Chapter 12
Infectious Complications of Biologics

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Abbreviations

CDI	*Clostridium difficile* infection
CI	Confidence interval
CMV	Cytomegalovirus
DNA	Deoxyribonucleic acid
EBV	Epstein-Barr virus
FDA	Food and Drug Administration
HBc	Hepatitis B core
HBsAb	Hepatitis B surface antibody
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HR	Hazard ratio
HSV	Herpes simplex virus
IBD	Inflammatory bowel disease
JC	John Cunningham
OR	Odds ratio
PCP	*Pneumocystis* pneumonia
PML	Progressive multifocal leukoencephalopathy
PYF	Patient-years of follow-up

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SIR	Standardized incidence ratio
TNF	Tumor necrosis factor
TOUCH	Tysabri Outreach: Unified Commitment to Health
TREAT	[Crohn's] Therapy, Resource, Evaluation, and Assessment Tool
USA	United States

Introduction

Infection is the most frequently encountered consequence of biologic therapy and a major concern for both patients and healthcare providers. Biologic agents suppress immune function to mitigate aberrant and unregulated inflammatory activity but can also predispose to serious, sometimes fatal, consequences including newly acquired infections, opportunistic infections, or reactivation of latent disease. The risk of such infections reflects a variety of external factors including biologic type and the use of concomitant immunosuppressant medication(s) as well as host-specific variables such as age, inflammatory bowel disease (IBD) severity, underlying nutritional status, medical comorbidity, and history of bowel surgery [1]. Other considerations include history of malignancy, presence of cytopenia (i.e., leukopenia or neutropenia), geographic location, previous infectious exposure(s), and vaccination status, among others. Appropriate screening with identification and stratification of at-risk patients, the use of primary or secondary chemoprophylaxis, and close clinical and laboratory surveillance with early recognition and timely goal-directed therapy for both common and opportunistic infections may optimize patient outcomes and decrease associated morbidity and mortality.

Defining an Immunocompromised Host

Genome-wide association studies have demonstrated increasing evidence of an aberrant immune response in IBD, with susceptibility loci incorporating innate and adaptive immune responses toward diminished diversity of commensal microbiota [2]. Although impaired innate mucosal immunity has been linked to the pathophysiology of IBD, particularly Crohn's disease [3, 4], the population is not considered immunocompromised on this basis alone. A systemic immune defect has not been established in IBD patients except in subjects who become immunocompromised as a result of immunosuppressant therapy or who have predisposing medical comorbidities [1].

While IBD may independently predispose to certain infectious processes, such as primary and recurrent *Clostridium difficile* infection (CDI) and invasive pneumococcal disease (particularly within the first 6 months of diagnosis) [5, 6], immunosuppression in the setting of biologic therapy may also heighten the risk for a variety of infections caused by viral, bacterial, fungal, mycobacterial, or parasitic organisms

including opportunistic infections. Lowered host resistance may not only influence the development of infection but may also allow for advanced progression not otherwise seen in immunocompetent persons. Additional contributory factors including age, malnutrition, total parenteral nutrition, comorbidity, and bowel surgery appear independently associated with infection-related hospitalizations among IBD patients as demonstrated in a large US nationwide inpatient sample [7].

Overview: Biologic Therapy and Infection Risk in IBD

Infection risk is a primary concern surrounding biologic therapy though may be most significant with the use of corticosteroids, particularly in doses equivalent to prednisone >20 mg/day for 2 weeks or more [1]. Serious and opportunistic infection risks appear increased not only with corticosteroid use but also with combination therapy including multiple immunosuppressants or concomitant narcotics [8–11]. Unfortunately, there is currently no functional assay to quantify immunosuppressive effects in patients with IBD. Based on limited data, increased infection risk appears to occur early in the course of biologic therapy. In one study, almost 70% of infections occurred after three infliximab infusions or less [12]. A Danish nationwide analysis found that the risk of serious infections (associated with hospitalization) was significantly increased in IBD patients who received one anti-tumor necrosis factor (TNF) dose (hazard ratio [HR] 1.64, 95% confidence interval [CI] 1.06–2.53) and subsequently decreased in patients who received two or three doses (1.18, 95% CI 0.79–1.78) and four or more doses (1.06, 95% CI 0.66–1.69) [13].

Explicit links between immunosuppressant class and specific infection have not been well described [1, 8, 10]. A study from the Mayo Clinic reported specific infection types related to individual immunosuppressant classes (used as monotherapy). Biologic therapy with infliximab was more commonly associated with the development of fungal and mycobacterial infections; corticosteroid therapy and azathioprine therapy were more commonly associated with fungal (*Candida* species) and viral infections, respectively, although considerable overlap was noted and firm conclusions could not be drawn [10]. Of note, this study included a variety of opportunistic infections occurring on a spectrum of severity, ranging from milder infections such as mucosal herpes simplex virus (HSV) to life-threatening disseminated fungal infections.

Epidemiology of Infection with Biologic Therapy in IBD: Collective Data

Biologic agents exert immune system effects through a variety of mechanisms. Studies regarding infection risk with TNF antagonists have shown inconsistent results, with some reporting an increased infection risk and others reporting findings to the contrary [14–20].

A recent systematic review and meta-analysis (including 49 randomized placebo-controlled studies with 14,590 participants) supported that biologic agents (infliximab, adalimumab, certolizumab, golimumab, natalizumab, and vedolizumab) appear to moderately increase the risk of any infection (odds ratio [OR] 1.19; 95% CI, 1.10–1.29) and significantly increase the risk of opportunistic infections (OR 1.90; 95% CI, 1.21–3.01) but do not influence the risk of serious infections in patients with IBD [21]. Interestingly, serious infection risk appeared significantly decreased with biologic use in studies with a low risk of bias (OR 0.56; 95% CI, 0.35–0.90) [21].

A systematic review and network meta-analysis investigating the safety profile of biologics used in the treatment of ulcerative colitis found no significant difference in adverse event rates among patients treated with infliximab, adalimumab, golimumab, and vedolizumab. The most favorable safety profiles were seen with vedolizumab in the induction phase and infliximab in the maintenance phase [22]. Agents with the highest probability of being safest were vedolizumab in the induction phase and adalimumab in the maintenance phase [23].

The assessment of risk with anti-TNF agents varies [9, 24–27]. A meta-analysis of anti-TNF agents used in Crohn's disease found no increase in the risk of serious infection (requiring antimicrobial therapy or hospitalization) among 21 studies enrolling 5356 patients and 3341 controls over a median follow-up of 24 weeks [24]. This applied to the overall analysis as well as subgroup analysis for short-term induction trials, short- and long-term induction trials, and maintenance trials with randomization after open-label induction [24]. A pooled analysis of primary safety data across ten IBD clinical trials (including five pivotal randomized, controlled phase 3 clinical trials, ACCENT I, ACCENT II, and SONIC trials in Crohn's disease and ACT 1 and ACT 2 trials in ulcerative colitis) conducted among adults treated with infliximab and immunomodulator therapy also found no increase in the risk of infections or serious infections with long-term infliximab treatment (5 mg/kg or 10 mg/kg, with or without azathioprine; $n = 1713$) compared to placebo (with or without azathioprine; $n = 406$) [9]. Patients with ulcerative colitis (but not Crohn's disease) who received immunomodulator treatment (versus treatment without immunomodulator) demonstrated an increased incidence of infections [9].

Infection Risk with Biologic Therapy in IBD: Focus on Specific Agents

Anti-TNF Therapy

Infliximab

In contrast to the aforementioned clinical trial data, a nationwide, register-based, propensity score-matched cohort study from Denmark (2000–2012; final cohort $n = 3086$, with 1543 anti-TNF users and 1543 anti-TNF nonusers) demonstrated a 63% increase in the risk of serious infections (associated with hospitalization) for

anti-TNF users within the first 3 months of treatment compared to anti-TNF nonusers, followed by a subsequent risk decline. Over a 1-year risk period, the HR decreased and was no longer significant [13]. Similarly, increased infection risk was detected in an analysis of prospective observational safety data from the Crohn's Therapy, Resource, Evaluation, and Assessment Tool (TREAT) registry, evaluating 6273 patients with Crohn's disease (3420 who received infliximab with a total of 17,712 person-years and 2853 who received conventional nonbiological medications only [other-treatments-only group] with a total of 13,251 person-years) over a mean follow-up of 5.2 years. This study found an increased risk for serious infection in patients treated with infliximab (HR 1.43, 95% CI 1.11–1.84, $P = 0.006$). Almost 90% of infliximab-treated patients received at least two infusions, a majority (81.5%) of whom were dosed at 5 mg/kg. There was no evidence to support that greater numbers of infliximab infusions or infliximab dose escalation (from 5 mg/kg to 10 mg/kg) influenced serious infection risk [8]. Multivariate regression analysis from the TREAT registry found that moderate-to-severe Crohn's disease activity was the strongest significant predictor for serious infection (HR 2.24, 95% CI 1.57–3.19, $P < 0.001$), while isolated colonic Crohn's disease involvement (compared to both ileum and colon involvement) appeared to be protective against serious infection (HR 0.73, 95% CI 0.54–1.00, $P = 0.046$) [8].

Adalimumab

The overall safety profile of adalimumab in global clinical trials of Crohn's disease (involving 3160 patients representing 3401.9 patient-years of drug exposure) was reported to be comparable to that of other anti-TNF agents used for the same indication. Adverse event rates were similar to those described in other studies of adalimumab used for alternate approved indications covering a clinical follow-up period over 10 years. The most frequently reported serious adverse event was serious infection, most commonly due to abscess (intra-abdominal and gastrointestinal related). The incidence of opportunistic infections including tuberculosis was low [27].

A systematic review and meta-analysis including three randomized controlled trials (conducted from drug inception to January 2015) comparing adalimumab with placebo for moderate-to-severely active ulcerative colitis reported no significant difference in adverse events (over 8 weeks, including infection and tuberculosis) or serious adverse events when comparing induction therapy with adalimumab (dosed 160/80 mg at weeks 0/2 and then 40 mg at weeks 4 and 6) versus placebo [28]. Adalimumab maintenance therapy (40 mg every other week) increased the risk of adverse events (over 1 year) compared with placebo (risk ratio 1.28, 95% CI 1.06–1.54) [28].

Certolizumab

Safety data pertaining to infection risk with the use of certolizumab is limited. Three meta-analyses using randomized controlled trial data for certolizumab suggested that the risk of infection with long-term therapy was not clearly increased [29–31].

A pooled analysis showed that the incidence rate for serious infectious complications was higher in short-term studies of certolizumab treatment versus placebo, but the risk did not heighten with long-term certolizumab therapy (up to 7 years) [31].

Golimumab

Golimumab safety evaluated in the PURSUIT trials revealed that adverse events in golimumab treatment groups appeared similar to those observed with other anti-TNF agents and with golimumab used for other approved indications [32, 33]. Results from the PURSUIT-SC induction study found the overall incidence of adverse events through week 6 was similar for golimumab- and placebo-treated patients, with serious infection reported in 0.5% versus 1.8%, respectively [32]. Overall rates of infections, serious infections, and infections warranting antimicrobial therapy per 100 patient-years of treatment did not increase with continued golimumab exposure [33, 34].

Anti-TNFs: Summary

Although varied reports exist regarding serious infection risk, most data support a potentially increased risk for opportunistic infections with anti-TNF agents. The US Food and Drug Administration (FDA) has issued a boxed warning for the anti-TNF class as presenting a risk for the development of a variety of infections, particularly opportunistic pathogens such as tuberculosis and invasive fungal infections [35, 36]. The anti-TNF agents used for the treatment of IBD appear to have similar risks, although that for certolizumab is less clear. Higher drug doses do not appear to be associated with greater infection risk. While this seems surprising, there may be a threshold effect, or the risk may be minimal and would require larger databases than thus far utilized to display this. The overall risk of serious infection with maintenance anti-TNF therapy among the IBD population appears limited, particularly during follow-up over long-term exposure, and may be fueled by other patient factors influenced by disease state and concomitant medication use (i.e., steroids).

Anti-Integrin Agents

A systematic review and meta-analysis of randomized placebo-controlled trials using anti-integrin antibodies in adults with IBD (including 12 eligible trials, four with natalizumab, six with vedolizumab, and two with etrolizumab) reported no significant difference in the risk of opportunistic infections among patients treated with gut-specific and non-gut-specific anti-integrin antibodies, both compared to placebo [37].

Natalizumab

Natalizumab, a humanized monoclonal antibody against alpha-4 integrin, received initial FDA approval for use in multiple sclerosis but was temporarily withdrawn from the market in 2005 due to the risk of progressive multifocal leukoencephalopathy (PML), a serious opportunistic infection of the central nervous system caused by reactivation of the John Cunningham (JC) virus in chronically treated patients. One case of PML was reported in a Crohn's disease patient on combination therapy with azathioprine [38]. In 2008, natalizumab was reapproved in the USA under a specialized distribution program (TOUCH, Tysabri Outreach: Unified Commitment to Health) and FDA approved for the treatment of active Crohn's disease. Natalizumab-associated risk of PML has been most dramatically demonstrated in the multiple sclerosis literature. Among 99,571 multiple sclerosis patients treated with natalizumab (representing 209,123 patient-years), there were 212 reported PML cases (2.1 cases per 1000 patients); 22% of the affected patients died [39]. The risk of PML was lowest among patients who tested negative for anti-JC virus antibodies (estimated incidence 0.09 cases per 1000 patients, 95% CI 0–48). The highest estimated risk was seen among patients with the following factors (alone or in combination): positive anti-JC virus antibody status, immunosuppressant use prior to natalizumab initiation, and increasing duration of therapy (with greatest risk at 25–48 months and very few infections under 12 months). In the highest-risk subgroup of patients with all three risk factors, the estimated incidence was 11.1 cases per 1000 patients (95% CI 8.3–14.5) [39]. Natalizumab is generally prescribed with reservation due to this risk profile, and the availability of vedolizumab has further limited natalizumab use in IBD.

Vedolizumab

The advent of vedolizumab presented a favorable alternative to natalizumab as a gut-selective anti-alpha-4 beta-7 integrin agent. Integrated safety data from six trials of vedolizumab used in Crohn's disease and ulcerative colitis (2380 patients with 4811 person-years of vedolizumab exposure) found no associated increased risk of infection or serious infection, reinforcing the presumed gut specificity of the therapy [40]. Systemic infections may still be a concern, however, with gastrointestinal infections as a potential risk. Serious infections including clostridial infections, sepsis, and tuberculosis were rarely reported in $\leq$0.6%. Independent risk factors for serious infection were corticosteroid use, narcotic analgesic use and younger age in Crohn's disease, and narcotic analgesic use and prior anti-TNF failure in ulcerative colitis [40]. A retrospective cohort study assessing vedolizumab safety for moderate-to-severe Crohn's disease from seven medical centers (May 2014–December 2015) reported 21 serious infections (requiring antibiotics or resulting in discontinuation of vedolizumab, hospitalization, or death) [41]. There have been no associated reports of PML.

Interleukin 12/23 Monoclonal Antibody

Ustekinumab

Safety data of ustekinumab for induction of remission in Crohn's disease indicated no significant difference in adverse events or serious adverse events when comparing ustekinumab to placebo; based on limited data, the assessment of rare adverse events could not be determined [42]. A multicenter, double-blind, placebo-controlled phase 3 study of ustekinumab for the treatment of moderate-to-severely active Crohn's disease refractory to anti-TNF therapy (741 patients, 51% of whom had previously failed two or more anti-TNFs) reported similar proportions of patients with infections in ustekinumab versus placebo groups. Tuberculosis was not reported to have occurred in ustekinumab-treated patients through week 20 [43].

Infection Risk Linked with Combined Medication Use

The risk of serious opportunistic infections (such as tuberculosis or histoplasmosis) as a consequence of anti-TNF therapy appears to be increased with concomitant immunosuppressants, particularly corticosteroids [8]. Data from the Crohn's TREAT registry with over 5 years of follow-up revealed that factors independently associated with serious infection included prednisone treatment (HR = 1.57, 95% CI 1.17–2.10, $P = 0.002$) and narcotic analgesic treatment (HR = 1.98, 95% CI 1.44–2.73, $P < 0.001$). Moderate-to-severe disease activity was the strongest independent predictor of serious infection and was significantly greater among patients treated with infliximab than among patients treated with other medications [8]. In a pooled analysis, ulcerative colitis patients on combined immunosuppressant therapy with infliximab and azathioprine demonstrated an increased incidence of infections compared with infliximab monotherapy; this was not detected in Crohn's disease patients [9].

A case-control study from the Mayo Clinic demonstrated (univariate analysis) that use of infliximab (OR 4.4; 95% CI 1.2–17.1), azathioprine/6-mercaptopurine (OR 3.1; 95% CI 1.7–5.5), and corticosteroids (OR 3.4; 95% CI 1.8–6.2) was each independently associated with significantly increased odds for the development of opportunistic infections relative to medication nonuse. Multivariate analysis confirmed that the use of any one of these immune suppressants (relative to immunosuppressant nonuse) was associated with increased odds for the development of opportunistic infection (OR 2.9; 95% CI 1.5–5.3), while the use of multiple (two or three) agents profoundly increased the odds for opportunistic infections (relative to immunosuppressant nonuse) with an OR of 14.5 (95% CI 4.9–43). Neither methotrexate nor mesalamine was significantly associated with the risk of developing opportunistic infections [10].

Host Factor of Age: Infection Risks in Pediatric and Elderly Populations

Older age appears to increase the risk of infectious complications with anti-TNF agents and possibly other biologics. A significantly increased risk for opportunistic infections has been associated with advanced age over 50 years among IBD populations [10, 11].

Pediatric

There is a paucity of robust clinical data on the risk for infection with biologic therapy in the pediatric population. A systematic review was performed to quantify the incidence of serious infection among 5528 pediatric IBD patients who received anti-TNF therapy over 9516 patient-years of follow-up (PYF). The rate of serious infection in pediatric patients treated with anti-TNFs (352/10,000 PYF) was similar to that in patients treated with immunomodulator monotherapy (333/10,000 PYF; standardized incidence ratio [SIR] 1.06; 95% CI 0.83–1.36) but significantly lower than the expected rate in pediatric patients treated with steroids or adults treated with anti-TNF therapy [44].

Elderly

Certain infections appear more common among elderly compared to younger populations regardless of IBD or immunosuppressed status. These include reactivation of latent tuberculosis and bacterial infections such as community-acquired pneumonia and urinary tract infections. Viral infections occur less commonly in the elderly with the exceptions of viral gastroenteritis, influenza, and varicella zoster virus [1]. Immunosenescence leading to functional alterations in innate and adaptive immune cells may contribute, although there is limited evidence for a direct relationship [45].

Among IBD populations, advanced age appears to be a significant risk factor for infection-related hospitalizations and inhospital mortality as well as postoperative mortality and complications [46, 47]. A US national inpatient cohort study found that inhospital mortality among IBD patients was increased among elderly patients over 65 years of age compared to younger patients (OR 3.91, 95% CI 2.50–6.11), a difference that persisted after adjusting for medical comorbidities and complications. The highest mortality was noted in the oldest age group and was significantly increased among IBD patients who did not undergo surgery compared to those who did [46].

Specific Infection Risk with Biologic Therapy

Mycobacterial Infections and Invasive Fungal Infections

Pathogen exposure and geographic clustering may heighten the risk for certain endemic infections including granulomatous infectious (such as tuberculosis) or opportunistic fungal infections. Native birthplace and background, residence, and travel to endemic areas are thus important historic elements when considering patients for biologic therapy. Anti-TNF agents, in particular, may prevent an effective granulomatous response [48], leading to susceptibility to mycobacterial infections such as tuberculosis and opportunistic fungal infections including histoplasmosis, coccidiomycosis, and cryptococcus, among others [49].

Mycobacterial Infections

Tuberculosis

The risk of tuberculosis is increased with anti-TNF agents. Infection typically presents within the first few months of initiating anti-TNF therapy but may occur up to 2–3 years later or even following treatment for tuberculosis. Although pulmonary infections are classic, atypical sites can be involved [50, 51].

Detection of latent tuberculosis infection or active disease among patients receiving anti-TNF therapy became an issue of notable importance after the US FDA Adverse Events Reporting System found higher tuberculosis rates among patients exposed to infliximab compared to background population rates [52]. Most patients (56%) had extrapulmonary tuberculosis, and 24% had disseminated disease. Not only did the frequency of tuberculosis infection appear increased compared to other opportunistic infections reported in association with infliximab but also 64/70 cases (91%) manifested in countries with a low incidence of tuberculosis suggesting disease reactivation [52]. The risk of tuberculosis has been confirmed in other studies of TNF-alpha antagonist exposure, particularly with the use of monoclonal antibodies [53, 54].

Not only is the risk for reactivation of latent tuberculosis increased among anti-TNF-treated patients but the disease may also be more severe than in the general population [1]. Active tuberculosis can present in IBD patients undergoing anti-TNF therapy despite negative screening tests for latent tuberculosis and can also be seen in those who have completed tuberculosis treatment or received latent tuberculosis prophylaxis [55]. A recent retrospective study conducted at GETAID centers investigated all IBD patients undergoing anti-TNF therapy who developed tuberculosis despite negative screening tests. Among 44 patients identified, the median interval from initiation of anti-TNF therapy to diagnosis of tuberculosis was 14.5 months (interquartile range 25–75, 4.9–43.3). Tuberculosis involvement included pulmonary site in 57% with extrapulmonary involvement in 91%. Tuberculosis exposure

was thought to be implicated in 32% of the cases. Anti-TNF therapy was re-initiated in 27 patients approximately 11.2 months (interquartile range 25–75: 4.4–15.2) following tuberculosis diagnosis, and infection recurrence was not detected [56].

Generally, standard and complete treatment for latent tuberculosis infection (such as isoniazid for 6–9 months) [57] should be commenced prior to anti-TNF therapy, which should not be initiated until at least 3–4 weeks after introduction of the antituberculosis agent(s). Anti-TNF therapy should be stopped if active tuberculosis is detected and may be resumed after approximately 2 months of antituberculosis therapy [1, 57]. Restarting anti-TNF therapy following adequate treatment for tuberculosis appears safe [56].

Invasive Fungal Infections

Patients undergoing biologic therapy, particularly with anti-TNFs, are at increased risk for the development of invasive fungal infections [58]. The US FDA issued a black box warning in 2008 for the class of anti-TNF agents regarding this serious infectious consequence. Invasive or disseminated fungal infections have been reported among patients treated with anti-TNFs (commonly in combination with other immunosuppressants) across indications and may be associated with severe infections and high morbidity and mortality [1, 58–60]. Histoplasmosis [61–65], coccidiodomycosis [65–70], aspergillosis [71–73], cryptococcus [74, 75], and candidiasis [76] infections have been described and are commonly reported in patients on combination immunosuppression in endemic areas. Ten cases of *Histoplasma capsulatum* were reported with anti-TNF use (nine infliximab, one etanercept); all patients resided in histoplasmosis-endemic areas and were on combined immunosuppressive therapy. Infectious manifestations were noted within 1–24 weeks following anti-TNF initiation; nine of the patients required intensive care unit admission, and one patient died [77]. A multicenter retrospective review (January 2000–2011) of 98 patients on anti-TNF therapy (most commonly with infliximab in 67.3%) identified concomitant steroid use as a predictor of severe infection. Disease outcomes were generally favorable, although the mortality was 3.2%. Resumption of anti-TNF therapy occurred in 33.8% at a median of 12 months (range 1–69 months) and appeared overall safe [78].

Pneumocystis jiroveci (*carinii*)

Immunosuppression is a predisposing factor for the development of *Pneumocystis jiroveci* pneumonia, previously known as *Pneumocystis carinii* pneumonia (PCP). *Pneumocystis* pneumonia (PCP) infection appears increased among IBD patients, particularly in association with combination immunosuppressive therapy including infliximab [79–82]. The mean time from infliximab infusion to pneumonia symptom onset

was 21 ± 18 days ($n = 40$), and patients had an average of 2.1 ± 1.3 infusions ($n = 76$) prior to symptom development. The mortality rate was 27% [82].

Prophylactic treatment for PCP (such as trimethoprim/sulfamethoxazole) should be considered for patients on triple immunosuppression (i.e., corticosteroids, biologic, and immunomodulator therapy). Additional risk factors for the development of PCP that may necessitate prophylaxis include lymphopenia (total lymphocyte count <600 cells/mm) and age over 55 years [83]. Primary chemoprophylaxis is not recommended for fungal infections other than *Pneumocystis jiroveci,* and there are no vaccinations available for disease prevention [1].

Bacterial Infections

Legionella

Patients on anti-TNF therapy appear to be at heightened risk for *Legionella pneumonia* infection, particularly with combination immunosuppressant therapy and among elderly populations aged over 65 years [36]. The relative risk of *L. pneumophila* infection was increased in patients exposed to anti-TNF therapy (relative risk 16.5–21) compared with that in the overall population in France [84]. Cases of legionella have similarly been reported in association with anti-TNF therapy used for the treatment of IBD [6, 85–88]. In 2011, the FDA issued a boxed warning regarding the risk of *Legionella* for the TNF-alpha inhibitor class [36]. Immunosuppressant therapy should be held until the acute infection has resolved. Recurrent *Legionella* infection has also been reported and may influence reintroduction of immunosuppressant therapy [1, 89].

Listeria

Patients on anti-TNF therapy appear to be at heightened risk for *Listeria* infection, particularly with combination immunosuppressant therapy and elderly populations aged over 65 years [36, 90]. Several cases of listeriosis have been reported among patients treated with anti-TNF therapy for IBD [91–96] and rheumatoid arthritis [97, 98]. In 2011, the FDA issued a boxed warning regarding the risk of *Listeria* for the TNF-alpha inhibitor class [36].

Nocardia

The risk of systemic and cutaneous nocardia infection has been recognized in association with anti-TNF therapy [99], particularly with concomitant corticosteroid therapy. A review of the literature (1980–2014) pertaining to nocardial infections among immunosuppressed IBD patients reported nine cases (six associated with anti-TNFs, two associated with prednisone plus thiopurine, one associated with cyclosporine).

Clostridium difficile

CDI has become an epidemiologic phenomenon as a leading cause of hospital-associated gastrointestinal illness [100]. It is well established that patients with IBD, particularly those on chronic immunosuppressive therapy with certain agents such as corticosteroids, are at increased risk for the development of CDI [101]. Furthermore, IBD patients who develop CDI have increased risks for severe infection, gastrointestinal surgery, and greater hospital length of stay compared to IBD patients without CDI along with increased inhospital mortality compared to *C. difficile*-infected patients without underlying IBD and IBD patients without CDI [100, 102, 103].

CDI should be excluded (or empirically treated in some cases) prior to initiation of biologic or other immunosuppressant therapy. No meaningful association linking infliximab with serious bacterial infections including CDI was seen in a large retrospective cohort study involving 10,662 patients with IBD, while corticosteroid therapy was associated with an over threefold increased relative risk for CDI (RR 3.4, 95% CI 1.9–6.1) compared with other immunosuppressants [101]. A subsequent retrospective cohort study of 503 patients with CDI identified IBD patients as 33% more likely than the general population to experience recurrent infection. Among this IBD cohort (n = 110), patients with recurrent CDI were significantly more likely than those without recurrent CDI to have reported exposure to biologic therapy (48.6 versus 40.0%, $P < 0.01$). Infliximab use (compared to nonuse) significantly elevated the risk of recurrent CDI (34.3% versus 17.3%, respectively, $P < 0.01$), while adalimumab use did not. Steroid therapy, recent antibiotic exposure, and 5-aminosalicylic acid use also significantly increased the risk for recurrent CDI, while immunomodulators (azathioprine, methotrexate, and cyclosporine) did not appear to influence this risk [5]. Treatment with two or three immunomodulators increased the risk, independent of disease severity at presentation [104]. Chemoprophylaxis for CDI is not recommended [1].

Streptococcal pneumoniae

An increased risk of *Streptococcal pneumoniae* has been established in association with anti-TNF agents, as demonstrated in several large studies in Denmark and in the USA [6, 105]. The risk of invasive pneumococcal disease appears increased among IBD patients compared to controls, not only following but also in years prior to IBD diagnosis [6]. The risk of invasive pneumococcal disease in IBD versus control groups was increased twofold for Crohn's disease and 1.5-fold for ulcerative colitis; this risk was greatest during the first year after IBD diagnosis and decreased 2–4 years after IBD diagnosis. Exposure to anti-TNF agents did not influence the risk of invasive pneumococcal disease in the IBD population (nor did exposure to oral or topical corticosteroids or 5-aminosalicylates/sulfasalazine) [6]. Anti-TNF treatment, either alone or in combination with immunomodulator therapy, has been associated with diminished antibody response to pneumococcal vaccination [106, 107].

Viral Infections

Influenza

Immunosuppressed patients may be at increased risk for developing complications related to influenza infection [1, 108]. Influenza virus infection may be severe or fatal and may be complexed by secondary bacterial infection(s). Additional risk factors for influenza-related mortality include extremes of age (young and elderly) as well as medical comorbidities [109]. Inactivated trivalent influenza vaccine is recommended for patients undergoing immunosuppressant therapy. Lower immune response rates to vaccination [110–112] and persistence of seroprotection have been detected in IBD populations, particularly in association with anti-TNF treatment [113, 114] or combination immunosuppressant therapy [111, 112, 115]. Timing of influenza vaccination relative to infliximab dosing in pediatric and adult patients receiving maintenance IBD therapy does not appear to influence immune response [116]. Influenza vaccination appears safe and well-tolerated among IBD patients [117] and does not appear to be associated with disease flare [111, 113, 117, 118].

Hepatitis B Virus

The prevalence of hepatitis B virus (HBV) infection among patients with IBD appears similar to that of the general population in some studies [119–121] and increased in IBD patients compared to non-IBD patients in others [122, 123]. Hepatitis B reactivation is an important concern among immunosuppressed populations, widely reported among patients undergoing cytotoxic chemotherapy (particularly for hematologic malignancies) and solid organ or stem cell transplantation and also reported in association with biologic treatments for autoimmune conditions and IBD [124]. Immunosuppressive treatment (e.g., with TNF inhibition) can reduce viral clearance, exhaust HBV-specific T-cell responses, and enhance viral load, leading to immune-mediated liver damage particularly after immunosuppression is withdrawn [125–127]. Reactivation of viral replication and flares of HBV thus reflect immune reconstitution and can occur even after short courses of immunosuppression. Occurrence of this preventable consequence has been associated with significant morbidity and mortality that may be mitigated by the use of prophylactic antiviral therapy among at-risk patients [1, 128].

Testing

All IBD patients should receive HBV serologic testing prior to immunosuppressant therapy to assess HBV exposure or vaccination status. Patients should receive the initial HBV vaccination at least 2 weeks prior to initiation of immunosuppressant therapy. Testing to confirm serologic response may be performed approximately 1–2 months after the final vaccination; levels of hepatitis B surface antibody (HBsAb

or anti-HBs) > 100 international units/liter (IU/L) should ideally be maintained during biologic therapy to achieve adequate protection against HBV [1, 129]. Higher doses of the immunizing antigen or a second HBV vaccination course may be required for patients whose response to the previous series is inadequate [130].

Prophylaxis

IBD patients with active HBV infection should receive treatment, with delay of biologic therapy and/or immunomodulators until acute infection or reactivation (HBV deoxyribonucleic acid [DNA] < 2000 IU/mL) resolves [1]. Patients at moderate or high risk for HBV reactivation should be considered for antiviral prophylaxis prior to the initiation of immunosuppressant therapy according to published guidelines from the American Gastroenterological Association. Patients with positive hepatitis B surface antigen (HBsAg) and positive hepatitis B core (anti-HBc) (+HBsAg/+anti-HBc) serologies or with negative HBsAg and positive anti-HBc (−HBsAg/+anti-HBc) planned to undergo treatment with anti-TNF agents, anticytokine agents (such as ustekinumab), or anti-integrin agents (such as natalizumab or vedolizumab) are categorized as moderate risk for HBV reactivation (anticipated incidence 1–10%), and HBV antiviral prophylaxis is suggested (weak recommendation based on moderate-quality evidence). Patients with positive HBsAg and positive anti-HBc (+HBsAg/+anti-HBc) serologies undergoing treatment with low-dose corticosteroids (<10 mg prednisone/day or equivalent) for ≥4 weeks as well as patients with negative HBsAg and positive anti-HBc (−HBsAg/+anti-HBc) serologies undergoing treatment with moderate-dose (10–20 mg prednisone/day or equivalent) or high-dose (>20 mg prednisone/day or equivalent) corticosteroids for ≥4 weeks are also considered to be at moderate risk for HBV reactivation. Patients at high risk for HBV reactivation (anticipated incidence >10%) in whom HBV antiviral prophylaxis is advised (strong recommendation based on high-quality evidence, respectively) include patients with positive HBsAg and positive anti-HBc serologies undergoing treatment with moderate-dose (10–20 mg prednisone/day or equivalent) or high-dose (>20 mg prednisone/day or equivalent) corticosteroids for ≥4 weeks [128].

Prophylactic antiviral treatment should generally be maintained for a minimum of 6 months following discontinuation of immunosuppressant therapy (as recommended by the European Crohn's and Colitis Organisation) [1]. Patients at low risk for HBV reactivation (anticipated incidence <1%) in whom antiviral prophylaxis is not routinely recommended (weak recommendation based on moderate-quality evidence) include patients with positive HBsAg and positive anti-HBc (+HBsAg/+anti-HBc) serologies or negative HBsAg and positive anti-HBc (−HBsAg/+anti-HBc) serologies undergoing immunosuppressive treatment with azathioprine, 6-mercaptopurine, methotrexate, or any oral corticosteroid dose lasting for ≤1 week; others in this low-risk category include patients with negative HBsAg and positive anti-HBc (−HBsAg/+anti-HBc) serologies undergoing treatment with low-dose (<10 mg prednisone/day or equivalent) corticosteroids for ≥4 weeks.

Hepatitis C Virus

The prevalence of hepatitis C virus (HCV) among patients with IBD appears similar to the general population as confirmed in several studies [119–121, 123]. Biologic therapy does not appear to influence the short-term course or reactivation of HCV. Reports suggest that anti-TNF therapy is generally considered safe with appropriate clinical monitoring in HCV patients [131–136]. The long-term effect of therapy on the course of HCV has not been determined [137].

Cytomegalovirus

The presence of cytomegalovirus (CMV) infection among IBD patients has been described in association with the use of corticosteroid and azathioprine therapy [138]. A prospective observational study of 69 ulcerative colitis patients with moderate-to-severe disease activity under immunosuppressive treatment with steroids and/or other immunosuppressants reported that CMV is frequently reactivated in the setting of acute colitis but often resolves without antiviral treatment [139].

The association of CMV infection with biologic therapy has been less frequently described. Systemic CMV reactivation causing severe infections has been infrequently reported in association with anti-TNF therapy, including retinitis [140], colitis [141], hepatitis [142], and disseminated disease [143]. A prospective observational study investigating the association between colonic CMV reactivation and the use of anti-TNF versus azathioprine therapy among 73 ulcerative colitis patients with 109 flare-ups reported that patients undergoing maintenance therapy with anti-TNF agents were not at increased risk of CMV reactivation compared to patients on azathioprine [144]. CMV reactivation was similarly identified in 35% and 38% of patients receiving anti-TNF agents and azathioprine, respectively [144].

Screening for CMV infection is not necessary prior to initiation of immunosuppressive therapy. However, as CMV may complicate disease course in the setting of severe acute or steroid-refractory colitis, infection should be excluded with colonic biopsy particularly during acute colitis flares and prior to increasing immunosuppressant therapy. Among IBD patients, the prevalence of CMV in colonic tissue has been reported in 21–34% of patients with severe colitis and 33–36% of patients with steroid-refractory colitis [145].

Immunosuppressant therapy may generally be continued in cases of mild CMV reactivation. In cases of CMV gastrointestinal disease associated with steroid-refractory colitis, antiviral therapy should be initiated with consideration for discontinuation of immunosuppressant therapy until acute infection resolves. Immunosuppressant therapy should be discontinued [1, 146], and prompt antiviral treatment with ganciclovir (2–3 weeks) should be initiated in the setting of severe or systemic CMV infection; oral valganciclovir may be considered after 3–5 days to complete a 2–3 week treatment course. Foscarnet may be considered as a treatment alternative in cases of ganciclovir resistance or intolerance [1].

Epstein-Barr Virus

Reactivation of Epstein-Barr virus (EBV) has been reported to be more frequent among IBD patients compared to controls and is influenced by therapeutic regimens. A prospective study of 379 outpatients (treated with 5-aminosalicylates, $n = 93$; azathioprine, $n = 91$; infliximab, $n = 70$; combination infliximab plus azathioprine, $n = 43$; healthy controls, $n = 82$) found that over 90% had previous EBV exposure. Only six IBD patients were undergoing steroid therapy. The overall prevalence of EBV-DNA detected in blood was 35% with a significantly greater prevalence in IBD patients, independent of medication regimen, compared to controls. Infliximab (monotherapy or in combination with azathioprine) compared to azathioprine monotherapy or 5-aminosalicylate monotherapy ($P < 0.05$) was associated with higher EBV prevalence. Age was a risk factor for EBV-DNA positivity (OR 1.021, 95% CI 1.002–1.040); older age (>60 years) was related to EBV positivity with specificity of 92%. Ulcerative colitis was a risk factor for high EBV levels (>1000 and 2500 copies/mL). There was no clinical consequence of this EBV-positive status in the short-term follow-up period of this study [147].

Asymptomatic EBV screening should be considered prior to the initiation of immunosuppressive therapy among inflammatory bowel disease patients and can guide therapeutic management strategies, particularly in deferring thiopurine use among patients unexposed to EBV in whom primary infection has been associated with the risk of lymphoproliferative disorders such as EBV-positive lymphoma [148, 149]. Immunosuppressive therapy should be discontinued in cases of severe primary infection or EBV-mediated lymphoproliferative disorders [1].

Varicella Zoster Virus

IBD patients, particularly those on immunosuppressants, are at increased risk for herpes zoster infection compared to the general population [150]. A large, retrospective cohort study using a US administrative healthcare claims database (January 1997–December 2009) including 108,604 adults (<64 years of age) with IBD (56,403 with ulcerative colitis; 50,932 with Crohn's disease; 1269 with unspecified IBD) matched to 434,416 controls without IBD demonstrated that the risk of herpes zoster was increased in the IBD population compared to controls with an incidence rate ratio of 1.68 (95% CI 1.60–1.76). The risk of herpes zoster infections was highest with combination of anti-TNF and thiopurine therapy (OR 3.29, 95% CI 2.33–4.65) after controlling for comorbidities, healthcare utilization, and other medication use [151].

Immunosuppressants should not be commenced during active infection with varicella or herpes zoster virus. Antiviral agents should be dosed promptly if infection occurs while on immunosuppressant therapy, which should be discontinued in severe cases. Reintroduction of immunosuppressant therapy may be considered once the patient is afebrile and vesicular crusting of lesions has occurred.

Herpes Simplex Virus

Immunosuppressed patients may experience more severe, frequent, and extensive manifestations of primary or recurrent herpes simplex virus (HSV) disease [152–154]. Disease manifestations, including HSV-associated esophagitis [155], encephalitis [156], fulminant colitis [157, 158], hepatitis [159, 160], sepsis [161], and disseminated cutaneous infection [162, 163], among others, have been described in IBD patients on immunosuppressant regimens. Reports of localized HSV, HSV encephalitis, and disseminated cutaneous HSV have been described in association with the use of anti-TNF agents [25, 152, 153, 163–166].

Screening for HSV is not necessary prior to initiation of biologic therapy. HSV is not a contraindication to immunosuppressive therapy, although viral reactivation yielding frequently recurrent oral or genital HSV lesions may require episodic or chronic daily antiviral prophylaxis (e.g., with valacyclovir, acyclovir, or famciclovir). Cases of suspected HSV, especially severe or disseminated HSV infection, should prompt antiviral therapy with discontinuation of immunosuppressant(s) until resolution of the acute infection.

Managing Infectious Risks with Biologic Therapy in IBD

Clinician awareness of infectious risks and individual host variables is paramount when considering initiation of biologic therapy. Due to the potential risk for serious infections associated with biologic therapy, adherence to preventive screening and surveillance guidelines are advised. Vaccinations should be advocated for all IBD patients, particularly for patients early in the disease course who may be particularly susceptible to certain infections and who may promptly require immunosuppressant therapy. Most immunizations, except for live virus vaccines, may be safely administered to IBD patients on biologic therapy. Annual tuberculosis risk assessment should be performed with retesting in high-risk situations [1]. Patients being considered for natalizumab therapy should be enrolled in the TOUCH program; JC virus status should be established prior to initiation of therapy (with treatment if negative) and retested periodically at 4–6 month intervals [167].

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