Gastroenterology 2021;161:47–65

REVIEWS IN BASIC AND CLINICAL GASTROENTEROLOGY AND HEPATOLOGY

Douglas J. Robertson and Vincent W. Yang, Section Editors

Approach to the Management of Recently Diagnosed Inflammatory Bowel Disease Patients: A User's Guide for Adult and Pediatric Gastroenterologists

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Inflammatory bowel diseases (IBDs), including Crohn's disease and ulcerative colitis, are chronic, progressive, immune-mediated diseases of adults and children that have no cure. IBD can cause significant morbidity and lead to complications such as strictures, fistulas, infections, and cancer. In children, IBD can also result in growth impairment and pubertal delays. IBD is highly heterogenous, with severity ranging from mild to severe and symptoms ranging from mild to debilitating. Delay in IBD diagnosis, especially in Crohn's disease, is common and associated with adverse outcomes. Early diagnosis and prompt institution of treatment are the cornerstones for improving outcomes and maximizing health. Early diagnosis requires a low threshold of suspicion and red flags to guide early specialist referral at the primary provider level. Although the armamentarium of IBD medications is growing, many patients will not respond to treatment, and the selection of first-line therapy is critical. Risk stratification of disease severity, based on clinical, demographic, and serologic markers, can help guide selection of first-line therapy. Clinical decision support tools, genomics, and other biomarkers of response to therapy and risk of adverse events are the future of personalized medicine. After starting appropriate therapy, it is important to confirm remission using objective end points (treat to target) with continued control of inflammation with adjustment of therapy using surrogate biomarkers (tight control). Lastly, IBD therapy extends far beyond medications, and other aspects of the overall health and wellbeing of the patient are critical. These include preventive health, nutrition, and psychobehavioral support addressing patients' concerns around complementary therapy and medication adherence, prevention of disability, and ensuring open communication.

Keywords: Inflammatory Bowel Disease; Crohn's Disease; Ulcerative Colitis; Early Diagnosis; Early Therapy; Personalized Therapy; Adult; Pediatric.

Inflammatory bowel diseases (IBDs), including the main subtypes Crohn's disease (CD) and ulcerative colitis (UC), are chronic, progressive, immune-mediated diseases of the intestinal tract that have no cure.[1,2] IBDs are associated with significant morbidity, disability, and risk of complications.[3,4] Although they can occur at any age, IBDs are most common among adolescents and young adults. In developed counties, IBD incidence, although stable at approximately 1%, is higher than mortality, leading to compounding prevalence and rising burden of IBDs.[5] In developing countries, IBD incidence and prevalence are also on the rise, especially in the last few decades.[6] Direct and indirect costs of IBD are substantial. Within the United States, direct health care costs among IBD patients are 3 times as high compared as those among non-IBD patients.[7,8]

Early management of IBD, including both diagnosis and treatment, are critical to improve quality of life and prevent complications. This review summarizes the existing literature on, and proposes a framework for how to best manage, CD and UC early in the disease course in adult and pediatric patients.

Early Diagnosis and Treatment: Gateways for Improved Prognosis in Inflammatory Bowel Diseases

Inflammatory Bowel Diseases Are Progressive Diseases

The natural history of both CD and UC can vary from mild disease with few symptoms to complicated disease with strictures and fistulas. In a French population-based study of incident CD, the cumulative probability of

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Abbreviations used in this paper: ADA, adalimumab; AGA, American Gastroenterological Association; CD, Crohn's disease; CDST, clinical decision support tool; CI, confidence interval; CRP, C-reactive protein; EEN, exclusive enteral nutrition; EIM, extraintestinal manifestation; FC, fecal calprotectin; HR, hazard ratio; IBD, inflammatory bowel disease; ICR, ileocolic resection; IFX, infliximab; IMM, immunomodulator; IQR, interquartile range; MRI, magnetic resonance imaging; NUDT15, nudix hydrolase; OR, odds ratio; SUCRA, surface under the cumulative ranking; TDM, therapeutic drug monitoring; TPMT, thiopurine methyltransferase; TNFi, tumor necrosis factor inhibitor; UC, ulcerative colitis; UST, ustekinumab; VDZ, vedolizumab.

Most current article

0016-5085/$36.00
https://doi.org/10.1053/j.gastro.2021.04.063

perianal CD varied between 11% and 19% at 1–10 years after diagnosis.[9] In a study of 983 patients with CD in Asia, stricturing or penetrating CD occurred in 41% and perianal disease in 25% of patients.[10] At the other end of the spectrum, incidental terminal ileitis can be diagnosed in 1.6% of individuals undergoing nondiagnostic colonoscopy, with an uncertain but likely low rate of progression to overt CD.[11] With respect to UC, most patients have mild to moderate severity and 10%–15% of patients can experience a severe course.[12] In a population-based cohort study, proctosigmoid location of colitis occurred in 73% of patients; of these, disease extension occurred in 23% of patients at 7 years of follow-up and it was a marker of worse prognosis.[13] The risk of surgery for CD and UC can be up to 46.6% and 15.6% 10 years after diagnosis, respectively, and has decreased significantly during the last 6 decades.[14]

The symptoms associated with IBD can be waxing and waning, but the underlying systemic inflammation can lead to progressive, cumulative, and often irreversible intestinal damage and risk of complications if not treated adequately.[15] Complications associated with ongoing inflammation in CD include strictures, obstructions, fistulas, abscesses, and surgery,[3,16] and those associated with UC include loss of colonic and anorectal function, surgery, and colorectal cancer.[2,4,17] Other complications include anemia, nutritional deficiencies, loss of bone density, and progressive loss of quality of life. In children, persistent inflammation is associated with growth impairment, risking permanent loss of height.[18] Similar to other chronic diseases, such as rheumatoid arthritis, the concept of cumulative damage is now acknowledged in IBD and can be measured using validated tools, such as the Lemann Index.[19]

Limited Correlations Among Inflammation, Symptoms, and Complications

The concordance between intestinal inflammation and symptoms can be limited, especially in CD.[20,21] In a population-based cohort, more than 20% of CD patients were found to have strictures and penetrating disease at the time of diagnosis, suggesting that clinically silent inflammation may precede formal diagnosis.[22] The STRIDE (Selecting Therapeutic Targets in Inflammatory Bowel Disease) recommendations, updated recently, are meant to target endoscopic healing, minimize disability, and restore quality of life and adequate growth in children, in addition to control of symptoms.[23] Therefore, rather than a gradual "step-up" approach, in which treatment adjustment is based on the severity of symptoms, the recommended treat-to-target approach aims to achieve endoscopic healing and control of inflammation and involves early, aggressive treatment in appropriate patients.[23]

Delay in Diagnosis Leads to Adverse Outcomes

Delay in diagnosis is more common in CD than UC (median delay, 7.6 months; interquartile range [IQR], 3.1–15.0 months and 3.3 months; IQR, 1.9–7.3 months, respectively; $P < .001$).[24] Data from the Swiss IBD cohort demonstrate that CD diagnosis can be delayed in pediatric and adult patients by 3 months (IQR, 1–9 months) and 6 months (IQR, 1–24 months), respectively. Adults were more likely to present with strictures ($P < .001$) and require bowel surgery ($P < .001$). Furthermore, the duration of diagnostic delay has been associated with complications such as strictures and internal fistulae.[25] In a study, of adult CD patients in France, delay in diagnosis longer than 13 months was associated with higher risk of a major surgery ($P = .05$).[26]

Evidence of Disease Activity Before Diagnosis

There is a significant increase in gastrointestinal symptoms before IBD diagnosis (9.6% and 10.4% 5 years before CD and UC diagnosis, respectively, compared with 5.8% of controls).[27] In addition, patients who were diagnosed with irritable bowel syndrome or depression were less likely to receive timely specialist referral (irritable bowel syndrome: hazard ratio [HR], 0.77; 95% confidence interval [CI], 0.60–0.99, depression: HR, 0.77, 95% CI, 0.60–0.98), suggesting that delays in IBD diagnosis may be related to focusing on comorbid or inaccurate diagnoses.[27] In a population-based study using data from the Danish registry, Vadstrup et al[28] found a significant increase in costs associated with health care services, prescription medicine, home care services, and labor productivity loss in the 10 years before IBD diagnosis.

Growth Impairment and Pubertal Delays in Children

IBD and ongoing inflammation can lead to impairment of growth and pubertal development to children. Impaired linear growth may be the only presenting symptom of IBD in pediatric patients.[29,30] Growth impairment is multifactorial in nature, representing the summation of nutritional deficiencies, altered eating habits, inflammatory cytokines, and corticosteroid use. Marked growth impairment at diagnosis, defined as a height z-score < -2.5, is a poor prognostic sign.[31] Furthermore, IBD patients exhibit "catch up" growth beyond the typically expected age for growth plate closure (median additional years to reach adult height: male patients with CD, 1.9 years and male patients with UC, 2.5 years; female patients with CD: 2.6 years and female patients with UC, 2.8 years), suggesting that achieving remission even after reaching adolescence may allow for maximal growth potential.[18]

Early Management Can Alter Disease Course and Prevent Complications

Data have consistently demonstrated that long-term IBD complications are mitigated by early treatment and remission. In the long-term follow-up data from the CALM trial, patients with early CD who achieved deep remission, compared to those who did not, had a significantly lower risk of new fistulas, abscesses, hospitalization, or surgery for CD (adjusted HR, 0.19; 95% CI, 0.07–0.31) during a median 3 years' follow-up.[32] Other CD studies have similarly demonstrated that early treatment is independently

associated with improved long-term outcomes.[33] Data on the impact of early therapy in UC are more limited, but, as UC is also a progressive disease with risk of colorectal cancer, surgery, and loss of colonic function, it is reasonable to treat early to mitigate these risks.

How to Diagnose Inflammatory Bowel Disease Early

IBD is heterogenous with wide variation in presentation. Disease activity at presentation can range from mild to severe and, as discussed, symptoms may be mild to none. These can make the IBD diagnosis challenging, especially at a primary care level. Danese et al[34] have proposed a Red Flags Index consisting of a 21-item questionnaire to help providers triage and identify patients with concerning symptoms in a timely manner and refer to specialists appropriately. A useful adjunct to symptom-based criteria is fecal calprotectin (FC), a stool marker of inflammation; in a large meta-analysis, FC $\leq$ 40 μg/g carried a $\leq$1% probability of IBD, effectively excluding the diagnosis of IBD.[35] Similarly, in the Red Flags Index validation study, combining the index with FC (Red Flags Index $\geq$8 and/or FC $>$250 μg/g) increased the positive predictive value from 4% to 21% and negative predictive value from 97% to 100%.[36] Diagnostic criteria for IBD involve a composite of clinical symptoms, endoscopic, biomarker, and cross-sectional imaging features, which are beyond the scope of this review. We refer readers to the excellent guidelines laid out by the American College of Gastroenterology, European Crohn's and Colitis Organization, and British Society of Gastroenterology.[37–40]

Risk Stratification and Prognostication at Diagnosis

Appropriately risk-stratifying prognosis in patients recently diagnosed with IBD is essential to inform selection of the most appropriate treatment and monitoring strategies. CD and UC phenotype and disease activity at initial presentation can vary widely from limited and mild to extensive and complicated. Certain baseline clinical features are associated with a more aggressive disease course with higher risk of progression and complications. In higher-risk patients, early control of inflammation with immune-modifying therapies is critical. However, immunosuppressive therapies are associated with safety concerns in the short- and long-term, and entail significant health care costs. Therefore, a consideration of risks, benefits, and alternatives is key to develop an individualized therapeutic plan for the informed patient.

It is important to differentiate between disease activity and severity. Although the former refers to the burden of inflammation at any given point in time, the latter takes into account the disease phenotype and course, and is helpful in determining prognosis and predicting complications (Figure 1). For example, a patient with low disease activity (little to no symptoms and low inflammatory markers) may actually have high severity (due to disease history or behavior) increasing the risk for disease progression, and should be managed more proactively and aggressively. We will review predictors of IBD severity and activity.

Age of Inflammatory Bowel Disease Diagnosis

Numerous studies suggest that younger age at diagnosis is tied to adverse outcomes in both CD and UC.[41] In CD, being diagnosed before the age of 40 years is associated with an increased risk (odds ratio [OR], 2.1; 95% CI, 1.3–3.6) of disabling disease 5 years after diagnosis, including higher rates of surgery, hospitalization, steroid dependence, and disease recurrence.[42,43] In UC, younger age at diagnosis is linked to more frequent relapses, colectomy, and colorectal cancer.[44,45] There are conflicting data on the disease course in the very-early-onset IBD population of patients diagnosed before age 6 years, with studies reporting both similar and worse outcomes in very-early-onset IBD compared to the general pediatric population.[46] Similar to the youngest patients with IBD, elderly-onset IBD (diagnosed at 60–65 years of age) has conflicting evidence on prognosis, with 1 study reporting fewer hospitalizations and less frequent requirement of immunosuppression in patients diagnosed after age 60 years,[47] and a meta-analysis suggested that, although elderly IBD presents less commonly with complications, there are similar or higher rates of surgery compared to a nonelderly population.[48] It is being increasingly recognized that frailty, rather than chronologic age, may be the driver of adverse outcomes in this group.[49,50]

Other Demographic Variables

There are significant differences in IBD phenotype and outcomes based on race and ethnicity, likely due to a multitude of factors, both social and biologic. Emergency department use, hospitalization, complicated disease course, and IBD-related disability are more common in minority and lower socioeconomic status groups.[51,52] In a study of 770 patients with IBD, South Asian immigrants living in the United Kingdom were more likely to have extensive UC and colonic CD compared with their native counterparts,[53] which might be related, in part, to limited access to care.[54] Genes implicated in IBD risk also differ in non-White compared with White patients with IBD.[55] Being aware of the higher vulnerability to adverse IBD-related outcomes in these vulnerable groups should prompt careful monitoring to limit adverse outcomes.

There are increasing data on sex-based differences in IBD phenotype and outcomes, which may signal differences in pathogenic pathways and progression. Of note, extra-intestinal manifestations (EIMs) consistently tend to be more common in female patients (CD: OR, 2.3; 95% CI, 1.9–2.8 and UC: OR, 1.5; 95% CI, 1.1–2.3, in a large Dutch BioBank).[56] Similarly, in a retrospective pediatric study of nearly 1000 patients with CD, girls were more likely to have EIMs and less likely to have growth impairment compared with boys,[57] the latter is possibly related to lower insulin-like growth factor-1 level in boys.[58]

Disease severity variables	CD	UC
Clinical		
Limited anatomic extent	X	X
Growth impairment (pediatric)	X	
Age at diagnosis <14 years	X	X
Age at diagnosis <40 years (adults)	X	X
Smoking history	X	
Perianal or severe rectal disease	X	
Penetrating disease	X	
Stricturing disease	X	
Multi- or long-segment ileal (>20 cm), disease proximal to TI	X	
Extensive bowel involvement	X	X
Emergent diagnosis, hospitalization	X	X
Delay in diagnosis	X	X
Need for systemic steroids	X	X
C difficile, cytomegalovirus infection		X
Serologies		
ASCA (+)	X	
ANCA (+)	X	X
Anti-Cbir (+) (UC: pediatric)	X	X
Anti-GMCSF (+)	X	
Genetic		
NOD2 mutation	X	

* Based on data from Torres et al, Lancet, 2017 (CD) and Rubin et al, AJG, 2019 (UC)

Disease activity variables*
Clinical
Symptoms
Biomarkers
C-reactive protein
Fecal calprotectin
Albumin
Hemoglobin
Endoscopic
Disease activity scores

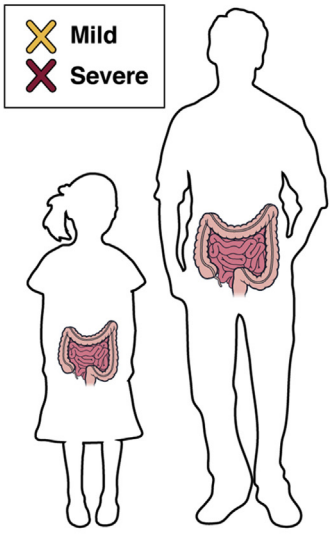


Figure 1. Inflammatory bowel disease severity vs disease activity variables. ASCA, anti-*Saccharomyces cerevisiae* antibodies; ANCA, anti-neutrophil cytoplasmic antibodies; GMCSF, granulocyte-macrophage colony-stimulating factor; TI, terminal ileum.

Disease Phenotype and Clinical Characteristics

The International Organization for the Study of Inflammatory Bowel Disease and the American Gastroenterological Association (AGA) provide a framework for categorization of CD and UC severity into mild-, moderate-, and high-risk groups based on phenotype and other characteristics.[59,60]

In CD, the presence of large or deep mucosal lesions on endoscopy or magnetic resonance imaging (MRI), history of a fistula, abscess, or intestinal resection are predictors of worse outcomes.[59,60] In a prospective population-based inception cohort of 213 patients with CD, penetrating behavior was associated with a higher risk of progression to perianal disease (HR, 5.65; 95% CI, 2.65–12.03) and was a risk factor for resection (HR, 3.92; 95% CI, 1.86–8.67) and hospitalization (HR, 1.01; 95% CI, 1.00–1.01).[16] Ileal and upper gastrointestinal disease location and extensive disease are also markers of severe disease.[61] Cigarette smoking is associated with complications and need for therapy escalation.[61]

In CD, the threshold of suspicion should be low for high-quality imaging of the pelvis, such as MRI, to rule our perianal CD. In a retrospective study of 136 pediatric CD patients, presence of anal fissures and skin tags, non-White race, and elevated C-reactive protein (CRP) were risk factors for perianal CD.[62] In another study of 274 patients in China with recently diagnosed CD, all of whom underwent MRI pelvis, asymptomatic perianal fistulas were diagnosed in 17.5% of patients and colonic location of CD was a risk factor for asymptomatic perianal fistulas.[63]

In UC, corresponding predictors of aggressive disease advised by the International Organization for the Study of Inflammatory Bowel Disease include active colonic ulcers and prior use of biologics.[59] Extensive colitis, deep ulcers, need for corticosteroids, hospitalization, *Clostridium difficile*, and cytomegalovirus infection also indicate higher colectomy risk.[64] Of note, disease extension from limited disease to extensive or pancolitis is associated with worse prognosis.[45,65]

In addition, co-occurrence of other immune-mediated inflammatory diseases can occur, most commonly with psoriasis and asthma, but also, in more rare instances, with other gastrointestinal diseases (eg, celiac, nonalcoholic fatty liver disease,[66] and eosinophilic esophagitis).[67,68] Presence of a concomitant immune-mediated inflammatory disease is

associated with worse outcomes. In a systematic review of 93 studies, the risk of extensive or pancolitis and IBD-related surgery was higher in IBD patients with immune-mediated inflammatory diseases (risk ratio, 1.38; 95% CI, 1.25–1.52; $P < .01$; $I^2 = 86\%$ and risk ratio, 1.17; 95% CI, 1.01–1.36; $P = .03$; $I^2 = 85\%$, respectively).[69]

Serologic Biomarkers

Of routinely available serologic biomarkers, CRP, an interleukin-6–dependent acute-phase reactant, is correlated with inflammatory burden, albeit nonspecifically, and is used for IBD risk stratification, with higher CRP (≥5 mg/dL) consistent with moderate to severe disease.[59,70] In addition, commercially available IBD serologic markers can help with prognostication. These include perinuclear antineutrophil antibody and several antimicrobial antibodies, notably anti-*Saccharomyces cerevisiae* antibody, antibody to *Escherichia coli* outer-membrane porin C, and antibody to flagellin (CBir1). In the Pediatric RISK Stratification study, a large prospective study of CD, patients positive for 2 or more serologic markers (anti-*Saccharomyces cerevisiae* antibody, outer-membrane porin C, and/or CBir1) progressed to a penetrating or stricturing complication more quickly than those with only 1 serologic marker, and those receiving anti-TNF in this cohort had a reduced likelihood of progression to penetrating complications, indicating a window to change disease complication.[41] Another autoantibody of interest is that to granulocyte-macrophage colony-stimulating factor, of which high expression has been associated with stricturing and penetrating behavior in adult and pediatric CD.[71,72]

Fecal Calprotectin

Stool markers of inflammation, of which FC is the most widely used, are more specific for bowel inflammation compared to serum markers.[73] FC is limited by patients' reticence to collect stool and lack of specificity for IBD, but it remains an important tool for stratifying newly diagnosed patients with IBD for risk of progression and response to first therapy. Practically, it is important to discuss the collection with patients, highlighting that the sample can be from any time, only a small amount of stool is necessary for the analysis and, given instability at room temperature leading to falsely low values, it should be remitted to the laboratory immediately or placed in the refrigerator,[74] not the freezer, for the most accurate results. If the result is unexpectedly high, it is appropriate to repeat based on clinical judgment, as there can be variability among measurements within the same individual even on the same day.[75] Lastly, there is variability between assays and it is important to use assay-specific cutoff values until there is standardization.[76]

FC has been shown to accurately discriminate between endoscopic disease severity in both UC[73] and CD.[77] Kennedy et al[78] demonstrated that an elevated FC (>250 μg/g) at index visit for CD was associated with increased rates of disease progression. More recently, the same group reported that achieving an FC <250 μg/g within 12 months of diagnosis was associated with a reduction in the risk of disease progression.[79]

Genetic Risk Predictors

There are more than 200 identified risk loci for IBD.[55,80] IBD susceptibility mutations in nucleotide-binding oligomerization domain 2 (*NOD2*), which is involved in the host–microbe immune response, were the first identified and confer the greatest risk for IBD.[81,82] In a large genotype–phenotype study of CD, NOD2 was noted to be strongly tied to ileal disease location and younger age at diagnosis and, when accounting for ileal disease location, an association with stricturing disease no longer remained.[83]

Polygenic risk scores (a summation of risk alleles weighted by effect size derived from genome-wide association studies) have been studied, but the methods used to create the scores vary widely. Within the RISK cohort, neither a polygenic risk score nor NOD2 were associated with stricturing or fistulizing behavior.[41] As more expansive, genome-wide polygenic risk scores improve and evolve with the help of more sophisticated techniques, they continue to warrant further exploration as a prognostic test.[84]

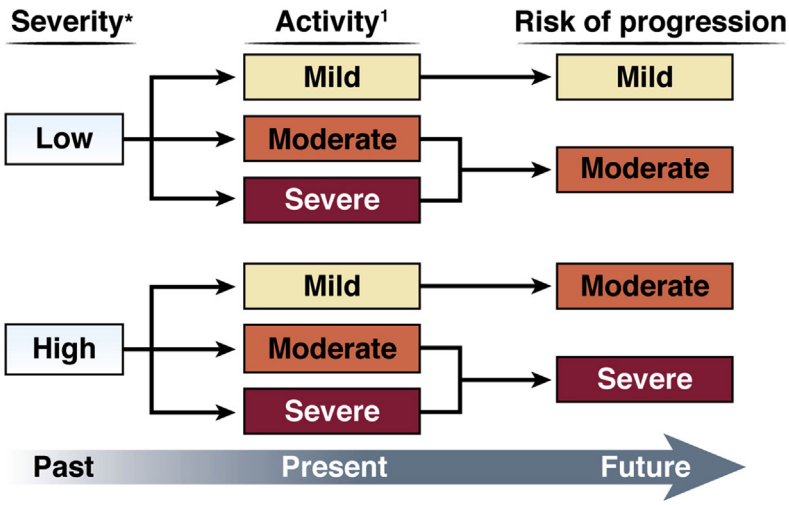
Risk Prediction Tools

Risk prediction models are being incorporated consistently across diseases toward risk stratification and shared decision-making at the individual level. For CD patients, Siegel et al[85] developed and validated a web-based prediction tool (PROSPECT) to individualize risk of complications using clinical, serologic, and genetic markers. Variables in the prediction tool included the presence of small bowel disease (HR, 2.12; 95% CI, 1.05–4.29), left colonic disease (HR, 0.73; 95% CI, 0.49–1.09), perianal disease (HR, 4.12; 95% CI, 1.01–16.88), anti-*Saccharomyces cerevisiae* antibody (HR, 1.35; 95% CI, 1.16–1.58), anti-CBir1 (HR, 1.29; 95% CI, 1.07–1.55), anti-neutrophil cytoplasmic antibody (HR, 0.77; 95% CI, 0.62–0.95), and the NOD2 frameshift mutation/SNP13 (HR, 2.13; 95% CI, 1.33–3.40), with a predictive accuracy of 73% and 75% in adults and children, respectively. This is expected to be available for clinical use in early 2021.

Clinical risk features (disease severity), as well as degree of intestinal inflammation (disease activity), can be very useful to stratify outcomes of IBD and guide personalized therapy. Newer biomarkers, serologic and genetic, will help improve the precision of IBD therapy.

Early Therapy of Inflammatory Bowel Disease

Risk stratification is a key element of determining the initial selection of IBD therapy. Medication safety profile, patient preference, and payer preference are other important variables to consider. For the purpose of this discussion, we risk-stratify patients into mild, moderate, or severe disease based on guidance laid out by the AGA (Figure 2)[60,64] and illustrate therapeutic options for CD and UC in Figures 3 and 4, respectively.



[1]Grading disease activity in Crohn's disease**

Mild	Moderate	Severe
CDAI 150–220	CDAI 220–450	CDAI > 450
• Ambulatory • Eating and drinking • < 10% weight loss • No features of obstruction* • No fever • No dehydration • No abdominal mass or tenderness • CRP usually increased above the upper limit of normal	• Intermittent nausea or vomiting • > 10% weight loss • Treatment for mild disease ineffective, or tender mass • No overt obstruction • CRP elevated above the upper limit of normal	• Cachexia (BMI < 18 kg/m²) • Significant weight loss • High fever • Evidence of obstruction or abscess • Persistent symptoms despite intensive treatment • CRP increased

[1]Grading disease activity in ulcerative colitis***

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

* Refer to Figure 1
**Adapted with permission from Torres, J., et al. (2017). "Crohn's disease." *Lancet* 389(10080): 1741–1755.
***Adapted with permission from Rubin, D. T., et al. (2019). "ACG Clinical Guideline: Ulcerative Colitis in Adults." *ACG.* 114(3): 384–413.

Figure 2. Stratification of inflammatory bowel disease risk of progression based on disease severity and activity. BMI, body mass index; CDAI, Crohn's Disease Activity Index; ESR, erythrocyte sedimentation rate; UCEIS, Ulcerative Colitis Endoscopic Index of Severity. *Refer to Figure 1. **From Torres et a1,[1] adapted with permission. ***From Rubin et al,[38] adapted with permission.

Early Therapy for Crohn's Disease

Medical therapy. There is good evidence-based guidance for the management of moderate to severe CD, but the treatment of mild CD is less clear in the absence of clinical trials devoted to this group of patients. In a small minority of cases that have mild inflammatory CD with mild endoscopic activity, no symptoms and no evidence of stricturing or fistulizing, the risk of progression is likely to be low.[86] It

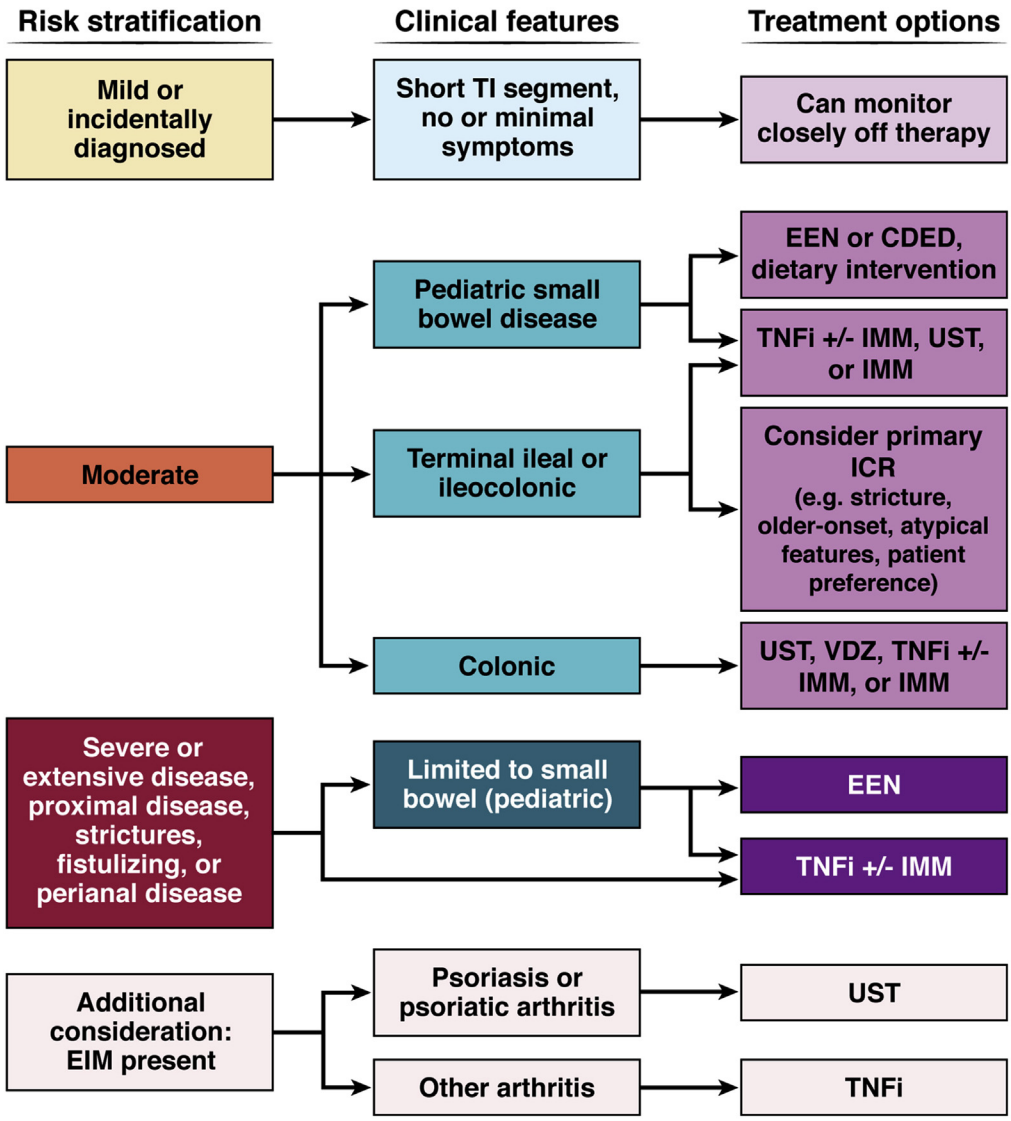


Figure 3. Therapeutic strategies for the management of recently diagnosed CD. IMMs include thiopurines and methotrexate. CDED, Crohn's disease exclusion diet; TI, terminal ileum.

may be reasonable to monitor such patients off therapy with close follow-up and frequent symptom reassessment and monitoring of FC and CRP. If patients have mild disease activity, then an 8-week course of budesonide can be tried and patients can be monitored off therapy after stopping steroids. Immunomodulators (IMMs) may be a consideration in moderate disease nonresponsive to budesonide; however, long-term safety concerns limit this approach.[60]

Due to lack of head-to-head trials, biologic positioning is reliant on indirect data, such as network meta-analyses and real-world retrospective studies. In the former, the surface under the cumulative ranking (SUCRA), a measure of the relative ranking of each treatment, is used for comparisons. SUCRA ranges from 0 to 1, with a higher number indicating higher ranking. For the management of early moderate to severe CD, tumor necrosis factor inhibitors (TNFis) remain the mainstay of treatment. In a network meta-analysis of randomized controlled trial data,[87] infliximab (IFX) and adalimumab (ADA) were superior to other therapies for moderate CD (SUCRA 0.93 and 0.75, respectively). Of note, biosimilars are approved as inexpensive alternatives to IFX.[88] Ustekinumab (UST) was associated with a lower risk of serious adverse events and infections (SUCRA 0.72 and 0.71, respectively), and may be a consideration among risk-averse patients. In moderate CD, especially when limited to the colon and no high-risk features, vedolizumab (VDZ) and UST are efficacious first-line options with good safety profiles. In addition, although response to VDZ is lower among TNFi exposed, biologic-naïve patients have higher rates of response. Results from ongoing head-to-head trials such as UST vs adalimumab (ClinicalTrials.gov ID: NCT03464136) and risankizumab vs UST (ClinicalTrials.gov ID: NCT04524611) will help clarify the positioning of biologics.

In the case of severe CD, or when particularly high-risk features, such as fistulizing or stricturing disease, or proximal involvement, a TNFi, particularly IFX, remains the first choice. Of note, there is no benefit of concomitant mesalamine with biologic therapy in CD and it should be stopped at the time of escalation to a biologic.[89]

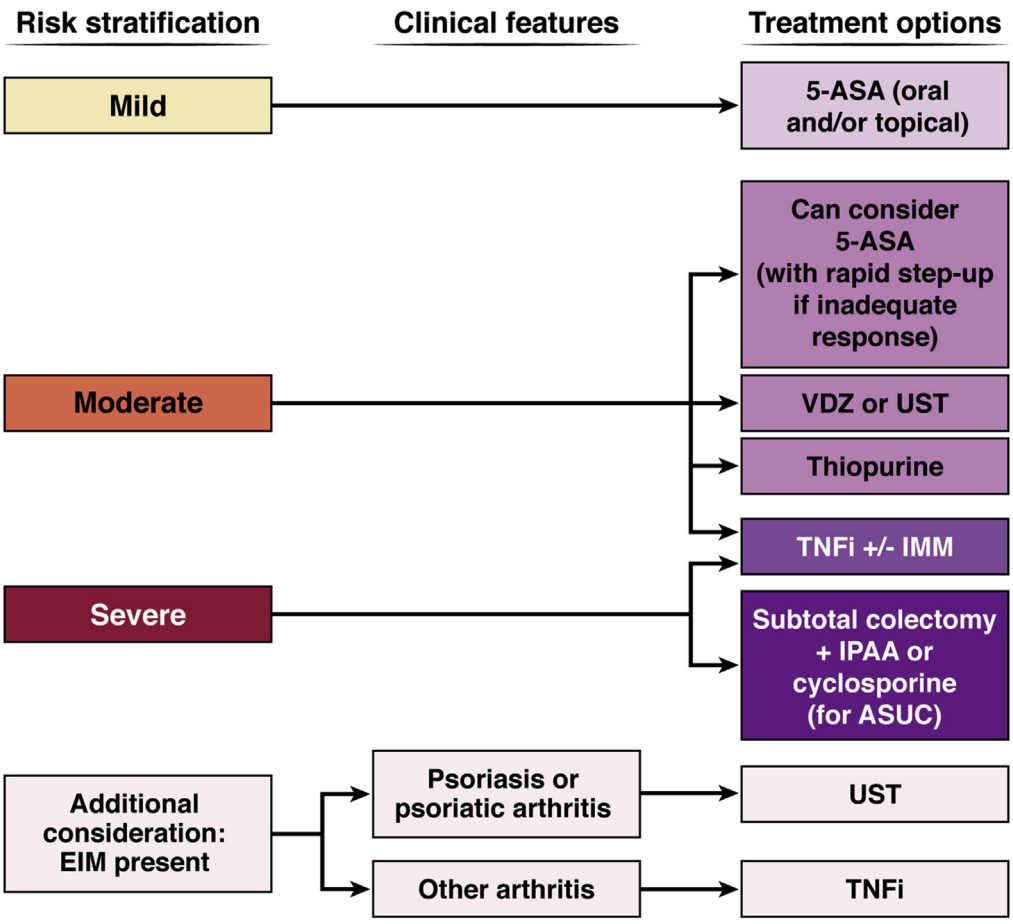


Figure 4. Therapeutic strategies for the management of recently-diagnosed ulcerative colitis. IMMs include thiopurines and methotrexate. 5-ASA, 5-amino salicylic acid; ASUC, acute severe ulcerative colitis; IPAA, ileal pouch anal anastomosis.

Combination therapy of a biologic with IMM, best-studied with TNFi, is an important consideration in severe disease, especially penetrating or perianal disease. It is associated with improved outcomes, a decrease in loss of TNFi response, and fewer long-term complications.[90,91] The mechanism of action may be due to decrease in immunogenicity and impact on drug level. Similar effects have not been seen with adding IMM to UST of VDZ therapy, possibly due to a lower role of immunogenicity in drug metabolism.[92] For patients with perianal CD, a multidisciplinary approach with early referral to a colorectal surgeon is key to improved outcomes.[93]

Ileocolic resection as a first-line therapy. Surgery is often viewed as a late-stage therapeutic option for CD, to be positioned after medical therapies, and the rate of surgery for CD has declined over time.[94] The LIR!C (Laparoscopic Ileocolic Resection Versus Infliximab Treatment of Distal Ileitis in Crohn's Disease) trial, a randomized controlled trial of IFX vs laparoscopic ileocolic resection (ICR) in adult patients with limited terminal ileal disease, found no difference in safety or measures of quality of life at 1 year between the 2 groups.[95] Furthermore, on long-term follow-up (median 5 years), the ICR group had no subsequent resection, 42% received no treatment at all, and 74% received no biologic treatment.[96] More recent cost-effectiveness analyses found that ICR is more cost-effective than IFX.[97] ICR should be considered a viable initial treatment modality not only in patients presenting with a complication at diagnosis, but also in those with limited nonpenetrating ileocecal CD in the setting of shared decision-making or when concerns about biologic safety are a significant consideration.

Dietary therapy. Exclusive enteral nutrition (EEN**)** is the use of polymeric or elemental formula typically for 8–12 weeks to induce remission in CD. European Pediatric Consensus guidelines recommend EEN as the first-line therapy to induce remission in pediatric patients with luminal CD.[31] This is based on numerous randomized controlled trials demonstrating that EEN is as effective as corticosteroids. Meta-analyses of these randomized controlled trials have reported clinical remission rates of 73%–95%.[98,99] Relapse after this period of induction is common, typically leading to maintenance management with IMM or biologics.[100] To increase adherence, a combination of partial enteral nutrition and the CD exclusion diet may be more tolerable and as effective in inducing remission in mild to moderate pediatric CD.[101] Studies on EEN in adults are limited and have shown mixed results but warrant consideration in select cases.[102]

The modification of whole foods in diet as a therapeutic strategy in IBD is an emerging area of interest, such as the Trial of Specific Carbohydrate and Mediterranean Diets to Induce Remission of CD (DINE-CD).[103] Dietary studies are highly heterogenous due to the relevance of macro- and

micronutrients in diet, as well as food additives, processing, and packaging.[104] Currently, there is no recommendation for whole foods–based management of IBD, but future studies will delineate this further.

Early Therapy of Ulcerative Colitis

In UC, mild disease can be managed with oral and/or topical mesalamine therapy, generally with adequate control of disease.[38] For moderate UC, VDZ and UST are effective options,[105,106] and may be better first-choice options than TNFi, given safety profile. In the VARSITY trial, the only head-to-head trial of 2 biologics (n = 769), VDZ was superior to ADA in achieving clinical remission (31.3% vs 22.5%; $P = .006$) and endoscopic improvement (39.7% vs 27.7%; $P < .001$) in moderate to severe UC.[105] In case VDZ or UST may not be feasible due to payer preference, TNFi, particularly IFX, is an effective option with good safety profile.[107] Thiopurines may be considered in moderate UC after weighing risks against benefits.[64] In patients with severe UC requiring hospitalization, IFX is the preferred biologic for induction and maintenance of remission, with or without IMM. Combination therapy in the SUCCESS trial was associated with improved clinical, but not endoscopic, outcomes compared to IFX monotherapy.[108] When using IFX as a monotherapy in moderate to severe UC, given the potential for the colon to act as a "sink" for drugs, we advocate for checking early drug concentrations to ensure proper dosing and detecting immunogenicity early along with other pharmacokinetic and safety-related variables.[109] There is no clear benefit of concomitant mesalamine with biologic therapy in UC and it can be stopped in patients escalating to biologics.[110] Some patients may present with acute severe UC where TNFi, cyclosporine, or subtotal colectomy followed by ileal pouch anal anastomosis can be a good initial strategy; discussion of management of acute severe UC is beyond the scope of this article.

Taking Extraintestinal Manifestation Into Consideration

EIMs are common in IBD, estimated to affect 30%–40% of patients.[111,112] In a Swiss cohort study, symptoms of EIMs before IBD in one-quarter of the patients[113]; collaboration across specialties, including but not limited to rheumatologists, dermatologists, ophthalmologists, is vital not only to prompt referral of patients with EIM suspicious for IBD to allow for expedient initiation of therapy for both conditions, but also to allow for consideration of both in the selection of therapy, dose, and chronicity of treatment. For example, VDZ, which is gut-selective, is associated with an increased risk of de novo or worsening EIM.[114,115] In patients with significant symptoms of EIM, one should weigh the potential benefit of VDZ against another therapy, such as TNFi, that might more broadly target gut and systemic inflammation.[116]

Predictors of Response to Inflammatory Bowel Disease Therapy

The number of therapeutic agents in the IBD armamentarium are numbered, and each agent has limited efficacy. In addition, the first biologic, regardless of choice, has the highest probability of success. For all of these reasons, it is important to be thoughtful in selecting the initial therapy. Clinical decision support tools (CDSTs) and prediction models are being developed to help with this.

Smoking has been associated with lower response to TNFi, and among responders, shorter response duration.[117] Using ACT1 and ACT2 trial data, Vande Casteele et al[118] developed a CDST incorporating IFX clearance, stool frequency, rectal bleeding scores, white blood cell count, and body weight to predict endoscopic healing in UC at different time points, with accuracy in the range of 80% or higher. External validation models, however, had lower predictive value, with an area under of the curve of 0.67 (95% CI, 0.61–0.74). Similar CDSTs have been developed to predict response to CD and UC with VDZ.[119,120] Such tools require clinical variables that are widely available, have no associated costs, and are feasible to incorporate in discussions with the patient. Ultimately, biomarkers that are specific to underlying mechanisms of action may be most accurate in helping select the right therapy for the patient. Although these CDSTs and predictors show promise, none have been prospectively validated and are not yet ready for full incorporation into routine clinical care.

Predictors of Adverse Events With Inflammatory Bowel Disease Therapy

Genetic heterogeneity pertaining to drug metabolism impacts adverse events and can be leveraged to guide therapy. Thiopurine methyltransferase (TPMT), the first identified variant impacting IBD therapy, is involved in thiopurine metabolism with decreased activity resulting in severe leukopenia. Thiopurines should be avoided or the dose lowered based on genotype and the associated TPMT activity.[121] Nudix hydrolase (NUDT15) mutations have been implicated in leukopenia risk with thiopurine in European and Asian populations.[122,123] A combination of TPMT and NUDT15 mutations accounts for nearly 50% of cases with severe thiopurine-induced leukopenia.[123] Testing for TPMT genotype or enzyme level and NUDT15 genotype before initiating thiopurine therapy is recommended. In addition, polymorphism in the HLA class II region (rs2647087) is associated with pancreatitis risk in thiopurine-treated individuals, 9% risk in heterozygotes and 17% risk in homozygotes.[124]

Beyond IMMs, there is promise in using genetic variants to further aid in identification of adverse events with biologic therapies. Most notably, in a genome-wide association study of 1240 biologic-naïve, primarily European patients, the Personalising Anti-TNF Therapy in Crohn's disease (PANTS) Consortium found that the allele HLA-DQA1*05 significantly increased the risk of anti-drug antibody development to TNFi drugs (HR, 1.90; 95% CI, 1.60–2.25).[125] Additional analyses have revealed that differences in haplotypes are associated with differences in immunogenicity to IFX vs ADA.[126] More recently, enrichment in a polymorphism in *TNF-α* (rs1799964) was found in patients with paradoxical psoriasis with TNFi compared to those

without in a small cohort of 53 patients with IBD.[127] Further study to validate these findings is needed, but genetic variants may have an expanded role in future selection of early therapies.

Treat-to-Target Strategy

Choice of initial therapy should be accompanied by a plan for a treat-to-target strategy with decisions made about how response to therapy will be assessed, how therapy will be optimized, and long-term monitoring strategies to be undertaken after achieving target goals to support continued tight control.

Selecting the Target

The STRIDE program, initiated by the International Organization for the Study of Inflammatory Bowel Disease, published a consensus statement on treat-to-target strategies with the primary therapeutic goal being clinical and endoscopic remission.[128] This was recently updated to include normalization of biomarkers as a short-term target following the landmark CALM trial.[23] CALM, a randomized controlled trial of 244 patients with recently diagnosed moderate to severe CD treated with TNFi early in their disease course, showed a treat-to-target strategy of escalating TNFi and thiopurine therapy based on clinical symptoms and biomarker normalization resulted in more patients achieving the primary end point (mucosal healing [Crohn's Disease Endoscopic Index of Severity <4] with absence of deep ulcers) at week 48 compared to using clinical symptoms alone (adjusted risk difference, 16.1%; 95% CI, 3.9–28.3; $P = .010$).[129] The long-term extension of CALM has further demonstrated that attainment of target goals of either endoscopic or deep remission by week 48 led to reduction in progression of disease during a median 3 years' follow-up.[32]

Given the issue of nonadherence with collecting a stool sample to measure FC, there is increasing interest in identifying serum-based biomarkers as therapeutics targets. A serologic panel of 13 protein markers, the Endoscopic Healing Index (Monitr, Prometheus Biosciences, San Diego, CA), validated in CD to distinguish endoscopic activity, is comparable to FC and likely superior to CRP alone.[130] Another modality of interest is point-of-care intestinal ultrasound, which allows for noninvasive and inexpensive evaluation of variables correlated with disease activity (bowel wall thickness, Doppler signal, and wall layer stratification) and has been used to measure initial response to therapy,[131] as well as ongoing assessment of disease activity in both CD and UC.[132,133] MRI is a reasonable alternative monitoring modality, with 2 small studies reporting the ability of MRI to accurately discriminate mucosal healing based on cut points of MaRIA and Nancy scores.[134,135]

We recommend identifying an appropriate target, depending on disease characteristics, availability of resources and patient preference, and treating to achieve normalization of the target, followed by periodic reassessment.

Achieving the Target: Therapy Optimization and Drug Monitoring

Whatever the choice of initial therapy, it is important to optimize it to achieve maximal benefit to the patient as well as to fully exploit its efficacy in the setting of expanding, but still limited, therapeutic choices. This optimization entails dose and interval adjustments or the addition of a medication to use in combination and is often based on therapeutic drug monitoring (TDM). This can be as simple as dose escalation of mesalamine (defined as increasing dose by 2.4 g/day), which, even in clinically quiescent patients, led to reduction of calprotectin levels to <100 μg/g and was tied to longer time to relapse.[136]

TDM is typically used to optimize both thiopurines and biologics (Table 1). With thiopurines, monitoring metabolites has long been accepted.[137] AGA guidelines currently recommend the use of TDM to achieve target drug concentrations and assess for presence of high-level neutralizing anti-drug antibodies at time of treatment failure for TNFi therapies.[121] However, controversy remains over the utility of proactive TDM with TNFi agents.[138] Proactive TDM for biologics may also offer a cost benefit compared to empirical adjustments of therapy.[139] A further nuance to TDM with biologics is the choice of target concentration. Both the AGA[121] and the BRIDGe (Building Research in IBD Globally) Group have suggested target concentrations based on the currently available literature; BRIDGe offers a web-based tool to assist in choosing target drug concentrations based on patient characteristics (Table 1).[140,141] If these targets are not achieved, escalation of dose, shortening of interval, and/or adding an immunomodulator, in the case of TNFi, are recommended, with subsequent reassessment of drug concentration until targets are reached.

Maintaining the Target: Tight Control

Once achieving target goals, patients should continue to be monitored serially every 3–6 months with clinical visit and noninvasive inflammatory markers (FC and CRP). Prospective studies show that FC can increase and predict relapse 3–4 months before clinical symptoms in both UC and CD, making it a viable biomarker for monitoring, even in the quiescent state.[142] In the post-hoc analysis of the TAILORIX (Drug Concentration Versus Symptom-Driven Dose Adaptation of IFX in Patients With Active CD) study, FC was highly predictive of mucosal healing in their cohort after week 2, and, in the setting of a persistently abnormal FC, they recommended assessing a drug concentration at the same time to determine a possible pharmacokinetic cause of failure to achieve endoscopic and histologic remission.[143] Future studies will determine the role of the Endoscopic Healing Index as a biomarker to monitor tight control.

360-Degree Inflammatory Bowel Disease Care

Beyond prognostication and medical and surgical management, outcomes in IBD are improved when there is a

Table 1. Target Thiopurine Metabolite Levels and Biologic Trough Concentrations

Drug	Target	BRIDGe[141]	AGA Guideline[121]
Thiopurine monotherapy	Clinical remission	—	6-TGN 230–450 pmol/8 × 10^8
Infliximab (and biosimilars)	Clinical remission Endoscopic healing	wk 14 and beyond: ≥3 μg/mL[a] ≥7 μg/mL	≥5 μg/mL
Adalimumab[b]	Clinical remission Endoscopic healing	wk 4 and beyond: ≥5 μg/mL[a] ≥7 μg/mL	≥7.5 μg/mL
Certolizumab	Clinical remission	wk 6: ≥32 μg/mL Remission: ≥15 μg/mL	≥20 μg/mL
Golimumab	Clinical remission	wk 6: ≥2.5 μg/mL Remission: ≥1 μg/mL	No recommendation
VDZ[c] and UST[d]		No recommendation	No recommendation

BRIDGe, Building Research in IBD Globally.
[a]If active, do not abandon therapy unless >10 μg/mL.
[b]Adalimumab, on achieving a steady state in maintenance, does not need to be a trough concentration.
[c]Suggested targets for VDZ[163]: wk 6 ≥25 μg/mL; maintenance ≥15 μg/mL.
[d]Suggested targets for UST[164]: wk 8: 3.7–8.7+ μg/mL; maintenance ≥1.3 μg/mL.

360-degree approach to care of the patient (Figure 5), interweaving preventative care, nutrition, psychobehavioral management, and socioeconomic considerations, as well as fostering open communication with the patient and family. An interdisciplinary care team, often described as a "medical home," should include services to address all of these facets of care and, when implemented early in the disease course, has been shown to improve patient outcomes.[144,145] There is potential, with the rise of telemedicine and remote monitoring tools, to expand comprehensive services for patients with IBD to locations formerly with issues of access.[146,147]

Preventative Care

There are well-accepted guidelines for preventative care in IBD,[148,149] but it has also been shown that preventative care is often overlooked.[150,151] It is important for the gastroenterologist to engage in preventative care for their patients with IBD, whether it be by informing the primary physician of services needed, informing the patient and empowering them to seek the preventative services, or offering those services themselves in clinic, for example, vaccinations. Early in the disease course, preventative care, in particular vaccinations, should be highlighted as strategies that are important in reducing the risk of disease and treatment-related complications. Supplementary Figures 1–7, which include detailed sections on preventative care, are comprehensive checklists to promote 360-degree care starting from the very first visit.

Nutrition

Nutritional services should be offered to patients with IBD to address nutritional deficiencies, aid in catch-up growth in pediatrics, provide support for enteral nutrition as needed, and explore any specific patient concerns about diet. There is burgeoning patient interest in the use of specialized diets (eg, specific carbohydrate diet and anti-inflammatory diet) as an adjunct to medical therapy.[152] It is useful to be open to discussion and provide referral to a well-informed nutritionist to provide accurate information and support.

Psychobehavioral Support

There is a well-described increase in anxiety and depression in IBD patients, and patients with psychological comorbidities are more likely to be hospitalized (OR, 4.13; 95% CI, 1.25–13.61).[153] When a biopsychosocial integrated care model that included cognitive behavior therapy was instituted for IBD patients, there were improvements in disease activity and quality of life, with significant reductions in the use of opioids ($P = .037$), hospitalizations (48% to 30%), and inpatient care costs ($P = .005$).[154] High resilience, or an ability to recover from adversity, has been shown to be associated with lower disease activity, improved quality of life, and fewer operations in CD.[155] Screening for psychological comorbidities and low resilience early in the disease course with referral for psychobehavioral support could lead to improvements in outcomes among patients with IBD.

Complementary Therapies

Complementary treatments are also commonly pursued by patients with IBD[156] and, just as with diet and nutrition, it is important to engage with your patient in open discussion about these therapies to foster a therapeutic relationship.[157]

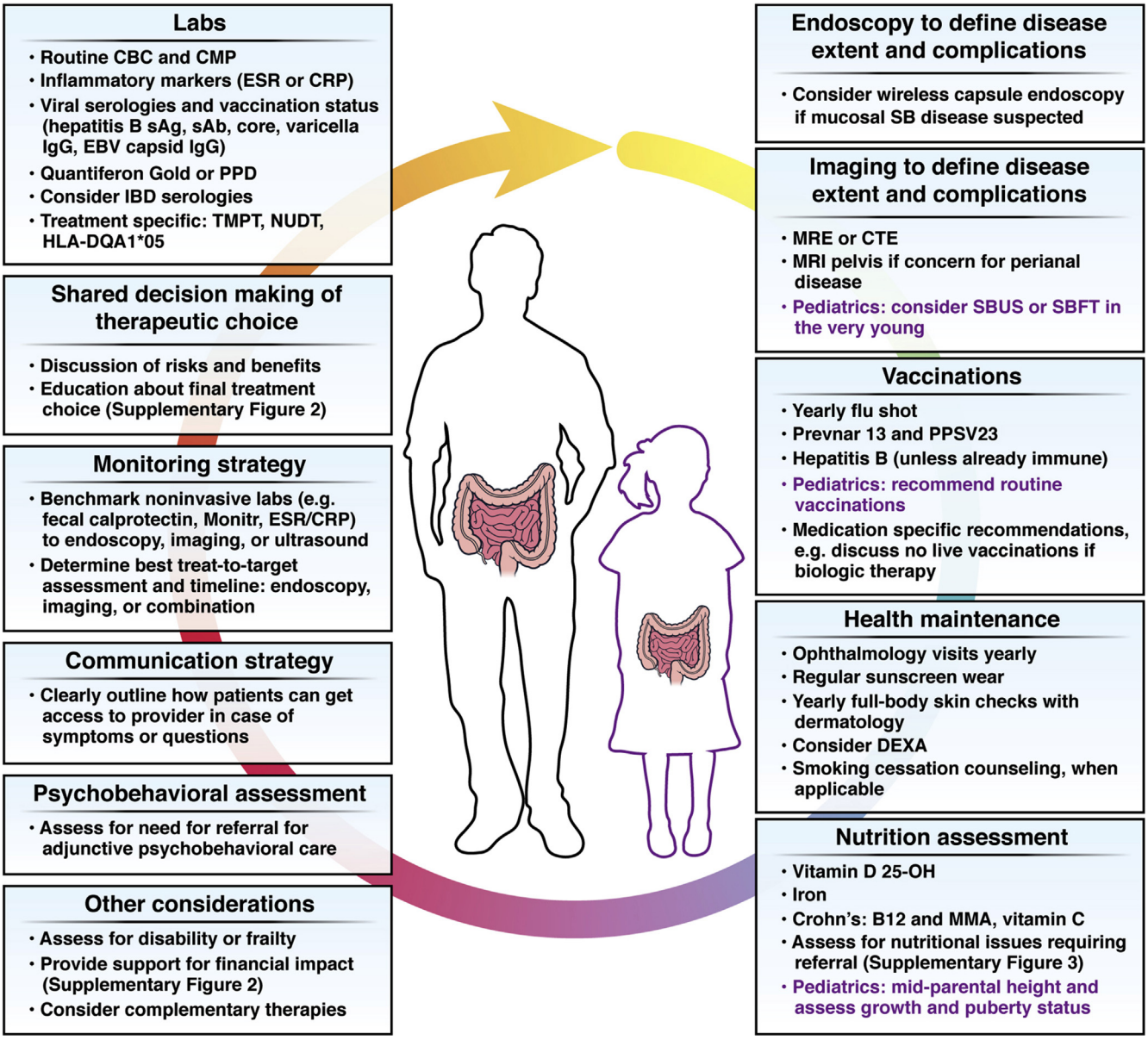


Figure 5. 360° care of the patient with IBD. Please see Supplementary Figure 1 for screening tool to identify patients who may need 360-degree care services. CBC, complete blood count; CMP, comprehensive metabolic panel; CRP, C-reactive protein; CTE, computed tomography enterography; DEXA, dual energy X-ray absorptiometry; EBV, Epstein-Barr virus; ESR, erythrocyte sedimentation rate; IgG, immunoglobulin G; MMA, methylmalonic acid; MRE, magnetic resonance enterography; PPD, purified protein derivative; ; PPSV23, pneumococcal polysaccharide vaccine 23; sAb, surface antibody; sAg, surface antigen; SB, small bowel; SBFT, small bowel follow through; SBUS, small bowel ultrasound.

Medication Management

Medications in IBD need to be taken long-term and require a high level of adherence to be effective and to avoid relapse and/or development of anti-drug antibodies. Patient understanding and "buy-in" to therapy is critical. A clinical pharmacist, if available, can facilitate a discussion with patients regarding these medications to promote understanding.[158] Furthermore, there are available resources to off-set the financial burden from medications.[7] Numerous advocacy groups (eg, Crohn's and Colitis Foundation; AGA; and North American Society for Pediatric Gastroenterology, Hepatology & Nutrition) have useful resources for education and support, directing patients to these trusted sources can be invaluable.

Providing Support for Disability

IBD takes a toll on school and work life. Absenteeism and presenteeism are common in patients with active IBD.[159,160] In pediatrics, discussion about the need for accommodations at school should be routinely asked and a plan provided as needed. For adults, physicians should

devise a plan with the patient how to best address their concerns and needs for support based on their specific situation and preferences.

Communication

Lastly, open communication between the patient and provider is key to success.[161] Effective shared decision-making is important in fostering satisfaction with treatment decisions, reducing decisional conflict and regret,[162] and improving adherence.

Conclusions

In summary, early diagnosis and early management of IBDs are critical to minimizing complications and ensuring positive outcomes. Selection of appropriate first-line therapy should be based on risk assessment, disease activity, and clinical characteristics of the patient. Ongoing head-to-head trials will provide further clarity as to the relative positioning of available therapies. Comprehensive care of the IBD patients involves a thoughtful, individualized, and well-rounded assessment and treatment plan, taking into consideration feedback from the patient. Personalized IBD care is fast-evolving, and sophisticated prediction models incorporating multi-omic platforms are likely to be the future of IBD therapeutics.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at http://dxdoi.org/10.1053/j.gastro.2021.04.063.

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Received January 6, 2021. Accepted April 27, 2021.

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Acknowledgments
The authors thank Jill Gregory, certified medical illustrator, Icahn School of Medicine at Mount Sinai, for the illustrations.

Author contributions: Manasi Agrawal and Elizabeth A. Spencer: concept, literature search, drafting of manuscript and critical revision of the manuscript for important intellectual content; Jean-Frederic Colombel and Ryan C. Ungaro: concept and critical revision of the manuscript for important intellectual content.

Conflicts of interest
These authors disclose the following: Jean-Frederic Colombel has received research grants from AbbVie, Janssen Pharmaceuticals and Takeda; has

received payment for lectures from AbbVie, Amgen, Allergan, Bristol-Myers Squibb Company, Ferring Pharmaceuticals, Shire, Takeda and Tillots; has received consulting fees from AbbVie, Amgen, Arena Pharmaceuticals, Boehringer Ingelheim, Bristol-Myers Squibb Company, Celgene Corporation, Celltrion, Eli Lilly, Enterome, Ferring Pharmaceuticals, Genentech, Gilead, Iterative Scopes, Ipsen, Immunic, Imtbio, Inotrem, Janssen Pharmaceuticals, Landos, LimmaTech Biologics AG, Medimmune, Merck, Novartis, O Mass, Otsuka, Pfizer, Shire, Takeda, Tigenix, Viela bio; and hold stock options in Intestinal Biotech Development. Ryan C. Ungaro has served as a consultant and/or advisory board member for Bristol Myers Squibb, Eli Lilly, Janssen, Pfizer, and Takeda. He has received research support from AbbVie, Boehringer Ingelheim, and Pfizer. The remaining authors disclose no conflicts.

Funding

Manasi Agrawal receives research support from the Dickler Family Fund, New York Community Trust, and the Helmsley Charitable Trust Fund for SECURE-IBD. Elizabeth A. Spencer receives research support from an National Institutes of Health T32 (5T32GM082773-13), NY Crohn's Foundation, and the Goldsmith Family Fund. Ryan C. Ungaro is supported by an National Institutes of Health K23 Career Development Award (K23KD111995-01A1).