Management Considerations for the Older Adult With Inflammatory Bowel Disease

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Abstract: As the prevalence of older adults with inflammatory bowel disease (IBD) is rising, understanding the unique challenges in both diagnosis and management is becoming increasingly important. Knowledge of phenotypic differences as well as overlapping symptoms with other medical conditions is critical to obtaining a timely diagnosis of IBD in older adults. Although older adults with IBD are at higher risk for adverse events compared with younger adults with IBD, recent data have suggested that ongoing disease activity may be a significant driver of adverse clinical outcomes rather than use of current treatment modalities. Ultimately, earlier and effective treatments can improve outcomes and quality of life for older adults with IBD. However, to help improve medical decision-making, clinicians must move away from the use of chronological age alone and begin to integrate measures of biological age, such as frailty and sarcopenia, into risk stratification tools. This article reviews the management considerations for older adults with IBD and provides the rationale for incorporating measures of biological age into current practice.

Inflammatory bowel disease (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), is a chronic inflammatory disorder of the gastrointestinal tract that arises from an immune response to environmental triggers among genetically susceptible individuals.[1] Classically, IBD has been thought of as a disease of the young. More recently, there has been an epidemiologic shift, with older adults representing the fastest-growing subpopulation of individuals with IBD. This shift is particularly owed to the rise in incidence among older adults, coupled with the aging of the population.[2] As a result, it is estimated that approximately one-third of the IBD population will soon be comprised of adults 60 years and older, with approximately 15% newly developing IBD during this time frame.[3-6]

Although data exploring treatment and management are present for younger adults with IBD, there is a dearth of these data for the older-adult

IBD patient population. As a result, treatment decisions are largely based upon age and comorbidities alone, without consideration of important geriatric principles such as frailty, sarcopenia, and polypharmacy. Thus, it is important to detail what is known in this area as well as highlight knowledge gaps in clinical practice. This article discusses the unique clinical presentations for older adults, the impact of treatment decisions on clinical outcomes, and the rationale for incorporating biological age into medical decision-making for older adults with IBD.

Disease Course and Clinical Presentation in Older Adults With Inflammatory Bowel Disease

Among older adults who developed IBD earlier in life, there is a commonly discussed notion that the disease burns out over time. However, a French study on the long-term natural history of CD showed that after 20 years, a similar percentage of individuals experienced a disease flare in the 12 months prior compared with just 3 years after diagnosis (24% vs 34%, respectively).[7] Additionally, a study comparing the postoperative recurrence rate in older adults undergoing ileocolic resection found no significant difference in 5-year recurrence rates compared with their younger counterparts when evaluated radiologically (33% younger vs 20% older), endoscopically (46% younger vs 40% older), or surgically (16% younger vs 9% older).[8] Thus, ongoing disease activity needs to be treated among older adults, and the expectation that disease is likely to burn out in time should be cast aside. Treatment of older adults with IBD is critically important, as disease-related adverse events can lead to more severe consequences in this subpopulation.

Clinical Phenotype of Older Onset
In addition to individuals who develop IBD earlier in life and are now aging, there is a clinically distinct population of older adults who develop incident IBD later in life.[1] Typically, this bimodal peak of incidence occurs around age 60 years, and it is associated with a higher proportion of individuals having UC and a lower proportion having CD.[9,10]

The location and extent of disease also differs based upon age of IBD onset. More specifically, population-based studies have found that UC more often presents as left-sided disease among older adults, with fewer older adults presenting with proctitis or pancolitis.[9,11,12] The type of presentation, however, may also be specific to region, as older individuals who live in Asia are more likely to present with ulcerative proctitis (37.4%), with a similar proportion also presenting with left-sided colitis (31.8%) and pancolitis (30.8%). Similarly, among

older individuals who newly develop CD, those in the Western hemisphere more often present with colonic disease, whereas those in Asia may present with ileocolonic disease.[9,13] The phenotype of CD also appears to differ between individuals with older- and younger-onset IBD. Adults who develop CD later in life are more likely to have inflammatory and penetrating disease but less likely to develop stricturing disease.[9] These disease locations and phenotypes are also more likely to remain stable among older individuals with new-onset IBD, compared with individuals with younger-onset IBD in which these characteristics may change over time.[9,12,13]

Risk Factors
As clinical characteristics differ between older- and younger-onset IBD, so do the risk factors for IBD development. Approximately 5% to 16% of individuals with younger-onset disease have a family history of IBD, in contrast to approximately 7% and 3% of older adults with CD and UC, respectively.[9,14] This finding has been confirmed by genetic studies demonstrating a much stronger association between particular mutations (eg, *NOD2*) and development of earlier-onset IBD than development of older-onset IBD.[15]

Regional differences in the presentation of older-onset IBD suggest that environmental factors may play an increasingly important role in the development of IBD as people age. One environmental risk factor that appears to be more strongly associated with the development of older-onset IBD is antibiotic use.[16,17] From a Danish cohort of over 6 million individuals, use of antibiotics, particularly an antibiotic impacting the gastrointestinal microbiome, was associated with an increased risk of incident CD and UC, with the greatest effect seen among individuals aged 40 to 60 years and 60 years or older.[18] In contrast, preliminary data suggest that statin use may reduce the odds of IBD development, particularly among older adults; however, further data are needed.[19]

Diagnostic Delays
As clinical presentations can vary and as older adults are more likely to have additional comorbid conditions, making a timely diagnosis of older-onset IBD can be challenging. Consequently, initial misdiagnoses are more common among older adults. A study from 1998 showed that 51% of adults older than 40 years received an incorrect initial diagnosis compared with 39% of younger individuals.[20] Further, diagnostic delays are longer for older adults, with one study showing 16 months of delay among older adults compared with 5 months among younger adults with IBD.[21] Diagnostic delay, in part, is a result of an overlapping presentation of older-onset IBD with

other conditions, such as segmental colitis associated with diverticulosis, ischemic colitis, medication-associated colitis (eg, from nonsteroidal anti-inflammatory drug use), infectious colitis, radiation proctitis, and immune checkpoint inhibitor colitis.[22]

Treatment Considerations for the Older Adult

Although many of the same principles apply when treating older and younger adults with IBD, there are important considerations that must be integrated into the care for older adults. These are generally represented by the 5Ms (Mind, Mobility, Medications, Multicomplexity, Matters Most), which have been developed by the geriatric community and integrated into practice.[23]

The 5Ms of Geriatric Care

With an increasing number of older adults being seen in medical clinics across the globe, health care professionals in gastroenterology need to push beyond the consideration of age and comorbidities alone. Although comorbidities can help dictate appropriate medical therapy (eg, heart failure is generally a contraindication to anti–tumor necrosis factor [TNF] therapy), they alone offer only one piece of the puzzle. Multicomplexity, which focuses more on the biopsychosocial model of an illness, requires consideration of how ongoing medical issues impact an individual's daily life. To truly understand this, providers must consider living conditions (eg, does an adult with ongoing urgency and diarrhea live in a one-story or multi-story home?), social support, as well as the ability to cope and adapt with changes in disease status (eg, periods of remission or flares). This can impact medication choices, as well as treatment goals, and is fundamental to the care of older adults with IBD.

When deciding upon medication choices, it is important to consider not only the modality in which the medication is delivered (eg, enema in someone with limited mobility, injection in someone with arthritis and limited social support) but also the concept of polypharmacy. Polypharmacy, most commonly defined as the use of 5 or more medications, has been shown to be associated with an increasing number of adverse events, particularly among older adults.[24] More specifically, polypharmacy has been associated with increased drug interactions, medication side effects, medication nonadherence, hospitalization, and death.[25-27] This is particularly important within the older-adult IBD patient population, as prior data have found that 43% of older adults with IBD had severe polypharmacy (≥10 medications). Moreover, 35% were given at least 1 potentially inappropriate medication (listed in the Beers criteria), with 10% on long-term narcotics.[28] In a more recent study, 29% of older adults with IBD experienced severe polypharmacy, with this number increasing to 39% at subsequent visits.[29] Severe polypharmacy was also associated with an increased risk of hospitalization within 1 year (adjusted hazard ratio, 1.85; 95% CI, 1.13-3.01). These data highlight the impact that medication choices have on individual outcomes and argue against the reliance on mesalamine therapies (up to 4 pills a day, with possible rectal therapy) as well as prednisone tapers, which are commonly prescribed for older adults with IBD.[9,11,30]

When evaluating older adults with IBD, consideration should be given to any currently prescribed medications that may be contributing to symptoms. Discontinuing these medications and limiting the number of newly prescribed medications can help prevent polypharmacy and lead to improved outcomes.[31] Deprescribing efforts have, therefore, been a recent focus within geriatric care and may have particular benefit in the older-adult IBD patient population who are at high risk for polypharmacy.

Cognition and mobility are critical in determining the appropriate medical management of older adults with IBD. In a study of 405 older adults with IBD, 10% were noted to have cognitive impairments, 6% were noted to have reduced gait speed, and 20% had reduced grip strength.[32] Although there is currently a dearth of data exploring the impact of these factors on clinical and treatment-related outcomes, there is a need to incorporate these assessments into clinical decision-making (eg, individuals with cognitive impairment may benefit from infusion therapy more than oral agents or injectables, when considering advanced therapies). Understanding an older patient's cognitive function and mobility is also important when considering the impact of frailty and sarcopenia (as discussed in a later section) on both disease course and clinical management.

The consideration of what matters most is of particular importance to older adults. Based upon individual preferences, as well as the varying time horizon of follow-up treatment goals, management decisions for older adults may differ from those for younger adults. Accordingly, the preservation of functional status and minimization of clinical symptoms may take precedence over the achievement of deep remission in certain cases. Additionally, frequency of endoscopic evaluation, both for disease activity and dysplasia assessment, should be based upon individual characteristics and preferences (eg, risk of dysplasia, mobility [risk of fall when completing preparation]). However, further work is needed to understand outcomes based on the preferences of older adults, as in the case of colorectal cancer screening in patients over 75 years.[33]

Table. Key Facts About IBD in Older Adults

One-third of the IBD population will soon be comprised of adults 60 years and older, with approximately 15% newly developing IBD at this age.
Individuals with older-onset IBD are significantly less likely to be treated with anti-TNF therapy or immunomodulators and more likely to receive mesalamines and corticosteroids.
Ongoing disease activity may represent a significant driver of adverse clinical outcomes in older adults with IBD.
Older adults with IBD are more likely to develop anti-TNF antibodies compared with their younger counterparts, arguing against the concept of immunosenescence.
Early surgery among older adults who will require it, as well as elective surgical resection in select cohorts of older adults with IBD, may lead to improved outcomes.
Frailty is common in older adults with IBD and associated with IBD-related adverse events, but treatment of inflammation may lead to improvement in frailty.
Sarcopenia may be present in approximately 4 in 10 adults with IBD (42%) and is associated with an increased risk of adverse surgical outcomes, including infection, deep vein thrombosis, readmission, and longer length of hospital stay.

IBD, inflammatory bowel disease; TNF, tumor necrosis factor.

Medical Management for the Older Adult

Older adults with IBD are often undertreated, as a lack of data has led management decisions to largely be based upon chronological age and comorbidities alone. Health care professionals who are concerned about the safety of advanced therapies and surgical intervention may preferentially treat older-adult IBD patients with mesalamines and intermittent courses of corticosteroids. In a 2014 study by Charpentier and colleagues, individuals with older-onset IBD were significantly less likely to be treated with anti-TNF therapy or immunomodulators and significantly more likely to be treated with mesalamines and corticosteroids.[9] Further, when evaluating the cohort with older-onset CD, almost 90% were given mesalamines by 20 years of follow-up, despite mesalamines being shown to have limited efficacy in the treatment of CD.[9] Additionally, a multicenter study demonstrated that almost one-third of older adults with IBD were prescribed corticosteroids for at least 6 months, with this number doubling from 36% between 1991 and 2000 to 64% between 2001 and 2010.[30,34] Although updated data are needed, particularly given the relatively recent approval of additional advanced therapies (eg, vedolizumab [Entyvio, Takeda], ustekinumab [Stelara, Janssen], risankizumab [Skyrizi, AbbVie]), it is likely that there is a similar reluctance to use treatments such as anti-TNF therapy, Janus kinase inhibitors, or combination therapy in older adults owing to concerns about safety.

Risks vs Benefits of Using Advanced Therapies

Despite concerns regarding the safety of advanced therapies among older adults with IBD compared with younger adults with IBD, recent data have suggested that ongoing disease activity may represent a more significant driver of adverse clinical outcomes.[35-37] In a study by Cheng and colleagues, pooled data from randomized clinical trials have demonstrated that anti-TNF therapy compared with placebo among older adults with moderate-to-severe UC did not result in an increased risk of serious adverse events. In fact, treatment with anti-TNF therapy resulted in lower rates of serious adverse events (20% anti-TNF agents vs 25.4% placebo), lower rates of hospitalization (14.4% anti-TNF agents vs 21.1% placebo), and lower rates of severe infection (2.5% anti-TNF agents vs 5.6% placebo).[38,39] These results support the notion that the safer treatment option for older adults with IBD is likely the more efficacious one.

Analogous results were seen in a nationwide Denmark study assessing the efficacy and safety of vedolizumab vs anti-TNF therapy among older adults with IBD.[40] In a propensity-matched analysis, there was no difference in 1-year infectious risks between the 2 treatments; however, individuals treated with anti-TNF therapy were less likely to require IBD-related surgery, IBD-related hospitalization, or need for corticosteroids compared with individuals treated with vedolizumab. It should be noted that although propensity-matched scoring may account for many potential baseline differences between patients, there are likely additional unmeasured items (eg, social support) that may account for treatment decisions and potential outcome differences.

A risk of using anti-TNF therapy in older patients with IBD is that older adults are more likely to develop anti-TNF antibodies compared with their younger counterparts. Among 22,197 individuals using infliximab, 18.1% of older adults developed antibodies to infliximab therapy compared with 15.0% among younger individuals ($P<.01$). However, among individuals who were dose escalated (change in dose or frequency to achieve ≥10 mg/kg every 8 weeks), this difference was less apparent (10.6% with antidrug antibodies among older adults vs 9.9% among younger adults). The finding that older adults are more likely to make antidrug antibodies than younger adults, argues against the notion of immunosenescence and emphasizes that when using anti-TNF therapy among older adults with IBD, caution needs to be given to not underdose.[41]

When considering combination therapy (anti-TNF agent + immunomodulator) among older adults, similar
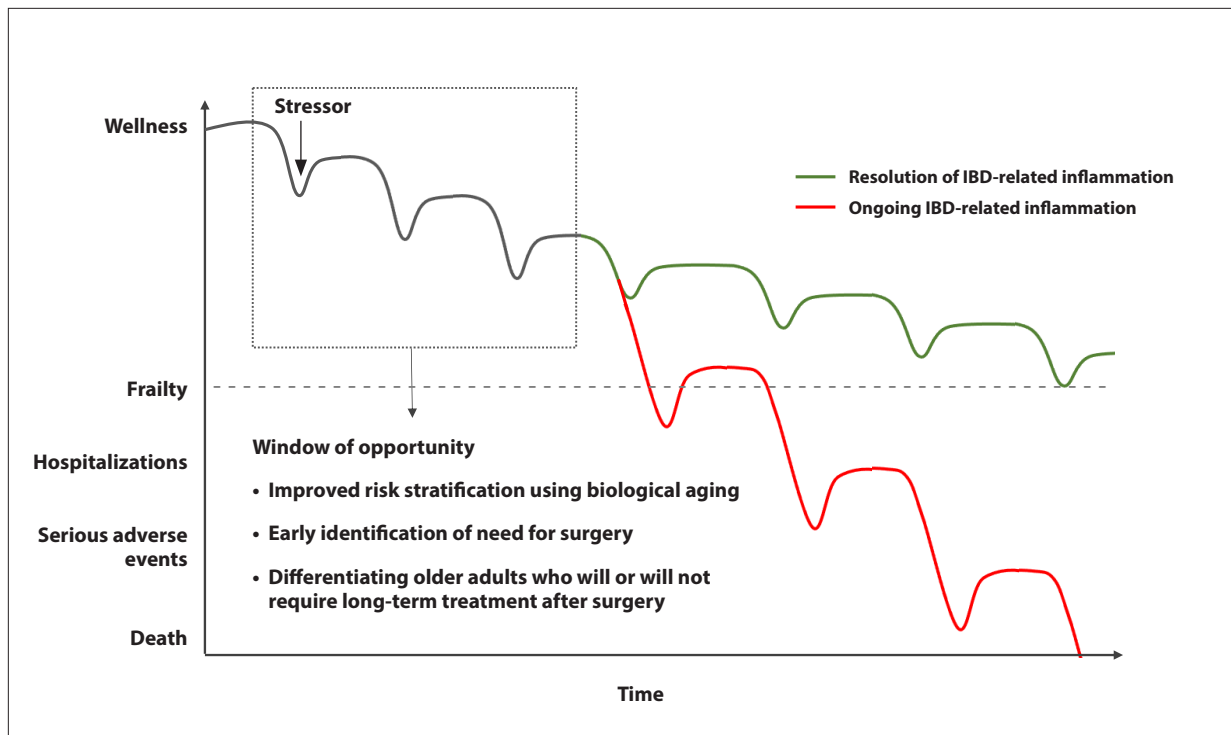
Figure. Natural progression of frailty in older adults with IBD in relation to stressors and response to treatment. An IBD patient's wellness state decreases naturally from inflammaging and is affected by stressors (eg, disease flare, minor injury or illness), which cause temporary decreases in wellness over time. A patient with resolution of IBD-related inflammation in response to treatment is more likely to maintain wellness and recover adequately from stressors, whereas a patient with ongoing IBD-related inflammation despite treatment is more likely to become frail and respond poorly to stressors. If clinicians apply risk stratification strategies in the early stages of IBD management (window of opportunity), they can potentially have a positive impact on an IBD patient's trajectory.

Modified from Fried LP et al.[64]

IBD, inflammatory bowel disease.

results have been noted. In a post-hoc analysis of the REACT trial, Singh and colleagues found that there was no increased risk of complications among older adults who received combination therapy compared with those who received conventional management. Further, when assessing mortality, although older adults had a higher overall mortality compared with younger adults (4.5% older adults vs 0.2% younger adults), more deaths were observed in older adults on conventional management than on combination therapy. These results in conjunction with the aforementioned studies suggest that ongoing disease activity as opposed to the medications themselves may be a more significant driver of adverse clinical outcomes among older adults with IBD (Table).[42,43]

Surgical Management of the Older Adult

A higher rate of adverse outcomes has been observed in older adults with IBD who underwent surgery. This finding has led to a deferral of surgical interventions in older patients owing to age and comorbidities alone. However, when considering risk factors contributing to an adverse 30-day surgical outcome, similar results are seen independent of age. More specifically, the presence of malnutrition, dependent functional status, preoperative sepsis, and need for emergency surgery carry similar odds for an adverse postoperative event among both older (≥60 years) and younger (<60 years) adults with IBD, although these factors are more common among older adults.[44] The higher adverse event rate among older IBD patients may be a consequence of initial surgical deferral. To avoid surgery, given the higher risk of adverse outcomes, older individuals with IBD may preferentially be continued on medications with limited efficacy. The continuation of ineffective medication can paradoxically increase the risk of an adverse postoperative event, as ongoing inflammation and malnutrition may precipitate functional and cognitive decline. Therefore, an older-adult–specific IBD

surgical risk stratification tool is urgently needed to help mitigate delays among individuals at lower operative risk and highlight potentially modifiable factors for individuals at higher operative risk.

Earlier IBD-related surgery, particularly before older individuals develop physiologic decline from ongoing inflammation, may be associated with improved outcomes. A study by Bewtra and colleagues found that elective colectomy compared with medical therapy for UC was associated with improved all-cause mortality among individuals 50 years and older.[45] A recent LIR!C-like study that assessed real-world data from patients who underwent ileocecal resection or received anti-TNF therapy further supports the potential benefit of earlier IBD-related surgery.[46,47] Among a Danish cohort of individuals with ileal CD, early surgical resection was associated with a 33% lower risk of the composite outcome (hospitalization, need for corticosteroids, need for surgery, development of perianal disease) compared with anti-TNF therapy. On subgroup analysis, individuals 40 years and older derived the most benefit from early surgical resection, with an associated hazard ratio of 0.56 (95% CI, 0.39-0.80) compared with anti-TNF therapy.[46]

These data support the notion that for older adults with IBD, earlier surgery in patients who require it and elective surgical resection in select cohorts may lead to improved outcomes.

Incorporating Measures of Biological Age Into Risk Stratification Tools

To improve current medical decision-making for older adults with IBD, there is an urgent need for accurate risk stratification tools. Because chronological age alone is a poor predictor of clinical outcomes, measures of biological age must be incorporated into current practice. Two such measures, frailty and sarcopenia, have both shown promise in this domain.

Frailty

Frailty is a state of vulnerability that leads to a rapid decline when faced with a clinical stressor (Figure). Frailty is present in approximately 11% of older community dwellers but is more common within the older-adult IBD patient population. In a recent population-based study in Sweden, 49% of older adults with IBD were at low risk and 12% at high risk for frailty, compared with 21% and 6%, respectively, among older-adult non-IBD population controls.[48] Additionally, in the geriatric literature, frailty has been associated with a number of adverse clinical outcomes among older adults, including hospitalization, falls, and mortality. Similar results have been observed in the IBD patient population, as frailty has been associated

with adverse events from medical therapy, rehospitalization, and mortality.[49-52] Recent data have also suggested that treatment of ongoing inflammation may improve frailty, as 27% of all adults with IBD who had ongoing inflammation developed frailty within 1 year compared with only 7% who had response to therapy.[53,54] These data, however, are retrospective and evaluate frailty as an accumulation of deficits. Further work prospectively using the frailty phenotype (to measure weight loss, exhaustion, weakness, gait speed, and physical activity) is underway, and should provide additional data that can be incorporated into older-adult IBD–specific risk stratification tools.[55]

Recent data from other subspecialties have also added to what is known about frailty.[56,57] In contrast to what had been previously thought, frail individuals derived greater benefit as a result of advanced heart failure therapies compared with individuals who were not frail.[58] This finding challenges the current paradigm of conservative care among frail individuals, and highlights that treating an underlying condition may mitigate, or even reverse, the development of frailty among older adults. Further data exploring this concept within the older-adult IBD patient population are therefore needed.

Sarcopenia

Another closely related but clinically distinct marker associated with biological age is sarcopenia. Sarcopenia, defined as the loss of muscle mass, strength, and function, is an important predictor of clinical outcomes among older adults and has been widely studied within the preoperative state. Yet, data assessing sarcopenia in the older-adult IBD patient population are limited, despite its high overall prevalence, which has been reported as 42% among adults (median age, 33 years) with IBD.[59] From the data available on all adults with IBD, several studies have shown that preoperative sarcopenia is associated with an increased risk of adverse surgical outcomes, including infection, deep vein thrombosis, readmission, and longer length of hospital stay.[60,61] However, it should be noted that as with frailty, not all IBD studies have shown a positive association between the presence of sarcopenia and the development of adverse clinical outcomes.[62] This heterogeneity is likely explained by the differing measures of muscle mass, the varying cutoffs and methodologies used to define low muscle mass in the IBD patient population, and the overall lack of functional assessments.

Recent data assessing older adults with IBD prior to surgery have found that skeletal muscle mass, as opposed to psoas mass alone, may be a stronger predictor of adverse postoperative events.[63] Furthermore, on multivariable analysis of 121 older adults with IBD, increasing skeletal muscle mass was associated with a lower risk of adverse

postoperative outcomes. Future prospective work must: (1) validate these findings, (2) incorporate additional measures of muscle strength and function, (3) develop an older-adult–specific IBD preoperative risk calculator, and (4) explore the role of prehabilitation to improve sarcopenia in the preoperative state.

Conclusion

As the population of older adults with IBD continues to rise, it is important for clinicians to make a timely diagnosis in patients with older-onset IBD and not delay the appropriate treatment modality. Clinicians must also limit polypharmacy and understand what matters most to the patient. For clinicians to effectively manage older adults with IBD, they need: (1) further data to develop treatment-related risk stratification tools that incorporate measures of biological age, (2) qualitative data regarding patient preferences, and (3) data describing which population of older adults can undergo surgical resection without need for further advanced therapies. Obtaining these data has the potential to change the current paradigm of practice and, in doing so, improve care for the growing population of older adults with IBD.

Disclosures

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