AGA Clinical Practice Update on Management of Inflammatory Bowel Disease in the Elderly: Expert Review

Ashwin N. Ananthakrishnan, M.D., M.P.H., Geoffrey C. Nguyen, M.D., Ph.D., F.R.C.P.(C), Charles N. Bernstein, MD

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Ashwin N Ananthakrishnan, M.D., M.P.H.[1]

Geoffrey C Nguyen, M.D., Ph.D., F.R.C.P.(C)[2]

Charles N Bernstein, MD[3]

[1] Division of Gastroenterology, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts, USA

[2] Mount Sinai Hospital Centre for Inflammatory Bowel Disease, University of Toronto, Toronto, Ontario, Canada.

[3] University of Manitoba IBD Clinical and Research Centre, Section of Gastroenterology, University of Manitoba, Winnipeg, Canada

Corresponding author:

Charles N. Bernstein, MD
University of Manitoba Inflammatory Bowel Disease Clinical Research Centre,
Section of Gastroenterology
804F - 715 McDermont Avenue
Winnipeg, MB R3E 3P4
CANADA

Email: Charles.Bernstein@umanitoba.ca

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Table 1: Best Practice Advice Statements – Management of IBD in older patients

Diagnosis

1. A diagnosis of inflammatory bowel disease (IBD; Crohn's disease (CD), ulcerative colitis (UC)) should be considered in older patients who present with diarrhea, rectal bleeding, urgency, abdominal pain, or weight loss as up to 15% of new diagnoses of IBD occur in individuals over the age of 60 years.
2. Fecal calprotectin or lactoferrin may help prioritize patients with a low probability of IBD for endoscopic evaluation. Individuals presenting with hematochezia or chronic diarrhea with intermediate to high suspicion for underlying IBD, microscopic colitis, or colorectal neoplasia should undergo colonoscopy.
3. In elderly patients with segmental left sided colitis in the setting of diverticulosis, consider a diagnosis of segmental colitis associated with diverticulosis in addition to the possibility of Crohn's disease or IBD-unclassified (IBDU).

Treatment – General principles

1. A comprehensive initial assessment of the older patient is important to collaboratively establish short- and long-term treatment goals and priorities.
2. Clinicians should risk stratify patients based on likelihood of severe clinical course including assessment of perianal or penetrating phenotype, long-segment small bowel involvement (CD), extensive colitis (UC), anemia, hypoalbuminemia, elevated inflammatory markers and weight loss, to determine an appropriate therapeutic strategy.
3. Systemic corticosteroids are not indicated for maintenance therapy. When used for induction therapy, when possible, clinicians should prefer non-systemic corticosteroids (like budesonide) or even early biological therapy initiation if budesonide is not appropriate for the phenotype of the disease being treated.
4. Candidacy for immunosuppression should be based on chronologic age, as well consideration for the patient's functional status, comorbidity including prior neoplasia and potential for infectious complications, and frailty.
5. When possible, immunomodulatory treatments with lower overall infection or malignancy risk (vedolizumab, ustekinumab) may be preferred in older patients. However, choice of treatment must also include assessment of clinical context, efficacy of treatments for specific phenotypes, rapidity of onset of action, and ability to achieve corticosteroid-free remission.
6. Consideration for thiopurine monotherapy for maintenance of remission in older patients should balance the convenience of its oral route of administration and lower cost with relatively lower efficacy, slow onset of action, and an increase in risk of non-melanoma skin cancers and lymphoma in this population.
7. Older patients with IBD have a greater burden of comorbidity than younger patients. Optimization of comorbidity is important to minimize risks associated with IBD and its treatment and guide selection of the appropriate agent.

8. The decision about timing and type of surgery in older IBD patients should incorporate disease severity, impact on functional status and independence, risks and effectiveness of medical therapy, candidacy for surgery, and risk of post-operative complications.
9. The increased risk of fracture, venous thromboembolism, infections including pneumonia, opportunistic infections, herpes zoster, and risk of skin- and non-skin cancers (including lymphoma) should be incorporated in therapeutic decisions.
10. Care for the older IBD patient should be multidisciplinary, actively engaging gastrointestinal specialists, primary care providers (including geriatricians), other medical subspecialists (e.g. cardiologists) mental health professionals, general or colorectal surgeons, nutritionists, and pharmacists. Engaging with family and caregivers may also be appropriate in formulating a plan.

Health Maintenance

1. Clinicians should facilitate adherence to vaccination schedules; including influenza, pneumococcal, and herpes zoster vaccines in older patients with IBD. If possible, vaccination should be scheduled before starting immunosuppression.
2. The decision to continue or stop colorectal cancer surveillance in older patients with long-standing ulcerative colitis or Crohn's colitis should be made incorporating age, comorbidity, overall life-expectancy, likelihood of endoscopic resectability of the lesion, and candidacy for colon resection surgery.

INTRODUCTION

Inflammatory bowel disease (IBD), comprising Crohn's disease (CD) and ulcerative colitis (UC) can present at any age including in the elderly, commonly defined as 60 years of age and older. Hence, considering both incident elderly patients with IBD and the aging prevalent IBD population, there will be increasing numbers of elderly IBD patients. The care of elderly IBD patients poses unique challenges with respect to diagnosis and therapeutic decision-making.

Approximately, one out of every 160 elderly individuals are affected by IBD. The prevalence of IBD amongst the elderly appears to be incrementally rising by 5.2% annually. Up to 15% of IBD in North America and Asia is diagnosed after the age of 60 years[1]. Incidence rates vary from 4 to 8 per 100,000 for persons over age 60 years. Clinicians must be prepared to newly diagnose IBD in the elderly and initiate therapy in the context of other health issues experienced by the elderly.

Common comorbidities, especially malignancy and increased disposition to infections, can render elderly patients more vulnerable to complications of immunosuppression[2]. Observational studies suggest that the risk of infection with anti-tumor necrosis factor (TNF) therapy and lymphoma with thiopurines is considerably higher in the elderly IBD population[3, 4]. Surgical management of IBD in elderly populations can also be associated with high risk due to high comorbidity. Further, while there is no difference in mortality rates for older versus younger age of onset in UC, the elderly are more likely to die of CD (33/10000 person-yrs) compared with their middle-age (5.6/10000 p-yrs) or young counterparts (1/10000 p-yrs).

It is becoming apparent that treatment of IBD in the elderly requires special consideration while accounting for effectiveness of immunosuppressive therapies in this subpopulation and

less favorable safety profiles. In this review, we present best practice advice statements on the diagnosis and management of IBD in the elderly (**Table 1**). It should be noted that most clinical data to inform these practices are based on observational data or indirect evidence as elderly IBD patients comprise a very small proportion of subjects enrolled in IBD clinical trials or long-term pharmacovigilance initiatives. This expert review was commissioned and approved by the AGA Institute Clinical Practice Updates Committee (CPUC) and the AGA Governing Board to provide timely guidance on a topic of high clinical importance to the AGA membership, and underwent internal peer review by the CPUC and external peer review through standard procedures of the Gastroenterology journal.

Diagnosis of IBD in the Elderly (Figure 1)

When elderly persons present with any constellation of symptoms that may include diarrhea, rectal bleeding, abdominal pain, and weight loss, providers should have a strong clinical suspicion for IBD. However, compared with persons under the age of 40 years, persons over 60 years are more likely to have other diagnoses that may mimic symptoms of IBD such as colorectal cancer, ischemic colitis, segmental colitis associated with diverticulosis, non-steroidal anti-inflammatory drug induced pathology, radiation enteritis or colitis, or microscopic colitis. Because the medical and surgical management of these conditions varies substantially, a vigorous approach to confirming the diagnosis of IBD is important in the elderly population.

The first diagnostic steps should include laboratory investigations that include a complete blood count, serum albumin, serum ferritin, and C-reactive protein (Figure 1). Liver enzymes and urea and creatinine levels serve to assess for underlying comorbidities as well as a baseline

for toxicity monitoring. Stool testing for *Clostridium difficile* in all new presentations of diarrhea, regardless of antibiotic use history, and selective testing of stool for culture and ova and parasites may be appropriate. Cross sectional imaging with computerized tomography (CT scan) is appropriate in elderly persons who present with acute symptoms especially when abdominal pain is a prominent symptom because it can also rule out other diagnoses (e.g., ischemic colitis, diverticular disease). Colonoscopy with histologic confirmation remains a cornerstone of diagnosis. However, there should be additional consideration of procedural risks and tolerance for anesthesia in the presence of comorbidities and polypharmacy in elderly patients. In cases where the indication for colonoscopy is equivocal or is associated with relatively high-risk, the use of non-invasive stool markers of inflammation such as fecal calprotectin and imaging may aid in decision-making.

Disease Presentation and Disease Course

The initial presenting phenotype may differ between elderly-onset IBD and younger onset of the disease. In CD, the elderly may be more likely than younger patients to present with isolated colonic disease (44%) and less likely to have penetrating disease or perianal disease[5-7]. Compared with their younger counterparts, elderly persons with UC are more likely to have left sided disease, occurring in 40%[6]. Presenting with more benign phenotypes may suggest patients with elderly-onset IBD may have more favorable outcomes compared with their younger counterparts. While some initial epidemiological studies may support this notion, others have suggested that those with elderly-onset UC were more likely than younger IBD patients to undergo colectomy[5]. Thus, in attempting to predict disease course, it may be more prudent to consider specific disease characteristics rather than chronologic age.

Multidisciplinary Approach to Management (Figure 2)

Managing an older individual diagnosed with IBD warrants a multidisciplinary approach. In a sample from the National Social Life Health and Aging Project nearly a third (29%) of persons aged 57-85 years were using at least 5 prescription drugs, and 4% of this elderly cohort were at risk of major drug-drug interactions emphasizing the importance of pharmacist support. Multiple co-existing chronic diseases may warrant co-management with a geriatrician to integrate frequently complex care and polypharmacy. Moreover, access to mental health providers may be helpful due to the high prevalence of depression and other mental health disorders in the elderly population. Because physical and cognitive decline can increase with age, social workers or health care navigators may work closely with health providers to enable reliable access to care as well as supportive care at home.

Medical Therapy in Elderly Inflammatory Bowel Disease (Figure 2)

The principles behind selection of optimal medical therapy in elderly IBD patients based on disease presentation and prognostic factors is similar to that of the general population. Though there is little evidence for age-related differences in efficacy of various therapeutic agents, there are safety considerations that may be warranted given the higher frequency of malignancy and the effects of immunosenescence among the elderly. Unfortunately, safety data among the elderly are relatively sparse as this population is underrepresented in clinical trials and registries. In addition to chronologic age, clinicians should also assess overall fitness and frailty in considering selection of treatments. Pre-treatment frailty was associated with an increased risk of infections following immunomodulator or anti-TNF treatment or following surgery[8].

Interventions aimed to ameliorate physical and nutritional frailty including physical therapy and nutritional support may thus be an important part of care of the older IBD patient. Screening prior to initiation of medical therapy for IBD including assessment of hepatic and renal function, presence of latent tuberculosis or hepatitis B infection, and assessment of TPMT status prior to thiopurine use is similar in the older IBD patient as in younger patients. Despite the potential risks for immunomodulatory therapy in the elderly, therapy choices should not be delayed and/or corticosteroid therapy prolonged out of concerns for immune therapy-associated risks.

Aminosalicylates:

Aminosalicylates have proven efficacy for the induction and maintenance of remission in mild-to-moderate UC. In contrast, though widely used, their efficacy is less well established in CD with most clinical trials demonstrating either no or a modest benefit over placebo. Their lack of a systemic immunosuppressive effect has made them a frequently relied upon option for treatment of the older IBD patient. Population-based cohorts have demonstrated that over two-thirds of older patients with UC and CD receive 5-ASA therapy.[5, 6] Though side effects from 5-ASA use are infrequent, the rare complication of interstitial nephritis may be especially pertinent in older patients due to superimposed age-related decline in renal function.

Corticosteroids

Despite limited evidence-based data, corticosteroids seem to have similar efficacy in elderly IBD patients as their younger counterparts[9]. They are frequently used in the management of older adults with IBD. They are more likely to be used for maintenance therapy in the elderly compared with younger IBD patients,[10] despite some evidence that elderly IBD patients are less likely than younger IBD patients to be corticosteroid dependent (21% vs 30%)[7]. While

corticosteroid-related adverse effects may not be more frequent in the elderly compared with younger IBD patients, older patients also have a greater prevalence of diabetes, hypertension, glaucoma, cataract, osteoporosis, and cognitive impairment all of which may be exacerbated by corticosteroid use. Corticosteroid use may also lead to increased risk of anxiety, depression, fatigue, and poor sleep quality. Initiation of therapies (biologic or small molecule) with rapid onset of action may reduce or eliminate the need for use of corticosteroids.

Budesonide is an oral corticosteroid with a high-first pass metabolism that has been shown to have only a modestly lower efficacy than conventional systemic corticosteroids in CD with lower adverse effects. Similarly, budesonide-MMX has been shown to be effective for mild-to-moderate left-sided UC. Long-term budesonide is less likely to lead to adrenal axis suppression than systemic corticosteroids[11]. Thus, budesonide may be preferred over conventional corticosteroids in older patients with ileocolonic or right-sided luminal CD or left-sided UC. Any use of systemic corticosteroids should prompt consideration for corticosteroid-sparing therapy and measures to mitigate risk for osteoporosis should a prolonged course be required.

Topical corticosteroids (or aminosalicylates) may be effective for distal colonic disease but may be poorly tolerated in older patients with limited mobility or weak sphincter tone. In such situations, formulation with lower volume (such as foam) may be preferred. Clinical trials have not demonstrated efficacy of corticosteroids in maintaining remission in IBD in any age group[11]. Given the potentially higher risk adverse effects outlined above, corticosteroid use for IBD maintenance therapy should be avoided.

Thiopurines and Methotrexate

While thiopurines are effective in maintaining remission in both CD and UC, the data are limited, particularly in the elderly[12]. More than a third of the elderly have been exposed to thiopurines in one cohort within 5 years of IBD diagnosis[7]. Among the elderly, a higher frequency of adverse events including hepatoxicity may be seen, though acute pancreatitis was less likely to occur[7].

An increase in the absolute risk of thiopurine-related malignancy in elderly IBD patients has raised concerns about their use in this population. Thiopurine use is associated with a higher absolute risk of non-melanoma skin cancer (NMSC) among those older than 65 years compared with those younger than 50 years (4.04 vs. 0.66 per 1000)[13]. The absolute incidence of lymphoproliferative disorders in the presence of thiopurine use has also been shown to be increased in elderly IBD patients compared to those younger than 50 years (5.41 vs. 0.37/1000 person years) while the age-related difference was less pronounced in thiopurine non-users (1.68 vs. 0 person-years)[14].

On balance, thiopurines by virtue of their oral administration are convenient and inexpensive options for many older patients with IBD. However, their inferior efficacy when compared to other therapies, their delayed efficacy (thereby potentially prolonging corticosteroid exposure), and the higher absolute risk of potentially serious treatment-related malignancies in older IBD patients makes prudence about new initiation of thiopurines important. Nonetheless, routine discontinuation or absolute avoidance of its use solely based on chronologic age is not appropriate and consideration of thiopurine use should be on a case-by-case basis. Methotrexate also represents an attractive option in older patients with Crohn's disease with data supporting its role in inducing and maintaining remission. It can also be an alternative to thiopurines when used

for combination therapy in individuals considered to be at high risk for thiopurine-related adverse effects including malignancy.

Anti-TNF biologics

Effectiveness studies of anti-TNF therapy in elderly IBD populations have demonstrated mixed results. A study of 114 biologic-naïve patients who were started on anti-TNF therapy showed they had lower persistence with therapy and were more than half as likely to achieve corticosteroid-free remission at 12 months compared to younger patients (31% vs. 67%)[15]. Lobaton *et al*. similarly found lower rates of clinical response at 10 weeks in older patients on anti-TNF therapy compared to controls but no difference at later time points[16]. A meta-analysis found no difference in efficacy of infliximab and golimumab in CD and UC between older and younger IBD patients[17].

There have been a number of reports on anti-TNF related complications in the elderly IBD population. One observational study of 95 elderly IBD patients who were initiated on anti-TNF therapy, had higher rates of severe infections (11% vs. 2.6%), cancer (3% vs 0%), and death (10% vs. 1%) when compared with 190 matched younger controls though the cause of mortality was not specified[3]. The rate of these adverse events was also higher among older anti-TNF users compared to older non-anti-TNF users (0.5% severe infections, 2% cancer, 2% death). Another observational study revealed that a fifth of elderly patients discontinued anti-TNF therapy within 12 months of initiation[18]. In a multi-center Spanish cohort study, older onset IBD patients were more likely to experience any infection (46% vs. 26%) and malignancy (7.6% vs. 1.8%) compared with younger IBD patients [7]. A meta-analysis that compared the safety of anti-TNF therapy across age groups for all indications of use showed that the pooled prevalence

of infection was higher in older biologic users (13%) compared to younger users (6%) (OR 2.28, 95% CI 1.57 – 3.31) and older controls not using biologics (OR 3.60, 95% CI 1.62 – 8.01)[4]. There was also a three-fold higher risk of malignancy in older compared to younger biologic users (OR 3.07, 95% CI 1.98 – 4.62) but not when compared to older controls**.** Limitations of these studies include inability to separate out the independent effect of anti-TNF from either concomitant steroid or immunomodulator therapy. In many older patients, particularly those who are not frail, the benefit of anti-TNF biologic therapy will likely outweigh the small increase in risk.

The evidence for the safety of the combination of an immunomodulator with anti-TNF biologic therapy in older patients is mixed. While a post-hoc analysis of the REACT trial by Singh *et al*. concluded that the benefit of early combined intervention was similar in older and younger patients with no increase in risk[19], Desai *et al.* noted that older patients on combination therapy were twice as likely to stop therapy early than those on anti-TNF monotherapy (HR 2.20, 95% CI 1.12 – 4.32)[18]. Combination therapy may be appropriate in those with severe disease including deep ulceration, extensive bowel involvement, and penetrating phenotype, while in others, anti-TNF monotherapy may be a preferred initial option, particularly in the setting of significant frailty, comorbidity or infection risk.

Vedolizumab, Ustekinumab, Tofacitinib, and other medications:

Limited clinical trial data suggest that the effectiveness of vedolizumab in CD and UC is similar between older and younger patients. There was no age-related difference in the rate of any adverse events including infections and serious infections. Because of its gut-specificity, vedolizumab use is associated with less systemic immunosuppression and should have a

favorable safety profile. However, a comparison of 131 IBD patients initiated on anti-TNF therapy and 103 initiated on vedolizumab showed no difference in infection rates at one year in either CD or UC though confidence intervals were quite wide[20]. There are no published data examining the safety of ustekinumab specifically in older patients with IBD, but a limited cases series of 24 patients with psoriasis showed few infection events[21].

Most of the safety data on tofacitinib relies on indirect studies from rheumatology. While there is a higher frequency of serious infections in older patients on tofacitinib compared with those on placebo, it was similar to risks observed in younger individuals. Pooled analysis of clinical trials in rheumatoid arthritis has been informative regarding the safety of this therapy in older patients. Curtis et al. pooled data from phase 3 and long-term effectiveness studies, identifying 16% of patients in these studies to be aged $\geq$ 65 years[22]. While serious adverse events were more common in older tofacitinib users than younger users with both the 5mg or 10mg BID dose, a similar effect was also noted among placebo users suggesting no incremental age-related increase in risk. Specifically, there is a higher risk of herpes zoster among older patients receiving 5mg and 10mg of tofacitinib compared with placebo (5.5 and 3.1 per 100 p-y vs. zero, respectively). An interim analysis reported an increased risk of venous thromboembolism including pulmonary embolism among older patients with rheumatoid arthritis with cardiovascular risk factors with tofacitinib 10mg BID (0.4 per 100 p-y) compared with anti-TNF therapy (0.07 per 100 p-y) leading to placement of a black-box warning. Cyclosporine is rarely used in older patients with IBD but may be considered for acute severe ulcerative colitis as rescue therapy in individuals where anti-TNF biologics may be contraindicated or previously failed.

Safety of surgery in older patients with IBD

The data on whether older age is associated with higher risk of post-operative complications following surgery in patients with IBD has yielded conflicting results. Some small studies suggested no difference in postoperative complications between elderly patients with IBD and younger patients. However, a larger study analyzing the ACS NSQIP database found that post-operative mortality at 30 days was higher in older patients with both CD and UC compared to younger controls[23]. The frequency of post-operative complications was higher in older compared to younger patients (34.5% vs. 21.3%). Older patients also had higher rates of post-operative infection, venous thromboembolic events, bleeding requiring blood transfusion as well as cardiac, renal, and neurologic complications including stroke and coma. Independently, undergoing emergent surgery was associated with an increase in mortality. Additionally, the greater comorbid burden in older patients also increases risk of post-operative complications and mortality. The preferred surgery may also be different in older patients, particularly among those with ulcerative colitis. Due to reduced anal sphincter tone, older patients may have worse functional outcomes from an ileal-pouch anal anastomosis. An end-ostomy may offer more functional independence in select patients. Pharmacologic thromboprophylaxis is important in older patients undergoing surgery due to higher risk for venous thromboembolism. In addition, assessment and optimization of nutritional status prior to surgery may be important in reducing post-operative morbidity and facilitating recovery.

Health Maintenance

Soon after diagnosis it is important for clinicians to discuss health maintenance issues with older patients. Older patients are at a higher risk for vaccine preventable illnesses,

particularly in the setting of systemic immunosuppression. It has been shown that influenza vaccine and herpes zoster vaccine are underutilized including in persons with IBD where the risk for influenza, pneumococcal pneumonia or shingles is increased especially in persons using immunomodulatory drugs[24, 25]. Clinicians should facilitate adherence to recommended vaccination schedules including influenza, pneumococcal, and herpes zoster vaccines as the risk for serious sequelae of these infections is increased among elderly patients. While gastroenterologists often defer routine health maintenance such as vaccinations to primary care providers, it is not uncommon for IBD patients of any age to find themselves without a primary care provider, and for primary care providers to have some uncertainty regarding the safety and timing of certain vaccines in persons on immunomodulatory drugs. It is also important to ensure the older IBD patient is up to date with age-appropriate cancer screening recommended for the general population.

Persons with chronic colitis (usually of at least 8 years duration) either related to UC or CD are at approximately a two-fold risk of developing colorectal cancer compared to age matched community counterparts. While the relative risk is higher in younger patients with IBD the absolute risk is higher in the elderly as colorectal cancer becomes increasingly common. Hence, vigilance is needed toward ongoing surveillance colonoscopies and clinicians should be prepared to adequately address dysplastic lesions in these patients. Like colorectal cancer, adenomas and serrated polyps are more common in the elderly. However, as with all decisions in medicine and the decisions regarding therapy choice in the elderly, the persistence with surveillance colonoscopy with advancing age should consider anesthesia and perforation risks

associated with the procedure itself, comorbidity, overall life-expectancy, and candidacy for colon resection surgery.

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