2017-2019 Guidelines for the Clinical Preventive and Management Care of Patients With Inflammatory Bowel Disease

(Excerpted Sample)

BACKGROUND

Inflammatory bowel disease (IBD) is a chronic autoimmune disease affecting the gastrointestinal tract (GIT) and encompasses both ulcerative colitis (UC) and Crohn's disease (CD).[1,2,3] IBD incidence has increased globally over recent decades and affects as many as 1.4 million people in the US.[2,3,4] The disease etiology is not fully understood; although studies indicate that it consists of a multifactorial interaction between genome, enteric microbiota, environment, and a deregulated immune system.[1,4] Age of onset for IBD is younger than 30 years, and there is an increasing incidence of pediatric diagnoses.[2,5,6] CD and UC, though compartmentalized under IBD, typically differ in affected GIT regions and in their responses to therapeutics.[5,7,8]

Symptoms of CD commonly include chronic diarrhea, abdominal discomfort (often with postprandial intensity), and weight loss.[1,8] Up to half of CD patients will develop intestinal complications such as abscesses, fistulas, and strictures, and a similar number will likely require abdominal surgery during the course of the disease.[8] CD is transmural and can affect the entirety of the GIT in an interrupted pattern.[1] It can present as a multisystem disease and include arthropathy, thromboembolic, and metabolic bone diseases.[8] In addition, a recent cohort study found an association between CD and an increased risk of chronic fatigue syndrome.[7] There is also an increased risk of intestinal cancer for patients with CD and UC.[2,8]

Unlike transmural CD, UC inflammation is limited to the mucosa.[1] UC's symptoms include diarrhea, increased bowel movement frequency, hematochezia, and it can manifest beyond the intestine.[1,5] Mucosal lesions in patients with UC originate in the rectum and extend in an uninterrupted pattern into the colon.[1] Lichtenstein et al noted that "[d]istinguishing Crohn's disease from ulcerative colitis can be challenging when inflammation is confined to the colon…," and that "[t]he presence of ileitis in a patient with extensive colitis…can also make determination of the IBD subtype challenging."[8] Although endoscopy remains the standard diagnostic tool for IBD evaluation, biomarker development and use are emerging as diagnostic possibilities for clinical practice.[1]

The available treatment options complicate IBD management, as iatrogenic adverse events can occur during disease management. Steroids,, historically a first-line therapeutic class, decrease bone mineral density (BMD) and affect behavior, blood pressure, and blood glucose levels.[8] More recently developed immunosuppressive therapeutics may increase the risk of a variety of cancers.[4,8] Surgical treatment can be curative in certain cases of UC, but can result in loss of GIT function as well as surgery-related morbidity.[7,8]

The chronicity and complications of IBD require long-term management and routine follow-up coordinated among gastroenterologists, primary care physicians, dieticians, and mental health care specialists.[9] Routine monitoring permits the detection of not only changes in the disease but also comorbidities that can affect disease course and prognosis.[9] In recent guidelines for the long-term management of IBD, the American College of Gastroenterology noted a lack of coordination among clinicians caring for patients with the disease.[9] Other recently issued guidelines have outlined preventative care measures, in terms of routine vaccinations, smoking intervention, orthopedic evaluation, and mental health care, that may help improve the disease prognosis and patient quality of life.[5,8,9] As part of patient preventive care and management, recently reviewed dietary considerations for patients with IBD are in the following educational analyses.

EDUCATIONAL ANALYSIS

Gap #1: Clinicians may be unfamiliar with recent American College of Gastroenterology (ACG) CD and UC clinical management guidelines.

Learning Objective #1: Define the goals of IBD management and list the therapeutics for IBD and their related considerations.

The goals for IBD management are to induce or maintain remission, promote mucosal health and healing, and avoid disease complications.[8] Endoscopic (or cross-sectional) imaging is recommended for objectively assessing a patient's reported symptom resolution.[8] Response to treatment should occur in a 2- to 4-week period following treatment initiation with peak improvement reached by 16 weeks.[8]

Despite the popular demand for using therapeutics perceived to be natural IBD treatments, including probiotics, curcumin, and fecal microbiota transplantation, the evidence to support their indication is lacking.[5] Although microbiota transfer is used in cases of IBD involving *Clostridioides difficile* infection (in a trial context), there is no evidence to support its use in uninfected patients.[5] Consequently, no recommendations have been made as to the use of probiotics, curcumin, and microbiota transfer.[5] There is a phase 2 study of the supplement, Mastiha, for IBD treatment underway in Greece.[10]

Glucocorticoid use for decreasing UC flare symptoms was first studied in the mid-1950s.[3] From there, steroids evolved into a first-line treatment for IBD by the 1970s.[3] Although steroids decrease the symptoms of IBD, they do not heal intestinal mucosa.[8] Therefore, their use is recommended for no longer than 3 months, since they can alter behavior, sleep patterns, increase blood glucose and blood pressure, and decrease bone density.[2,3,8,9] ACG guidelines advise that "clinicians should avoid repeated courses of corticosteroids…and consider escalation of therapy in patients who frequently need corticosteroids for disease control."[5] Steroid use may not alleviate symptoms or can be too effective at doing so, as one-fifth of patients will not respond to steroids, and one-third will develop steroid dependence.[8]

Less bioavailable second-generation steroids, such as budesonide, have been studied with the hope of decreasing the systemic adverse effects observed with the first generation (which includes prednisone and methylprednisolone).[3] Although these second-generation steroids have resulted in fewer adverse effects, any improved efficacy has yet to be shown.[3,8] In addition, it is recommended that the first-line therapeutic for mild to moderate UC remains a 5-aminosalicylate (5-ASA) medication, rather than budesonide multi matrix system (MMX), despite the latter's approval for UC treatment by the US Food and Drug Administration.[5] This recommended first-line 5-ASA class includes sulfasalazine, mesalamine, and the prodrug diazo-bonded 5-ASAs balsalazide and olsalazine.[5] Patients aged less than 40 years at the time of UC diagnosis who have severe endoscopic activity and extensive disease, according to the ACG guidelines, "may benefit from more aggressive initial therapy…."[5]

The immunomodulators, including methotrexate and thiopurines azathioprine (AZA) and 6-mercaptopurine (6-MP), can be implemented into medical management during periods of remission or used with a steroid to induce remission, since immunomodulators' effects are not clinically apparent for up to 12 weeks.[4,8] Methotrexate should be considered only with concurrent contraception in adult patients of child-bearing age because of its teratogenic property.[8] Myriad adverse effects from immunomodulators range from vomiting to malignancy and can comprise bone marrow suppression.[4,8] Consequently, routine blood screening is recommended for patients who are administered these therapeutics.[4,8]

Nonmelanoma skin cancer (NMSC) risk is increased in thiopurine-treated patients who have a history of or proclivity towards sun exposure, and lymphoma risk is increased in thiopurine-treated patients under 30 years of age.[4] Although thiopurines are teratogens in other animals, no similar effects have been demonstrated in humans.[4] Thiopurine use has, though, been linked to an increased percentage of neonatal anemia.[4] In addition, thiopurine-induced pancreatitis is the most frequent cause of pancreatitis in patients with IBD.[4] Hence, its use is discouraged in treating pregnant women.[4] Methotrexate, a known teratogen, is contraindicated for use in pregnant women with IBD.[4] Cyclosporine has been effective in inducing remission for patients with UC, but it is ineffective in the treatment of CD.[2,8]

For patients who do not respond to steroids or immunomodulators, anti-tumor necrosis factor (TNF) treatment has been effective.[8] Anti-TNF therapy such as infliximab is recommended in conjunction with immunomodulators because combined therapy has shown improved efficacy over singular treatment with these drug classes.[8] Infliximab has shown varying efficacy, with as much as 30% of treated patients showing no response following an induction phase and 50% of patients discontinuing the treatment because of adverse effects or loss of drug efficacy.[11] To improve these results, routine therapeutic drug monitoring is recommended to evaluate for anti-therapeutic antibodies and appropriate drug concentration; this approach has produced encouraging long-term results for patients.[12]

Anti-TNF antibodies, infliximab, adalimumab, and certolizumab, are approved for use in treating moderate to severe CD (fistulizing CD, in the case of infliximab).[8] As with the immunomodulators, it is recommended that the infection and malignancy risks of anti-TNF therapy be considered for each patient—particularly those with a history of congestive heart failure, malignancy, or demyelinating disease.[4,8] No guidelines currently advise clinicians on switching from a reference biologic product such as infliximab to biosimilar products (infliximab-abda, infliximab-qbtx, infliximab-dyyb, or CT-P13).[4] A cohort study did find similar efficacy and safety between infliximab and CT-P13.[13]

Recently-developed anti-integrin therapeutics, also known as leukocyte trafficking inhibitors, have been effective for patients unresponsive to other regimens.[8] These include the anti-α4 integrin antibody, natalizumab, and anti-α4β7 integrin antibody, vedolizumab.[8] However, patients with previous John Cunningham (JC) virus exposure can develop progressive multifocal leukoencephalopathy (PML) when treated with natalizumab.[4,8] It is therefore recommended that patients be tested for JC seropositivity prior to starting this treatment. Vedolizumab, on the other hand, has not been associated with PML and has enabled CD and UC patients to enter clinical remission following other treatments' failure.[4,8] Vedolizumab may also be considered as a treatment option prior to starting previously mentioned therapeutics.[8]

The anti-p40 antibody ustekinumab, an inhibitor of interleukins (IL) -12 and -23, has been efficacious in patients for whom anti-TNFs and other therapeutics have failed and has been relatively safe.[8] Investigation is underway on other potential therapeutics including the anti-integrin antibody, etrolizumab, the sphingosine-1-phosphate receptor modulator, ozanimod, IL-23 inhibitors brazikumab and risankizumab, and anti-Janus kinase 1 agents, upadacitinib and filgotinib.[8] A phase 2 study of GIT lesions in CD was recently completed using the IL-23 p19-targeting antibody, mirikizumab.[14]

Gap #3: Clinicians may be unfamiliar with recent ACG guidelines for appropriate preventative care specific to patients with IBD.

Learning Objective #3: Describe the recommended considerations in preventative vaccine selection and preventative care for patients with IBD.

Clinicians and gastroenterologists may be hesitant to initiate preventative vaccines for their patients with IBD out of concern for immunosuppression.[9] In a previous survey, vaccines were incorrectly selected by gastroenterologists for patients with IBD (20% to 30% selected live vaccines for immunosuppressed patients and 25% to 35% avoided the same vaccines for immunocompetent patients).[9] In general, patients with IBD, regardless of their immune status, can receive non-live vaccines as part of their preventative health care routine.[9]

Some confusion has surrounded clinician responsibility for executing the protocol and delivery of vaccinations.[9] The ACG recommends that gastroenterologists "clarify…the limits of [their] responsibilities and delegate routine health care issues to the primary care clinician…," and that "[i]t is equally important to educate the primary care clinician to the unique health maintenance needs of the IBD patient."[9]

Those patients with a low degree of immunosuppression may receive select live vaccines such as the herpes zoster vaccine.[8,9] Patients treated with low-immunosuppressive dose drugs, including corticosteroids, methotrexate, AZA, and 6-MP, fall into this category (depending upon their dosage).[9] Anti-TNFs produce a greater degree of immunosuppression.[9] Ideally, immunocompetent patients with IBD

should receive routine vaccinations more than 4 weeks prior to the start of immunosuppressive treatment if the vaccines are live and more than 2 weeks prior if the vaccines are inactivated.[8,9]

Patients with IBD carry a greater risk of influenza infection and, once infected, are also at an increased risk of pneumonia co-infection as well as of hospitalization.[4,9] It is therefore recommended that all patients with IBD receive an annual influenza vaccination.[9] For immunosuppressed patients, the trivalent inactivated form of the vaccine is recommended.[9] The ACG also recommends employing general guidelines for the following vaccines: hepatitis A and B, human papilloma virus (HPV), Haemophilus influenza B, pertussis, and tetanus.[9]

As mentioned, the risk of pneumonia is increased for IBD patients with influenza infection.[9] A cohort study reported an increased risk of pneumococcal pneumonia in particular among patients with IBD.[9] Even though patients who are immunosuppressed with thiopurine and anti-TNF therapeutics show a decreased immune response to the 23-valent pneumococcal polysaccharide vaccine, it is still recommended that these patients receive this vaccination and a booster injection 5 years after its initial administration.[9] It is recommended that administration of PCV13, the 13-valent pneumococcal conjugate vaccine, occurs either more than 8 weeks prior to or more than 1 year after vaccination with PPSV23.[9]

Additional vaccines should be considered for patients with IBD who have more specific risks, depending upon their age and activity. Adolescents and young adults are at a greater risk of meningococcal disease.[9] It is therefore recommended that patients in this age range receive meningococcal vaccinations per routine recommendations, which include the following options: MenACWY (Menactra; Sanofi, Paris, France, Menveo; GlaxoSmithKline, London, England), for serogroups A, C, W, and Y, or MPSV4, (Menomune; Sanofi, Paris, France), MenB-4C for serogroup B (Bexsero; GlaxoSmithKline, London, England), or MenB-FHbp (Trumenba; Pfizer, New York, NY).[9]

Patients with IBD aged over 50 years should be considered for vaccination against herpes zoster (HZ, commonly known as shingles), a dermatologic disease that occurs from recrudescence of varicella-zoster virus (VZV).[9] Patients with IBD are at increased risk for reactivations of VZV and it is recommended that the immunocompetent and those treated with low-dose immunosuppressants in this group be vaccinated against HZ.[9] The directive for immunosuppressed (in particular, anti-TNF-treated) patients with IBD is more equivocal, as the standard vaccine is live attenuated.[9] However, there is now also a recombinant adjuvanted vaccine available for use in the US.[15]

The VZV (chicken pox) vaccine, also live attenuated, is recommended for children not previously exposed, for unexposed adults aged over 13 years, and for patients with IBD prior to starting immunosuppressive treatment.[9] There is particular concern over acute infection of varicella in immunosuppressed patients, in whom multiple organs can be affected and the consequences fatal.[4]

Yet another live attenuated vaccine is the yellow fever vaccine, YF-Vax (Sanofi, Paris, France), to be cautiously considered for immunosuppressed patients planning to travel to (yellow fever) endemic areas.[9] In these instances, the endemic travel destination and the vaccine are discouraged because of a known adverse event risk associated with the vaccine.[9] As of June 2019, the US YF-Vax supply is deplete and an investigational (also live) vaccine, Stamaril (Sanofi, Paris, France), now has limited availability.[16]

Immunocompromised patients' (immunocompetent) household members are encouraged to receive routine (live as well as inactive) vaccines.[9] However, it is recommended that immunosuppressed patients abstain from contact with HZ-vaccinated individuals with subsequent skin lesions and from handling rotavirus-vaccinated infants' diapers for at least 4 weeks post-vaccination.[9]

In addition to the discussed preventative vaccine recommendations, recent guidelines also recommend routine screenings for patients with IBD, as they are at greater risk of cancer, decreased BMD, and depression.[4,8,9] Women with IBD should be screened annually for cervical cancer because immunocompromised women exposed to HPV are at greater risk of developing cervical cancer.[9] Patients with IBD should be routinely screened for both melanoma and NMSC, particularly as patients with IBD may be at greater risk of melanoma, and patients treated with immunosuppressants have an increased

risk of NMSC.[9] It is advised that patients treated with immunosuppressants take protective measures against sun exposure.[9]

Routine screenings for decreased BMD and osteoporosis are recommended for patients with risk factors beyond those associated with IBD.[9] Patients with IBD who smoke should receive medical guidance for smoking cessation, particularly as CD's onset and progression are associated with smoking as are the disease's reduced responses to medical and surgical treatments.[9] Mental health counseling for IBD-related depression or anxiety is also recommended for patients with IBD.[9]

CONCLUSION

IBD is a complex autoimmune disease with increasing global incidence. In managing patients with IBD, clinicians must be apprised of recent preventative health care and treatment guidelines to facilitate remission and decrease risk of complications and comorbidities. Clinicians can coordinate with dieticians to help patients distinguish popular diets from potentially beneficial dietary adjustments. Clinicians also should also be aware of adverse effects to consider with recent developments in immune system-targeting therapeutics in addition to the adverse effects possible with older treatments. Inter-clinician coordination can enhance a multifaceted approach to a complicated disease.

REFERENCES

[1] Titz B, Gadaleta RM, Lo Sasso G, et al. Proteomics and lipidomics in inflammatory bowel disease research: from mechanistic insights to biomarker identification. *Int J Mol Sci*. 2018;19(9):pii:E2775. doi:10.3390/ijms19092775

[2] Matsuoka K, Kobayashi T, Ueno F, et al. Evidence-based clinical practice guidelines for inflammatory bowel disease [published online February 10, 2018]. *J Gastroenterol*. 2018;53(3):305-353. doi:10.1007/s00535-018-1439-1

[3] Dubois-Camacho K, Ottum PA, Franco-Muñoz D, et al. Glucocorticosteroid therapy in inflammatory bowel diseases: from clinical practice to molecular biology. *World J Gastroenterol*. 2017;23(36):6628-6638. doi:10.3748/wjg.v23.i36.6628

[4] Cohn HM, Dave M, Loftus EV Jr. Understanding the cautions and contraindications of immunomodulator and biologic therapies for use in inflammatory bowel disease. *Inflamm Bowel Dis*. 2017;23(8):1301–1315. doi:10.1097/MIB.0000000000001199

[5] Ko CW, Singh S, Feuerstein JD, Falck-Ytter C, Falck-Ytter Y, Cross RK. AGA Clinical practice guidelines on the management of mild-to-moderate ulcerative colitis [published online December 18, 2018]. *Gastroenterology*. 2019;156(3):748-764. doi:10.1053/j.gastro.2018.12.009

[6] Kim J, Ye BD. Successful transition from pediatric to adult care in inflammatory bowel disease: what is the key [published online January 10, 2019]? *Pediatr Gastroenterol Hepatol Nutr*. 2019;22(1):28-40. doi:10.5223/pghn.2019.22.1.28

[7] Tsai SY, Chen HJ, Lio CF, et al. Increased risk of chronic fatigue syndrome in patients with inflammatory bowel disease: a population-based retrospective cohort study. *J Transl Med*. 2019;17(1):55. doi:10.1186/s12967-019-1797-3

[8] Lichtenstein GR, Loftus EV, Isaacs KL, Regueiro MD, Gerson LB, Sands BE. ACG clinical guideline: management of Crohn's disease in adults [published online March 27, 2018]. *Am J Gastroenterol*. 2018;113(4):481-517. doi:10.1038/ajg.2018.27

[9] Farraye FA, Melmed GY, Lichtenstein GR, Kane SV. ACG clinical guideline: preventive care in inflammatory bowel disease [published online January 10, 2017]. *Am J Gastroenterol*. 2017;112(2):241-258. doi:10.1038/ajg.2016.537

[10] Clinical Trials. A study on the effectiveness of a nutritional supplement with natural Mastiha in inflammatory bowel diseases. NIH U.S. National Library of Medicine. https://clinicaltrials.gov/ct2/show/NCT02796339?cond=Inflammatory+Bowel+Diseases&phase=12&rank=1. Updated May 8, 2018. Accessed June 12, 2019.

[11] Papamichael K, Lin S, Moore M, Papaioannou G, Sattler L, Cheifetz AS. Infliximab in inflammatory bowel disease. *Ther Adv Chronic Dis*. 2019;26;10:2040622319838443. doi:10.1177/2040622319838443

[12] Feuerstein JD, Nguyen GC, Kupfer SS, Falck-Ytter Y, Singh S. American gastroenterological association institute guideline on therapeutic drug monitoring in inflammatory bowel disease [published online August 3, 2017]. *Gastroenterology*. 2017;153(3):827-834. doi:10.1053/j.gastro.2017.07.032

[13] FDA approves biosimilar infliximab Ixifi. Generics and Biosimilars Initiative Online. http://www.gabionline.net/Biosimilars/News/FDA-approves-biosimilar-infliximab-Ixifi. Published December 1, 2018. Accessed June 11, 2019.

[14] Eli Lilly & Company. Lilly's mirikizumab met primary endpoint and key secondary endpoints in phase 2 study, including reductions of gastrointestinal lesions. Eli Lilly & Company. https://investor.lilly.com/news-releases/news-release-details/lillys-mirikizumab-met-primary-endpoint-and-key-secondary. Published May 21, 2019. Accessed June 11, 2019.

[15] Shingles (herpes zoster). Centers for Disease Control and Prevention website. https://www.cdc.gov/shingles/vaccination.html. Accessed June 12, 2019.

[16] Clinical update announcement: Temporary total depletion of US licensed yellow fever vaccine addressed by availability of Stamaril vaccine at selected clinics. Travelers' Health. Centers for Disease Control and Prevention website. https://wwwnc.cdc.gov/travel/news-announcements/yellow-fever-vaccine-access. Updated April 30, 2019. Accessed June 12, 2019.