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Infection Risk Among Elderly with Inflammatory Bowel Disease



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With an aging population, the number of older patients with Crohn's disease (CD) and ulcerative colitis (UC) and the health care costs associated with their care is expected to increase. This trend will lead to a subsequent rise in the use of immunosuppression. The risk of infection, particularly as a result of opportunistic infections in the setting of immune modifying and biologic therapy, is of utmost concern to providers and a common reason for hospitalization. In addition to medications, ongoing active intestinal inflammation, multimorbidity, malnutrition, immunosenescence, hospitalization and surgery all contribute to the predisposition to infection. Recognizing and addressing these risk factors is key to managing older IBD patients in a cost-effective manner.

BACKGROUND

The inflammatory bowel diseases (IBD), chronic inflammatory conditions of the intestine, are comprised of Crohn's disease (CD) and ulcerative colitis (UC). Long believed to be a disease of the young, a growing number of IBD patients are over the age of 65.¹ Compared to non-IBD elderly patients, the costs associated with caring for elderly IBD patients may be two fold higher.²

Unique challenges exist in the diagnosis and treatment of CD and UC in the elderly. Multimorbidities and atypical clinical presentations can cast doubt on the diagnosis. IBD management can be complicated by the patient's functional status and polypharmacy even as the disease course may be milder when diagnosed in advanced age. Additionally, the lack of medical efficacy trials and appropriate clinical endpoints (i.e., subjective versus objective) in older IBD patients adds to the complexity of treatment decisions. One of the

important considerations in the treatment of elderly patients is the development of serious infection. Multiple factors, often existing in tandem among elderly, increase the susceptibility to infection. These include ongoing active intestinal inflammation, polypharmacy, multimorbidities, poor nutrition, immunosenescence, hospitalization, and surgery. Immunosuppressive therapy, especially a combination of biologics (i.e., anti-TNF agents) and thiopurines (i.e., azathioprine, methotrexate), used to induce and maintain disease remission in adults, has been associated with an increased risk of infection and decreased response to vaccination in the elderly.^{3,4}

The spectrum of infections in IBD is wide and can vary from uncomplicated viral upper respiratory infections to gram-negative sepsis. Strategies to prevent infection through vaccination and universal precautions are key. Early recognition and management of risk

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factors is significant in blunting the effect of serious infections. In a health care system moving towards tying reimbursement to quality measures, prevention of infection in elderly IBD is part of sound medical practice and important in managing costs.

Epidemiology and Cost

Between 10-30% of individuals with IBD are over the age of 60, while 10-15% are diagnosed as elderly.^{1,5,6} As IBD prevalence rates increase and because the disease is associated with a relatively unchanged life expectancy, the number of elderly Crohn's disease and ulcerative colitis is expected to grow. Since many patients with IBD transition to old age with their disease, this necessitates a lifetime of care. By 2050, the US census bureau projects the expected number of elderly to double.⁷ Over the same time, Medicare spending will increase from 2.6% of the gross domestic product to 9.2%.⁸ Compared to non-IBD patients, IBD patients are seven times as likely to incur healthcare costs, five times more likely to have an outpatient clinic visit, and three times as likely to undergo an inpatient stay.²

Maintenance of disease remission in CD and UC is directly associated with improved patient outcomes and quality of life. In patients with moderate to severe active IBD, thiopurines and biologics may be the most effective options. Over the last two decades, the use of these medications has increased. While this has decreased IBD-related hospitalizations and surgeries, there has been an associated increased rate of adverse events attributable to immune suppression, namely malignancy and serious infections.^{10,11} Pneumonia, cellulitis, and perianal and intraabdominal abscesses are commonly cited serious infections, often leading to an inpatient stay.¹² Infection-related hospitalizations of IBD inpatients are associated with longer hospital days and higher hospitalizations costs.¹³

Risk Factors for Serious Infections in Elderly IBD

Multiple factors influence infection risk in elderly IBD patients. Multimorbidity, polypharmacy, immunosenescence, malnutrition, immunosuppressive agents, hospitalization and surgery all play important roles. When evaluating all potential factors, active intestinal inflammation is the strongest predictor of serious infection.¹² Treatment with infliximab, a biologic, is associated with a higher risk of infection in the absence of higher mortality, suggesting that

the mortality rate with treatment of active disease outweighs the risks associated with the anti-TNF, including infection.¹²

Persistent active gut inflammation can predispose to infection. Dysbiosis, or disruption of the gut microbiota, thought to be in part associated with pathogenesis and changing disease activity in IBD,¹⁴ predisposes to *Clostridium difficile* infection. *C. difficile* colitis, much like CMV colitis, is associated with more severe IBD and may reflect incompletely controlled active inflammation.^{15,16} Advanced age is a well-known risk factor for the development of *C. difficile* infection, which in the elderly is associated with significant morbidity and mortality, accounting for a 20% readmission rate and a 9% mortality rate in hospitalized patients.¹⁷

Multimorbidity

As the prevalence of many diseases rises with age, multimorbidity becomes more prevalent over time affecting 35% of Americans over the age of 65 and 70% of those over the age of 80.¹⁸ One third of patients over 65 have four or more comorbidities and both the number and proportion of patients with multiple comorbidities is expected to grow.^{18,19} The resulting costs are revealing, as two-thirds of Medicare patients with multimorbidity account for 96% of Medicare expenditures.¹⁸ In elderly IBD, the most common comorbid conditions, cardiovascular illness, chronic lung disease, and diabetes,²⁰ can increase susceptibility to complications and effect medical treatment options. Anti-TNFs, for instance, are contraindicated in New York Heart Association Class III/IV heart failure, while corticosteroids can worsen diabetes.²¹

Polypharmacy

Multimorbidity often requires several prescriptions, and older IBD patients take an average of 7 medications on a daily basis.²⁰ Additionally, older patients are at increased risk for adverse events due to the changes in drug metabolism and decreased drug clearance in the elderly. In the setting of a lower glomerular filtration rate, the clearance of corticosteroids in older patients is decreased, potentiating any systemic side effects, including infection.¹ Polypharmacy is associated with increased risk of drug-drug and drug-condition interactions which need to be carefully considered when managing older IBD patients. For example, antibiotic and proton pump inhibitor use can predispose to *C. difficile* colitis.²²

Malnutrition

In IBD, malnutrition may result from small bowel resection, malabsorption, medication side effects, and changes in diet. Comorbid conditions impact the nutritional state of elderly. In one study across Europe, the United States, and South Africa, over a third of hospitalized older adults met the criteria for malnutrition.²³ In active IBD, severe malnutrition affects a third of patients and serves as a risk factor for mortality in hospitalized patients.^{13,24} Poor nutrition is a recognized risk factor for opportunistic infections.²⁵

Immunosenescence

While poor nutrition is associated with an impaired immune system, aging is associated with immunosenescence, a gradual deterioration of the immune system associated with impaired stem cell regeneration, neutrophil and macrophage dysfunction, altered barrier function, and decreased production of B-cells and T-cells.²⁶⁻²⁸ These changes can increase the susceptibility to infection and the persistence of infections due to an inability to clear the pathogen. The elderly have been shown to have higher rates of bacteremia and sepsis and incident rates of sepsis have increased 20% faster in elderly when compared to younger patients.^{29,30} In older IBD patients on immunosuppression, the risk of severe infection is greater than younger patients.³

Overall, respiratory infections, including pneumococcal pneumonia and influenza, are the most common type of infection in IBD patients. Among opportunistic infections in CD and UC, herpes zoster may be most often seen.³¹ Many of the common infections in IBD are vaccine-preventable and in older adults, these infections tend to have a more severe disease course.⁴ Nonetheless, the vaccination rates in IBD patients are suboptimal, in part because it is not a point of discussion during office visits.³² Once patients are scheduled to undergo vaccination, immune suppression therapy can reduce their efficacy. Compared to patients on monotherapy with biologics or thiopurines, adults on dual therapy have a decreased response to vaccines.⁴

Medications

For many providers caring for elderly IBD, the potential adverse effects secondary to immune suppression are particularly concerning. In older patients, data regarding safety of anti-TNFs is derived mainly from

the rheumatology literature, where the results are mixed.^{33,34} In rheumatoid arthritis, infliximab at higher than standard dose (10 mg/kg) when combined with methotrexate led to more than a threefold increased risk of serious infection compared to those who received methotrexate alone ($P = 0.013$).³⁵ In IBD patients, a large retrospective study evaluating the use of infliximab and adalimumab found an increased rate of severe infection (11% vs. 0.5%) compared to patients treated with other IBD medications.³ A retrospective case-control study from the Mayo Clinic showed no increase in opportunistic infection with combination anti-TNF and thiopurine therapy.³¹ A community-based retrospective cohort study of patients on anti-TNF therapy found that 44% of older patients versus 32% of younger patients developed infection, but this was not statistically significant.³⁶ Another study examining claims data of >20,000 matched Crohn's disease patients found rate ratios of 6.18 and 1.75 for opportunistic infection and sepsis in patients on combination anti-TNF and thiopurine therapy, but this was not statistically significant. Other studies have suggested an increased risk of adverse events or an increased rate of anti-TNF discontinuation in patients > 60 years old.^{38,39} After 24 months, 47% of older anti-TNF users stopped therapy compared to 10% of younger patients.³⁹ Among the 38 older IBD patients who ceased therapy, 8 (21%) stopped therapy due to infectious complications. Six of the eight were either on concomitant thiopurines or corticosteroids.³⁹ Although dose or duration with monotherapy infliximab does not appear to increase the risk of serious infection, it's unclear if this holds true for combination infliximab and thiopurine therapy.¹²

Narcotic and corticosteroid therapy have consistently been associated with serious infections in IBD. Narcotics are associated with almost a two-fold increase in infections.¹² Meanwhile, corticosteroids appear to drive the infection risk among patients undergoing medical therapy, especially in two- or three-drug regimens that include thiopurines.^{12,31} A population-based cohort Canadian study revealed a time-dependent risk of infection among corticosteroid users in incident older IBD patients.⁴⁰ Despite these findings and guidelines that strongly state against the use of corticosteroids for maintenance therapy in CD and UC,^{21,41} one study showed that 32% of older IBD patients were on chronic corticosteroids while just 10% were treated with thiopurines or biologics.²⁰

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Hospitalizations and Surgery

Rates of hospitalization for UC and CD are rising and this has been associated with significantly increased costs.⁹ Infections account for over a quarter of all IBD hospitalizations and infection-related inpatient stays are associated with excess hospital stay, higher costs, and a four-fold increased mortality.¹³ Elderly patients account for an inordinately high percentage of IBD-related hospitalizations.^{1,42} These hospitalizations are associated with increased costs and mortality rates in older IBD patients even when adjusting for comorbidity.⁴²

Among elderly, nosocomial infections cause a particularly high disease burden. Older patients have longer length of stays and are more likely to be discharged to skilled nursing facilities.⁷ The inpatient elderly patient is at higher risk for *C. difficile*-associated diarrhea, nosocomial pneumonia, foley-associated urinary tract infections, and intravenous catheter-associated infections. These infections have been associated with worse patient outcomes in IBD patients.^{16,43}

Although most hospitalized and outpatient IBD patients can be treated effectively with medical therapy, surgical intervention is often required. Using the Nationwide Inpatient Sample, older patients were less likely to undergo nonelective surgery for UC but as likely to undergo CD-related surgery as their younger counterparts.⁴² The overall risk of complications between elderly and nonelderly patients was similar.⁴² A recent population-based cohort study found that elderly IBD patients prescribed corticosteroids were significantly more likely to have undergone surgery.⁴⁰ Few studies report on the non-medication related risk of infectious complications after IBD-related surgery. A single center study found that after controlling for duration of disease, previous surgery, medications, and comorbidity, patients ≥ 60 years old had a higher post-operation wound infection rate than younger patients (13% vs. 1%).⁴⁴

Most studies evaluating the risk of infection following IBD-related surgery have examined the effect of preoperative anti-TNF therapy on postoperative complications. A meta-analysis reported a significantly higher rate of infectious postoperative complications in anti-TNF treated CD patients (OR 1.45, 95% CI: 1.03-2.05) but not in UC.⁴⁵ The data regarding the preoperative use of corticosteroids and immunosuppressants and the associated postoperative complications is mixed,

especially in the elderly.⁴⁶ Part of the controversy with preoperative biologic and thiopurine therapy is that disease activity, itself a risk for postoperative infection, often is not accounted for in the studies examining postoperative infections.

Strategies Going Forward

Health care costs for chronic medical conditions like IBD are significant and are expected to grow with an aging population. Recognizing the factors behind these costs and minimizing their impact is key. Among elderly patients, the clinical and financial burden associated with adverse events like infection is substantial. Because clinical symptoms in IBD often do not correlate with active inflammation, an important strategy to balance the risk of therapy and potential infectious complications is objective assessment of disease activity through labs, imaging, and colonoscopy. Ongoing objective evaluation can help ensure that patients are adequately treated and decreases the risk of hospitalization and surgery. Due to the mild disease course of IBD and concern for adverse events associated with immunosuppressives in the elderly, a “step-up” treatment approach, utilizing nonimmunosuppressives before advancing therapy, often is used to treat underlying inflammation. Advanced age is not a contraindication for use of thiopurines and biologics, and in moderate to severe disease, these medications may be indicated. In general, monotherapy with either biologics or thiopurines, rather than the combination of the two, is typically preferred in older IBD patients.

Beyond assessing patients for appropriate therapy, other strategies to prevent infection among elderly IBD patients exist. In hospitalized patients, these include appropriate antibiotic use to avoid *C. difficile* and limiting urine foley catheters and the duration of mechanical ventilation to prevent hospital-acquired pneumonia.⁴⁷ Among IBD patients specifically, limiting corticosteroid use for induction of remission in IBD, updating vaccinations for influenza and pneumococcal pneumonia, and the use of sterile techniques for central venous catheters placement are not only imperative for effective patient care but are part of the Physicians Quality Reporting System (PQRS) by the Centers for Medicare and Medicaid Services (CMS).⁴⁸

Malnutrition and polypharmacy are potentially modifiable risk factors for infection in elderly IBD. Assessing nutritional status is an important aspect

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of care in IBD. Nutritional care involves identifying deficiencies and providing appropriate supplementation. Polypharmacy can provide challenges in IBD management and in the elderly, medication reconciliation can often identify unnecessary prescriptions.⁴⁹ Part of an effective approach to malnutrition and polypharmacy involves a multi-disciplinary collaboration between dietitians, pharmacists, primary care physicians, and gastroenterologists.

There is a paucity of data in elderly IBD and the risk of infection in the age group. Further research is needed examining the natural history of IBD, the efficacy and complications of various medical and surgical therapies, appropriate clinical goals of therapy, and the most common infections among elderly patients. Until then, guidelines and recommendations that direct the care of all adult IBD patients can be utilized in the elderly to prevent serious infections. The American College of Gastroenterology suggest testing for tuberculosis, hepatitis type B, and in endemic areas, specific fungal infections, prior to initiation of biologics.^{21,41} Additionally, the CDC recommends patients over the age of 65 undergo vaccinations for influenza, pneumococcal pneumonia, and zoster. In the setting of immunosenescence and multiple comorbidities, older adults may benefit from post-vaccination titers to determine if further booster shots are needed. ■

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Answers to this month's crossword puzzle:

