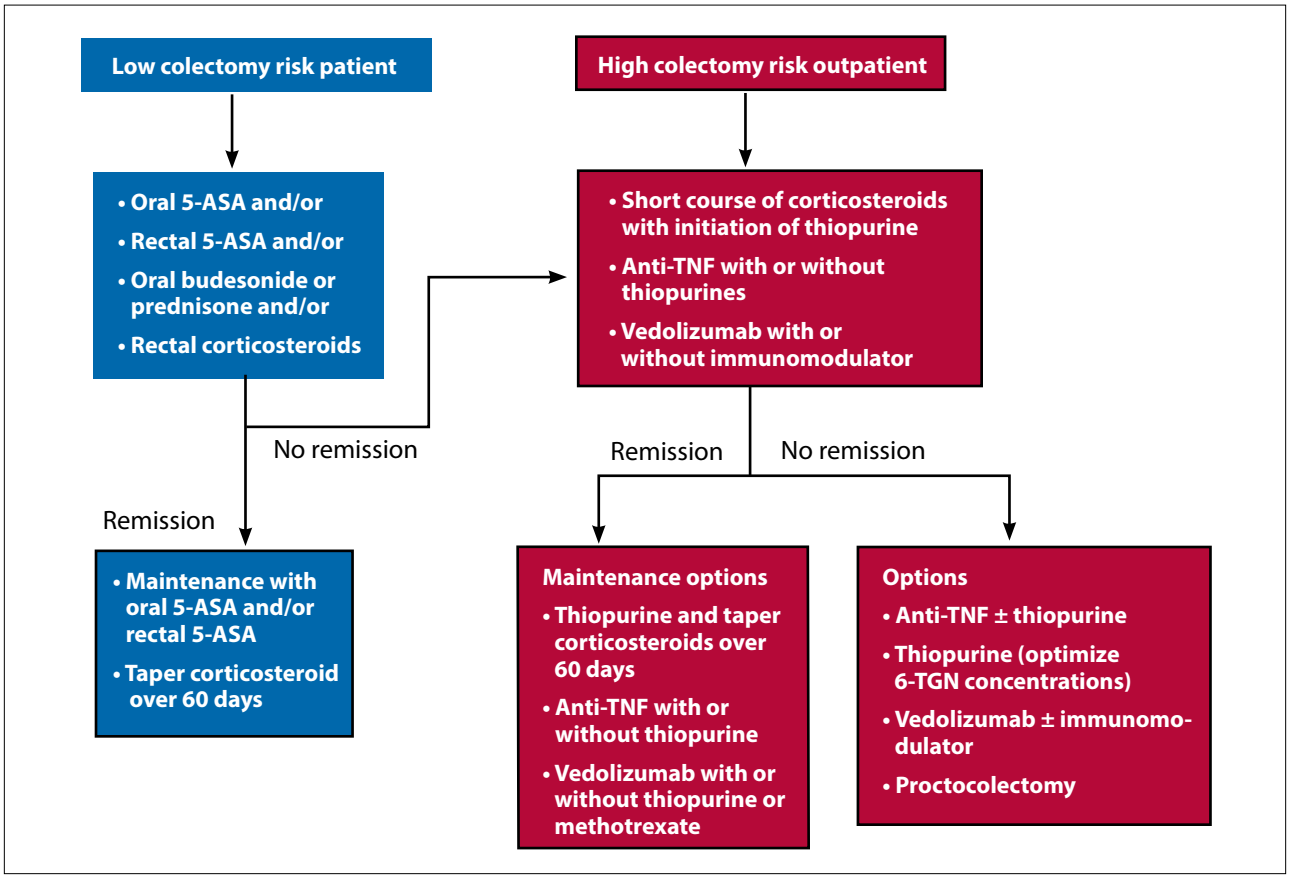



**Figure 1.** American Gastroenterological Association Clinical Pathway for ulcerative colitis: induction and maintenance therapy.[2]

5-ASA, 5-aminosalicylate; 6-TGN, 6-thioguanine nucleotide; TNF, tumor necrosis factor.

earlier and greater symptom relief in both distal[5] and extensive[6] disease.

Although oral corticosteroids are effective for inducing rapid remission in active UC,[7,8] significant safety concerns limit their use for patients who have failed 5-ASA agents or those with moderate to severe disease who need a prompt response.[1,2,4] Corticosteroid side effects affect multiple organ systems and include Cushingoid features, emotional and psychiatric disturbances, metabolic disturbances, bone disease, and increased risk of opportunistic infections.[1,9] Further, corticosteroids are associated with a high rate of dependence,[10] with only a third of UC patients in the prebiologic era having continued response after a course of corticosteroids within a year of initiating these agents and an equal proportion eventually requiring colectomy.[10,11] Even with the advent of biologics, fewer than one-third of patients with UC have a prolonged, corticosteroid-free remission.[12]

Unlike systemic corticosteroids, oral budesonide is a topically acting corticosteroid with low bioavailability and few systemic effects owing to its high first-pass metabolism in the liver to metabolites with minimal to no activity.[13-15] Controlled ileal-release budesonide uses a pH-mediated delivery system to release drug into the distal ileum and proximal colon. While this formulation is effective in mild to moderate ileocolonic Crohn's disease (CD), it appears to be significantly less likely to induce remission than oral mesalamine in patients with UC.[16] In contrast, a newer extended-release formulation of oral budesonide (budesonide MMX) that uses a colonic release technology to release drug progressively throughout the entire colon has been approved for mild to moderate UC.[13,15,17] The AGA Clinical Pathway guidelines recommend this agent as an option for first-line therapy of mild to moderate UC.[2] Although more data are needed to determine the efficacy of budesonide MMX relative to standard budesonide, mesalamine, or oral corticosteroids,[18] current data suggest that this agent may be an appropriate alternative to systemic corticosteroids in patients with mild to moderate UC who have failed maximal 5-ASA therapies.[15]

## Patient Case: Initial Therapy and 8-Week Follow-Up

The patient was started on oral mesalamine 4.8 g/day and topical mesalamine 4 g/day, and after 3 weeks, his symptoms improved but did not resolve. Extended-release budesonide 9 mg/day was started. Approximately 2 months later, the patient returns to the office and reports that his symptoms have worsened over the last month. He is currently experiencing 9 bloody bowel movements per day with severe urgency and incontinence. He is having difficulty functioning because of severe fatigue.

Physical examination is notable for tachycardia and tenderness in the left lower quadrant. Laboratory results reveal anemia and an elevated erythrocyte sedimentation rate. Sigmoidoscopy reveals large deep ulcers, and biopsies are consistent with severely active colitis.

***What is your next step in managing this patient?***

Patients who fail to respond to conventional treatment with 5-ASAs and/or corticosteroids are considered at high risk for colectomy and should be treated accordingly (Figure 1). Such patients are usually treated with a short course of systemic corticosteroids to induce remission. The thiopurines azathioprine and 6-mercaptopurine have significant corticosteroid-sparing effects in UC and are considered first-line maintenance therapies in patients who flare when corticosteroids are withdrawn.[1,4,19] However, because these agents have a relatively slow onset of effect (up to 3-6 months), patients with active disease despite corticosteroid therapy also require appropriate induction therapy.[1,20] For patients who do not respond to corticosteroids or for those who become corticosteroid-dependent despite using a thiopurine,

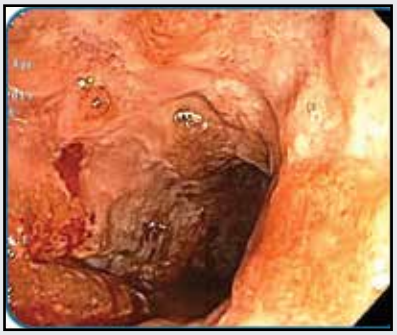
**PATIENT CASE: Initial Therapy and 8-Week Follow-Up**

**Presentation**

- Symptoms have worsened over the last month
- Currently having 9 bloody BMs per day with severe urgency and incontinence
- Waking 1-2 times per night to defecate
- Moderate abdominal pain with and before defecation
- Severe fatigue

**Laboratory**

- ESR: 55 mm/hr
- CRP: 15.4 mg/dL
- FC: 782 mcg/g
- Hb: 10 g/dL
- Albumin: 3.0 g/dL



**Imaging**

Sigmoidoscopy reveals large deep ulcers, spontaneous bleeding, and absence of anatomic landmarks. Biopsies are consistent with severely active colitis without evidence of CMV.

BMs, bowel movements; CMV, cytomegalovirus; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; FC, fecal calprotectin; Hb, hemoglobin.

biologic agents—either an anti–tumor necrosis factor (TNF) agent or anti-integrin—should be introduced, with or without an immunomodulator.

Since the introduction of infliximab in 1998, many large randomized, controlled trials have confirmed the efficacy of anti-TNF agents in inducing and maintaining remission in UC.[12,21-24] Additionally, these agents have been proven to achieve mucosal healing,[12,23-25] have corticosteroid-sparing properties,[12,23,26] and improve patient quality of life.[23,27]

***What induction regimen should be used in this patient?***

Although use of anti-TNF agents has become standard of care in managing moderate to severe UC, the optimal induction regimen for patients with acute severe UC remains uncertain. Growing evidence indicates an increased rate of infliximab clearance in patients with acute severe UC, necessitating an intensified induction regimen.[28,29] A number of pharmacokinetic factors are known to increase the clearance of infliximab, including high inflammatory load with high baseline C-reactive protein (CRP) and TNF concentrations, low serum albumin, male sex, large body size, and antidrug antibodies.[29,30] Further, a severely damaged mucosal barrier can lead to efflux of infliximab into the colonic lumen and fecal loss of the drug.[29,31] Recognizing the frequency of these factors in severe UC, accelerated infliximab dosing strategies have been increasingly used in this setting. A recent literature review of 76 studies concluded that total inflammatory burden and colonic leakage of infliximab drive increased infliximab clearance in patients with acute severe UC.[28] Cohort studies suggest that infliximab dose intensification may be beneficial to at least half of patients with acute severe UC, while case-controlled studies suggest that intensified dosing regimens with 1 to 2 additional infusions in the first weeks of treatment can reduce the early (3-month) colectomy rate by up to 80%. Although prospective data are needed to clarify the optimal dosing strategies in these patients, Dr Maria T. Abreu noted that "we want to hit them hard at the beginning, sometimes giving infusions of infliximab every few days in a hospitalized patient." Monitoring CRP can be helpful, and, assuming an initial drop in CRP after an inductive dose of infliximab, a subsequent rise should lead to consideration of an additional dose earlier than the intended 2-week infusion.

## Patient Case: Follow-Up

The patient received 2 infusions of infliximab 10 mg/kg intravenous (IV) and gradually improved over a week. He received a subsequent infusion 6 weeks later. About 10 weeks later, he feels well overall and reports having 4 formed stools per day without bleeding. He does experience mild urgency, but denies having incontinence or nocturnal awakenings. Physical examination is normal, and CRP has decreased to 1.5 mg/dL.

***Should infliximab concentrations and antidrug antibodies be obtained now?***

Numerous studies have demonstrated a correlation between high serum anti-TNF concentrations and favorable outcomes, including clinical, biomarker, and endoscopic remission.[32-38] Conversely, the presence of antidrug antibodies has been linked to lower serum drug concentrations, reduced clinical response, and infusion reactions.[39-43] Given these exposure-response relationships, checking drug trough concentrations and evaluating for the presence of antidrug antibodies (ie, therapeutic drug monitoring) can be used to optimize drug concentrations and clinical improvement in patients with inflammatory bowel disease (IBD).[44]

Therapeutic drug monitoring can be used at any point in induction or maintenance therapy, either in a proactive routine fashion when the patient is in remission or as a reactive strategy, to help guide treatment in cases of suboptimal response.[44] Although most current evidence has explored reactive therapeutic drug monitoring, recent retrospective data suggest that proactive monitoring of serum infliximab concentrations may be associated with better clinical outcomes and less need for IBD-related surgery or hospitalization compared with reactive monitoring.[45] In a retrospective multicenter study, 264 patients receiving infliximab maintenance therapy received proactive or reactive drug monitoring based on first infliximab concentration and antibodies to infliximab. Proactive monitoring was used in patients without any IBD-related symptoms to prospectively titrate infliximab to a target therapeutic window of 5 to 10 μg/mL, while reactive monitoring was used to guide treatment decisions in patients with symptoms suggestive of loss of response or drug intolerance due to acute or delayed infusion reactions. Multiple Cox regression analyses independently correlated proactive drug monitoring with reduced risk for treatment failure compared with reactive monitoring (hazard ratio, 0.16; 95% CI, 0.09-0.27; $P<.001$) (Figure 2). Additionally, when compared with reactive monitoring, proactive monitoring was independently associated with reduced risk of IBD-related surgery, IBD-related hospitalization, lower antibodies to infliximab, and serious infusion reaction. Although these data highlight potential benefits of optimizing maintenance infliximab prior to loss of response, due to an absence of prospective, randomized data supporting prospective therapeutic drug monitoring, the AGA guidelines on therapeutic drug monitoring consider current evidence insufficient to inform the use of routine proactive monitoring in patients who are being treated with anti-TNF agents.[44]

***Should an immunomodulator be started?***

Current evidence suggests that combination therapy is superior to monotherapy in patients who are naive to either biologics or immunosuppressive

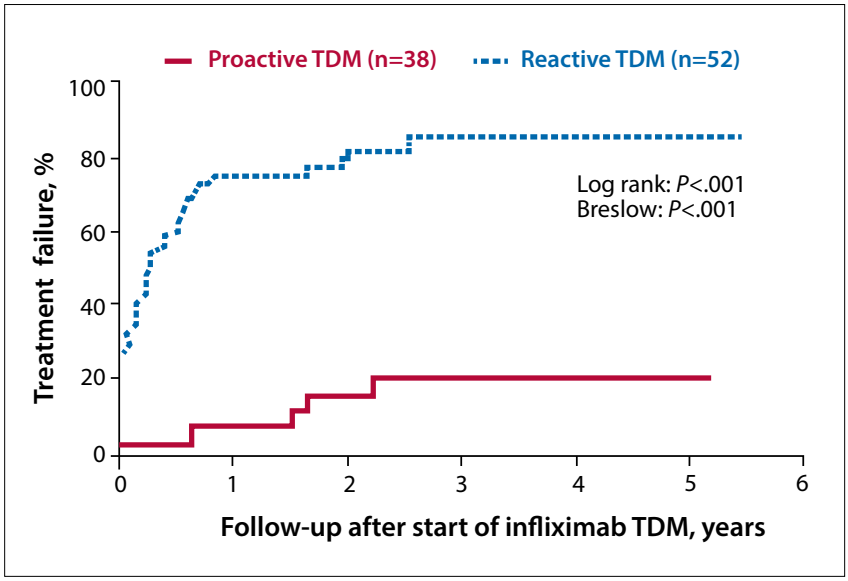



**Figure 2.** Kaplan-Meier cumulative probability of treatment failure in patients with ulcerative colitis undergoing either reactive (dotted line) or proactive (solid line) therapeutic drug monitoring (TDM) based on the first infliximab concentration.[45]

agents.[46,47] In a double-blind, double-dummy trial (UC SUCCESS), 239 anti–TNF-naive patients with moderate to severe UC were randomized to infliximab, azathioprine, or combination therapy for 16 weeks.[46] At week 16, 39.7% of patients receiving combination therapy had achieved corticosteroid-free remission (the primary endpoint) compared with 22.1% of those receiving infliximab alone (*P*=.017) and 23.7% of those receiving azathioprine alone (*P*=.032). A higher percentage of patients receiving combination therapy also achieved mucosal healing, although the difference was statistically significant between that group and the azathioprine monotherapy group only (*P*=.001). Importantly, fewer patients receiving combination therapy developed antidrug antibodies compared with those receiving infliximab monotherapy (3% vs 19%, respectively). Consistent with previous observations, this finding underscores the well-recognized efficacy of immunomodulators in suppressing antidrug antibody formation, leading to higher biologic drug levels, improved clinical response, and reduced infusion reactions.[33,38,48-50] Commenting on the reasons to include an immunomodulator with a biologic, Dr Abreu noted that "in the era of biologics, a primary reason is to keep stable, steady, higher levels of the anti-TNF agent."

## Patient Case: Follow-Up

Thiopurine methyltransferase test demonstrates normal activity, and azathioprine 2.5 mg/kg/day is started. Prior to his next infusion, a trough infliximab level is 8 µg/mL (target trough concentration ≥5 µg/mL), and there are no antibodies to infliximab. Three months later, a sigmoidoscopy demonstrates moderate endoscopically active disease. The patient reports having 8 bowel movements per day, with occasional blood in stools, urgency, and nocturnal awakenings to defecate.

***How can therapeutic drug monitoring guide your treatment decision?***

Despite the efficacy of anti-TNF agents in managing IBD, a considerable proportion of patients do not respond initially, lose response to therapy, or are intolerant to therapy.[33,39,51] Indeed, it is estimated that over 30% of patients with CD who respond initially will lose response within the first year of therapy, and secondary nonresponse rates as high as 50% per year have been observed in placebo-controlled trials in patients with IBD.[39,52,53] While loss of response to biologic therapy can be due to a variety of clinical factors (eg, superimposed infection, irritable bowel syndrome, fixed stenosis, partial obstruction), drug-related factors such as inadequate serum drug concentrations or immunogenicity may also be involved.[30,37,54,55] Accordingly, consideration for factors that influence the pharmacokinetics of anti-TNF agents is important when assessing patients with loss of response to these therapies.

With this in mind, the clinical utility of combining anti-TNF concentrations and antidrug antibody measurements in managing patients with loss of response to these agents (ie, reactive drug monitoring) has been increasingly explored.[37,38,55,56] Overall, current evidence has demonstrated that patients with subtherapeutic drug levels but without antidrug antibodies benefit more from dose escalation than switching to another antiagent. Conversely, as in this patient, those with adequate drug concentrations are more likely to respond to changing to a biologic with a different mechanism, as inflammation may no longer be driven by TNF in these settings.[37] Strategies recommended for patients with antidrug antibodies include increasing the dose of the anti-TNF agent (if antidrug antibody concentrations are low), adding an immunomodulatory, or, in the case of high antidrug antibody concentrations, switching to another anti-TNF agent or another class of biologic.[37] As Dr Abreu noted, the presence of antidrug antibodies "is a bit of a gray zone. If the level of the antidrug antibody is low, dose escalation is an option. On the other hand, if the level is already really high, and certainly if the patient has had an infusion reaction, you're done with that agent."

***What do you do next?***

Given that this patient has active inflammation in the presence of adequate infliximab trough concentrations and concomitant immunosuppression,

switching to a biologic with a non–anti-TNF mechanism is a reasonable strategy. Vedolizumab is a humanized monoclonal antibody that binds to $\alpha_4\beta_7$ integrin, a receptor found on the surface of gut-homing leukocytes.[57] Blocking these receptors results in decreased migration of leukocytes across blood vessels at the inflammatory site and a decreased inflammatory response.[57] Importantly, vedolizumab selectively blocks gut lymphocyte trafficking without interfering with trafficking to the central nervous system.[58] This is an important difference from natalizumab, the first drug in this class, which blocks lymphocyte trafficking to multiple organs (including the brain) and has been associated with progressive multifocal leukoencephalopathy (PML), a serious and usually fatal brain infection.[58] However, although no cases of PML were reported in clinical trials with vedolizumab, the product labeling does carry a class warning regarding the risk of this infection.[59]

Vedolizumab was approved in 2014 for use in patients with moderately to severely active UC.[59] This approval was based on the results of a large randomized, controlled trial (GEMINI 1) that demonstrated clinical response in 47.1% of patients after 6 weeks of vedolizumab therapy compared with 25.5% of placebo-treated patients, as well as 52-week corticosteroid-free remission rates in up to 45% of patients receiving the drug every 4 weeks compared with 16% of patients who switched to placebo.[58] Further, post hoc analysis of data from this study demonstrated vedolizumab to be effective induction and maintenance therapy in patients with prior anti-TNF exposure,[60] as is the case with this patient.

### *What other therapeutic strategies are being studied for UC?*

With increased understanding of the pathogenic mechanisms in IBD has come a broader spectrum of inflammatory mechanisms that can be targeted pharmacologically. Although a full discussion of the many emerging therapeutic targets for IBD is beyond the scope of this article, several agents are currently undergoing phase 2 or 3 investigation in UC. The important role of leukocyte recruitment across intestinal tissue in perpetuating chronic inflammation in UC makes lymphocyte trafficking a rational target for therapy.[58,61] Similar to vedolizumab, a number of alternative anti-integrin agents are under development and represent a promising strategy for UC. Etrolizumab, a humanized monoclonal antibody to $\beta_7$ integrin, is a second-generation anti-integrin currently being studied in phase 3 trials for UC.[62,63]

Another antitrafficking approach that is being explored in UC involves modulating sphingosine-1-phosphate (S1P), a sphingolipid metabolite that regulates key cellular activities such as proliferation and migration, vascular integrity, and lymphocyte trafficking.[62,64,65] Binding S1P receptors can prevent lymphocytes from exiting lymph nodes, leading to a reduction in circulating lymphocytes in the blood.[62,64] Ozanimod is an oral S1P1-receptor and S1P5-receptor modulator that is currently undergoing phase 3 study in UC. In a randomized, controlled phase 2 trial (TOUCHSTONE), ozanimod improved rates of clinical remission in patients with moderate to severe UC, with continued safety and efficacy recently demonstrated in an ongoing open-label extension of this trial.[64,66]

Another novel approach for treating UC is to inhibit members of the Janus kinase (JAK) family, proteins that facilitate signal transduction of several cytokines that are needed for lymphocyte activation and proliferation as part of the immune response.[62,65] Inhibiting JAK leads to downstream modulation of a number of inflammatory cytokines that are implicated in the pathogenesis of IBD.[62,67] Tofacitinib, an oral, small molecule JAK inhibitor that is currently approved for treating rheumatoid arthritis and psoriatic arthritis, has been shown to have dose-dependent efficacy as induction therapy for UC in a phase 2 trial.[68,69] More recently, the efficacy and safety of tofacitinib as induction and maintenance therapy in moderate to severe UC has been demonstrated in a large phase 3 clinical program (OCTAVE).[67] In the OCTAVE Induction 1 and 2 trials, tofacitinib 10 mg twice daily was superior to placebo in achieving remission (18.5% vs 8.2%; *P*=.007), clinical response (59.9% vs 32.8%; *P*<.001), and mucosal healing (31.3% vs 15.6%; *P*<.001) at

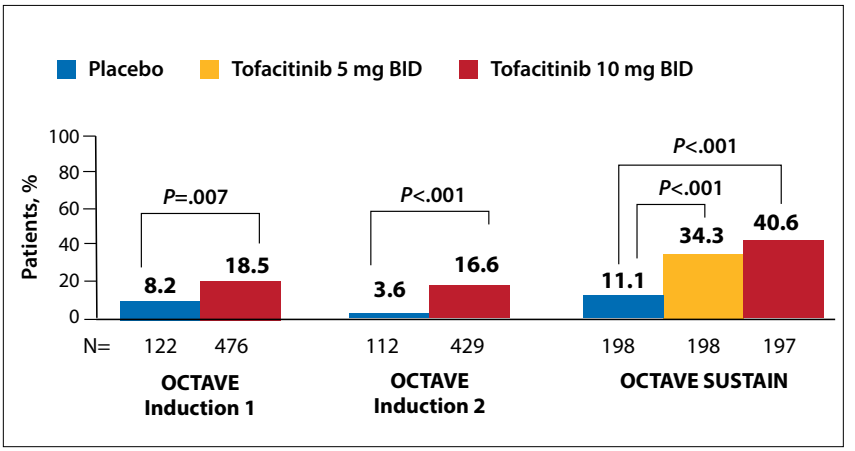



**Figure 3.** Clinical remission rates in the OCTAVE program. Remission is defined as a total Mayo score of no more than 2, with no subscore greater than 1 and a rectal bleeding subscore of 0 at 8 weeks in OCTAVE induction trials and at 52 weeks in OCTAVE SUSTAIN.[67]

BID, twice daily.

8 weeks. Commenting on these data, Dr Abreu noted that "separation among responders was seen as early as 8 weeks, which is really a very striking thing. I think this is something that hopefully will be part of our armamentarium that works quickly and orally." Indeed, recent data presented at the 13th Congress of the European Crohn's and Colitis Organisation suggest clinical improvement as soon as 3 days after initiating tofacitinib.

Further, in the longer-term OCTAVE SUSTAIN trial, over one-third of patients receiving tofacitinib maintained clinical remission and mucosal healing at 52 weeks, significantly higher than placebo-treated patients ($P$<.001 for each comparison) (Figure 3).[67] The most frequently reported adverse events, excluding worsening UC, were nasopharyngitis, arthralgia, and headache. However, tofacitinib was associated with a higher rate of overall infection and herpes zoster infection than placebo, as well as increased lipid levels. Other JAK inhibitors currently under investigation for UC include filgotinib and upadacitinib.[70]

> "It's important to remember that addressing anemia is considered a quality metric by several different organizations, including the CCFA."
> – Edward V. Loftus Jr, MD

## Patient Case: Follow-Up

The patient responded to vedolizumab induction therapy, and is continued on 300 mg IV every 8 weeks. Four months later, his symptoms remain under control, and fecal calprotectin has normalized. However, he continues to complain of extreme fatigue, and repeat laboratory tests demonstrate severe anemia.

***What causes anemia in IBD?***

Anemia is by far the most common extraintestinal manifestation of IBD, occurring in approximately one-third of patients.[71,72] Although the cause of anemia in IBD is multifactorial, by far the 2 most frequent causes are iron deficiency anemia (IDA) and anemia of chronic disease, or anemia of chronic inflammation.[71,73] Iron deficiency in IBD results from intestinal bleeding as well as inhibition of iron absorption due to hepcidin production.[73,74] Hepcidin, an acute-phase protein synthesized primarily by hepatocytes, exerts its activity by binding to ferroportin and preventing iron entry into plasma.[75] Hepcidin expression is upregulated during infection and inflammation, such as occurs in active IBD, leading to reduced iron absorption in the duodenum and reduced iron availability for heme formation in the bone marrow.[72] Dr Edward V. Loftus Jr explained that "in inflammatory states, increased levels of hepcidin cause degradation of ferroportin, essentially trapping iron inside enterocytes and preventing iron from being mobilized into the blood and into the rest of the body." Accordingly, serum hepcidin has been shown to correlate positively with disease activity and negatively with ferroportin in patients with UC.[76]

***What are the consequences of anemia in IBD?***

The symptoms of IDA—primarily fatigue, reduced performance, and even dyspnea—can be significant and add to the already considerable quality-of-life burden associated with IBD. Commenting on this patient's symptoms, Dr Loftus noted that "as gastroenterologists, we tend to focus on the GI issues, but we can't forget about patients' fatigue, which I would argue is one of the cardinal symptoms of IBD." Further, the presence of anemia has been shown to be an independent predictor of poor outcomes (hospitalization and surgeries) and health care resource utilization (visits to gastroenterology clinics, telephone calls) in patients with IBD.[77] Given the enormous impact of anemia on patient quality of life as well as clinical outcomes, treatment of anemia has become an independent treatment target and quality metric in IBD.[73]

***How should this patient's anemia be managed?***

According to the recent Anemia Care Pathway developed by the Crohn's & Colitis Foundation, iron supplementation should be administered in all cases of manifest anemia and inadequate iron stores (Figure 4).[71,73] Despite a common perception that anemia is a secondary problem in IBD patients, treatment of anemia should not be delayed during active disease and can

**PATIENT CASE: Follow-Up 4 Months After Vedolizumab Initiation**

**Presentation**

- UC symptoms have improved, but patient complains of severe fatigue

**Laboratory**

- ESR: 15 mm/hr
- CRP: 8.0 mg/dL
- FC: 50 mcg/g
- Hb: 9.1 g/dL
- MCV: 78 fL/rbc
- Albumin: 3.8 g/dL

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; FC, fecal calprotectin; Hb, hemoglobin; MCV, mean corpuscular volume; UC, ulcerative colitis.

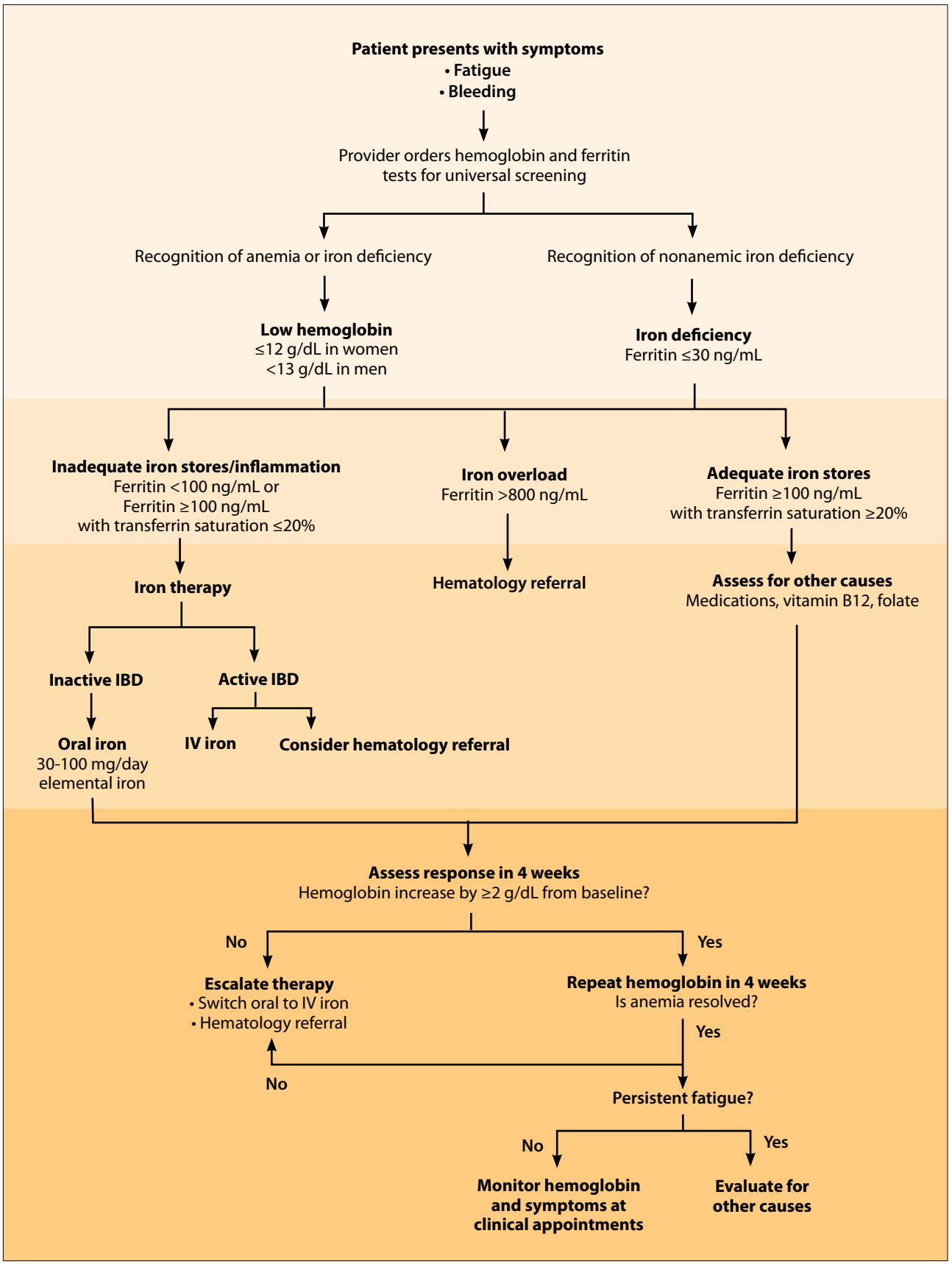



**Figure 4.** Crohn's & Colitis Foundation Anemia Care Pathway.[73]
IBD, inflammatory bowel disease; IV, intravenous.

**Table 2.** IV Iron Preparations Available in the United States[73,82-93]

| | Iron Dextran | Iron Sucrose | Ferric Gluconate | Ferumoxytol | Ferric Carboxymaltose |
|---|---|---|---|---|---|
| **Approved for General IDA Treatment** | ✓ | | | ✓ | ✓ |
| **Test Dose Recommended** | ✓ | | ✓[a] | | |
| **Administration** | Slow IV injection | Slow IV injection or IV infusion ≥15 min | Slow IV injection or IV infusion | IV infusion over 15 min | Slow IV injection or IV infusion ≥15 min |
| **Observation** | 1 hour after test dose | ≥30 min during and after administration | ≥30 min during and after administration | ≥30 min during and after administration | ≥30 min during and after administration |

[a]Recommended in patients with a history of drug allergies.
IDA, iron deficiency anemia; IV, intravenous.

be provided concurrently with IBD therapy.[73]

Oral iron supplementation has been the therapy of choice for many years and is recommended for patients with quiescent IBD at a dose of 30 to 100 mg/day of elemental iron.[73] Given that more than 90% of ingested iron remains unabsorbed, however, oral iron supplementation can cause a number of gastrointestinal effects such as nausea, flatulence, diarrhea, and even gastric erosion.[71] Accordingly, tolerance of oral iron may be a particular concern in the setting of active IBD.

Although traditionally avoided for fear of hypersensitivity reactions,[71,78] several factors favor IV iron supplementation in patients with IBD.[79] In addition to the potential inability to compensate ongoing blood loss, oral iron may not be absorbed in patients with active inflammation in IBD due to a hepcidin-mediated mechanism.[79,80] Comparative studies have generally found IV iron to be faster, more effective, better tolerated, and able to improve quality of life to a greater extent than oral iron supplementation.[79,81] Accordingly, IV iron is recommended for patients with IDA and active IBD.[71,73,79]

A number of IV iron preparations are available in the United States, all of which differ considerably with respect to their formulation, dosing, pharmacokinetic properties, and indications (Table 2).[73,82-93] Iron dextran preparations have demonstrated considerable efficacy in both children and adults with IBD.[82-84] However, these preparations are associated with a significant rate of immunoglobulin E–mediated anaphylactic reactions, in some studies approaching 6%, despite successful test infusions. Commenting on iron dextran, Dr Loftus added that although "a large amount can be given at once, it may take multiple hours, and then the patient must be observed afterwards." Ferumoxytol is an iron polyglucose sorbitol carboxymethyl ether complex that was approved in 2009 by the US Food and Drug Administration for the treatment of IDA in adult patients with chronic kidney disease and in 2018 for treating IDA in adults who have unsatisfactory response or intolerance to oral iron.[85] Ferumoxytol can be injected rapidly intravenously at doses of 510 mg with no test dose, and, therefore, a full treatment course (1.02 g) can be administered in 2 clinic visits. Subgroup analyses of data from phase 3 studies have found ferumoxytol to be safe and effective in patients with IBD and IDA who had been unsuccessfully treated with oral iron. In an analysis of 231 patients with IDA and gastrointestinal disorders, treatment with ferumoxytol (510 mg × 2) was effective and generally well tolerated, achieving a mean increase in hemoglobin of 28.0 g/L at week 5 after administration (vs -1.0 g/L with placebo; $P<.001$).[86] Additionally, patients treated with ferumoxytol experienced significant improvement in most patient-reported outcomes, including Functional Assessment of Chronic Illness Therapy–Fatigue scores and various domains of the Short Form-36 Health Survey. More recently, analysis of 93 patients with IBD in a large phase 3 trial indicated that patients responded to ferumoxytol and ferric carboxymaltose with a significant increase in hemoglobin and a safety profile comparable to that seen in the overall study population.[87]

Ferric carboxymaltose, the first high-dose nondextran IV iron available,[88] is unique in that it allows administration of up to 1000 mg within 15 minutes, making it suitable for intensive iron repletion. This formulation has been found to be safe and effective specifically in patients with IBD.[89,90] In one study involving 200 patients with IDA and IBD, patients treated with ferric carboxymaltose achieved response (defined as hemoglobin increase of ≥2.0 g/dL) significantly faster than those receiving oral ferrous sulfate.[81] Further, fewer patients treated with ferric carboxymaltose discontinued therapy due to adverse events than those receiving ferrous sulfate (1.5% vs 7.9%, respectively).

According to the Crohn's & Colitis Foundation Anemia Care Pathway (Figure 4), patients who have not responded with 4 weeks of treatment with an increase of hemoglobin by at least 2 g/dL should be changed from oral to parenteral iron and/or referred to a hematologist.[73] Patients who have responded should continue to be followed every 4 weeks until fatigue and

anemia have resolved (hemoglobin ≥12 g/dL in women, hemoglobin ≥13 g/dL in men).

## Patient Case: Follow-Up

The patient received a dose of ferric carboxymaltose following vedolizumab infusion and a subsequent dose 1 week later. One month later, he reports resolution of fatigue, and hemoglobin has increased to 13.1 g/dL.

***What other considerations are important for this patient?***

Given the chronicity of IBD, young age of many patients, and multiple potential comorbidities, preventive care is an essential component of managing patients with IBD.[94,95] Further, the increasing use of corticosteroids, immunomodulators, and biologic agents as a mainstay of therapy in IBD places IBD patients at increased risk of various infections, many of which are preventable by prior vaccination.[96] Given these considerations, a working knowledge of the special health maintenance needs of this population is important.[94,95] In addition to immunizations, key aspects of preventive care in IBD patients include bone health, depression screening, smoking cessation, and cancer surveillance (particularly for cervical cancer, skin cancer, and colorectal neoplasia).[97] To that end, the ACG has recently issued guidelines for preventive care in patients with IBD.[97]

***What vaccinations should this patient receive?***

Although adherence to age-appropriate vaccination schedules is generally recommended for IBD patients, special consideration should be given to patients receiving or initiating immunosuppressive therapies.[97] All adult IBD patients regardless of immunosuppression status should receive nonlive vaccines per national guidelines issued by the Centers for Disease Control and Prevention, Advisory Committee on Immunization Practices, and the Infectious Disease Society of America.[97-99] Recommendations for inactivated vaccines are listed in Table 3.[97]

Recommendations for live vaccines (measles, mumps, rubella [MMR]; varicella; and herpes zoster) vary based on the type of immunosuppression that patients are receiving (Table 4). While the MMR vaccine is contraindicated in patients receiving immunosuppressive agents, some live vaccines are recommended for patients receiving low-level immunosuppression, defined as those who have received certain regimens of systemic corticosteroids (eg, <20 mg prednisone), methotrexate at doses used to treat IBD, or thiopurines (<2 mg/kg/day) within the previous 3 months.[97] Anti-TNF therapy is generally considered to be high-level immunosuppression.[97,98] Although the ACG guidelines did not define the use of vedolizumab with respect to vaccination, other experts characterize this agent as high-level immunosuppression.[100]

Patients with IBD, particularly those receiving immunosuppressive therapies, are at increased risk of several vaccine-preventable diseases, including influenza, pneumococcal pneumonia, and herpes zoster.[97] Of these, the increased risk of herpes zoster in this population has garnered increasing attention over the past decade.[101,102] In a large retrospective cohort and nested case-control study involving over 100,000 patients with IBD matched to 434,416 individuals without IBD, the risk of herpes zoster was significantly higher among IBD patients (incidence rate ratio, 1.68; 95% CI, 1.60-1.76) compared with controls.[102] This risk increased considerably with the use of anti-TNF agents, corticosteroids, and thiopurines, with the highest risk associated with combination anti-TNF and thiopurine therapy (odds ratio, 3.29; 95% CI, 2.33-4.65). An increased risk of herpes zoster has also been observed with the use of tofacitinib in both IBD[67,103,104] and rheumatoid arthritis patients.[105] Given these observations, the ACG recommends that herpes zoster vaccination be considered in all adults with IBD over the age of 50 years, including certain subgroups of immunosuppressed patients.[97] While low doses of methotrexate or thiopurines are not considered contraindications to live herpes zoster vaccine, the decision to vaccinate patients receiving anti-TNF therapies is decided on a case-by-case basis. An inactive subunit zoster vaccine (Shingrix™) has recently been approved by the US Food and Drug Administration for prevention of herpes zoster in adults age 50 years and older.[106] This recombinant vaccine has been found to be safe and remarkably effective in immunocompetent individuals 50 years and older,[107] as well as in patients 70 years and older.[108] Although not specifically tested in this population, the availability of this nonlive vaccine is anticipated to be advantageous for immunosuppressed patients with IBD.[97]

***What other screening should be performed for this patient?***

Screening for anxiety and depression is recommended for patients with IBD due to the high rates of these conditions and their potentially negative impact on disease activity and recurrence.[97,109,110] Commenting on the importance of screening, Dr Lichtenstein noted that "we ask simple questions, such as 'over the past month, have you felt down, depressed, or hopeless?' By asking patients directly, even during endoscopic procedures, we identify many patients who are depressed and need interventions." Given the frequency of reduced bone mineral density (BMD) and fractures in patients with IBD,[97,111,112] periodic screening for osteoporosis and BMD testing are recommended for patients with IBD and conventional risk factors, with a particularly low threshold for screening for patients who have used corticosteroids at any time.[97] Key risk factors for IBD-related osteoporosis include corticosteroid treatment, calcium and vitamin D deficiencies, malnutrition, and the systemic effects of chronic inflammation.

Recognizing that subgroups of patients with IBD are at increased risk

**Table 3.** Recommendations for Inactivated Vaccines

| Infectious Agent(s) | Target Population | Check Titer Before Immunization? | Dosing Regimen |
|---|---|---|---|
| *Corynebacterium diphtheriae*, *Clostridium tetani*, *Bordetella pertussis* | All patients | No | A single dose of TDap recommended at age 11 through 64 years; Td booster every 10 years |
| HAV | All patients | Yes | 2 doses at 0 and 6 months |
| HBV | All patients | Yes | 3 doses at 1, 1-2, and 4-6 months; check titers 1 month after the last dose; if no response, there are 3 options: revaccination, double-dose HBV vaccination, or combined HAV/HBV vaccination |
| Human papilloma virus | Female and male patients 11-26 years of age | No | 3 doses at 0, 2, and 6 months |
| Influenza | All patients | No | Annual immunization with trivalent inactivated influenza vaccine; "high-dose" vaccine for patients 65 years and older; live attenuated intranasal influenza vaccine is contraindicated in immunosuppressed patients |
| *Neisseria meningitides* | High-risk adults | No | 2 or 3 doses depending on vaccine |
| *Streptococcus pneumonia* | All patients | No | If no previous vaccination, PCV13 should be followed by a dose of PPSV23 after 2-12 months; if the patient received 1 or more doses of PPSV23, PCV13 should be administered 1 or more years after PPSV23; another dose of PPSV23 should be administered 5 years after the initial PPSV23 dose and at age 65 years or older if at least 5 years have elapsed since the previous PPSV23 dose |

HAV, hepatitis A virus; HBV, hepatitis B virus; PCV13, pneumococcal conjugate vaccine; PPSV23, pneumococcal polysaccharide vaccine; Td, tetanus and diphtheria; TDap, tetanus, diphtheria, and acellular pertussis.

**Table 4.** Recommendations for Live Vaccines

| Infectious Agent(s) | Target Population | Check Titer Before Immunization? | Dosing Regimen | If Patient Is Already on Immunosuppressive Treatment |
|---|---|---|---|---|
| Measles, mumps, rubella | If unknown vaccination history | Yes | 2 doses (>28 days apart) at least 6 weeks before starting immunosuppressive therapy | Contraindicated |
| Varicella | If unknown vaccination history | Yes | 2 doses (4-6 weeks apart) at least 1 month before starting immunosuppressive therapy | Depends on type of immunosuppressive medications |
| Herpes zoster | Patients ≥50 years | No | 1 dose at least 1 month before starting immunosuppressive therapy | Depends on type of immunosuppressive medications |

of certain cancers, cancer screening is essential in this population.[97,113] Melanoma screening is recommended for all patients with IBD, as both the disease itself and anti-TNF exposure have been linked to increased melanoma risk.[97,114] Screening for nonmelanoma skin cancer (NMSC) is also recommended for this patient, as thiopurines have been linked to an increased risk of NMSC, which can persist even after therapy is discontinued.[115] Colorectal cancer screening is paramount for all patients with IBD, with screening colonoscopy recommended within at least 8 years of symptom onset and repeat surveillance colonoscopies every 1 to 3 years thereafter.[116] Lastly, although not relevant for this patient, given the risk of cervical dysplasia with immunosuppressants, women with

IBD receiving immunosuppressive therapies should undergo annual cervical cancer screening.[97]

## Summary

Treatment of IBD has evolved considerably over the past decade. In an effort to change the natural history of the disease, therapy is guided by an individual's prognosis rather than symptoms alone.[2,117-119] While conventional therapies are recommended for patients with UC who are at low risk for colectomy, more aggressive therapy with biologics and/or immunomodulators is recommended for those with a poorer prognosis (ie, high risk of colectomy).[2] Although the introduction of anti-TNF agents has revolutionized IBD management, a considerable proportion of patients do not respond initially, lose response, or cannot tolerate these therapies.[33,39,51] Given the number of pharmacokinetic and clinical variables that can affect serum levels of anti-TNF agents, reactive therapeutic drug monitoring can be used to assess the mechanisms behind suboptimal response and guide treatment decisions. Further, emerging evidence suggests that proactive therapeutic drug monitoring in patients with quiescent disease can help prevent loss of response and may be associated with better clinical outcomes than reactive therapeutic drug monitoring.[45] In addition to strategies for optimizing current treatments, newer agents such as vedolizumab and emerging therapeutic targets (eg, lymphocyte trafficking, downstream signaling) are providing new avenues for targeted therapies.

In addition to treating intestinal inflammation, clinicians caring for patients with IBD must also recognize extraintestinal complications such as anemia and manage them effectively. Indeed, anemia occurs in approximately 30% of patients and is associated with high rates of IBD-related complications, resource utilization, and impaired patient quality of life.[72,73,77] Although oral iron may be useful in those with quiescent disease, IV iron is recommended in active disease, as it is more effective, is better tolerated, and improves quality of life to a greater extent than oral iron supplementation.[79,81]

Preventive strategies are also an essential component of caring for IBD patients. In addition to the chronicity of the disease, young age of many patients, and multiple potential comorbidities, the increasing use of corticosteroids, immunomodulators, and biologics places IBD patients at increased risk of various infections, many of which are preventable by prior vaccination.[94-96] In addition to immunizations, key aspects of preventive care in IBD patients include bone health, depression screening, smoking cessation, and cancer surveillance (particularly for cervical cancer, skin cancer, and colorectal neoplasia).[97]

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# NOTES

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