Serious and Opportunistic Infections in Elderly Patients With Inflammatory Bowel Disease

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Keywords
Inflammatory bowel disease, elderly patients, opportunistic infection, serious infection, vaccination, immunosuppression

Abstract: Inflammatory bowel disease (IBD) is often treated with biologics and immunomodulators, which can place elderly IBD patients at risk for serious and opportunistic infections. This article provides an updated account of research on therapies in IBD that are associated with an increased infection risk. Relevant serious and opportunistic infections in the elderly population are discussed along with methods for prevention and treatment. The incidence of infection increases with age and the degree of immunosuppression. Emphasis should be placed on performing vaccinations at the time of IBD diagnosis. Additionally, patients receiving immunosuppressive therapy should avoid live vaccines. Physicians should have a greater awareness of the increased risk of infection in elderly adults and the need for screening for infection prior to initiation of immunosuppressive IBD therapies.

Treatment of inflammatory bowel disease (IBD) has become increasingly dependent on newer biologics and immunomodulators. However, given these treatments' inherent immunosuppressive properties, their use creates an increased risk for serious and opportunistic infections. Opportunistic infections are caused by normally nonpathogenic organisms that are able to take advantage of immunocompromised states to cause disease requiring hospital admission. Serious infections result in death or hospitalization, or necessitate the use of intravenous antibiotics.[1,2] Elderly patients are at elevated risk of both such infections in the presence of IBD progression, comorbidities, and frailty. Diagnosing opportunistic infections in elderly patients is often challenging because symptoms tend to be nonspecific or mimic those of the underlying IBD. A 2014 review by Dave and colleagues[3] described many of the opportunistic infections seen in IBD patients on immunosuppressive agents and their diagnosis and treatment. This article updates that review with a summary of more recent factors that put IBD patients at risk for serious and opportunistic infections as well as highlights the opportunistic infections in elderly IBD patients that may be missed or misdiagnosed, and offers an approach to clinical diagnosis and management.

Age as an Independent Risk Factor for Opportunistic Infection

Approximately one-third of the IBD population is elderly, defined as older than 60 years. Over 20% of the elderly IBD population was diagnosed at an age greater than 60 years.[4,5] A recent retrospective cohort study of more than 60,000 IBD patients found that age was an independent risk factor for acquiring infections.[6] Specifically, 30.3% of patients in the elderly cohort had an infection compared to 19.1% of patients in the nonelderly cohort (adjusted hazard ratio [HR], 1.27; $P<.001$). Adjusted variables included IBD therapy, IBD type, sex, and comorbidities.

A large nationwide, population-based, cohort study in France showed an increased incidence of serious and opportunistic infections in patients 65 years or older compared with younger patients, with a 2- to 3-fold greater absolute risk of infection in the older population.[7] A pathophysiologic risk factor for opportunistic infection is immunosenescence, the gradual deterioration of the immune system as a consequence of aging. Age-related alterations in immunology, altered drug metabolism, and nonspecific symptoms of functional decline also make the elderly population more susceptible to infection.[8] In addition, elderly patients tend to have more serious infections and are hospitalized more often than younger patients.[9] Twenty-five percent of IBD-related hospital admissions in the United States are for patients older than 65 years who are typically more malnourished, anemic, and hypovolemic.[10]

Medical Management of Inflammatory Bowel Disease and Infection Risk in the Elderly

Medical management of IBD is frequently very nuanced, requiring consideration of multiple patient factors. Current management guidelines do not stratify by age; however, given that the elderly are more likely to be frail or take multiple agents that may impair immunity, extra caution should be paid to the risk of infection with the use of immunosuppressive therapies.[8,11] The response to treatment in elderly patients is slower than what may be seen in younger IBD patients.[12,13] Medical management in elderly IBD patients is further complicated by impaired functional status, medical comorbidities, and polypharmacy.[14]

Choosing which treatment to use in the elderly is challenging because patients older than 60 years are often excluded from randomized, controlled clinical trials. The Infectious Diseases Society of America defines certain biologics and immunomodulators, such as anti–tumor necrosis factor (TNF) α agents, as a source of high-level immunosuppression, which may lead clinicians to avoid using immunosuppressive therapy due to risk of infection.[15] Treatment with combinations of immunomodulators or suppressors also greatly increases the risk of infection. One study reported a 14.5-fold increased risk of infection with the use of 2 or more immunomodulators.[16] In addition, immunomodulators are linked to a higher risk of lymphoproliferative disorders, myelotoxicity, and nonmelanoma skin cancers, especially in the elderly.[8,17] Bautista and colleagues[18] found a decline in the use of immunomodulators, biologics, and prednisone in the elderly population, whereas mesalamine was more commonly used. Immunomodulators such as 6-mercaptopurine, azathioprine, and methotrexate are effective as corticosteroid-sparing therapies for the treatment of IBD in both elderly and younger IBD patients.[8]

5-Aminosalicylic Acid

5-aminosalicylic acid (5-ASA) is used in the treatment of active IBD and for maintenance of remission in ulcerative colitis (UC) and Crohn's disease (CD), and is commonly prescribed to patients over the age of 60 years. Use of 5-ASA is considered to be relatively safe with rare reports of nephrotoxicity and interstitial nephritis.[14] A meta-analysis by Wheat and colleagues[19] found that 5-ASA use in IBD patients was not associated with an increased risk of serious infection when compared to placebo (odds ratio [OR], 0.52; 95% CI, 0.09-21.47). 5-ASA therapies in combination with prednisone in IBD patients were also not associated with an increased risk of serious infection when compared to placebo (OR, 7.32; 95% CI, 0.06-832.34).[19]

Corticosteroids

Corticosteroids are commonly used in the treatment of IBD flares and to induce remission in IBD that is refractory to 5-ASA or in acute severe IBD. Corticosteroid use varies from 31% to 57% in the elderly population, and nearly one-third of elderly patients are on a prolonged course.[8] However, long-term use of corticosteroids has been associated with numerous adverse events, including osteoporosis, altered mental status, and depression.[14] Corticosteroid use in the elderly is associated with an increased risk of fractures, exacerbation of diabetes, predisposition to cataracts and glaucoma, tuberculosis, and fungal infections. The most common infections related to corticosteroid use stem from *Candida* species.[17] Simultaneous use of corticosteroids with ciprofloxacin increases the risk of tendonitis and rupture, especially in the elderly.[20] Among patients with elderly-onset IBD (diagnosis in patients older than 65 years), exposure to oral corticosteroids over a 6-month period had a greater risk of serious infection compared to nonexposed patients (adjusted rate ratio, 2.3; 95% CI, 1.8-2.9). Individuals currently exposed to corticosteroids had an even greater risk, with an adjusted rate ratio of 2.8 (95% CI, 2.1-3.7).[21] Prolonged use of corticosteroids should be avoided in the elderly.

Table 1. Incidence Rates Per 10,000 Person Years (Unadjusted)

	Thiopurine Monotherapy	Anti-TNFα Monotherapy	Combination Therapy
Serious Infections	105	190	224
Opportunistic Infections	17	21	41
Viral Infections	11	7	13
Bacterial Infections	2	5	11

TNF, tumor necrosis factor.

Adapted from Kirchgesner J et al.[7]

Methotrexate

Methotrexate is used in the treatment of moderate to severe CD.[14] Retrospective cohort data suggest that methotrexate has similar outcomes among elderly IBD patients and young IBD patients.[4] Significant adverse events among all individuals using methotrexate include hepatotoxicity, bone marrow suppression, and infections in the setting of immunosuppression.[22] An increased risk of infection among all IBD patients on methotrexate has not been established.[23] In a 2017 meta-analysis comparing methotrexate to placebo, methotrexate was not found to have an increased risk of serious infection among all IBD patients (OR, 0.52; 95% CI, 0.04-6.34).[19] However, there are no data on the safety profile of methotrexate in the elderly IBD population.[4]

Thiopurines

The thiopurine medication class includes 6-mercaptopurine and azathioprine, which are used in the treatment of moderate to severe IBD.[14] Thiopurines for the treatment of IBD are associated with an increase in benign and opportunistic infections, with studies showing increases in viral, fungal, parasitic, bacterial, and mycobacterial infections.[24] Toruner and colleagues[2] found that thiopurine use among IBD patients increased the risk of opportunistic infection 2- to 3-fold (OR, 3.8; 95% CI, 2.0-7.0), which then further increased with concomitant corticosteroid use (OR, 17.5; 95% CI, 4.5-68.0). When stratified by age, individuals older than 45 years at the time of IBD diagnosis had the greatest risk of opportunistic infections (OR, 2.3; 95% CI, 1.0-1.2) compared to individuals ages 30 to 44 years (OR, 1.0; 95% CI, 0.5-2.4).[2]

Cyclosporine

Cyclosporine inhibits calcineurin, leading to suppression of cell-mediated immunity.[25] It is used in cases of severe or fulminant IBD; however, it is rarely used due to toxicity.[14] Cyclosporine use has been associated with viral warts and gram-negative sepsis in IBD patients.[25] Due to its limited use, there are no data on the specific risk of infections in the elderly IBD population.

Anti–Tumor Necrosis Factor Alpha

The anti-TNFα drug class is composed of monoclonal antibodies including infliximab (Remicade, Janssen), adalimumab (Humira, AbbVie), certolizumab pegol (Cimzia, UCB), and golimumab (Simponi, Janssen). Anti-TNFα therapies are used both as monotherapy and in combination for the treatment of moderate to severe IBD. All individuals treated with anti-TNFα drugs were found to have a greater risk of hepatitis B virus (HBV) infection, tuberculosis, and endemic fungal infections.[14] Patients older than 65 years who were started on anti-TNFα monotherapy for IBD had an increased incidence of severe infection compared to younger patients (11.0% vs 2.6%, respectively).[14]

The risk of opportunistic and serious infections is further increased with combination anti-TNFα therapies. A population-based study[7] showed that among 190,000 adult IBD patients, the risk of serious and opportunistic infections varied according to IBD treatment exposure, with combination therapy as the greatest risk of infection compared to anti-TNFα or thiopurine monotherapy (Table 1). Increased risk was noted for viral, bacterial, and mycobacterial infections. In patients 65 years or older who received immunosuppressive treatment, the risk of serious infection during the study period was approximately 5% with a relative risk of infection 2- to 3-fold greater compared to younger patients.[7]

A 2019 systematic review and meta-analysis demonstrated that combination therapies for IBD that include anti-TNFα agents are associated with a higher risk of serious infection compared to monotherapy.[26] Risk of serious infection increased with the combination of an anti-TNFα agent with an immunosuppressive agent compared to anti-TNFα monotherapy (relative risk, 1.19; 95% CI, 1.03-1.37).[26] There was an even greater risk when anti-TNFα therapy was combined with a corticosteroid compared to anti-TNFα monotherapy (relative risk, 1.64; 95% CI, 1.33-2.03).[26] Overall, there is a higher risk of infection with anti-TNFα monotherapy compared to immunosuppressive monotherapy. The annual incidence of serious infection in the elderly population exposed to anti-TNFα therapy is roughly 5%.[27,28]

Integrin Receptor Antagonists

Natalizumab (Tysabri, Biogen) and vedolizumab (Entyvio, Takeda) are monoclonal antibodies that inhibit leukocyte extravasation by antagonizing integrin receptors. Vedolizumab also potentially provides gut-specific immunosuppression. A 2017 systemic review on the safety of vedolizumab found lower exposure-adjusted incidence rates of infection and serious adverse events compared to placebo.[29] However, there was a higher but statistically insignificant rate of enteric infections in vedolizumab-exposed patients (7.4/100 person years [PYs]; 95% CI, 6.6-8.3) compared to placebo (6.7/100 PYs; 95% CI, 3.2-10.1).[29] A 2019 retrospective cohort study of IBD patients older than 60 years found that 17% of patients on vedolizumab therapy were found to have a significant infection within 1 year of starting therapy, compared to 20% of patients on anti-TNFα therapy.[30] This difference was found to be insignificant. The most common infection among both groups was pneumonia. This study did not find a significant difference in rates of *Clostridium difficile* or other gastrointestinal infections between the anti-TNFα–treated group and the vedolizumab-treated group (21% vs 18%, respectively; *P*=.57). Notably, the most common reason for stopping therapy among the vedolizumab cohort was infection (14%).

Natalizumab is a recombinant humanized immunoglobulin (Ig) G4 monoclonal antibody that binds to the α4 integrin subunit on leukocytes and has been used in the treatment of multiple sclerosis.[31,32] It was the first anti-integrin molecule proven to be effective in the induction and maintenance of remission in patients with CD. However, clinical trials have shown that natalizumab increases the risk of John Cunningham (JC) virus activation, which leads to progressive multifocal leukoencephalopathy.[33,34] The risk of JC virus activation is especially high in immunocompromised patients who may be JC virus seropositive.[33,34]

Janus Kinase Inhibitors

At present, Janus kinase (JAK) inhibitors are effective medications in the treatment of rheumatoid arthritis and myelofibrosis. Their effect on the inflammatory response has led JAK inhibitors to be studied for the treatment of IBD. Tofacitinib (Xeljanz, Pfizer) has been approved by the US Food and Drug Administration (FDA) for use in patients with moderately to severely active UC.[35] Research has shown an increased risk of herpes zoster (HZ) infection but not Epstein-Barr virus or cytomegalovirus (CMV) infection when patients are treated with tofacitinib. Incidence rates for HZ were higher with 5 mg of tofacitinib (2.1; 95% CI, 0.4-6.0) and 10 mg of tofacitinib (6.6; 95% CI, 3.2-12.2) compared to placebo among UC patients.[36]

Physicians should avoid the use of live vaccines concurrently with tofacitinib. A 2019 FDA warning highlighted a risk of increased mortality, pulmonary emboli, and opportunistic infection at the 10-mg twice-daily dosing. These adverse events are particularly evident in older Asian males and diabetic patients.[37] As such, the FDA has recommended a reduction of tofacitinib dosing to 5 mg twice daily.[38] A large cohort study found that the number of serious infections was higher among individuals treated with tofacitinib (0.9%) compared to placebo (0%).[36] However, this difference was not found to be statistically significant. Tofacitinib use was also associated with an increased risk of opportunistic infections compared to placebo, the majority of which were HZ infections. Older age was found to be a significant risk factor for opportunistic infection among patients on tofacitinib.[36]

Filgotinib is a highly selective JAK1 inhibitor that was evaluated in a randomized, double-blind, placebo-controlled, phase 2 trial for IBD.[39] The percentage of adverse events was similar among patients treated with filgotinib compared to patients treated with placebo (75% vs 67%). However, serious infections occurred in 3% of patients treated with filgotinib, whereas the placebo group experienced no serious infections.

Anti-Inflammatory Cytokines

Additional drugs that are being developed and studied for their use in IBD include interleukin (IL) -6, -12, and -23 antibodies. Excessive production of IL-6 significantly contributes to the pathogenesis of IBD. PF-04236921 is a fully human monoclonal IL-6 antibody that completed a phase 2 study in 2017 in patients with CD who failed anti-TNFα therapy.[40] Dosing in the 200-mg arm was terminated due to high rates of serious adverse events, including infections such as gastrointestinal abscesses.[32] The 50-mg arm has shown promise in clinical response and remission, although 58 patients developed serious adverse events, including wide-ranging infections from abdominal abscesses to tuberculosis.[32]

IL-12 and -23 are cytokines that are upregulated in patients with IBD. Ustekinumab (Stelara, Janssen) has recently been approved as induction and maintenance therapy for adult patients with moderately to severely active CD who have failed other immunosuppressant therapies.[41] The UNITI-1 and UNITI-2 trials found that the proportion of patients who developed infections was similar between those taking ustekinumab and those taking a placebo.[42,43] Notably, *Listeria* meningitis was reported in the 6-mg/kg ustekinumab group.[32]

There is a paucity of data exploring the rates of serious infections among IBD patients treated with ustekinumab. However, there are surveillance data assessing the safety of ustekinumab use among psoriasis patients. A 2018 prospective cohort study based off of the British Association of Dermatologists' Biologic Interventions Register found that among psoriasis patients treated with ustekinumab,

the incidence rate of serious infection was 15.07 (95% CI, 10.77-21.09), with the most common infections being lower respiratory infection, skin infection, and soft tissue infection.[44] The incidence of serious infections among patients taking ustekinumab was similar to that among patients treated with etanercept (Enbrel, Amgen; 15.25; 95% CI, 11.56-20.12).[44] However, a 2015 cohort study utilizing the Psoriasis Longitudinal Assessment and Registry found that rates of serious infections were lowest among patients treated with ustekinumab for psoriasis (0.93/100 PYs) when compared to infliximab (2.91/100 PYs), nonbiologics such as methotrexate and cyclosporine (1.43/100 PYs), and other biologics such as adalimumab and golimumab (1.91/100 PYs).[45]

Finally, leukocytapheresis, an extracorporeal therapy for UC not used in the United States, has been demonstrated to be safe and tolerable in the elderly UC population.[46] The rate of infections following leukocytapheresis is low and similar to that in younger patients.

Serious and Opportunistic Infections in Elderly Patients With Inflammatory Bowel Disease

Immunosuppressants and biologics place elderly IBD patients at increased risk for infection. The most commonly cited infections in this population include pneumonia, cellulitis, and perianal and intra-abdominal abscesses. Given the immunosuppressive effects of IBD treatment, physicians should also be aware of opportunistic infections.[47] A diagnosis of infection may be more difficult in the setting of elderly patients with multiple comorbidities. The European Crohn's and Colitis Organisation (ECCO)[4] recommends both screening for opportunistic infections and documenting vaccination status at the time of diagnosis of IBD so that appropriate vaccines can be given (Table 2).

Overall, vaccination recommendations are similar for elderly patients with and without IBD, although there are exceptions that pertain to live vaccines. IBD patients should follow all age-appropriate vaccinations as recommended by the Advisory Committee on Immunization Practices.[48] One consideration for all immunosuppressed IBD patients is the type of vaccine to use. Patients with IBD can receive all inactivated vaccines; however, caution should be given to live vaccines, such as the measles, mumps, and rubella vaccine, as well as the live HZ vaccine (Zostavax, Merck).[49] It is also important to consider the timing of vaccination in regard to initiation of immunosuppressive therapy, as the use of immunosuppressive agents can lead to a decreased immune response to vaccination.[50,51] Specifically, the ECCO guidelines recommend that elderly IBD patients be vaccinated against varicella zoster virus prior to initiation of immunotherapy.[4]

Pneumococcus

Streptococcus pneumoniae, or pneumococcus bacteria, are the most common cause of respiratory infection in the world. Other presentations of pneumococcal infections include bacteremia, meningitis, and acute otitis media, although these presentations are more common among the pediatric population than in the elderly.[52] Both pneumococcal infection incidence and mortality are significantly higher in immunocompromised patients compared to those with intact immune systems. Immunocompromised individuals constitute 28% of those with invasive pneumococcal disease.[53] If an invasive pneumococcal disease is suspected, samples of cerebrospinal fluid or blood should be sent for testing.

The Centers for Disease Control and Prevention recommends that adults 65 years or older be vaccinated with the 13-valent pneumococcal conjugate vaccine (PCV13) and the 23-valent pneumococcal polysaccharide vaccine (PPSV23) regardless of immunocompromised status.[54] One dose of PCV13 should be administered to all adults 65 years or older who did not previously receive a dose. One dose of PPSV23 should be given to all adults 65 years or older at least 1 year after any prior PCV13 dose and at least 5 years after any prior PPSV23 dose.[54] Patients on immunomodulators or biologics can be vaccinated, but a blunted response should be expected.[53,55] Therefore, IBD patients should receive revaccination of PPSV23 every 5 years. PPSV23 should be administered before the start of immunomodulator therapy because of the suppressed immune response.

The principles of treating pneumococcal infection are similar to those of treating other bacterial infections. However, for most pneumococcal diseases, therapy is started even before the exact bacterial etiology is known. It is important to obtain infectious disease consult advice on resistance to penicillin given that immunosuppression is associated with a risk of penicillin resistance.[56]

Legionella

Legionella infections most commonly present as Legionnaires' disease and Pontiac fever. Legionnaires' disease is a primary cause of community-acquired pneumonia, sometimes presenting with gastrointestinal symptoms, hyponatremia, and elevated hepatic transaminases.[57] Pontiac fever often presents as an influenza-like illness, without signs of pneumonia.[58] Risk factors for a *Legionella* infection include elderly age, a history of smoking, chronic obstructive pulmonary disease, diabetes, renal failure, and use of glucocorticoids.[59] At present, there is no available vaccine or prophylactic medication to prevent *Legionella* infection. The diagnosis of *Legionella* infection is made through bacterial sputum culture or urine antigen detection. A sputum microbiologic culture has a wide sensitivity range from 25% to 75%, whereas antigen detection

Table 2. Vaccines Recommended in Elderly Patients With IBD

Disease	Type of Immunogen	General Recommendation(s) for Vaccination in Patients With IBD	Concerns With IBD Patients on Immunosuppressive Therapy
HBV	Recombinant protein	An accelerated double-dose regimen is recommended in all HBV anti-HBc–seronegative patients with IBD.	None
Influenza	Inactivated virus	1 dose annually	None
Pneumococcus	Polysaccharides, conjugated or not to a protein carrier	Patients should receive 1 dose of PCV13 followed by PPSV23 after 8 weeks if immunocompromised or after 1 year if immunocompetent, followed by PPSV23 dose every 5 years.	None
Tetanus	Inactivated toxoid	If a patient was previously vaccinated, administer 1 dose every 10 years. If a patient was not previously vaccinated or if his or her vaccination status is unknown, administer 3 doses. The first 2 doses should be administered 4 weeks apart, with the third dose administered 6-12 months following the second dose.	None
Varicella zoster virus	Live attenuated virus	Check titers and vaccinate if not immune 3 months prior to biologic/immunosuppression initiation. If a patient is nonimmunized, administer 2 doses (0 and 1-2 months).	Risks and benefits should be evaluated on an individual basis.
Herpes zoster virus	Live attenuated virus	ECCO guidelines: patients >60 years should follow the standard schedule. ACG guidelines: patients >50 years, including those on low levels of immunosuppression (methotrexate, <0.4 mg/kg/week; azathioprine, <3.0 mg/kg/day; 6-mercaptopurine, <1.5 mg/kg/day), should follow the standard schedule.	Risks and benefits should be evaluated on an individual basis.

ACG, American College of Gastroenterology; anti-HBc, hepatitis B core antibody; ECCO, European Crohn's and Colitis Organisation; HBV, hepatitis B virus; IBD, inflammatory bowel disease; PCV13, 13-valent pneumococcal conjugate vaccine; PPSV23, 23-valent pneumococcal polysaccharide vaccine.

Adapted from Mir FA and Kane SV.[91]

in the urine only detects 1 serogroup (*L pneumophila*), which accounts for 70% to 80% of infected patients.[56] If community-acquired pneumonia is suspected, treatment of *Legionella* infection with a macrolide or fluoroquinolone is indicated, especially in an immunocompromised patient. Immunomodulator therapy should be withheld until the infection resolves.

Listeria Monocytogenes

Listeria is an important bacterial pathogen to consider in immunosuppressed and elderly patients. *Listeria* infection can present in numerous ways, including febrile gastroenteritis, sepsis of unknown origin, meningoencephalitis, and cerebritis.[60] IBD patients receiving immunosuppressive agents are at risk of systemic and central neurologic infections with *L monocytogenes*. This risk is higher with anti-TNFα therapy as compared to other immunomodulators. Patients should avoid unpasteurized milk and cheese, uncooked meat, raw vegetables, and smoked seafood. *Listeria* infection may be diagnosed with stool culture, which has a sensitivity of 87%.[61] In terms of managing IBD treatment in patients infected with *Listeria*, anti-TNFα therapy should be discontinued during infection, although there are no definitive recommendations on the decision to hold immunomodulators. Antibiotics used for the treatment of *Listeria* infection include ampicillin, amoxicillin, and sulfamethoxazole/trimethoprim for patients who have a penicillin allergy.

Histoplasmosis

Among individuals who are symptomatic from *Histoplasma capsulatum* exposure, the most common clinical manifestations are pulmonary histoplasmosis and disseminated histoplasmosis. Pulmonary histoplasmosis presents with fever, malaise, headache, and dry cough, with imaging showing patchy pneumonia and mediastinal or hilar lymphadenopathy. Disseminated histoplasmosis can present with hepatosplenomegaly, lymphadenopathy, pancytopenia, mucous membrane ulcerations, and meningitis.[62] The most frequent sites of fungal infections are the pulmonary and gastrointestinal systems, with infection often occurring early in the treatment of IBD (within 12 months), especially with the use of anti-TNFα therapy.[63]

Histoplasmosis is the most common endemic mycosis in certain areas of Mexico, Central and South America, and the Ohio Valley in the United States. However, the disease is seen globally and should be investigated in patients with unexplained pulmonary or systemic illnesses.[64] The use of anti-TNFα therapy has resulted in more cases of histoplasmosis. Symptoms commonly found in infected elderly IBD patients include fever, chills, dyspnea, cough, chest pain, arthritis, arthralgia, and erythema nodosum. Histoplasmosis is not communicable from person to person but instead acquired from inhalation of infectious spores found in soil contaminated with bird or bat droppings. Anti-TNFα therapy increases the risk of serious *H capsulatum* infection with rates noted to be 3 times more frequent than tuberculosis in this immunocompromised population.[65] Diagnosis requires fungal blood cultures, urine, serum, and/or serology with bronchial lavage.

Compared to nonimmunocompromised patients in whom histoplasmosis resolves without treatment, the infection in actively immunosuppressed patients is progressive, and treatment is always recommended. In immunocompromised patients, azole antifungals are indicated. Individuals with severe symptoms may require amphotericin B and itraconazole maintenance for 12 months until the histoplasmosis antigen is no longer seen in blood or urine samples.[66] Physicians should be aware of an immune inflammatory syndrome upon discontinuation of histoplasmosis therapy.

Cryptococcal Infection

In general, *Cryptococcus neoformans* infection in UC patients using immunomodulators is rare, although multiple case reports describing its incidence exist.[67-69] *C neoformans* is ubiquitously present in the environment, with pigeon droppings providing the main source of infection. Clinically, exposure can present as pneumonia with single or multiple noncalcified nodules and pulmonary infiltrates on imaging, but it can also present as a central nervous system infection, skin infection, or prostate infection.[70] Cryptococcal infection is normally considered in patients receiving alkylating agents, antimetabolic drugs, or large doses of corticosteroid therapy. Infection occurs through inhalation of the pathogen in the lungs with subsequent hematogenous spread.[71] Rare sites of disease are the peritoneum, bones, and gastrointestinal tract. Diagnosis is based on culture of blood and/or cerebrospinal fluid, direct microscopic observation of the pathogen, and Periodic acid–Schiff stain positivity. Stain positivity on histochemical analysis may be useful in distinguishing damage from *C neoformans* in the gastrointestinal tract from effects of IBD.

Currently, there is no consensus on whether or not to continue immunomodulators during an active cryptococcal infection. However, patients described in case reports often refuse to continue using immunomodulator agents or will have their doses reduced.[67,69] Treatment of cryptococcal infection consists of antifungal drugs such as amphotericin B with or without flucytosine or fluconazole. Higher doses may be warranted if the nervous system is involved.

Pneumocystis jirovecii

Pneumocystis jirovecii is a fungus that causes pneumonia in immunosuppressed patients.[72] Although classically associated with HIV patients, *P jirovecii* has also been documented in IBD patients, especially in association with immunosuppressants.[73] Compared to non-IBD patients, in whom the incidence of *P jirovecii* is 3 per 100,000 PYs, the incidence in patients with IBD is estimated to be 10.6 per 100,000 PYs, which is increased to 32 per 100,000 PYs in patients taking immunosuppressants.[73] Multiple studies have also suggested that the elderly are especially vulnerable with an average age of *P jirovecii* cases in the sixth decade.[72,74]

In 2014, the ECCO recommended primary *P jirovecii* prophylaxis in patients on 3 immunosuppressants if one of those agents is a calcineurin inhibitor or an anti-TNFα agent.[4] Otherwise, the decision for prophylaxis can be left between the provider and patient. Diagnosis of *P jirovecii* often requires repeat and combination testing. Chest radiography may be normal in early stages of the disease, whereas computed tomography scans are more sensitive and will display predominant ground-glass opacification in *P jirovecii* infection.[75] *P jirovecii* is cultured from bronchoalveolar fluid, and results are used in conjunction with (1,3)-β-D-glucan serum tests. Trimethoprim, sulfa drugs, and pentamidine are the mainstays of treatment.[75] While corticosteroids are beneficial in the HIV-infected patient population, their role in the IBD population has not been defined.

Hepatitis C Virus Infection

Although the natural history of hepatitis C virus (HCV) in IBD patients is poorly understood, management of HCV in this patient population is important given the complicating factor of coexisting immunosuppressants and

Table 3. Screening Tests for Serious and Opportunistic Infections

Disease Being Screened	Screening Test(s)	When to Screen
HBV	• HBsAg • Anti-HBc • Anti-HBs • HBV DNA if HBsAg-positive or anti-HBc–positive and/or anti-HBs–positive	Before anti-TNFα, vedolizumab, or immunosuppressant use
HCV	• HCV antibodies • HCV RNA (if anti-HCV–positive)	Before anti-TNFα or immunosuppressant use
Latent tuberculosis	• Tuberculin skin test or QuantiFERON-TB Gold assay • Consider T-SPOT.TB assay if QuantiFERON-TB Gold is indeterminate. • Chest radiograph	Before anti-TNFα or vedolizumab use
HIV	• 4th-generation antigen/antibody HIV-1/-2 immunoassay; if positive, obtain plasma HIV RNA level	Before anti-TNFα or immunosuppressant use
HPV	• Papanicolaou test or HPV test (if available)	Before anti-TNFα or immunosuppressant use
VZV	• Obtain history of chicken pox or shingles. • IgM/IgG anti-VZV	Before anti-TNFα or immunosuppressant use
Epstein-Barr virus	• IgM/IgG anti–viral capsid antigen antibodies • IgM/IgG anti–Epstein-Barr nuclear antigen antibodies • IgM/IgG anti–early antigen antibodies • The Monospot test is not recommended for general use given its lack of specificity.	Before thiopurine use

anti-HBc, hepatitis B core antibody; anti-HBs, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; HPV, human papilloma virus; Ig, immunoglobulin; TNF, tumor necrosis factor; VZV, varicella zoster virus.

Adapted from Mazzola G et al.[111]

drugs that may result in liver toxicity.[76] The elderly IBD population is especially vulnerable due to the potential for prolonged treatment duration. Immunosuppression greater than 3 months represents the strongest risk factor for HCV infection.[35] HCV testing should be performed before starting immunosuppressive treatment in IBD (Table 3).[56]

The management of IBD during HCV treatment has been documented to be successful when also receiving anti-TNFα therapy. HCV treatment in these cases consists of interferon-free regimens, such as ledipasvir/sofosbuvir (Harvoni, Gilead) and sofosbuvir (Sovaldi, Gilead) as monotherapy. In general, anti-TNFα therapy should be continued even if HCV infection is diagnosed, except in cases of decompensated cirrhosis where anti-TNFα therapy is contraindicated.

Hepatitis B Virus Infection

Immunosuppressive treatment increases the risk of viral reactivation in HBV infection in a manner that is proportional to the level of immunosuppression achieved.[76] Thus, it is important that patients have an inactive virologic status prior to immunosuppressive therapy initiation, even though there is still an increased risk of HBV reactivation.[35] Patients in this setting have a greater than 20% risk of reactivation and require prophylaxis of HBV infection with nucleot(s)-ide analogues.[76] Another complicating factor in managing HBV in IBD patients is that patients on immunosuppressive therapy may have difficulty achieving appropriate postvaccination titers of hepatitis B surface antibodies. A 2017 meta-analysis showed that HBV vaccination response declines significantly in patients on immunosuppression.[77] As such, revaccination of immunosuppressed IBD patients may be appropriate to achieve sufficient titers. According to the ECCO guidelines, an accelerated double-dose regimen at 0, 1, and 2 months demonstrated better efficacy in IBD patients.[56] Importantly, administration of interferon is not recommended due to the risk of IBD exacerbations.[76]

Herpes Zoster and Varicella Zoster Virus Infections

HZ often presents after reactivation of the varicella zoster virus in the sensory ganglia. Initial symptoms include malaise, headache, photophobia, and itching that most commonly affects the face and chest, classically in a dermatomal distribution. Patients experience a maculopapular rash that may progress to pustules.[78]

In a 2018 retrospective cohort study, patients with IBD were found to have a higher incidence of HZ (7.55/1000 PYs) when compared to non-IBD patients

(3.22/1000 PYs).[79] The incidence of HZ in IBD patients varies from 437 to 856 cases per 100,000 PYs in patients aged 45 to 64 years.[80] In a subgroup analysis, the risk of infection increases with both age and immunosuppression. IBD patients treated with corticosteroids, thiopurines, and anti-TNFα therapy are more prone to complicated HZ infections that involve the central nervous system, eyes, esophagus, and pulmonary system.[35] A nationwide retrospective cohort study demonstrated that exposure to thiopurines (adjusted HR, 1.47; 95% CI, 1.31-1.65) or a combination of thiopurines and anti-TNFα therapy (adjusted HR, 1.65; 95% CI, 1.22-2.23) was associated with an increased risk of HZ when compared to exposure to 5-ASA alone.[79] IBD patients treated with 5-ASA treatment alone had a significantly increased risk of HZ compared to no 5-ASA treatment (adjusted HR, 1.72; 95% CI, 1.51-1.96).[79]

Tofacitinib has also been associated with an increased risk of HZ. Although the majority of data for HZ risk in tofacitinib-treated patients has been in rheumatoid arthritis, incidence rates observed in clinical trials for UC (4.07/100 PYs) have been similar to those previously seen in rheumatoid arthritis (4.0/100 PYs).[81,82] Among rheumatoid arthritis patients treated with tofacitinib, independent risk factors for HZ included increased age, corticosteroid use, and higher dosage.[83] Currently, there are no trials assessing the risk of HZ with tofacitinib compared to other immunomodulators in the IBD population. However, the risk of HZ in tofacitinib-treated rheumatoid arthritis patients may be similar to IBD patients treated with thiopurines. Patients treated for rheumatoid arthritis with 5- and 10-mg dosages of tofacitinib were found to have an increased risk of HZ (HR, 2.10; 95% CI, 0.83-5.34 and HR, 3.10; 95% CI, 1.15-7.87, respectively).[83] This was similar to rates of HZ in IBD patients treated with thiopurines. Long and colleagues reported an HR of 1.85 (95% CI, 1.61-2.13) and Gupta and colleagues reported an HR of 3.1 (95% CI, 1.7-5.6).[84,85] However, the significance of this comparison is currently unknown.

Varicella zoster virus infection has been preventable with vaccination since the development of the live attenuated varicella zoster virus vaccine in 1995.[86] Per the 2017 American College of Gastroenterology guidelines, shingles or HZ vaccine should be provided to all patients who have IBD and are older than 50 years.[87] Two HZ vaccines are currently on the market. Zostavax, a live vaccine, has been in use since 2006, and Shingrix (GlaxoSmithKline), an adjuvant, nonlive recombinant vaccine for adults ages 50 years and older, has been in use since 2017.[88] Currently, no data are available for the safety of Shingrix in the IBD population or for elderly patients on immunosuppressive therapy. An ongoing randomized, controlled trial is studying the safety of Zostavax in patients simultaneously on anti-TNFα therapy as well as a randomized, controlled trial evaluating the safety of Shingrix in patients with moderate to severe UC on tofacitinib.[89,90]

Antivaricella therapy should be prescribed within 72 hours of rash onset in IBD patients over the age of 50 years. Intravenous antiviral agents are generally used, and treatment duration in immunocompromised patients lasts from 7 to 14 days. The decision to withhold immunosuppression in IBD patients with HZ should be made on a case-by-case basis. The ECCO guidelines note that IBD patients receiving immunomodulators require significant immunomodulatory-free periods both before and after HZ vaccine administration because the efficacy and safety of HZ vaccination in this patient population is not clear.[56] If immunosuppression is withheld during infection, waiting for resolution of skin lesion vesicles may be a good marker to resume immunosuppressive treatment.[80] It is important to note that a negative antibody test for varicella zoster virus could be a false-negative result that causes undue anxiety in immunosuppressed IBD patients.[86] Breakthrough varicella zoster virus infections in these cases are rare, and stopping immunosuppressive therapy in the setting of a negative varicella antibody test may make patients susceptible to IBD flares.

Influenza

IBD patients who are immunosuppressed have increased morbidity and mortality rates as a result of influenza and experience a more severe course of hospitalization, often with bacterial pneumonia superinfection.[87,91] Studies show not only reduced influenza seroprotection rates when IBD patients are immunosuppressed, but also suggest that booster shots are ineffective.[35,92]

It is important to recognize that vaccinating IBD patients with influenza does not increase the risk of IBD flares.[91] IBD patients who are immunosuppressed can attain the same level of immunogenic response against influenza strain A.[93] On the other hand, seroprotection against strain B is impaired by immunosuppressive agents, especially in the setting of combination immunosuppression. Vaccines should be offered in the outpatient setting to improve the rate of compliance to vaccination. Immunocompromised elderly IBD patients should not receive the live attenuated influenza vaccine. Instead, a standard or high dose of inactive influenza vaccine is recommended annually in the fall and spring.[91,93] Of note, the influenza vaccine can safely be given with pneumococcal vaccines regardless of immunocompromised status.[91]

Tuberculosis

Anti-TNFα therapy increases the risk of development and reactivation of tuberculosis (TB). However, IBD itself is not considered a risk factor for TB.[94,95] Biosimilar anti-TNFα medications show a similar risk for TB as

existing anti-TNFα agents.[35] As noted by Tubach and colleagues, an analysis of the French Registry of Infections and Lymphoma found that infliximab and adalimumab pose the highest risk for TB development compared to other anti-TNFα agents.[96] This conclusion is limited by the study's small sample size of 69 cases. In a more recent meta-analysis, Zhang and colleagues found that the type of anti-TNFα therapy was not associated with any statistically significant differences in TB risk.[97] However, infliximab-based therapy is associated with a lower risk of serious infections compared to adalimumab-based therapy in patients with UC (relative risk, 0.57; 95% CI, 0.33-0.97), although not in patients with CD.[26]

TB screening in IBD patients is challenging because of the effect of corticosteroids and immunomodulatory drugs on screening test performance.[95] A 2017 cohort study of IBD patients treated with infliximab found that patients diagnosed with latent TB infection were more frequently male and had IBD for a longer time than those with negative TB screening test results throughout follow-up.[95] There are several important flaws in the diagnostic testing for TB among the immunosuppressed IBD population. The tuberculin skin test is not as specific as the interferon-γ release assay and may lead to more false-positive results. However, the inhibition of interferon-γ production in anti-TNFα–treated individuals may result in false-negative and indeterminate results.[98]

The 2017 Infectious Diseases Society of America guidelines recommend the use of interferon-γ release assay for the diagnosis of TB.[15] There is no clear consensus on the frequency of rescreening. Currently, the American College of Rheumatology recommends yearly screening for TB with use of biologics if risk factors for current or future exposure to TB are present.[99] Prophylaxis for TB is only indicated in patients who are diagnosed with latent TB. The ECCO guidelines dictate that anti-TNFα treatment can be started no earlier than 2 months after the beginning of treatment with anti-TB agents.[4] Several studies have shown that restarting anti-TNFα therapy after successful treatment of TB is safe with no documented recurrence in the 2.5- to 3-year follow-up period.[95,100]

Cytomegalovirus Infection

Although CMV infection is common and mostly asymptomatic in nonimmunocompromised individuals, such infection in an immunocompromised patient often results in a complicated course involving intestinal disease, pneumonia, and/or retinitis. CMV infection has also been associated with a high risk of colectomy.[101] In general, IBD patients have an increased rate of serum anti-CMV IgG compared to non-IBD controls.[102] Typical features of infection on colonoscopy include irregular ulcers and cobblestone-like changes.

Given the ability for CMV colitis to be masked as an IBD flare, screening for CMV infection in acute severe UC patients with glucocorticoid resistance should be performed. Currently, the gold standard for diagnosing CMV colitis is positive histopathology by hematoxylin and eosin stain along with positive immunohistochemistry or positive quantitative polymerase chain reaction (PCR) for CMV DNA in colonic mucosal tissues. In many cases, detection of CMV by PCR alone is insufficient for diagnosis of CMV gastrointestinal disease.[103] Thus, if the clinical situation deteriorates, antiviral treatment should be considered.

Overall, there are insufficient data to formally guide immunosuppressive strategy during or after treatment of CMV-mediated colitis. A study involving 9 patients with UC and positive CMV serology found that after 3 infusions of infliximab, none of the patients' disease had progressed.[104] Several studies have found an association between use of corticosteroids and CMV reactivation.[104,105] There are limited data showing that thiopurines do not increase the risk for CMV infection. Studies have yet to evaluate the effect of vedolizumab on CMV infection.

Enteric Infection Vs Inflammatory Bowel Disease Flare

Enteric infection is frequently identified in patients with IBD and may result in an exacerbation of IBD. Furthermore, elderly patients are at higher risk of enteric infections, such as *C difficile*. Nguyen and colleagues found that increasing age was a risk for in-hospital mortality and prolonged hospital stay among IBD patients infected with *C difficile*.[106] Enteric infection testing significantly affects IBD management; patients with an enteric infection are less likely to have IBD therapies added or escalated.[107,108] Current diagnostic, endoscopic, and histologic findings are largely unable to differentiate IBD flare from enteric infection.

In a 2018 cross-sectional analysis of 577 symptomatic IBD patients who underwent a gastrointestinal pathogen panel PCR test, non–*C difficile* enteric infections were identified in 18.1% of CD patients and in 16.1% of UC patients. The distribution of infections also differed between CD and UC patients. Among CD patients, norovirus and *Campylobacter* were more common, whereas bacterial species were more common among UC patients. *C difficile* infections were detected at a rate of 0.88% in CD patients and 2.5% in UC patients.[107]

Some evidence notes that long-term IBD outcomes (eg, hospitalizations, IBD therapy escalations) after initial symptom resolution are similar between patients with and without enteric infection, but the impact of specific enteric infections on patients with IBD is not well described.[107] Specific infections trend toward worse clinical outcomes

in patients with an IBD flare (eg, superimposed *Campylobacter jejuni* infection).[109] IBD patients with non–*C difficile* enteric infections are more likely to remain in remission within 1 year when compared to patients with *C difficile* infections.[109]

Diagnostic strategies for enteric infections include the BioFire FilmArray Gastrointestinal Panel (Biomérieux), a comprehensive molecular test that can detect many common agents of infectious diarrhea within 1 hour but does not detect CMV. PCR testing fails to discriminate between active *C difficile* infection and asymptomatic colonization.[110] However, in patients with an apparent relapse of IBD, PCR testing should be considered as a diagnostic step given that flare and infection appear similarly on endoscopy and histology.

Summary

The complexity of IBD care is compounded in elderly patients due to comorbidities, polypharmacy, and aging. Elderly patients are particularly vulnerable to serious and opportunistic infections when immunosuppressed. The most frequent infections in elderly IBD patients are pneumonia, sepsis, and candidiasis, although viral and mycobacterial infections are seen with the use of therapies such as anti-TNFα and immunomodulators. New drugs targeting ILs and their receptors appear to be associated with serious infections and require further studies to evaluate their safety. It is important to screen for infection prior to initiating therapy in elderly IBD patients, and to provide prophylaxis when indicated. Continued vigilance is required to monitor for infection in the setting of drug-drug interactions, a senescent immune system, altered drug metabolism, and increased neoplastic potential in the elderly.

The authors have no relevant conflicts of interest to disclose.

The authors are grateful to Robert S. Holzman, MD, of the Infectious Disease Division at NYU Langone Health for his review of the manuscript.

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