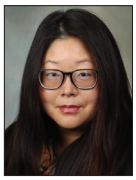
# ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Disease

Section Editor: Stephen B. Hanauer, MD

## Management of Patients With Mild Crohn's Disease



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**G&H** How can mild Crohn's disease be defined?

**CH** Mild Crohn's disease can be described in terms of severity, which means the likelihood of progression over time. There are not many factors associated with a low likelihood of progression. The factors are mainly older age at diagnosis, which tends to be more than 40 years of age at diagnosis, in combination with limited anatomic extent such as limited ileitis incidentally identified during colonoscopy or scattered aphthous erosions throughout the colon without larger or deeper ulcers or extensive involvement of the colon or the small bowel.

There is also mild Crohn's disease activity, which refers more to clinical presentation at a point in time. Health care providers stratify disease activity, especially when considering mild vs moderate to severe activity, by assessing if the patient has systemic signs of inflammation such as fevers or, in particular, weight loss. With mild Crohn's disease activity, there are no systemic signs of inflammation such as fevers, change in appetite, or unintentional weight loss, and there are no obstructive symptoms such as significant abdominal pain or cramping. In mild Crohn's disease activity, laboratory test results are typically normal, in particular complete blood count, albumin, C-reactive protein, and fecal calprotectin, and physical examination is normal.

**G&H** What are some challenges of making the correct initial diagnosis?

**CH** One of the most common difficulties is separating patients who have incidental ileitis from those who truly have Crohn's disease. For example, when performing a routine colonoscopy for another indication (eg, a screening colonoscopy) and intubating the ileum, a few scattered aphthous erosions may be seen. This could represent mild Crohn's disease, or it could be completely incidental. Another challenge is if symptoms are out of proportion to the endoscopic activity that is seen. For example, a patient may have significant abdominal pain, diarrhea, or constipation, but only a few aphthous erosions may be seen in the ileum or throughout the colon during colonoscopy. It can be difficult to determine whether mild Crohn's disease is driving all of those symptoms and if treatment for mild Crohn's disease will result in symptom resolution vs if a competing etiology is present that is driving the clinical presentation.

**G&H** When might treatment not be needed?

**CH** It is important to recognize that not all patients with mild Crohn's disease will progress. In fact, studies have shown that 40% to 50% of patients diagnosed with mild Crohn's disease will continue to have only mild disease up to 15 years after their diagnosis, especially if they were incidentally diagnosed and asymptomatic during their colonoscopy. If there is mild endoscopic activity, no significant symptoms, and no evidence of disease complications (eg, the risk of progression is low), providers should monitor patients periodically but medical therapy may not be necessary. Patients should undergo annual or semi-annual assessments and get biomarkers such as fecal calprotectin and C-reactive protein checked periodically. Two other metrics to include in evaluations are blood counts, namely iron status, as well as weight. If a patient's ferritin or iron stores are starting to decrease over time and their weight is also starting to change, additional evaluation may be needed. Otherwise, if everything else is stable, we would continue to monitor and watch the patient without medical therapy but focus on optimizing other variables such as diet and physical activity.

**G&H** How should providers identify the best therapeutic strategy for an individual patient with mild Crohn's disease?

**CH** This is where risk stratification based on risks of disease progression is important. The first thing I do is determine whether the patient's clinical symptoms match what is seen

endoscopically or on imaging. If they do, then I need to determine whether these patients are at higher risk for disease progression if they are untreated or undertreated. For example, pediatric patients and patients with younger age at diagnosis have a greater risk for developing complications over time. I then ask myself whether the endoscopic findings are perhaps an underestimate of the patient's overall disease burden. That is particularly true if I am noticing anemia, if weight loss is present, or if the patient has abnormalities in their fecal calprotectin or C-reactive protein results. If that is the case, I may pursue additional evaluation with upper gastrointestinal endoscopy, cross-sectional imaging with computed tomography or magnetic resonance enterography, or even a capsule endoscopy, especially if I am concerned that I may be underestimating the patient's disease activity or if the risks of progression are high.

I also ask myself whether there are signs of systemic inflammation. If those are present, especially anemia, abnormal biomarkers, and weight loss, I give the patient an initial course of budesonide, even if their endoscopic findings are fairly mild. Then I assess the patient's response to the treatment to determine which appropriate maintenance therapy strategies should be considered. These are patients with whom I am going to start an earlier conversation about future corticosteroid-sparing strategies.

### G&H Is there a role for corticosteroids other than budesonide?

**CH** Prednisone is certainly a reasonable option if the patient has more than just limited ileal disease or if access to budesonide is limited due to costs or coverage. Ileal-release budesonide and budesonide rectal foam are now available as generics, which may help improve access. Budesonide tends to be preferred because it is more targeted to the distal and terminal ileum, whereas prednisone is systemically available and has more adverse effects.

### G&H How has treatment for mild Crohn's disease changed, and how should patients be managed for second-line therapy?

**CH** In the past, guidelines recommended either a course of budesonide and supportive care or a course of budesonide and either sulfasalazine or immunomodulators such as thiopurines. Now with the expansion of the therapeutic toolbox for inflammatory bowel disease (IBD), there are more options. There are interleukin inhibitors such as ustekinumab (Stelara, Janssen) and risankizumab (Skyrizi, AbbVie) as well as anti-integrins such as vedolizumab (Entyvio, Takeda). Both of these mechanisms of action have a very favorable long-term safety profile for patients. Additionally, we are more thoughtful about the earlier use of anti–tumor necrosis factor (TNF) agents, especially for higher-risk patients, and with the availability of multiple biosimilars to anti-TNF agents, access to this class as an advanced therapy may be improved. Using thiopurines as monotherapy for maintenance is becoming less common as a strategy because of the risks associated with long-term use of thiopurines such as nonmelanoma skin cancer and lymphoproliferative disorders, particularly the longer the patient is taking the agent and with older age.

Because the goal of Crohn's disease treatment is not only to induce remission but also to maintain it, using strategies that are effective but also have a more favorable safety profile is preferred. How that decision is made depends on the patient's initial response to budesonide—was it complete, partial, or a nonresponse? Also, did that lead to additional evaluation? If additional evaluation identified more extensive disease, I am going to choose a strategy that is more effective over one that is more supportive.

### G&H Could you expand on the role of advanced therapies?

**CH** As mentioned, there is certainly a role for advanced therapies, but it depends on the patient's response to the initial course of corticosteroids, whether budesonide or systemic corticosteroids, as well as how extensive their Crohn's disease is on evaluation. If a patient has quite a few symptoms, is experiencing weight loss, has anemia, and has more small-bowel involvement, the threshold for using advanced therapies will be lower.

As an example, patients with pediatric-onset Crohn's disease are more likely to progress, and providers can use the prediction tools that are available to identify which patients should be initiating advanced therapies earlier. For Crohn's disease, the earlier appropriate treatment is initiated, the greater the likelihood of impacting the natural history of the disease and ideally preventing outcomes such as stricturing or fistulizing disease and surgery. This is especially true for pediatric-onset Crohn's disease where providers are additionally looking for abnormalities or changes in laboratory tests and developmental factors such as signs of growth delay. If pediatric patients with mild Crohn's disease are falling off their growth curve, providers may want to perform additional evaluation to make sure there is not more involvement than initially thought at face value, such as checking IBD serologies and genetics. If these patients have 2 or more of these serologies or genetics present, the likelihood they are going to progress to complicated Crohn's disease is greater. For those patients in particular, starting a conversation earlier on about adding biologics or other advanced therapies is going to be key.

### G&H Is there a role for using dietary therapy?

**CH** There is a lot of interest in dietary strategies for mild Crohn's disease. The majority of the evidence is in pediatric-onset Crohn's disease, particularly with exclusive

enteral nutrition. Using predominately enteral nutrition for the first 6 to 8 weeks has been shown to induce remission at rates similar to corticosteroids, and then foods are gradually reintroduced afterward. A dietary strategy such as exclusive enteral nutrition has been challenging for adults, namely because of adherence and cost. There are other strategies such as the Crohn's Disease Exclusion Diet, which uses partial enteral nutrition (approximately 50% of calories through enteral nutrition and 50% of calories through a whole-foods diet). This diet has shown potential effectiveness, both in the adult and pediatric patient populations, with reasonable remission rates around week 6 and some evidence of endoscopic healing by week 24.

As mentioned, one of the main obstacles to dietary-based strategies is adherence. Additionally, the patient's diet is somewhat limited, there may be concern for the development of malnutrition as a result of implementing these strategies, and cost can be a problem because nutritional supplements are not routinely covered by health insurance. Whole-foods diets tend to be more expensive to maintain, and there is a lot of variability in terms of access to optimal food choices based on socioeconomics and geographics. Therefore, while dietary strategies may be great to consider in concept and in ideal circumstances, they are harder to execute in everyday clinical practice.

### G&H Other than medical therapy, how should mild Crohn's disease be managed holistically?

**CH** Certainly, providers want to achieve mucosal healing in an ideal setting, but aside from just managing luminal disease activity, optimizing diet is important because diets high in saturated fats, ultra-processed foods, and certain emulsifiers or carrageenans may be associated with increased disease activity or likelihood of being diagnosed with Crohn's disease later in life. Therefore, dietary guidance early on is important. Additionally, anxiety, depression, and trauma are associated with a Crohn's disease diagnosis, so having access to psychosocial care is key.

Also, modifiable variables should be optimized. Smoking has a negative impact on Crohn's disease, so starting a conversation about smoking cessation for current smokers is important. The exact role of obesity in Crohn's disease and ulcerative colitis is unclear, but obesity in and of itself is an inflammatory state, so optimizing weight management is essential. Many of these patients have not started advanced therapies yet, so being on top of preventive care, especially vaccinations, is important because certain vaccines such as live vaccines (eg, measles, mumps, and rubella; chickenpox) may not be administered in the setting of immunosuppression. Being up-to-date on those vaccines is key in anticipation of future use of such treatment.

### G&H How can patients be best monitored for disease progression?

**CH** First of all, providers should see patients in the clinic for routine follow-ups at intervals based on their initial presentation. The main thing is to identify markers that can be assessed and followed over time. Having a baseline set of laboratory tests, including blood count, metabolic profile, liver chemistries, albumin, C-reactive protein, and fecal calprotectin, and following them will be helpful to determine objective changes over time. The 4 biomarkers that I follow the most are probably C-reactive protein, fecal calprotectin, hemoglobin, and iron. Additionally, I consider weight to be a critical vital sign for Crohn's disease. If patients are fairly asymptomatic and not on advanced therapies, I see them perhaps once or twice a year. If patients are symptomatic, I usually try to see them 2 to 3 times a year to try to capture changes in activity and implement therapies earlier rather than later.

### G&H Are there any common misconceptions about mild Crohn's disease?

**CH** Not all mild Crohn's disease patients require longitudinal or maintenance treatment, but all mild Crohn's disease patients should undergo long-term monitoring. Another issue, which is probably the bigger of the two, is undertreatment of mild Crohn's disease. Understanding risk stratification, especially for patients who are younger, is key because undertreatment of mild Crohn's disease for patients who are higher risk for progression may impact their natural history. The earlier treatment is started, the better long-term outcomes will be and the more likely patients will respond to treatment. What is tricky about Crohn's disease is that it is often clinically silent or indolent until it is not. If providers wait until patients have obstructive or fistulizing complications, the likelihood of successful therapy is lower, and the likelihood of needing surgery and increased health care utilization is higher.

***Disclosures***

*Dr Ha has served on consulting/advisory boards for AbbVie, Bausch Health, Janssen, Lilly, Bristol Myers Squibb, Roivant, Pfizer, and Takeda; the data and safety monitoring board for Takeda; and received educational grant support from AbbVie, Janssen, Takeda, Pfizer, and Helmsley Charitable Trust.*

## Suggested Reading

Agrawal M, Spencer EA, Colombel JF, Ungaro RC. Approach to the management of recently diagnosed inflammatory bowel disease patients: a user's guide for adult and pediatric gastroenterologists. *Gastroenterology*. 2021;161(1):47-65.

Claytor J, Kumar P, Ananthakrishnan AN, Colombel JF, Agrawal M, Ungaro RC. Mild Crohn's disease: definition and management. *Curr Gastroenterol Rep*. 2023;25(3):45-51.

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