ACG Clinical Guideline: Management of Crohn's Disease in Adults

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Am J Gastroenterol advance online publication, 27 March 2018; doi: 10.1038/ajg.2018.27

Abstract

Crohn's disease is an idiopathic inflammatory disorder of unknown etiology with genetic, immunologic, and environmental influences. The incidence of Crohn's disease has steadily increased over the past several decades. The diagnosis and treatment of patients with Crohn's disease has evolved since the last practice guideline was published. These guidelines represent the official practice recommendations of the American College of Gastroenterology and were developed under the auspices of the Practice Parameters Committee for the management of adult patients with Crohn's disease. These guidelines are established for clinical practice with the intent of suggesting preferable approaches to particular medical problems as established by interpretation and collation of scientifically valid research, derived from extensive review of published literature. When exercising clinical judgment, health-care providers should incorporate this guideline along with patient's needs, desires, and their values in order to fully and appropriately care for patients with Crohn's disease. This guideline is intended to be flexible, not necessarily indicating the only acceptable approach, and should be distinguished from standards of care that are inflexible and rarely violated. To evaluate the level of evidence and strength of recommendations, we used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system. The Committee reviews guidelines in depth, with participation from experienced clinicians and others in related fields. The final recommendations are based on the data available at the time of the production of the document and may be updated with pertinent scientific developments at a later time.

Introduction

Crohn's disease has been increasing in incidence and prevalence worldwide. At the same time, the number of therapeutic options is rapidly increasing. The purpose of this guideline is to review Crohn's disease clinical features and natural history, diagnostics, and therapeutic interventions.

To prepare this guideline, literature searches on the different areas were conducted using Ovid MEDLINE from 1946 to 2018, EMBASE from 1988 to 2018, and SCOPUS from 1980 to 2018. The major terms that were searched were Crohn's disease, inflammatory bowel diseases (IBD), regional ileitis, and regional enteritis. These were translated into EMTREE controlled vocabulary as enteritis and Crohn's disease. The remainder of the search included key words related to the subject area that included clinical features, natural history, diagnosis, biomarkers, treatment, and therapy. For each of the therapeutic sections, key words included the individual drug names. The results used for analysis were limited to primary clinical trials, meta-analyses, systematic reviews, and prior guidelines. Where

there were limited data, abstracts were used. In many areas reviewed, there were not available clinical trial data, and these areas are discussed as summary statements rather than GRADE statements.

To evaluate the level of evidence and strength of recommendations, we used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system (1). The level of evidence could range from "high" (implying that further research as unlikely to change the authors' confidence in the estimate of the effect), "moderate" (further research would be likely to have an impact on the confidence in the estimate of effect), "low" (further research would be expected to have an important impact on the confidence in the estimate of the effect and would be likely to change the estimate), or "very low" (any estimate of effect is very uncertain). The strength of a recommendation was graded as "strong" when the desirable effects of an intervention clearly outweigh the undesirable effects and as "conditional" when there is uncertainty about the trade-off s. We preferentially used metaanalyses or systematic reviews when available, followed by clinical trials and retrospective cohort studies. To determine the level of evidence, we entered data for the papers of highest evidence into the GRADE program (accessible at http://www.gradepro.org). The GRADE recommendations statements from this guideline are in **Table 1**. Summary statements are descriptive and do not have associated evidence-based ratings (**Table 2**). In this guideline, the numbered statements are the GRADE statements and the unnumbered statements relate to summary statements.

Table 1. Summary and strength of recommendations	
Diagnosis	
	Routine laboratory investigation
1.	Fecal calprotectin is a helpful test that should be considered to help differentiate the presence of IBD from irritable bowel syndrome (IBS) (strong recommendation, moderate level of evidence).
	Endoscopy
2.	In patients at particularly high risk for colorectal neoplasia (e.g., personal history of dysplasia, primary sclerosing cholangitis), chromoendoscopy should be used during colonoscopy, as it may increase the diagnostic yield for detection of colorectal dysplasia, especially compared with standard-definition white light endoscopy (conditional recommendation, low level of evidence).
3.	For patients undergoing surveillance colonoscopy there is insufficient evidence to recommend universal chromoendoscopy for IBD colorectal neoplasia surveillance if the endoscopist has access to high-definition white light endoscopy (conditional recommendation, moderate level of evidence).
4.	Narrow-band imaging should not be used during colorectal neoplasia surveillance examinations for Crohn's disease (conditional recommendation, very low level of evidence).
5.	Endoscopists who are sufficiently trained and comfortable performing chromoendoscopy may be able to forgo obtaining random surveillance biopsies and rely on targeted biopsies alone (conditional recommendation, very low level of evidence).
	Disease modifiers
6.	Nonsteroidal anti-inflammatory drugs (NSAIDs) may exacerbate disease activity and should be avoided when possible in patients with Crohn's disease (strong recommendation, low level of evidence).

Table 1. Summary and strength of recommendations *continued*	
7.	Cigarette smoking exacerbates disease activity and accelerates disease recurrence and should be avoided. Active smoking cessation programs should be encouraged (strong recommendation, low level of evidence).
8.	Usage of antibiotics should not be restricted in Crohn's disease patients in order to prevent disease flares (conditional recommendation, very low level of evidence).
9.	Perceived stress, depression, and anxiety, which are common in IBD, are factors that lead to decreased health-related quality of life in patients with Crohn's disease, and lead to lower adherence to provider recommendations. Assessment and management of stress, depression, and anxiety should be included as part of the comprehensive care of the Crohn's disease patient (strong recommendation, very low level of evidence)
Medical Therapy	
	Mild-to-moderately severe disease/low-risk disease
10.	Sulfasalazine is effective for treating symptoms of colonic Crohn's disease that is mild to moderately active and can be used as treatment for this patient population (conditional recommendation, low level of evidence).
11.	Oral mesalamine has not consistently been demonstrated to be effective compared with placebo for induction of remission and achieving mucosal healing in patients with active Crohn's disease and should not be used to treat patients with active Crohn's disease (strong recommendation, moderate level of evidence).
12.	Controlled ileal release budesonide at a dose of 9 mg once daily is effective and should be used for induction of symptomatic remission for patients with mild-to-moderate ileocecal Crohn's disease (strong recommendation, low level of evidence).
13.	Metronidazole is not more effective than placebo as therapy for luminal inflammatory Crohn's disease and should not be used as primary therapy (conditional recommendation, low level of evidence).
14.	Ciprofloxacin has shown similar efficacy to mesalamine in active luminal Crohn's disease but has not been shown to be more effective than placebo to induce remission in Crohn's disease and should not be used as therapy for luminal inflammatory Crohn's disease (conditional recommendation, very low level of evidence).
15	Antimycobacterial therapy has not been shown to be effective for induction or for maintenance of remission or mucosal healing in patients with Crohn's disease and should not be used as primary therapy (conditional recommendation, low level of evidence).
16	For patients with low risk of progression, treatment of active symptoms with anti-diarrheals, other non-specific medications, and dietary manipulation, along with careful observation for inadequate symptom relief, worsening inflammation, or disease progression, is acceptable (strong recommendation, very low level of evidence).

Table 1. Summary and strength of recommendations *continued*	
	Moderate-to-severe disease/moderate-to-high-risk disease
17	Oral corticosteroids are effective and can be used for short-term use in alleviating signs and symptoms of moderate to severely active Crohn's disease (strong recommendation, moderate level of evidence).
18	Conventional corticosteroids do not consistently achieve mucosal healing and should be used sparingly (weak recommendation, low level of evidence).
19	Azathioprine (at doses of 1.5–2.5 mg/kg/day) and 6-mercaptopurine (at doses of 0.75–1.5 mg/kg day) are not more effective than placebo to induce short-term symptomatic remission and should not be used in this manner (strong recommendation, low level of evidence).
20	Thiopurines (azathioprine, 6-mercaptopurine) are effective and should be considered for use for steroid sparing in Crohn's disease (strong recommendation, low level of evidence).
21	Azathioprine and 6-mercaptourine are effective therapies and should be considered for treatment of patients with Crohn's disease for maintenance of remission (strong recommendation, moderate level of evidence).
22	Thiopurine methyltransferase (TPMT) testing should be considered before initial use of azathioprine or 6-mercaptopurine to treat patients with Crohn's disease (strong recommendation, low level of evidence).
23	Methotrexate (up to 25 mg once weekly IM or SC) is effective and should be considered for use in alleviating signs and symptoms in patients with steroid-dependent Crohn's disease and for maintaining remission (conditional recommendation, low level of evidence).
24	Anti-TNF agents (infliximab, adalimumab, certolizumab pegol) should be used to treat Crohn's disease that is resistant to treatment with corticosteroids (strong recommendation, moderate level of evidence).
25	Anti-TNF agents should be given for Crohn's disease refractory to thiopurines or methotrexate (strong recommendation, moderate level of evidence).
26.	Combination therapy of infliximab with immunomodulators (thiopurines) is more effective than treatment with either immunomodulators alone or infliximab alone in patients who are naive to those agents (strong recommendation, high level of evidence).
27.	For patients with moderately to severely active Crohn's disease and objective evidence of active disease, anti-integrin therapy (with vedolizumab) with or without an immunomodulator is more effective than placebo and should be considered to be used for induction of symptomatic remission in patients with Crohn's disease (strong recommendation, high level of evidence).
28.	Natalizumab is more effective than placebo and should be considered to be used for induction of symptomatic response and remission in patients with active Crohn's disease (strong recommendation, high level of evidence).
29.	Natalizumab should be used for maintenance of natalizumab-induced remission of Crohn's disease only if serum antibody to John Cunningham (JC) virus is negative. Testing for anti-JC virus antibody should be repeated every 6 months and treatment stopped if the result is positive. (strong recommendation, moderate level of evidence).

Table 1. Summary and strength of recommendations *continued*	
30.	Ustekinumab should be given for moderate-to-severe Crohn's disease patients who failed previous treatment with corticosteroids, thiopurines, methotrexate, or anti-TNF inhibitors or who have had no prior exposure to anti-TNF inhibitors (strong recommendation, high level of evidence).
31.	Cyclosporine, mycophenolate mofetil, and tacrolimus should not be used for Crohn's disease (strong recommendation, moderate level of evidence).
	Severe/fulminant disease
32.	Intravenous corticosteroids should be used to treat severe or fulminant Crohn's disease (conditional recommendation, moderate level of evidence).
33.	Anti-TNF agents (infliximab, adalimumab, certolizumab pegol) can be considered to treat severely active Crohn's disease (strong recommendation, moderate level of evidence).
34.	Infliximab may be administered to treat fulminant Crohn's disease (conditional recommendation, low level of evidence).
Fistulizing Crohn's Disease	
	Perianal/fistulizing disease
35.	Infliximab is effective and should be considered in treating perianal fistulas in Crohn's disease (strong recommendation, moderate level of evidence).
36.	Infliximab may be effective and should be considered in treating enterocutaneous and rectovaginal fistulas in Crohn's disease (strong recommendation, moderate level of evidence)
37.	Adalimumab and certolizumab pegol may be effective and should be considered in treating perianal fistulas in Crohn's disease (strong recommendation, low level of evidence).
38.	Thiopurines (azathioprine, 6-mercaptopurine) may be effective and should be considered in treating fistulizing Crohn's disease (strong recommendation, low level of evidence).
39.	Tacrolimus can be administered for short-term treatment of perianal and cutaneous fistulas in Crohn's disease (strong recommendation, moderate level of evidence).
40.	Antibiotics (imidazoles) may be effective and should be considered in treating simple perianal fistulas (strong recommendation, moderate level of evidence).
41.	The addition of antibiotics to infliximab is more effective than infliximab alone and should be considered in treating perianal fistulas (strong recommendation, moderate level of evidence).
42.	Drainage of abscesses (surgically or percutaneously) should be undertaken before treatment of fistulizing Crohn's disease with anti-TNF agents (conditional recommendation, very low level of evidence).
43.	Placement of setons increases the efficacy of infliximab and should be considered in treating perianal fistulas (strong recommendation, moderate level of evidence).
Maintenance Therapy of Luminal Crohn's Disease	
44.	Once remission is induced with corticosteroids, a thiopurine or methotrexate should be considered (strong recommendation, moderate level of evidence).
45.	Patients who are steroid dependent should be started on thiopurines or methotrexate with or without anti-TNF therapy (strong recommendation, moderate level of evidence).

Table 1. Summary and strength of recommendations *continued*	
46.	Oral 5-aminosalicylic acid has not been demonstrated to be effective for maintenance of medically induced remission in patients with Crohn's disease, and is not recommended for long-term treatment (strong recommendation, moderate level of evidence).
47.	Corticosteroids are not effective for maintenance of medically induced remission in Crohn's disease and should not be used for long-term treatment (strong recommendation, moderate level of evidence).
48.	Budesonide should not be used to maintain remission of Crohn's disease beyond 4 months (strong recommendation, moderate level of evidence).
49.	Anti-TNF therapy, specifically infliximab, adalimumab, and certolizumab pegol, should be used to maintain remission of anti-TNF-induced remission (strong recommendation, high level of evidence).
50.	Anti-TNF monotherapy is effective at maintaining anti-TNF induced remission, but because of the potential for immunogenicity and loss of response, combination with azathioprine/6-mercaptopurine or methotrexate should be considered (strong recommendation, moderate level of evidence).
51.	Vedolizumab should be used for maintenance of remission of vedolizumab-induced remission of Crohn's disease (conditional recommendation, moderate level of evidence).
52.	Natalizumab should be considered for maintaining remission of natalizumab-induced remission of Crohn's disease patients only if John Cunningham (JC) virus is negative (conditional recommendation, moderate level of evidence).
53.	Ustekinumab should be use for maintenance of remission of ustekinumab-induced response of Crohn's disease (conditional recommendation, moderate level of evidence).
Postoperative Crohn's Disease	
54.	All patients who have Crohn's disease should quit smoking (conditional recommendation, very low level of evidence).
55.	Mesalamine is of limited benefit in preventing postoperative Crohn's disease, but in addition to no treatment is an option for patients with an isolated ileal resection and no risk factors for recurrence (conditional recommendation, moderate level of evidence).
56.	Imidazole antibiotics (metronidazole and ornidazole) at doses between 1 and 2 g/day can be used after small intestinal resection in Crohn's disease patients to prevent recurrence (conditional recommendation, low level of evidence).
57.	Thiopurines may be used to prevent clinical and endoscopic recurrence and are more effective than mesalamine or placebo. However, they are not effective at preventing severe endoscopic recurrence (strong recommendation, moderate level of evidence).
58.	In high-risk patients, anti-TNF agents should be started within 4 weeks of surgery in order to prevent postoperative Crohn's disease recurrence (conditional recommendation, low level of evidence).
59.	Although data are lacking in postoperative Crohn's disease, anti-TNF therapy should be combined with an immunomodulator to decrease immunogenicity and decrease loss of response (conditional recommendation, very low level of evidence).

Table 1. Summary and strength of recommendations *continued*	
When to refer to surgery	
60.	An intra-abdominal abscess should be treated with antibiotics and a drainage procedure, either radiographically or surgically (conditional recommendation, low level of evidence).
IBD, inflammatory bowel disease; IM, intramuscular; SC, subcutaneous; TNF, tumor necrosis factor.	

Table 2. Summary statements	
Clinical Features	
1.	Hallmark/cardinal symptoms of Crohn's disease include abdominal pain, diarrhea, and fatigue; weight loss, fever, growth failure, anemia, recurrent fistulas, or extraintestinal manifestations can also be presenting features.
2.	Crohn's disease is diagnosed clinically. There are no truly pathognomonic features. Endoscopic, radiographic, and histologic criteria with evidence of chronic intestinal inflammation will be present.
3.	Extraintestinal manifestations of Crohn's disease include the classic ones such as arthropathy (both axial and peripheral); dermatological (including pyoderma gangrenosum and erythema nodosum); ocular (including uveitis, scleritis, and episcleritis); and hepatobiliary disease (i.e., primary sclerosing cholangitis). Other extraintestinal complications of Crohn's disease include: thromboembolic (both venous and arterial); metabolic bone diseases; osteonecrosis; cholelithiasis; and nephrolithiasis. A number of other immune-mediated diseases are associated with Crohn's disease, including asthma, chronic bronchitis, pericarditis, psoriasis, celiac disease, rheumatoid arthritis, and multiple sclerosis.
Natural History	
4.	Crohn's disease, in most cases, is a chronic, progressive, destructive disease.
5.	The location of Crohn's disease tends to be stable, but can occasionally extend.
6.	Most, but not all, patients with Crohn's disease will present with nonpenetrating, nonstricturing disease behavior, but up to half of patients would have developed an intestinal complication (i.e., stricture, abscess, fistula, or phlegmon) within 20 years of diagnosis. Patients with ileal, ileocolonic, or proximal GI involvement are significantly more likely than those with isolated colonic disease to progress to an intestinal complication. Extensive anatomic involvement and deep ulcerations are other risk factors for progression to intestinal complications.
7.	Over long periods of observation, only 20–30% of patients with Crohn's disease will have a nonprogressive or indolent course. Therefore, the majority of patients will require active effort to identify therapies that achieve adequate control of bowel inflammation.
8.	Features that are associated with a high risk for progressive disease burden include young age at diagnosis (11), initial extensive bowel involvement, ileal/ileocolonic involvement, perianal/severe rectal disease, and patients presenting with a penetrating or stenosis disease phenotype (12). Visceral adiposity may be a marker for increased risk of penetrating disease (13).
9.	Symptoms of Crohn's disease do not correlate well with the presence of active inflammation, and therefore should not be the sole guide for therapy. Objective evaluation by endoscopic or cross-sectional imaging should be undertaken periodically to avoid errors of under- or over treatment.

Table 2. Summary statements *continued*	
10.	Perianal fistulizing Crohn's disease occurs in up to one-quarter of patients.
11.	Symptoms of Crohn's disease occur in most cases as a chronic, intermittent course; only a minority of patients will have continuously active symptomatic disease or prolonged symptomatic remission.
12.	In the absence of immunomodulator or biologic treatment, steroid dependency and/or resistance occurs in up to half of patients.
13.	Up to 80% of patients with Crohn's disease require hospitalization at some point during their clinical course, but the annual hospitalization rate decreases in later years after diagnosis.
14.	The 10-year cumulative risk of major abdominal surgery in Crohn's disease is 40% to 55%, although recent studies performed in the biologic era suggest that the 10-year risk may have decreased to 30%. The 10-year risk of a second resection after the first is 35%, although again more recent studies suggest that this may have dropped to closer to 30%.
15	In Crohn's disease, the 5-year rate of symptomatic postoperative recurrence is $\sim$ 50%.
16	Overall mortality in Crohn's disease is slightly increased, with a standardized mortality ratio of 1.4 times that of the general population. Causes of excess mortality include gastrointestinal disease, gastrointestinal cancer, lung disease, and lung cancer.
Intestinal Malignancy	
17	Patients with colonic involvement are at increased risk of colorectal cancer, and risk factors include duration of disease, extent of colonic involvement, primary sclerosing cholangitis, family history of colorectal cancer, and severity of ongoing colonic inflammation.
18	Patients with small bowel involvement are at increased risk of small bowel adenocarcinoma that can be difficult to diagnose preoperatively.
Diagnosis	
	Routine laboratory investigation
19	Initial laboratory investigation should include evaluation for inflammation, anemia, dehydration, and malnutrition.
20	In patients who have symptoms of active Crohn's disease, stool testing should be performed to include fecal pathogens, *Clostridium difficile* testing, and may include studies that identify gut inflammation such as a fecal calprotectin.
	Genetic testing
21	Genetic testing is not indicated to establish the diagnosis of Crohn's disease.
22	Certain genetic variants are associated with different phenotypic expressions in Crohn's disease but testing remains a research tool at this time.
	Serologic markers of IBD
23	Routine use of serologic markers of IBD to establish the diagnosis of Crohn's disease is not indicated.
	Endoscopy
24	Ileocolonoscopy with biopsies should be performed in the assessment of patients with suspected Crohn's disease.

Table 2. Summary statements *continued*	
25	Disease distribution and severity should be documented at the time of diagnosis. Biopsies of uninvolved mucosa are recommended to identify extent of histologic disease.
26.	Upper endoscopy should only be performed in patients with upper gastrointestinal signs and symptoms.
27.	Video capsule endoscopy (VCE) is a useful adjunct in the diagnosis of patients with small bowel Crohn's disease in patients in whom there is a high index of suspicion of disease.
28.	Patients with obstructive symptoms should have small bowel imaging and/or patency capsule evaluation before VCE to decrease risk of capsule retention.
29.	Deep enteroscopy is not part of routine diagnostic testing in patients with suspected Crohn's disease, but may provide additional information in patients who require biopsy/sampling of small bowel tissue to make a diagnosis.
	Imaging studies
30.	Small bowel imaging should be performed as part of the initial diagnostic workup for patients with suspected Crohn's disease.
31.	Computed tomography enterography (CTE) is sensitive for the detection of small bowel disease in patients with Crohn's disease and is comparable to magnetic resonance enterography (MRE).
32.	Because of the absence of any radiation exposure, MRE should be used preferentially in young patients (<35 years) and in patients in whom it is likely that serial exams will need to be performed.
33.	The decision for which small bowel imaging study to use is in part related to the expertise of the institution and the clinical presentation of the patient.
34.	Cross-sectional imaging with MRI of the pelvis and/or endoscopic ultrasound may be used to further characterize perianal Crohn's disease and perirectal abscesses.
35.	If an intra-abdominal abscess is suspected, cross-sectional imaging of the abdomen and pelvis should be performed.
	Determining disease activity and distribution
36.	IBD type, location, and disease activity should be documented in the medical record.
	Monitoring disease activity
37.	Fecal calprotectin and fecal lactoferrin measurements may have an adjunctive role in monitoring disease activity.
38.	Serum CRP is relatively nonspecific for the inflammation of Crohn's disease, but in select patients serial measurements may have a role in monitoring disease activity and response to therapy
39.	Periodic cross-sectional imaging (CTE, MRE) may be considered in monitoring response to therapy in certain patients with small bowel Crohn's disease.
40.	Mucosal healing as determined by endoscopy is a goal of therapy. a. Endoscopic scores have been developed that are reliable in measuring degree of mucosal healing and may be used to monitor response to therapy. b. Evaluation of the ileum for post-operative endoscopic recurrence by colonoscopy within a year after ileocolonic resection may help guide further therapy.

Table 2. Summary statements *continued*	
Management of Disease	
	Moderate-to-severe disease/moderate-to-high-risk disease
41.	Systemic corticosteroids are ineffective for maintenance therapy in patients with Crohn's disease. Topical corticosteroids, although commonly used in Crohn's disease, are of limited benefit.
42.	Azathioprine, 6-mercaptopurine, or methotrexate (15 mg once weekly) may be used in treatment of active Crohn's disease and as adjunctive therapy for reducing immunogenicity against biologic therapy.
	Biosimilar anti-TNF agents
43.	Biosimilar infliximab and biosimilar adalimumab are effective treatments for patients with moderate-to-severe Crohn's disease and can be used for *de novo* induction and maintenance therapy.
44.	Insufficient data exist to support the safety and efficacy of switching patients in stable disease maintenance from one biosimilar to another of the same biosimilar molecule.
Fistulizing Crohn's Disease	
	Perianal/fistulizing disease
45.	The presence of a perianal abscess in Crohn's disease should prompt surgical drainage.
Maintenance Therapy of Luminal Crohn's Disease	
46.	No maintenance treatment is a treatment option for some patients with asymptomatic (silent), mild Crohn's disease.
47.	Surgery may be considered for patients with symptomatic Crohn's disease localized to a short segment of bowel.
48.	Data are lacking demonstrating the effectiveness of sulfasalazine or of olsalazine for the maintenance of medically induced remission in patients with Crohn's disease and are these agents not recommended for long-term treatment.
Postoperative Crohn's Disease	
49.	Prophylactic treatment is recommended after small intestinal resection in patients with risk factors for recurrence.
50.	Risk factors for postoperative Crohn's disease recurrence should be taken into account when deciding on treatment.
	When to refer to surgery
51.	Surgery is required to treat enteric complications of Crohn's disease.
52.	A resection of a segment of diseased intestine is the most common surgery for a Crohn's disease.
53.	Crohn's disease patients who develop an abdominal abscess should undergo a surgical resection. However, some may respond to medical therapy after radiologically guided drainage.
CRP, C-reactive protein; GI, gastrointestinal; IBD, inflammatory bowel disease; MRI, magnetic resonance imaging; TNF, tumor necrosis factor.	

Future Directives

Despite the recent advances in the treatment of patients with CD, there still remains a large group of patients who do not respond adequately to our current medication armamentarium. We cannot selectively determine whether an individual will respond to a particular biologic, it is more of a "wait and see" approach. We are now entering an era of precision medicine and have begun to explore factors that predict response or nonresponse. In the future, biological therapies for IBD are likely to be used more selectively based on an individual patient's specific benefit/risk assessment, as determined by specific tissue signatures and reliable biomarkers, and will probably be adjusted throughout the course of their treatment. We will certainly expand our medical treatment war chest and uncover effective biologics with different mechanisms of action to treat our patients. If the initial biologic drug fails, patients will be able to switch to another agent and even combination biologics may become a reality.

Novel Agents

There are currently numerous novel agents in various phases of development being investigated for their ability to effectively treat patients with CD. There is an unmet need for the treatment of patients with CD. Approximately one-third of patients who are anti-TNF naive have a primary nonresponse to anti-TNF therapy. Among patients who are initial anti-TNF therapy responders, approximately one-third subsequently lose their response to therapy or become intolerant to therapy (secondary nonresponders). These secondary nonresponders can either escalate dose of their current medication, switch to another anti-TNF agent, or switch out of class (to an anti-integrin (natalizumab or vedolizumab), anti-IL-12 / 23 (ustekinumab), or to a novel mechanism. Those individuals who switch to therapy within class have less benefit than individuals who are TNF naive.

Some of the other agents under different stages of development for the treatment of patients with CD include other anti-integrins such as etrolizumab (which is a dual action anti-integrin that inhibits both α4β7 and αEβ7) or ozanimod (a potent sphingosine-1-phosphate receptor modulator that inhibits the egress of lymphocytes from lymph nodes) (370,371). Several other agents in early phases of development include the anti-IL-23 agents, risankizumab (372) and brazikumab (373), and the selective Janus kinase-1 inhibitors, filgotinib (374) and upadacitinib (formerly ABT-494) (375).