Chapter 6
Infectious Complications in Inflammatory Bowel Disease

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Introduction

The pathogenesis of inflammatory bowel disease (IBD), including onset, persistence, and recurrence, is intimately intertwined with infection. Much has been written and speculated about various infectious triggers of immune dysregulation, undoubtedly related to microbial imbalance [1]. Individuals diagnosed with ulcerative colitis (UC) or Crohn's disease (CD) are at increased risk of myriad infections by virtue of certain disease-related structural or anatomical abnormalities, such as abscess and fistula formation. Reactivation of certain viral infections such as herpes simplex or cytomegalovirus may predispose to other infectious complications, such as *Clostridium difficile* colitis (C. diff) [2]. C. diff has also been associated with relapse of IBD in several studies [3, 4]. The management and therapy of IBD have evolved considerably over the past decade, with significant associated improvement in the quality of life of affected individuals by virtue of manipulation of the immune system with biologic agents. However, with these benefits come tangible risks, most notably the increased risk of a variety of opportunistic infections [5]. This chapter will review state-of-the-art therapeutic approaches to IBD and associated risk of infectious complications and detail prevention strategies.

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Therapy for IBD and Infection Risk

Each biologic agent targets different mechanisms in the inflammatory cascade of IBD. This immunosuppression varies, with some biologics acting upon innate host defense mechanisms and others tailored to a more "gut-specific" response. To fully understand the risk of opportunistic infection (OI) in IBD patients treated with biologics, it is first important to evaluate their mechanisms of action.

Specific Drugs and Drug Classes for the Treatment of IBD

Anti-TNF Agents

Tumor necrosis factor (TNF) is a cytokine produced by numerous immune cells, most often by macrophages and T lymphocytes [6]. TNF has several intracellular and extracellular roles, with a high propensity to promote inflammation. It recruits component cells essential to the formation of granulomas and aids in the proliferation of fibroblasts, which are responsible for creating the capsule around granulomas. TNF is therefore important in both the development and maintenance of granulomatous host defense.

Anti-TNF agents have been utilized in therapy of IBD for over 20 years, making the drug class one of the most thoroughly researched biologics in post-marketing [7]. Infliximab was approved by the Food and Drug Administration (FDA) to treat CD in 1998, followed by the approval of adalimumab and certolizumab in 2007 [8].

While there is still some debate on the nuanced mechanisms of anti-TNF agents, it is generally well accepted that anti-TNF agents work to treat IBD primarily through (a) neutralization of TNF-α, which is responsible for signaling pro-inflammatory molecules to the gastrointestinal tissue; (b) initiation of reverse signaling, which suppresses cytokine activity; and (c) promotion of apoptosis of T lymphocytes in the lamina propria reducing T cell proliferation, thought to be the driving force behind inflammation in CD [6].

Anti-TNF treatment is not a targeted therapy, as evidenced by its ability to treat numerous autoimmune conditions such as rheumatoid arthritis, psoriasis, ankylosing spondylitis, as well as IBD. There are benefits to systemic immune suppression in management of IBD, specifically in certain manifestations of CD. Unlike UC, which is limited to colonic involvement, CD can affect any part of the gastrointestinal tract and, in some instances, requires a broader immunosuppressive agent in order to achieve disease remission. Additionally, providers may find themselves needing to select a biologic treatment that is effective for both IBD and another co-occurring autoimmune condition(s). While anti-TNF agents have well-documented successes in both mild and the most severe cases of IBD, treatment with these agents carries a greater risk of opportunistic bacterial, mycobacterial, viral, fungal, and parasitic infections, many of which may not otherwise occur in the immune-competent host.

Vedolizumab

Vedolizumab is a selective leukocyte adhesion molecule inhibitor, approved for use in both CD and UC in 2014 [8]. Based on animal models, vedolizumab is thought to work as a gut-specific monoclonal antibody, which targets α4β7 integrin, inhibiting memory T lymphocytes from migrating to the inflamed gastrointestinal mucosa [9]. Recent human research suggests the mechanism of action of vedolizumab may not be solely associated with intestinal T-cell trafficking but also works to suppress intestinal inflammation by acting on the innate immune system via boosting intestinal macrophages and changing the expression of innate effector molecules, chemokines, and recognition receptors [9]. Safety data from six vedolizumab trials over 4 years involving nearly 3000 patients showed no increased risk of any infection associated with vedolizumab treatment compared to placebo, which is thought to be due to the gut-specific targeting of immune suppression [10]. While the safety profile of vedolizumab is promising from clinical trials, more long-term safety trials are needed to fully establish vedolizumab's safety profile.

Ustekinumab

Ustekinumab was approved for use in CD by the FDA in 2016 [11] and for use in UC in October 2019 [12]. Ustekinumab is a monoclonal antibody that works by binding to the p40 subunit of both IL-12 and IL-23 [13]. This creates a blockade of the IL-12 and IL-23 cytokines, preventing them from binding with their respective receptors and thus effectively preventing inflammation signaling to the immune cells.

The pathogenesis of Crohn's disease is thought to largely involve overexpression of T cells in the intestinal lamina propria, which release large quantities of interleukin-12 [13], while interleukin-23 receptor appears to play a critical role in the genomics of IBD.

Ustekinumab has an anti-inflammatory effect that is systemic, leading to its use not only in IBD but also in psoriasis and psoriatic arthritis [13]. Despite its systemic effects, it appears to have low incidence of opportunistic infections (OIs) among IBD patients, with only three documented case reports (*Listeria* meningitis, esophageal candidiasis, and disseminated cutaneous herpes zoster) [14].

In the PSOLAR registry for psoriasis, of all the biologics, ustekinumab had the lowest rate of serious infection per 100 patient years [13]. Although this registry is primarily for psoriasis patients, 1% of participants (approximately 200 patients) have concurrent CD. While ustekinumab's long-term real-life safety profile is not yet fully established for UC, existing data for CD patients appears to bolster the reputation of low OI risk.

Janus Kinase (JAK) Inhibitor

In May 2018, a Janus kinase (JAK) inhibitor called tofacitinib was approved for treatment of moderate to severe UC [11]. Tofacitinib is not approved for use in CD as of the date of this publication. Unlike previous biologic treatments for IBD, which rely on intramuscular injection or IV infusion, tofacitinib is the first oral tablet biologic treatment for IBD.

Tofacitinib's biologic mechanism is not fully understood [15]. It is thought to play a role in the blockade of inflammatory cytokines, specifically IL-12 and interferon (IFN)-γ, which in theory may increase the risk of intracellular infections by similar processes of anti-TNF agents (e.g., interfering with the genesis of macrophages and diminishing the maintenance of existing macrophages).

To understand the proposed mechanism of tofacitinib, it is first important to review the function of the JAK-STAT pathway. Initially, cytokines phosphorylate JAKs, and then JAKs go on to phosphorylate STAT proteins. Once freed, these STAT proteins activate transcription of inflammatory cytokines [16]. Tofacitinib works by inhibiting all four JAKs, effectively stopping the inflammation cascade before it has a chance to begin. This blocking of the JAK-STAT pathway prevents the creation of numerous inflammatory cytokines, many of which play central roles in the pathogenesis of IBD but also appear to be essential in the function of our primary immune response and ongoing maintenance of the host defenses.

Similar to anti-TNF agents, JAK inhibitors induce systemic immune suppression, leading to a wide array of OI risks for the patient. Tofacitinib is a relatively novel therapy in its application for treatment of UC [11]. As such, the majority of the safety data for tofacitinib is derived from rheumatoid arthritis (RA) randomized controlled trials. Until post-marketing data is accumulated for tofacitinib with long-term safety trials for its use in IBD, we will be reliant upon extrapolating safety risks from the RA groups who have been more extensively studied.

Infection Risk Based on Organism and Organism Type

Bacterial

Mycobacterium tuberculosis

Tuberculosis (TB) remains one of the most lethal infectious diseases worldwide [17]. Approximately 25% of the world's population is infected with *Mycobacterium tuberculosis*. In 2018, an estimated ten million people developed active TB infection, with an associated 1.2 million deaths in the HIV-negative population. While the incidence of TB deaths has declined by 27% globally since 2000, TB remains the number one cause of infectious death from a single pathogen and remains in the top ten leading causes of death overall [17]. Regionally, TB is most common in

Southeast Asia (44%), Africa (24%), and the Southern Pacific (8%). India (27%) together with China (9%), Indonesia (8%), Pakistan (6%), and the Philippines (6%) accounts for 60% of the world's TB population. While TB is common worldwide, US rates have declined over the last 25 years [18]. In 2018, there were an estimated three per 100,000 cases of TB in the United States compared to 316 per 100,000 in Indonesia, 199 cases per 100,000 in India, and 61 per 100,000 in China. Data collected by the Center for Disease Control and Prevention (CDC) from tuberculin skin tests collected from 2011 to 2012 found that incidence of latent TB in the United States was more prevalent in non-US-born persons (20.5%) as well as non-Hispanic Asians (22.2%) and Hispanics (12.3%) [18].

M. tuberculosis most commonly affects the lungs, known as pulmonary TB. Airborne transmission of *M. tuberculosis* begins with inhalation of the bacilli that are deposited in alveoli, setting off an innate immune response to neutralize and destroy the pathogen [19]. Extra-pulmonary TB accounts for 15–20% of cases and occurs when the infection spreads from the alveoli to the lymph nodes and solid organs [20]. Both in pulmonary and extra-pulmonary TB, the host defenses respond to the bacilli by production of T lymphocytes and macrophages, which work together in creating granulomas to wall off and contain the infection [19]. If this initial containment is successful, the host does not develop active TB following exposure but instead carries the encapsulated bacilli in necrotic form, known as latent TB [21]. As long as the host immune system is competent, the granulomas go on to successfully contain the infection in an inactivated state.

TNF plays a critical role in both the formation and maintenance of the host defenses [6]. When TNF is suppressed, it leads the host to be susceptible to reactivation of TB through the disintegration of the existing infected granuloma, allowing the once inactivated bacilli to become reactivated into an incompetent defensive cellular response. The incidence of TB among patients treated with anti-TNF agents was found to be 0.28 per 100 patient years [22], with those on anti-TNF agents five to ten times more likely to have reactivation of *M. tuberculosis* compared to the general population. It appears patients on anti-TNF agents are at increased risk of TB even if they have a negative TB screening test prior to treatment induction, which demonstrates the need for ongoing surveillance for these patients [23].

The incidence of *M. tuberculosis* infection during tofacitinib treatment is similar to that which occurs on anti-TNF treatment (0.21 per 100 patient years [16] vs. 0.28 per 100 patient years [22], respectively). The blockade of JAK inflammatory cytokines prevents intracellular signaling of IL-12 and interferon (IFN)-γ, which are essential in the creation and function of macrophages [15]. Thus, similar to anti-TNF agents, JAK inhibitors interrupt the genesis of macrophages and interfere with the production of components required to maintain the function of the macrophage, allowing the once encapsulated and inactivated *M. tuberculosis* infection to become reactivated.

Clinical trial data do not suggest that vedolizumab increases patients' risk of TB; incidence rates among participants were congruent with the population incidence rates of the country of origin [23]. Additionally, in post-marketing data, patients who did develop TB while on vedolizumab were able to resume vedolizumab after finishing TB treatment.

In theory, there is a risk of TB reactivation for patients on ustekinumab, and although the degree of risk is uncertain, it appears to be low [14]. The incidence of TB in patients on ustekinumab was 0.02 per 100 patient years [22].

Nontuberculous Mycobacteria (NTM)

Nontuberculous mycobacteria (NTM) represent a group of numerous organisms, most of which do not pose a threat to immunocompetent persons [24]. NTM are found in soil, water, and animal vectors. NTM infections among patients with IBD have been less extensively studied in comparison to *M. tuberculosis*. Within the existing research, there are a few NTM infections identified specifically in IBD patients receiving biologics: *M. avium*, *M. marinum*, and *M. abscessus*.

M. avium is the most common NTM in the United States [22] and one of the most common NTM infections in severely immunocompromised persons [24]. *M. avium* is not thought to pose a risk to immune-competent persons [25]. It is found in water and collected rainwater is a common source. Infection with *M. avium* occurs with inhalation of aerosolized particles, such as water spray from an outdoor shower or mist from a water hose. Even point-of-use water filtration devices can become colonized.

M. avium complex (MAC) refers to both *M. avium* and *M. intracellulare* and is a thoroughly researched OI among AIDS patients, in part due to its incidence (3% among patients with CD4 counts between 100 and 199 cells/uL) [26], but mostly due to its reputation as clinical complex to treat with its multidrug-resistant strains [27]. Disseminated MAC occurs nearly exclusively in those with CD4 counts below 50 cells/uL [26].

M. abscessus is the second most common NTM infection in the United States and usually affects soft tissues, skin, and lungs (although it can affect any organ). *M. abscessus* is often multidrug resistant, which can pose a significant threat to the immunocompromised. It is found both in soil and water. There are case reports of *M. abscessus* transmission from gardening, acupuncture, and cosmetic mesotherapy involving the injection of various substances under the skin to produce a tightening effect. *M. abscessus* affects not only the skin and soft tissues but also causes serious lung infection, especially for those with preexisting lung diseases such as chronic obstructive pulmonary disease (COPD) or cystic fibrosis (CF) [28].

There are case reports of *M. marinum* among IBD patients, commonly acquired by aquarium owners or fishermen [29]. *M. marinum* infections are usually limited to the skin; seventy-five percent of cases present as a solitary lesion on the hand or digit [30]. Among those on anti-TNF treatment, the clinical presentation more often takes a sporotrichoid form whereby the infection extends beyond the lesion, producing several nodules along the lymphatic vessels, and spreads to regional lymph nodes. *M. marinum* can invade deeper tissues in 20–40% of cases (tenosynovitis, osteomyelitis, arthritis, and bursitis).

Among the research examining OIs in biologic therapy, NTMs are often examined as a category of OI [31]; less often the individual NTM infection is parsed out in the data. Furthermore, the data that is available on NTM incidence in biologic therapy frequently does not focus on the IBD population exclusively, which limits its salience for application in this population.

Data on NTM infections among IBD patients receiving anti-TNF treatment is limited; most research on the topic reports the total incidence of NTM infection among those receiving anti-TNF treatment for any indication (e.g., infection rates for those with RA, psoriasis, ankylosing spondylitis, and IBD are reported together). As such, this data should be interpreted with caution and may not accurately reflect the risk of opportunistic NTM infection among IBD patients on anti-TNF agents.

According to Shim et al. [22], overall NTM infection for those receiving anti-TNF has been estimated at a rate of 230.7 per 100,000 patient years, similar to numbers reported by Yoo et al.: 238.2 per 100,000 person-years [31]. One analysis of OIs among 1165 patients on anti-TNF treatment found that the most common NTM infections were *M. intracellulare* ($n = 3$) and *M. avium* ($n = 2$) [31]. In this same cohort, 83% of patients who developed NTM infection were receiving anti-TNF treatment for RA and not for IBD. Of the 422 IBD patients, only one was reported to have NTM infection, though the specific NTM infection was not reported. There are 30 case reports of *M. marinum* in those receiving anti-TNFs, with at least one case of disseminated disease [30].

There is limited data on NTM infection risk with tofacitinib use, but the risk appears to be low, with only two cases of pulmonary NTM infection documented among the 5671 patients enrolled in tofacitinib trials [15]. Only one case report of *M. abscessus* while on ustekinumab treatment [22] was identified.

Listeria monocytogenes

Listeria monocytogenes causes a foodborne illness that often results in self-limiting diarrhea, but in the immunosuppressed, it can lead to bacteremia, bacterial meningitis, and rhombencephalitis [32, 33].

L. monocytogenes is an intracellular pathogen; the growth of intracellular pathogens is inhibited by TNF-α; thus, when TNF-α is suppressed, the intracellular growth proceeds unchecked [32]. Studies examining *L. monocytogenes* risk specifically in the IBD population are limited, but listeriosis was found to be 20 times more common in RA patients treated with infliximab compared to the general US population (incidence of 61 per 1,000,000 person-years) [32].

Estimates of incidence of high-risk complications from *L. monocytogenes* are limited to case reports, such as 69-year-old male with CD on anti-TNF treatment who presented to the Emergency Department (ED) with acute central nervous system (CNS) changes and was diagnosed with Listeria rhombencephalitis [33].

Due to the gut-selective nature of vedolizumab, it is plausible that patients on treatment could be at increased risk for OIs of the gut such as *Listeria* [10]. In an

analysis of the 2830 patients across six safety trials, one patient developed *Listeria* meningitis, though this patient was also taking corticosteroids and azathioprine at the time of infection.

Streptococcus pneumoniae

Streptococcus pneumoniae is an opportunistic gram-positive extracellular pathogen that colonizes the mucosal surfaces of the nasal epithelium [34]. It is the causative bacterial agent of numerous infections ranging from mild (e.g., otitis media), moderate (community-acquired pneumonia) to severe (sepsis and meningitis). It is spread through both contact and airborne transmission. It is estimated that anywhere from 25% to 65% of children carry *S. pneumoniae* whereas less than 10% of adults are carriers [34]. If the carrier's immune system is compromised, it allows for dissemination of the bacterium into the lungs via aspiration, which can then lead to bacteremia, as well as spreading through the sinuses and inner ear.

TNF-α is essential to the host defense against extracellular bacteria, leaving those who are treated with anti-TNF agents inherently at increased risk for extracellular bacterial infections such as *S. pneumoniae* [32].

In an analysis of the 2830 patients across six safety trials for vedolizumab, 36 patients were documented as having infection with *S. pneumoniae*, which equates to an incidence of 0.8 per 100 patient-years [10].

Viral

Herpes Zoster (HZ)

Initial exposure to varicella zoster virus (VZV) causes primary varicella, commonly referred to as chicken pox [11]. Reactivation of VZV leads to herpes zoster (HZ), commonly referred to as shingles. Anyone with prior VZV exposure is at risk for developing HZ [35]. After initial exposure to VZV, varicella remains dormant in the dorsal root ganglia or cranial nerves [11]; reactivation causes a painful rash with hallmark distribution across dermatomes.

The risk of HZ infection among the general population is greatest in women, and incidence increases with age [36]. Analysis of nearly 40,000 IBD patient charts between 1996 and 2015 found HZ infection follows a similar pattern of increased incidence with age and among women, but not surprisingly authors found HZ affects the IBD population at a higher rate than the general population, especially in young persons [36]. Incidence of HZ among the general IBD population was found to be 0.7 per 100 patient-years.

Congruently, analysis of disease incidence among health insurance beneficiaries (specifically those with United Healthcare, Medicare, and Medicaid coverage

between 2007 and 2010) found that those with IBD under the age of 60 were twice as likely to be diagnosed with HZ compared to those without IBD over the age of 60 [35]. Some have proposed that the higher observed HZ incidence among younger patients with IBD is due to the use of biologic treatments [36]. Reoccurring HZ infection is higher in the IBD population compared to the general population, with more than half of the reoccurrence rates observed in patients over the age of 60 [36].

TNF is central to the TNFR1-mediated apoptotic death of cells infected with viruses [32]. In post-marketing research of anti-TNF safety in the French RATIO registry, most documented OIs were viral. While it is presumed that patients receiving anti-TNF treatment for IBD are at increased risk for HZ, the evidence has been contradictory, with some multi-institutional studies showing no increased risk of HZ on anti-TNF treatment and other country-specific databases in Europe showing statistically significant increased risks. There are several proposed reasons for this conflicting data, namely, the varying regional practices of using corticosteroids during the induction phase of anti-TNF treatment and perhaps the varying inclusion criteria of participants between the retrospective analyses interferes with the ability to draw direct comparisons. More research is needed in order to understand whether anti-TNF treatment alone in IBD is associated with increased risk of HZ infection.

Tofacitinib is thought to affect antiviral immune response in a more dismantling fashion compared to other biologic agents due to its action upon JAK1 [16]. Theoretically, tofacitinib diminishes type 1 (IFN-α and IFN-β) and type 2 (IFN-γ) viral responses, leaving the JAK1 receptor inactivated, rendering the host response to viral infection as inept [15]. HZ infection poses arguably the greatest risk for patients treated with tofacitinib. Those on JAK inhibitors are more than six times as likely to have HZ infection as compared to the general population [36].

UC patients treated with tofacitinib appear to have much higher incidence of HZ compared to the general population, with some studies demonstrating incidence of four per 100 patient-years [11] up to 7.6 per 100 patient-years [37].

Disseminated Herpes Zoster (DHZ)

In most cases, HZ is controlled quickly and succinctly by the immune system, but in certain instances, the HZ infection spreads and is termed disseminated disease when more than 20 vesicles appear beyond the initial dermatome and/or more than two dermatomes are affected, signaling the presence of persistent viremia [38]. Unlike HZ, the incidence of DHZ appears to be the same between males and females. The relative risk of DHZ while on anti-TNF treatment for IBD is not reported.

In the UC clinical trials of tofacitinib, there was a documented increased risk of HZ compared to placebo, but none of the participants had more than one or two dermatomes affected, and the participants did not need to discontinue tofacitinib as a result of the infection [37].

It has been observed that of those on tofacitinib who develop HZ, the risk of complications from HZ was highest among those older than 65, Asians, or those with a history of prior anti-TNF treatment failure [39]. It is not clear why the Asian population may be disproportionally at increased risk for complications from HZ while on tofacitinib treatment, but it may be a result of regional variance. For example, population studies have found HZ incidence in China and Taiwan to be much higher (51% and 66%, respectively) compared to relatively lower rates in Western Europe (7–26%) [40].

Chronic Hepatitis B Virus (HBV)

It is estimated that 240 million people have chronic HBV worldwide, with close to 700,000 deaths annually due to HBV complications [41]. North America and Western Europe are relatively low-endemic regions with estimated prevalence of chronic HBV between 0.5% and 2%, compared to the high-endemic regions of China, Indonesia, Southeast Asia, and sub-Saharan Africa, which all report greater than 8% incidence rates. In recent years, there has been a documented increase in HBV infection among European populations, thought to be a result in part to the migration of refugees from endemic areas into Europe [42]. Epidemiologists anticipate rates of HBV infection may rise over the next few years as a result of this migration. Refugees with chronic HBV are younger, more likely to have coinfection with HIV, and are more vulnerable to suffering long-term complications from HBV due to limited access healthcare.

HBV can cause both acute and chronic diseases [41]. The infectivity of HBV is more than 100 times that of HIV, with those most at risk including IV drug users, those who practice unprotected intercourse with multiple partners, healthcare workers with needle-stick injuries, and the incarcerated [43]. Transmission of HBV occurs through blood, sexual, or vertical route [41]. Acute infection is characterized by a positive HB surface antigen (sAg) and a viral load (HBV DNA level) over 2000 IU/mL. If the HBsAg is detectable for greater than 6 months, the person is considered to be chronically infected. Patients who have no detectable HBsAg after 6 months are considered to have “cleared” the infection and are categorized as potential or occult carriers. Antibodies against surface antibody (HBsAb) sometimes develop in potential carriers, but not always.

In 2008, the CDC recommended all persons who are receiving immunosuppressive treatments should be screened for HBV prior to starting treatment [44]. This recommendation for screening was due to concerns for increased rates of reactivation of HBV in immunosuppressed persons. The term “reactivation” in reference to HBV generally means either (a) patients with chronic HBV experience increased viral replication and activity of once controlled disease; (b) patients who had been exposed to HBV and cleared the infection test positive for HBV sAg, suggesting they have reverse-seroconverted to chronic infection; or (c) patients who had been exposed to HBV and cleared the infection now have detectable HBV DNA levels on quantitative testing but remain sAg negative [41]. There is a general consensus that

HBV reactivation is significantly higher in patients receiving combination immunosuppressive therapies than single agents alone [23].

Patients on anti-TNF treatment are thought to be at greater risk of reactivation of chronic HBV [32], though there is conflicting data on the validity of this statement [44]. Some studies show no significant increased risk of reactivation of HBV for patients receiving anti-TNF therapy, while other studies show up to 25% of patients with a positive hepatitis B surface antigen (HBsAg) prior to treatment went on to experience reactivation. Screening for HBV prior to initiating treatment with anti-TNF agents for IBD has increased over time [44], and this variance in pre-screening of patients may in part account for the conflicting data on risk of HBV reactivation in this patient population. In 2008, the same year the CDC recommended HBV screening for immunosuppressed persons, IBD practice guidelines also included this recommendation.

In an analysis of over 3000 IBD patients from the Veterans Health Administration datasets between 2003 and 2011, Shah and Ho et al. found that only 8.9% of IBD patients were screened for HBV prior to anti-TNF initiation, compared to 43.2% who were screened in 2011 [44]. Additionally, they did not find any documented cases of clinically significant HBV reactivation among this group, which was the first study to specifically examine the risk of HBV reactivation among IBD patients receiving anti-TNF.

Although vedolizumab is not thought to increase the risk of opportunistic infections [10], clinical trials for vedolizumab excluded patients with chronic HBV [23]. In the Global Safety Database examining patients who received vedolizumab, 14 patients out of 114,971 patient years were identified as having a history of HBV infection, and three of these had confirmed chronic HBV. There were no liver-related adverse events reported in these 14 patients, and more than half had prior or current use of anti-TNF agents. It is generally accepted among gastroenterologists that single-agent immunosuppression with vedolizumab is unlikely to increase the risk of HBV reactivation, but further safety trials are needed in order to strengthen the validity of this observation.

There is limited data on the risk of HBV reactivation with the use of tofacitinib, and even less is known about how this possible risk affects the IBD population specifically [40]. Data gleaned from the rheumatoid arthritis trials suggest the risk of HBV reactivation on tofacitinib is real, although the incidence is low [40]. These findings may be in part due to the geographical variances of HBV, with low incidence in the United States. Further longitudinal analysis will be needed to fully establish the degree of risk.

Chronic Hepatitis C (HCV)

It is estimated that four million people in the United States have chronic HCV [43]. As with HBV, transmission of HCV occurs through blood, sexual, and perinatal routes. Unlike HBV, there is no vaccine active against HCV. Prior to 1992, blood

products for transfusion were not screened for HCV in the United States. Acute infection with HCV can be cleared or go on to develop into chronic infection [43]. Treatment for HCV in the last decade has made tremendous progress to the extent that the overwhelming majority of patients with chronic HCV can be cured.

Anti-TNFs may allow for proliferation of viral replication in HCV, but the available data is limited and often based on short-term observations [45]. The blockade of TNF-α may actually benefit patients with HCV since TNF-α contributes to the development of liver fibrosis through recruitment of pro-inflammatory molecules [45], although it is not known to what extent (if any) that this mechanism is protective. Overall, limited data exists on the risk of worsening HCV infection on anti-TNF therapy, but it appears the risk is low [32]. Whether this low apparent risk is due to under-reporting or due to actual low incidence is not known. Since eradication of HCV is now widely accessible and successful and the duration of treatment is relatively short (8–12 weeks depending on the agent), it is possible there is under-reporting of HCV incidence among patients receiving anti-TNF.

Clinical trials for vedolizumab excluded patients with HCV [23]. In the Global Safety database, 15 patients out of 114,971 patient years were identified as having a history of HCV infection. There were two liver-related events reported: one liver neoplasm categorized as "serious" and one liver mass categorized as "not serious." Similar to the limitations with research on HBV, the use of tofacitinib in the IBD population and the subsequent risk of HCV have not yet been fully examined.

Fungal

In a large retrospective analysis of IBD hospitalizations between 2002 and 2014 from the National Inpatient Sample (NIS) database, the prevalence of opportunistic fungal infections among IBD patients was around 2% [46]. As with all OIs, the combined use of biologics plus corticosteroids increases the risk of fungal infections and associated mortality among the IBD population [47]. Anti-TNF agents are the most often noted biologic agents associated with fungal infections, likely a function of their systemic immunosuppressive effects, although the long history of their use in IBD does render them the most well studied in post-marketing [48]. Histoplasmosis and candidiasis are the most frequent opportunistic fungal infections for patients on anti-TNF agents [32, 46]. The risk of opportunistic fungal infection with vedolizumab was not higher compared to placebo in trials [46].

Candidiasis

Candida albicans is an extremely common commensal microorganism [49]. *C. albicans* is responsible for mucosal infections such as vulvovaginal candidiasis and esophageal candidiasis as well as systemic infections including sepsis [49]. Among

the IBD population, candida most frequently affects the respiratory and gastrointestinal tracts, but it can lead to bloodstream infection as well [48]. In a systematic review of fungal infections in the IBD population, approximately 10% of candida infections lead to sepsis. The mortality from candidiasis-induced sepsis is estimated to be approximately 40%, and it is the fourth leading cause of sepsis overall [49].

Invasive fungal infections can occur in patients on anti-TNF therapy, though the vast majority of the literature notes that concurrent use of corticosteroids and anti-TNF agents poses the greatest risk [50]. Systemic candidiasis is theoretically more likely in those with suppression of TNF levels, specifically due to the subsequent reduced production of IFN, increased apoptosis of monocytes, and reduced granuloma maintenance; these three mechanisms render the host defenses unable to contain the spread of the infection and allow for fungal proliferation in several organs [50].

Histoplasmosis

Histoplasma capsulatum is found most often in bird and bat droppings, and while cats can develop histoplasmosis, cats cannot infect humans [51]. It is the second most common fungal infection among the IBD population in the United States where it is considered endemic. There are regional variances of incidence within the United States, with histoplasmosis more commonly found in IBD patients hospitalized in the Midwest [46]. Those who keep chicken coops or frequent caves for recreation or occupation are at greatest risk [51]. Symptoms of histoplasmosis include fever, chills, extreme fatigue, cough, headache, chest pains, and body aches [52]. Onset of symptoms can occur 3 days after inhalation of the spores up to 17 days later. It is usually a short-lived illness, although it is possible the lung infection can be long term in the immunocompromised or spread to the CNS.

Coccidioidomycosis

Coccidioides immitis and *C. posadasii* are organisms that cause coccidioidomycosis, more commonly known as valley fever [53]. It is common in the southwest United States, as well as Mexico and South America. The spores of *Coccidioides species* reside in dust and soil, although there have been rare cases of valley fever occurring after exposure to a wound infected with *Coccidioides* and from exposure to shoes and rocks contaminated with spores.

Among patients hospitalized with IBD, the incidence of coccidioidomycosis was most common in the western United States, which follows the same pattern of its regional prevalence [46]. Like other fungal infections, anti-TNF increases the risk of reactivation of coccidioidomycosis, although the incidence is limited to case reports [32]. Symptoms of valley fever include rash (erythema nodosum) on upper

body or legs, cough, shortness of breath, fever, fatigue, night sweats, muscle aches, joint pain, and headaches [54]. Onset of symptoms occurs anywhere from 7 to 21 days after exposure and will last a few weeks to a few months. Five to 10% of those with valley fever develop chronic lung disease as a result of infection.

Blastomycosis

Blastomyces are fungi that live in moist decomposing organic matter such as leaves and woods and can be found most commonly in forest soil in the areas of the United States that surround the Great Lakes and the Ohio, Mississippi, and Saint Lawrence River [55]. Infection with blastomycosis occurs after inhaling the spores from disrupted soil. Activities that can result in exposure include hiking, camping, and hunting in wooded areas of the Midwest. In a review of the NIS database, it was found that blastomycosis was more common in IBD patients hospitalized in the Midwest [46]. Symptoms of blastomycosis are similar to the flu, including fever, cough, night sweats, muscle aches, joint pain, weight loss, chest pain, and extreme fatigue [56]. Symptoms start 21–90 days after inhalation of the spores, and disseminated infection can occur.

Aspergillosis

Aspergillus is a mold, transmitted through airborne inhalation of conidia [57]. Most immune-competent individuals do not develop illness as a result of *Aspergillus* exposure; however, those that are immunosuppressed are at risk of developing invasive infection. In the immunocompromised, *Aspergillus* is the leading cause of fatal pneumonia [47]. Invasive pulmonary aspergillosis can then lead to disseminated disease involving the brain, skin, and bones [57]. Exposure to high quantities of *Aspergillus* is thought to occur during building construction or renovations, but it is also found throughout the indoor and outdoor environment as household dust and decomposing plant matter.

Estimates of the incidence of aspergillosis among the IBD population are limited to case reports and appear to occur in the setting of simultaneous corticosteroid use with biologics [47, 48].

Cryptococcosis

Cryptococcosis is an invasive fungal infection, acquired through inhalation of airborne propagules, which deposit into pulmonary alveoli [58]. Cryptococcosis poses significant risk among the severely immunocompromised, with reports of nearly

one million annual cryptococcal meningitis infections worldwide. Around 95% of all cryptococcosis infections derive from *C. neoformans*, which is found in the excrement of pigeons and other birds, amoebas, and sow bugs and lives within hollows of trees. Regionally, cryptococcosis is more common among IBD patients in the South [46].

Cryptococcosis infection is contained through granulomas, making TNF, interferon-y, and interleukin-2 critical in the host defense against cryptococcocal infection [58]. As such, those on anti-TNF treatment are at increased risk of developing the infection.

Parasitic

Leishmaniasis

Leishmaniasis is a parasitic infection caused by many different species of *Leishmania* [59]. It is widely endemic throughout both hemispheres, including in the Mediterranean, India, Africa, and across South and Central America. *Leishmania* species are associated with cutaneous, mucosal, and visceral disease most often in immune incompetent hosts. In the cutaneous presentation, leishmaniasis causes large treatment-resistant skin lesions which can be mistaken for other diverse cutaneous presentations of CD. While most persons exposed do not go on to develop infection, it is thought that the parasite can remain dormant and pose a threat for reactivation [59]. Although the risk of reactivation among IBD patients on biologics is largely unknown, it is a growing area of research and may be included in future screening guidelines prior to biologic initiation.

Strongyloides

Strongyloides stercoralis is an intestinal nematode found in tropical and subtropical areas. It most commonly results in a mild or subclinical gastrointestinal infection with skin manifestations in immunocompetent individuals but can result in severe disease in the immunocompromised [60]. Hyperinfection is most commonly identified in patients receiving chronic corticosteroid therapy but is theoretically possible in other forms of immunosuppression and has been rarely reported [61, 62]. In this type of presentation, patients are gravely ill and may develop gram-negative bacteremia and meningitis with multiorgan failure in the most severe cases. As such, many experts recommend consideration of screening individuals with a history of residence in or travel to endemic areas [63].

Preventing Infections in IBD

Taking a History from an Infectious Disease (ID) Perspective

Prior to starting immunosuppressive therapy for IBD, a complete history should be performed. Review of the indications for treatment as well as the mode of action of the drug used will lead to a better understanding of infectious risks for the patient. Firstly, any current or recent infections should be ruled out by reviewing signs and symptoms that the patient may be experiencing. A thorough travel, social, and exposure history may provide clues as to a potential causative agent. Once active infection is ruled out and immunosuppressive therapy is considered, future risks of infection can be identified by a complete exposure history. A history of past infection, in childhood or in household members, should be elicited as well. History of prior blood transfusions or organ transplants is also important as it can increase the risk of infections such as hepatitis B and C.

Travel History and Future Plans

An effective ID history always includes a detailed travel history. As noted above, treatment with immunosuppressive therapy may increase the risk of infection acquired in certain endemic areas. It is therefore important to obtain information about patients' recent travel as well as areas of prolonged residence. Plans for future travel should be discussed as well to determine if the patient will be at risk for exposure to additional infectious agents.

Occupation

Certain occupations may place the patient at risk for particular infections. An example would be dimorphic fungi present in soil where activities such as farming, soil excavation, and construction/demolition may place the patient at increased risk in the setting of immunosuppressive therapy [64, 65].

Patients working in healthcare may be at increased risk through interaction with patients harboring communicable diseases, such as tuberculosis. They are also more likely to be exposed to blood-borne pathogens in the setting of needle-stick injuries, with concern for hepatitis B and C, as well as HIV. In one retrospective study, though healthcare workers on immunosuppressive therapy were found to have a high number of *Clostridium difficile* and Epstein-Barr virus (EBV) or cytomegalovirus (CMV)-related infections, no significant risk was found compared to the control group without IBD [66]. Similar to healthcare workers, patients that were recently hospitalized or residents of nursing homes may be at increased of *C. difficile* infection [67]. Another occupational infection to be aware of is *Legionella*, acquired through exposure to aerosolized water sources. Exposure to air

conditioners, water fountains, or cooling towers may place the patient at an increased risk while on immunosuppressive therapy [68].

Hobbies and Activities

Like occupational activities, some hobbies may increase the exposure to specific pathogens though the route of exposure may differ. For example, histoplasmosis can be associated with spelunking through contact with soil that has been contaminated with bird or bat droppings [64]. Farming, as mentioned above, can also increase the risk of fungal infection by disturbing the soil. Farming as well as gardening can be associated with sporotrichosis, a fungal infection caused by *Sporothrix schenckii*, which can cause lymphangitis or pneumonitis [69].

Diet

Patients' dietary habits may also represent a source of infection, for example, the consumption of undercooked meat or unpasteurized dairy products. Immunosuppressed patients who ingest these types of foods can develop listeriosis, caused by the gram-positive bacterium *Listeria monocytogenes*, which can eventually lead to CNS disease [70]. Nondairy foods, such as cantaloupe, have been also known to cause sporadic listeriosis outbreaks [71]. Consumption of poultry, meats, and dairy products has been known to be associated with salmonellosis, caused by the gram-negative rod, *Salmonella* species. In immunocompetent patients, it can be associated with gastroenteritis but can lead to bacteremia, osteomyelitis, and endovascular infections in the immunocompromised [72].

Animal Exposures

In patients starting immunosuppressive therapy, it is important to gather information about any animal exposure, including house pets, farm animals, as well as any possible indirect contact, such as with rodents or bats in the home. Infections can be transferred from animal to human (zoonoses), or the pathogen may reside in the animal's environment. Immunosuppressed patients can be at risk for *H. capsulatum* infection, which is a dimorphic fungus found in soil that has been contaminated with bird or bat droppings. Patients owning birds or chickens, as well as spending time near chicken coops, may be at increased risk for histoplasmosis. Another agent associated with bird droppings is the fungus *Cryptococcus neoformans*, which can cause CNS, pulmonary, and disseminated infections in immunocompromised patients [73]. Patients receiving immunosuppressive therapy appear to be at increased risk of nontuberculous mycobacteria such as *Mycobacterium marinum* [74]. This acid-fast nontuberculous mycobacterial species is usually seen in aquatic environment and can cause skin lesions after breaks in skin are exposed to ocean, salt, or fresh

aquarium water, causing so-called "fish-tank granulomas." Immunosuppression particularly increases the risk of disseminated infection [75, 76]. Toxoplasmosis, which is caused by the protozoan *Toxoplasma gondii*, is associated with hand-to-mouth contamination with cat feces or consumption of raw meat. Exposure may cause a subclinical or mild influenza-like or mononucleosis-like illness from which healthy hosts recover with no complications. In immunocompromised hosts, the parasite may reactivate and may be disseminated to the CNS, eyes, heart, liver, or lungs [77]. Patients with pet reptiles, such as lizards, snakes, and turtles, as well as amphibians, such as frogs, are at increased risk of S*almonella* infection [78].

Sexual History

A comprehensive sexual history is necessary to identify possible sexually transmitted infections and to address any risk factors. The risk of HIV, HCV, and HBV is increased in men who have sex with men and in patients with multiple sexual partners. As noted above, reactivation of hepatitis B is a concern in IBD patients receiving certain therapies. Human papillomavirus (HPV) is the most common sexually transmitted infection (STI), and incidence may also be affected by immune status. The virus can cause infection of the skin and mucous membranes, leading to formation of warts and anogenital condylomas. Certain strains of HPV can be associated with malignancies of the cervix, vulva, penis, anus, or oropharynx. Though immune suppression may increase the risk of anogenital warts, there is currently no evidence that risk of malignancy is increased as well [79]. Herpes Simplex Virus (HSV) is also known to cause oral and genital lesions and, in some cases, can cause CNS infections. Patients undergoing immunosuppressive therapy may be at increased risk of developing herpes encephalitis [80].

Substance Use and Other Practices

Substance use, particularly intravenous drug use, is known to be associated with increased infection risk. As discussed above, HIV and viral hepatitis may be transmitted through sharing of needles, and IBD patients receiving biologic agents may carry an increased risk of progression and complications. Skin and soft tissue infections can also occur in the setting of IV drug use with the most typical organisms being *Staphylococcus aureus* and *Streptococcus pyogenes*. Similarly, patients who have tattoos placed using contaminated equipment are at risk for acquiring HBV and HCV, as well as skin and systemic bacterial infections [81–83]. Cigarette smoking is known to increase susceptibility to a variety of respiratory tract infections, including bacterial pneumonia caused by *Streptococcus pneumoniae* [84]. Infection with this organism can lead to meningitis in severe cases, particularly in immunocompromised patients. Proper vaccination as discussed below may prevent infection. Cigarette smoking can also increase the risk of pulmonary tuberculosis [85].

Table 6.1 represents an example of a complete history sheet to elicit important information prior to starting immunosuppressive therapy.

Table 6.1 Example of items to assess during a visit with an IBD patient planning to start immunosuppressive therapy

Exposure	Yes	No	Comments
Medical history Do you have any history of prior infections, including hepatitis and tuberculosis? Anyone in your household with a history of prior infections? Have you been recently hospitalized? Any history of organ transplant? Any history of blood transfusion? Any history of malignancy and prior cancer screenings?			
Travel and residence Have you traveled or lived outside the United States? Where? When? Have you traveled or lived outside your state of residence? Do you have future domestic or international travel plans? Does your home have known mold problems? Do you have well water?			
Occupation What do you do for a living? Do you work outdoors? Are you involved in farming, soil excavation, or construction/demolition? Do you work in health care? Are you a caretaker for the very young or elderly?			
Hobbies and activities Do you spend a lot of time outdoors? Where? Do you spend time in caves? Are you exposed to a lot of freshwater or saltwater? Do you do a lot of gardening? Do you wear gloves?			
Diet Do you consume raw/undercooked meat or fish? Do you consume processed meats? Do you consume unpasteurized dairy products? Do you consume soft cheeses?			
Animals and pets Do you have any pets in your home? Have you been in contact with farm animals? Any other recent animal contact, including wild animals or birds?			
Sexual history Are you sexually active? Do you use barrier protection? Do you have multiple sexual partners? Men, women, or both? Do you have any history of sexually transmitted infections (examples are herpes, syphilis, gonorrhea, and chlamydia)? Have you ever been tested for HIV or hepatitis? Have you ever had an abnormal pap smear?			
Substance use and other Do you smoke? Tobacco? Vaping? Other? Do you or have you ever used drugs? Intravenous? Shared needles? Do you have any tattoos? Sterilized equipment?			

Screening Methods for Specific Infections

A detailed discussion about any past or current infections is essential prior to starting any patient on immunosuppressive therapy. Additionally, there are several screening methods available that should be offered during the initial evaluation under appropriate clinical circumstances.

Tuberculosis

All patients with IBD should be screened for latent tuberculosis infection (LTBI) prior to starting immunosuppressive therapy. Reactivation of LTBI is a risk for patients starting on immunomodulatory agents, and early screening may prevent development of active TB with appropriate treatment. Though recommendations for treatment are consistent, there are no clear guidelines as to the gold standard for diagnosing LTBI. Recommended tests include the tuberculin skin/Mantoux test or Quantiferon-TB Gold/interferon gamma release assay (IGRA), followed by a screening chest radiograph if positive. In the setting of immunosuppression, a positive result for either of these tests is considered diagnostic of LTBI, although immunosuppression may significantly reduce their sensitivity. Once patients are started on immunosuppressive therapy, while most authors agree screening should be based on the individual patient and his or her level of risk, in general, patients should be screened annually at a minimum [86]. Several equivalent regimens are available for the treatment of LTBI and include the medications isoniazid, rifapentine, and rifampin used individually or in combination. Both the CDC and National Tuberculosis Controllers Association (NTCA) now recommend rifamycin-based treatment, which is shorter in course compared to the 6- or 9-month isoniazid monotherapy (6H and 9H). The three different short-course regimens include a 3-month period of once-weekly isoniazid plus rifapentine (3HP), a 4-month period of daily rifampin, and a 3-month period of daily isoniazid plus rifampin (3HR). The shorter-course treatments have been shown to be effective and safe as well as exhibit higher completion rates compared to the longer isoniazid-based regimens [87]. The longer 6H and 9H regimens have also been associated with higher risks of hepatotoxicity. Once LTBI is diagnosed and therapy is initiated, it is recommended to wait at least a month prior to starting immunosuppressive therapy for the patient with IBD [88].

Histoplasmosis and Coccidioidomycosis

Patients on TNF inhibitors are thought to be particularly susceptible to histoplasmosis and coccidiodomycosis because of TNF-α's role in the host's defense against fungal organisms [89]. While there are no clear screening recommendations for endemic mycoses prior to starting therapy, patients who have lived or are currently

living in endemic areas could be at risk. A high degree of suspicion is required when a patient from an endemic area participating in high-risk activities presents with consistent symptoms; a chest radiograph can be pursued to look for active or old disease, and certain serologic studies may prove valuable, such as a urine histoplasma antigen [90]. At this time, antifungal prophylaxis is not recommended for asymptomatic patients in endemic areas, but prompt therapy for suspected active infection in the context of an appropriate clinical presentation in an immunosuppressed individual is critical.

Hepatitis B

Immunosuppression poses a significant risk for reactivation of hepatitis B virus (HBV) and flare of HBV disease, leading in some cases to severe liver failure and death if left untreated [91]. A recent review from the Royal College of Physicians by Apostolos et al. [92] summarizes screening recommendations as well as appropriate antiviral prophylaxis if required. All patients starting immunosuppressive therapy should be tested for evidence of HBV infection with serologic testing, including HBV core antibody (anti-HBc) and HBV surface antigen and surface antibody (HBsAg and HBsAb). As a reminder, HBsAg is a marker of infection with anti-HBs representing either recovery from infection or immunity following vaccination. Anti-HBc is expected to be positive in acute (IgM) or chronic (IgG) infection and may be positive during viral reactivation. Patients with a positive HBsAg or anti-HBc should then have their HBV DNA measured as well as HBV e antigen and antibody (HBeAg and anti-HBe) to evaluate for a high replicative state and e antigen seroconversion, respectively. Serologic studies will help determine, along with the type of immunosuppressive therapy, the level of reactivation risk, with positive HBsAg conferring a higher risk [92]. Reactivation of HBV is eventually diagnosed by noting an increase in the HBV DNA level. Antiviral therapy is recommended for all patients with HBV reactivation, with first line being treatment with nucleos(t)ide therapy such as tenofovir and entecavir. Careful case-by-case review is recommended when there are questions regarding the necessity to interrupt immunosuppressive therapy once HBV reactivation is diagnosed. Patients deemed to be at moderate-to-severe risk of flare may need to temporarily hold or reduce therapy while being treated for HBV reactivation. A similar nucleos(t)ide regimen is recommended for prophylactic treatment for HBsAg-positive patients planning to start immunosuppressive therapy. Some patients may have a negative HBsAg but a positive anti-HBc suggestive of past exposure though lacking protective immunity. These individuals are, in theory, at risk for reactivation. Though the reactivation risk is relatively low for those patients when starting immunosuppressive therapy, many experts recommend antiviral prophylaxis, depending on the immunosuppressive regimen planned [90]. For patients with no evidence of past HBV infection or immunity, vaccination prior to initiation of immunosuppressive therapy is strongly recommended, as discussed below.

Strongyloides

Strongyloides infection, if left untreated, can be severe and, in the case of disseminated strongyloidiasis or hyperinfection syndrome, can be fatal [93]. Patients starting immunosuppressive therapy are at increased risk of infection, and screening for latent infection in endemic areas may be beneficial to prevent progression of disease. Though the gold standard diagnostic test for *Strongyloides* infection is serial stool examination, sensitivity is low in asymptomatic individuals, and serologic tests have become more widely available. Serologic tests have a high sensitivity but a low specificity as the tests can cross-react with other parasitic infections. If diagnosed, patients with chronic asymptomatic infections should receive prophylaxis to prevent disseminated disease, most often with ivermectin [60].

Vaccines

As discussed above, most treatments for IBD place the patient at increased risk of infection secondary to drug-induced immunosuppression. Several studies suggest that IBD itself increases the risk for various vaccine-preventable infections such as pneumococcal pneumonia, influenza, and hepatitis B, and immunosuppressive treatment exacerbates that risk [94]. It is important to note that immune dysregulation is present in IBD patients on immunosuppressive therapy as well as in treatment-naive patients. As such, these patients may have a diminished immune response to vaccinations compared to the general population [95]. Gastroenterologists are therefore strongly encouraged to discuss and, if able, provide vaccination during outpatient visits at IBD centers. Here, we review recommended vaccinations in patients with IBD as well as the notable contraindications. Due to the nature of the immunosuppressive drugs used in IBD, live vaccines can only be administered prior to initiating treatment.

Inactivated Vaccines

Inactivated vaccines contain viral or bacterial components that cannot replicate. As such, they are generally well tolerated and safe for patients with IBD who are on immunosuppressive therapy. There are also no contraindications for household members or other close contacts to receive such vaccines. Inactivated vaccines will typically produce a weaker immune response compared to live vaccines and will often require a booster administration.

Tetanus, Diphtheria, and Pertussis Vaccination

The recommendations for the DTaP vaccine are similar to the general population. The recommended timeline of administration starts between the age of 6 weeks and 6 years old with a series of five doses. This is followed at the age of 11 by a single booster of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) and then the tetanus and diphtheria toxoid booster (Td) every 10 years, as per the Advisory Committee on Immunization Practices (ACIP). There is currently inconclusive data regarding whether IBD patients' response to the vaccine is appropriate [96, 97].

Influenza

Patients with IBD are at increased risk for influenza infection, particularly when immunocompromised [98]. The vaccine is available as an inactivated intramuscular or intradermal form as well as a live intranasal form. As recommended by the ACIP, annual vaccination is recommended for all patients 6 months and older. Unfortunately, several studies have shown that patient with IBD tend to mount a weaker response to the influenza vaccine [95, 99]. A booster vaccination did not increase antibody concentrations. Although the inactivated form is safe to administer in patients with IBD on immunosuppressive therapy, it is recommended to vaccinate the patients prior to starting therapy. The live intranasal vaccine, on the other hand, should be avoided in immunosuppressed patients. Additionally, household and close contacts of immunosuppressed IBD patients should only receive the inactivated vaccine as well. If there is suspicion for contact with infected individuals, chemoprophylaxis with antivirals can be considered [100].

Streptococcus pneumoniae

IBD patients are at increased risk of pneumococcal pneumonia compared to the general population, with an even higher risk once started on immunosuppressive therapy [101, 102]. Per ACIP guidelines, the pneumococcal vaccine is recommended in patients with IBD with patients requiring both the 13-valent pneumococcal conjugate vaccine (PCV13) and the 23-valent pneumococcal polysaccharide vaccine (PPSV23). One dose of the PCV13 vaccine should be administered to all IBD patients followed by a dose of the PPSV23 at least 8 weeks later in immunosuppressed patients or at least 12 months in immunocompetent patients. A booster dose of PPSV23 should then be administered 5 years after the first dose as well as an additional dose after the age of 65 [103]. If an IBD patient was previously vaccinated with PPSV23, then PCV13 should follow at least 12 months after. Immunocompetent IBD patients appear to have an intact response to the PPSV23 vaccine, though response can be diminished when treated with immunosuppressive therapy [104].

Hepatitis A

Hepatitis A vaccine is recommended in all children aged 12–23 months as well as older children that have not received the vaccination. Adults at risk of hepatitis A are injection drug users, men who have sex with men, those with chronic liver disease, or anyone traveling to endemic regions. The vaccination series consists of two doses separated by a period of 6–18 months. An adequate response to the vaccine has been shown in IBD patients, though seroconversion rates were overall decreased in patients on immunosuppressive therapy [86, 105].

Hepatitis B

All patients with IBD should receive the hepatitis B vaccine series regardless of immune status. Several studies have shown that patients starting anti-TNF therapy are at risk of reactivation of hepatitis B infection with some reports of fatal cases [87, 88, 106]. It is therefore important to obtain hepatitis B antibody levels before initiation of anti-TNF or any other immune-suppressive therapy. The vaccination schedule in patients with IBD, regardless of their immune status, is the same as the general population as advised by ACIP guidelines. It consists of a series of three doses at 0, 1, and 6 months for the Engerix-B or Recombivax vaccines versus two doses 4 weeks apart for the newer Heplisav-B vaccine. Titers should ideally be checked 1–2 months after the final dose to confirm seroprotection. A titer of the hepatitis B surface antibody equal or greater than 10 mIU/mL is considered adequate for protection against the virus [93]. In the case that titer levels are found to be too low, patients may require a double dose of the vaccine series. Alternatively, a combination vaccine for both hepatitis A and B (such as Twinrix) may provide higher immunogenicity than the hepatitis B vaccine alone [103]. Several studies have looked at the efficacy of the hepatitis B vaccine in patients with IBD compared to a healthy population, with one showing significantly lower hepatitis B surface antibodies in patients with IBD [99]. A meta-analysis by Jiang et al. revealed that older age and immunosuppressive treatment were the two biggest determinants of a poor response to the vaccine [102]. The type of immune-suppressive regimen is also associated with the response, with infliximab showing a lower seroprotective response compared to other drugs like vedolizumab, which was not shown to significantly affect the response to the vaccine [86, 104].

Herpes Zoster

Regardless of immune status, patients with IBD are at an increased risk of developing herpes zoster infection compared to the general population [107]. Those on immune-suppressive therapy are at an even higher risk, with most of the manifestations being

limited to cutaneous findings, although some cases of disseminated zoster have been reported [108]. Until 2017, only a live attenuated vaccine for herpes zoster was available (Zostavax), which was not recommended for patients on immunosuppressive therapy. An inactivated adjuvanted recombinant vaccine (Shingrix) is now available and recommended for immunocompromised patients. It consists of two doses, to be given 8 weeks apart. As in the general population, the vaccine is recommended in adults aged 50 and older.

Human Papillomavirus

Female patients with IBD, particularly on immunosuppressive therapy, have been found to be at an increased risk of developing cervical dysplasia and are therefore strongly advised to undergo annual cervical cancer screening [109, 110]. In patients with CD, there is an additional risk for anal neoplasia, and patient should be appropriately monitored as well [111]. The recommendations for the HPV vaccine are the same in patients with IBD as the general population, regardless of immune status. The HPV vaccine (Gardasil or Cervarix) is recommended for both males and females between the ages of 11 and 26, though vaccination can be started at age 9, per the CDC. If given between the ages of 9 and 14, the patients receive two doses at 0 and 6 months. If started after the age of 15, then the patients receive three doses at 0, 2, and 6 months. No difference in immunogenicity was noted in patients on immunosuppressive therapy [112].

Meningococcal Disease

There is currently no evidence that patients with IBD are at increased risk for *Neisseria meningitidis* infection, which can lead to meningococcal meningitis. There are two available vaccines in the United States, the meningococcal conjugate or MenACWY vaccines (Menactra or Menveo) as well as the serogroup B meningococcal or MenB vaccines (Bexsero and Trumenba). The vaccine recommendations are the same as the general population per ACIP guidelines. Preteens aged 11–12 are advised to obtain the meningococcal conjugate vaccine with a booster at 16 years old. The conjugate vaccine is also recommended for high-risk patients such as asplenic individuals, patients with complement deficiencies, those living in close proximity (college dormitories or military housing), and those traveling to endemic areas. The serogroup B meningococcal vaccine is also recommended in those aged 10 years and older who are at increased risk [113].

Table 6.2 summarizes recommendations for inactivated vaccines in patients with IBD.

Table 6.2 Recommended inactivated vaccines in patients with IBD

Vaccine	Check titers before immunization	OK for immunosuppressed	Vaccination recommendations
Tetanus, diphtheria, and pertussis	No	Yes	All patients with IBD with a Td booster every 10 years, one-time dose of Tdap
Influenza	No	Only inactivated vaccine	Recommended yearly in all patients with IBD during flu season
Pneumococcal pneumonia	No	Yes	If no prior vaccination, one-time dose of PCV13 followed by PPSV23 after 8 weeks if immunocompromised or 12 months if immunocompetent; another dose after 5 years and at the age of 65 (with at least 5 years elapsed since the last dose). If one dose of PPSV23 was already received, wait at least 1 year before administering PCV13
Hepatitis A	No	Yes	2 doses separated by at least 6 months
Hepatitis B	Yes	Yes	3 doses at 0, 1, and 6 months. Recheck titers 1–2 months after final dose. If nonimmune, booster with double dose or combination hep A/B vaccine
Herpes zoster	No	Only inactivated (Shingrix)	2 doses 8 weeks apart in adults aged 50 years and older. Live vaccine *not* recommended
Human papillomavirus	No	Yes	Males and females. 2 doses at 0 and 6 months if given between ages 9 and 14; 3 doses at 0, 2, and 6 months if age >15
Meningococcal disease	No	Yes	Meningococcal conjugate vaccine in high-risk individuals or preteens aged 11–12 with booster at age 16. Serogroup B meningococcal vaccine in high-risk individuals over the age of 10
Typhoid fever	No	Only inactivated injectable vaccine	Recommended in patients 2 years and older at least 2 weeks before travel to endemic areas

Adapted from https://www.cdc.gov/vaccines/schedules/hcp/imz/adult.html

Live Vaccines

Live vaccines are developed using an attenuated form of the infectious organism and tend to induce a stronger and longer-lasting immune response. These are generally not recommended in patients with IBD who are immunosuppressed due to the risk of disseminated infection.

Measles, Mumps and Rubella (MMR)

The ACIP guidelines recommend the measles, mumps, and rubella vaccine series for the general population, which consists of an initial dose starting at the age of 12–15 months followed by a second dose between the ages of 4 and 6. If there is no documentation of prior vaccination, MMR titers should be tested during initial office visits. If patients are found to lack immunity to any of the three viruses, they can be vaccinated if they are not on any current immunosuppressive therapy or plan to start in the next 6 weeks. Immunosuppressive therapy in the past 3 months is a contraindication as well [103]. Nonimmune patients should receive two doses 4 weeks apart. Additionally, the MMR vaccine series is safe for all household contacts of immunocompromised patients.

Varicella

In the general population, the varicella vaccination series consists of two doses starting at the age of 12–15 months with a subsequent dose between 4 and 6 years old [114]. Similar to MMR, if there is no documented history of varicella zoster vaccination, titers should initially be obtained. In nonimmune adults not on immune-suppressive therapy, the two doses should be given 4–8 weeks apart [115]. For those planning on starting immune-suppressive therapy, the vaccine series should be given at least 4–6 weeks prior to starting therapy. Vaccination should be delayed for 3 months if immunosuppressive therapy is discontinued [116]. It is safe for household contacts to receive the vaccine series though in the case of a vaccine-related rash, the affected individual should avoid contact with the immunocompromised patient [114]. The varicella vaccination is particularly important in IBD patients. Several studies have shown that patients with IBD are at an increased risk of primary varicella infection, leading occasionally to severe and sometimes fatal cases [115, 117], with an even higher risk in immunocompromised patients [118].

Herpes Zoster

Compared to the general population, patients with IBD, particularly when immunocompromised, are at an increased risk of herpes zoster infection secondary to reactivation of the varicella zoster virus [107]. As discussed above, there is now an inactivated vaccine for herpes zoster that is the preferred regimen for patient on immune-suppressive therapy. The ACIP recommends routine zoster vaccination for patients over the age of 50 for the inactivated vaccine (Shingrix) as opposed to over the age of 60 for the live attenuated vaccine (Zostavax). This live attenuated vaccine is still available, and though it is contraindicated in patients on high-level immunosuppressive therapy, those on low-level immunosuppression can safely receive this live vaccine. Patients should not receive the live vaccine if they received high-level immunosuppressive therapy in the past 3 months or are planning to start in the next

Table 6.3 Recommended live vaccines in patients with IBD

Vaccine	Check titers before immunization	OK for immunosuppressed	Vaccination recommendations
MMR	Yes	No	2 doses given at age 12–15 months and 4–6 years old, or in immunocompetent adults at least 4 weeks apart. Wait 6 weeks prior to starting immunosuppressive therapy
Varicella	Yes	No	2 doses at age 12–15 months and 4–6 years old, or in immunocompetent adults at least 4–8 weeks apart. Wait 4–6 weeks prior to starting immunosuppressive therapy
Herpes zoster	No	Live vaccine OK on low-dose immunosuppression, contraindicated on high-dose Inactivated vaccine recommended and safe	Live vaccine recommended in immunocompetent patients over the age of 60, or inactivated vaccine in all patients over the age of 50
Yellow fever	No	No	Recommended in immunocompetent patients 9 months and older travelling to endemic regions of South America and Africa
Typhoid fever	No	No. inactivated vaccine recommended and safe	Live oral vaccine only in immunocompetent patients 6 years and older who are travelling to endemic areas, particularly Southeast Asia. One capsule taken every other day, a total of 4 capsules, last dose at least a week before travel

Adapted from https://www.cdc.gov/vaccines/schedules/hcp/imz/adult.html

6 weeks. For household contacts, the live vaccine is safe for administration, but like varicella, household members who develop a vaccine-related rash should avoid contact with the immunocompromised patient.

Table 6.3 summarizes recommendations for live vaccinations in patients with IBD.

Conclusions

Biologic agents targeting various inflammatory cytokines have emerged as a standard of care for managing IBD and have drastically improved quality of life in many patients. With the widespread use of these agents, however, comes the need for awareness of risks and mechanisms to prevent them, most notably a myriad of

infections. A general understanding of infectious risks is warranted, including the spectrum of organisms that have the potential to cause disease, the circumstances that predispose patients to, and protect them from such infections. Involvement of infectious diseases specialists during the planning phases, prior to initiating these highly effective, yet high-risk therapies, may result in comprehensive and longitudinal assessment and abatement of infectious risks.

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