The treatment of inflammatory bowel disease (IBD) has changed dramatically over the last decade. With increasing evidence that a “top-down” approach may alter the natural history of disease, a more aggressive treatment approach, including the use of combination immunomodulator and biologic therapy, is being advocated. Immuno-modulator therapy includes the use of azathioprine (AZA), 6-mercaptopurine (6-MP), and methotrexate (MTX). Biologic therapy includes the use of anti–tumor necrosis factor (TNF-α) agents, and more recently the use of a humanized monoclonal antibody against the cellular adhesion molecule α4 integrin.

With the increasing use of immunomodulator and biologic therapy in the treatment of IBD, it is vitally important that the safety profile of these agents be carefully reviewed, particularly in terms of infectious risks. Corticosteroids (CS), which have been a mainstay of IBD treatment for many years, have increasingly been shown to be a major risk factor for the development of infectious complications. A recent case-control study demonstrated that the use of CS, thiopurines (AZA/6-MP), and anti–TNF-α agents were each individually associated with a threefold increased risk of developing opportunistic infections and that the combination of these agents dramatically increased the risk.

It is with this backdrop that this article reviews the infectious risks of IBD therapeutic agents. Throughout this article, serious infections are defined as those that lead to prolonged hospitalizations, are fatal or life threatening, result in significant disability, or are opportunistic in nature. Opportunistic infections include viral infections (eg, cytomegalovirus, Epstein-Barr virus, herpes simplex virus, and varicella zoster); bacterial infections (tuberculosis [TB] and streptococcal); and fungal infections (histoplasmosis, aspergillosis, candidiasis, and blastomycosis).
The first section of this article assesses the risk of serious infections with IBD therapeutic medications and the second section focuses on specific infectious diseases and particular circumstances.

PHARMACOEPIDEMIOLOGY

There are several challenges in determining the infectious risk of any given therapy. Briefly, the determination of whether a particular adverse event is related to a specific treatment is difficult if the event in question occurs infrequently. Serious and opportunistic infections in patients with IBD fall into this category. In addition, in patients with IBD, the underlying disease process can complicate interpretation because the disease itself may increase the risk of developing an adverse event.

The strongest evidence that an adverse event is related to a particular therapy is best demonstrated through randomized controlled trials. These randomized controlled trials are not powered to assess adverse events, however, especially those that occur rarely or over a longer period of time. Large observational cohort data or registry data can help to detect infrequent events, but they are neither randomized nor controlled and can be subject to bias. Case-control studies are an effective tool to study the risk of adverse events, but the identification of proper controls can be difficult and time-consuming.

CORTICOSTEROIDS

Population-based studies have shown that 42% of patients with Crohn disease are on CS within the first 3 years of diagnosis, and that 39% to 56% are on CS at some point during the course of their disease. The absolute infectious risk of CS in IBD is difficult to quantify, but there is significant evidence that they increase the risk of infection.

A meta-analysis of 71 controlled trials assessed the association between CS and subsequent infections. The overall risk of infectious complications was 12.7% in the CS group and 8% in the controlled group (relative risk [RR], 1.6; 95% confidence interval [CI], 1.3–1.9). In those receiving CS, there was a significantly increased risk of death (RR, 2.6; 95% CI, 1.2–5.3). The risk of infections in the intestinal disease subgroup was lower but still significant (RR, 1.4; 95% CI, 1.1–1.7). The rate was not increased in those patients receiving less than 10 mg/day of prednisone or those who had a cumulative dose of less than 700 mg.

Increased risks of serious infection and mortality secondary to CS use were demonstrated specifically in patients with Crohn disease through the Crohn Therapy, Resource, Evaluation, and Assessment Tool (TREAT) registry. This registry was initially created to monitor the toxicity of therapy with infliximab, and is an ongoing, prospective, observational, multicenter registry of North American patients with Crohn disease. There are approximately 6000 patients in the registry, half of whom are on other therapies aside from infliximab. Analysis of the TREAT registry demonstrated that in multivariate logistical analysis, CS were associated with an increased mortality risk (odds ratio [OR], 2.10; 95% CI, 1.15–3.83). Out of the 2142 patients on CS, 2.85% developed serious infections compared with 1.09% of patients not on CS. Serious infection risk was independently associated with CS use (OR, 2.21; 95% CI, 1.46–3.34), but not with infliximab treatment. Although this estimate of increased risk seems quite robust, it is important to note that this registry had a dropout rate of 20%, and that the reporting of adverse events was based primarily on the review of gastroenterologists’ medical records, raising concerns about the completeness of safety data.

Several studies have characterized the risk of CS in specific clinical circumstances. The European Cooperative Crohn Disease Study demonstrated that 3 out of the 43
patients who presented with an abdominal (phlegmonous) mass and were treated with CS died from sepsis. A retrospective case-control study examined the effect of CS on intra-abdominal and pelvic abscess formation. Systemic CS therapy was associated with an increased rate of intra-abdominal and pelvic abscesses in patients with perforating disease (OR, 9.03; 95% CI, 2.40–33.98) and in patients with nonpenetrating disease (OR, 9.31; 95% CI, 1.03–83.91). There was a trend toward an increased rate of abscess formation in patients receiving more than 20 mg per day of prednisone (OR, 2.81; 95% CI, 0.99–7.99).

Combined, all of these findings demonstrate the increased infectious risk with CS use and support the recommendation that patients who require frequent CS to control their disease should be considered for steroid-sparing therapy with immunomodulators or biologic agents.

**Budesonide**

Budesonide, a highly potent 17-α substitute glucocorticoid with a reduced bioavailability caused by rapid first-pass hepatic metabolism, has been used in the induction of remission in patients with mild to moderate ileal or proximal colonic Crohn disease. A meta-analysis to assess the safety of budesonide in patients with Crohn disease showed that the CS-related adverse event profile, including infectious complications, was similar to that of placebo. Unfortunately, budesonide has a limited role in the treatment of Crohn disease because it is significantly less effective than conventional CS for inducing remission in patients with active inflammatory disease.

**IMMUNOMODULATOR THERAPY**

**AZA and 6-MP**

Immunomodulator therapy with thiopurine agents (AZA and 6-MP) has been shown to be effective in the induction and maintenance of remission in patients with Crohn disease and ulcerative colitis (UC). Although effective, they can cause multiple adverse events that can lead to drug discontinuation.

Treatment with AZA in patients with rheumatoid arthritis (RA) has been shown to increase the risk of serious infections. In a nested case-control study of a cohort of more than 23,000 patients between 1980 and 2003, AZA was associated with an increased risk of serious infections requiring hospitalizations (RR, 1.52; 95% CI, 1.18–1.97). This risk was less than that of patients receiving CS (RR, 2.56; 95% CI, 2.29–2.85).

In patients with IBD, the risk of infection associated with thiopurines is less clear. A meta-analysis of patients with Crohn disease treated with AZA and 6-MP found that adverse events requiring withdrawal from a trial were increased as compared with placebo (OR, 3.01; 95% CI, 1.30–6.96). The most common side effects were allergic reactions (2.3%); leukopenia (1.4%); and nausea (1.4%). In a recent review of 66 studies (8302 patients), the cumulative incidence rate of drug-induced myelotoxicity with AZA and 6-MP in 9103 years of patient follow-up was 7% (95% CI, 6%–8%). Leukopenia was not associated with drug dosage and occurred most frequently within the first year of treatment. The cumulative incidence of infections in patients with AZA and 6-MP–induced myelotoxicity was 6.5% (95% CI, 3.2–9.8).

Whether leukopenia is directly associated with infectious complications is somewhat unclear. Many infectious complications in patients on AZA and 6-MP can occur in the absence of leukopenia, and as such it is difficult to assess the rate of infection based on risk of leukopenia alone.
The rate of adverse events and infection may be higher in the “real-world” clinical setting when there is longer follow-up. In one study of 396 patients on 6-MP with 1800 patient-years of follow-up, the adverse event rate was reported to be as high as 15%. In this same study, the reported incidence of infection was found to be 7.4% and the incidence of serious infection to be 1.8%. In another study, 410 patients with IBD treated with 6-MP were assessed from 1980 to 1999. Fifty-eight (14.1%) patients experienced an infection while on 6-MP. Pneumonia was seen in 16 patients (3.9%), which is similar to the normal population (1.2%–5%). Herpes zoster was seen in 12 patients (2.9%) and occurred at a mean of 32.5 months (range, 0.6–226 months) after initiation of treatment. Upper respiratory infections were seen in 29 patients (7.1% of patients).

In the two retrospective studies just mentioned, the risk of infection may be increased, but this is difficult to confirm because there was no specific control group. Data from the TREAT registry showed that in multivariate analysis, the use of immunomodulator therapy did not play a role in the development of serious infections. The limitation of this database analysis is that it does not take into account likely contributing risk factors, such as the duration of use or cumulative exposure to a particular agent.

In the previously described study by Agrawal and colleagues, which assessed the risk of abdominal abscess in patients with Crohn disease, there was no increased risk of infection in those treated with AZA. Another study assessed the risk of developing benign infections in 230 IBD patients receiving AZA. The incidence of benign viral upper respiratory tract infections (compared with controls) was 2.1 ± 2.2 per observation year and there was no increased risk in patients on AZA (P = 0.77). There was an increased incidence of benign oral and genital herpes simplex virus flares in patients on AZA (1 ± 2.6 vs 0.2 ± 0.8 per year; P = 0.04), however, and an increased rate of worsening viral warts (human papillomavirus [HPV]) (17.2% vs 3.3%; P = 0.004).

Together, these studies suggest that the risk of infectious complications with AZA and 6-MP in patients with IBD may be limited to mild infections in most cases.

**MTX**

MTX is a folate antimetabolite that inhibits DNA synthesis and has been shown to be effective in the induction and maintenance of remission in two separate trials in patients with Crohn disease. Although these trials were not powered to assess safety, of the 134 patients who received intramuscular and oral MTX, there was only one infectious complication reported (mycoplasma pneumonia). In one study of 54 patients with Crohn disease that compared 6 months of treatment with AZA with MTX (intramuscular followed by oral), no serious infectious complications were identified. Another study involving 49 Crohn disease patients who received MTX (intramuscular) for a median duration of 18 months (range, 7–59 months) showed that although adverse reactions occurred in 24 patients (49%) and five patients (10%) withdrew from the study, no infections complications were identified. A retrospective study of 39 Crohn disease patients receiving intramuscular followed by oral MTX, however, showed that 10 (26%) patients developed infections and 2 (5%) withdrew secondary to infectious compilations. In this study population, however, more than 50% were taking concomitant CS, which could certainly confound the risk of infectious complications.

The safety experience with MTX in the RA literature is vast and lessons can be drawn from this literature. In the previously described nested case-control study of more than 23,000 RA patients, MTX treatment was associated with a modestly increased risk of pneumonia (RR, 1.6; 95% CI, 1.02–1.33), but not with serious
infections requiring hospitalizations. An extensive review of the infectious complications of MTX in RA concluded that MTX was associated with a minimal increased risk of infections, and that treatment was likely not associated with an increased risk of opportunistic or serious infections. In RA registry data including almost 8000 patients, although there was a slightly increased risk of developing an infection compared with patients not on biologic or MTX therapy (RR, 1.3; 95% CI, 1.12–1.50), there was no increased risk of developing opportunistic infections. This latter finding was in contrast to patients on CS (>10 mg/day) who did have an increased risk of opportunistic infections (RR, 1.30; 95% CI, 1.11–1.53).

Overall, the data from the RA and Crohn disease literature demonstrate that treatment with MTX in patients with Crohn disease is likely safe from an infectious point of view, and does not increase the risk of serious or opportunistic infections. The use of MTX can be associated with liver and lung toxicity. Although MTX may be relatively safe to use in patients with CD, thiopurines have been used preferentially because they have been more extensively studied.

**ANTI–TNF-α THERAPY**

At present there are three different anti–TNF-α agents approved for the treatment of Crohn disease: (1) infliximab (Remicade, Centocor, Horsham, Pennsylvania); (2) adalimumab (Humira, Abbott Laboratories, North Chicago, Illinois); and (3) certolizumab pegol (Cimzia, UCB, Smyrna, Georgia). Infliximab is the only anti–TNF-α agent approved for use in the treatment of UC. There has been increasing use of these agents over the last decade, and multiple studies have examined the risk of infectious complications. There is definite evidence that anti–TNF-α agents are associated with an increased rate of serious infections in patients with RA. A meta-analysis of nine placebo-controlled trials of infliximab and adalimumab in RA involving over 5000 patients yielded a pooled OR for serious infection of 2.01 (95% CI, 1.31–3.09).

In terms of patients with IBD, the association between anti–TNF therapy and serious infection is not as clear and may relate to the fact that the patients with IBD are generally younger and have less comorbid disease, compared with patients with RA. Individual randomized trials in Crohn disease have not demonstrated an elevated risk of serious infection. In a recently published meta-analysis, 21 trials with a total of 5356 patients were reviewed to assess the safety of anti–TNF-α agents. There were 3341 patients in the anti–TNF-α group and 2015 patients in the control group, with a median follow-up of 24 weeks (range, 4–60 weeks). There was no significant difference in the risk of serious infection in the anti–TNF group versus the control group (2.09% versus 2.13%, respectively; 95% CI, 0.45–0.65). In subgroup analysis, there were no differences in infectious risk between anti–TNF-α and control groups whether they were induction or maintenance trials.

Data from the TREAT registry assessed the infectious complications of IBD therapeutic medications. The risk of serious infection 3 months after an infliximab infusion was compared with the risk of infection 3 months before an infusion. In univariate analysis, serious infections were more than twice as likely to occur in the 3 months after an infliximab infusion (OR, 2.15; 95 CI, 1.44–3.21). After controlling for other factors, however, such as disease duration and severity, concurrent use of CS, immunomodulators, and narcotic analgesics, the association between infliximab and serious infection was no longer significant (OR, 0.99; 95% CI, 0.64–1.53). An update of the TREAT registry, now with 24,575 patient years of follow-up, was recently presented in abstract form. Infliximab-treated patients had an increased risk of serious infections (RR, 1.57; 95%
CI, 1.16–2.14); however, multivariate analysis again suggested that this increased risk was independently associated with prednisone and not infliximab.

Several retrospective referral-center–based studies have assessed the risk of anti–TNF-α agents in patients with IBD. In one study, among the first 500 Crohn disease patients treated with infliximab at Mayo Clinic, serious infections occurred in 20 (4%), including four deaths caused by infection (0.8%). In a study of 202 patients with UC and Crohn disease who had a median follow-up of 2.4 years (range, 1–4.9; 620 patient-years), 42 patients (20.8%) experienced an infectious event including 22 patients (10.9%) with a serious infection. The safety of more than 3000 patients treated with adalimumab in clinical trials was recently assessed. The incidence of opportunistic infections was 1.8%, with oral candidiasis being the most commonly reported infection (1.2%). Serious infections were seen 5.8% of patients (incidence rate of 6.6 cases per 100 person-years) but almost half of those were intra-abdominal (2.5%). It is important to note that these three studies had no control group and did not take into account concomitant medications and so direct causality cannot be established.

More recently, in a single-center experience from Leuven, Belgium, the long-term safety of anti–TNF-α agents was assessed in 1400 patients with Crohn disease (of whom 734 received infliximab). Patients who received anti-TNF therapy were followed for a median of 58 months (interquartile ratio, 33–88 months). The percentage of patients who developed serious infections was 6% in the infliximab group and 9% in the control group. The incidence rate of serious infections in the two groups was not significantly different (1.6 per 100 patient-years in infliximab group versus 1.1 per 100 patient-years in control group).

Two population-based studies have reported on the safety of infliximab. The first, a population-based cohort from Stockholm County, examined 217 patients who received infliximab between 1999 and 2001. Eighteen patients (8.3%) developed severe infectious complications (seven were postoperative) and there were two deaths related to infection (both on CS, none on AZA and 6MP). In this cohort, 51% of the patients were on concomitant immunomodulators, 54% were being treated with CS, and 25% were on both immunomodulators and CS. Given that both of these agents increase infectious risk, the exact role of infliximab with regards to infection can not be determined from this study. The second population-based cohort examined the association between infliximab and other immunosuppressive agents in a cohort of 10,662 IBD patients in British Columbia, Canada. In patients receiving infliximab, the event rate of serious bacterial infection was 4.28 per 1000 patient-years (95% CI, 0.11–23.8) but this was not significantly increased compared with patients receiving CS or immunomodulators.

The risk of infectious complications with anti–TNF-α monotherapy in patients with Crohn disease does not seem to be increased in terms of overall infections. These studies may not be large enough, however, to detect rarer opportunistic infections (see later sections on TB and fungal infections). In a referral center–based case-control study of risk factors for opportunistic infections in patients with IBD, infliximab was associated with a fourfold increased risk of opportunistic infection (OR, 4.4; 95% CI, 1.2–17.1).

**COMBINATION THERAPY**

A recent randomized controlled trial published in abstract form demonstrated that in patients with moderate to severe Crohn disease, combination therapy with AZA and infliximab was superior in achieving clinical and endoscopic remission compared with either drug alone. Other studies have shown that the combination therapy reduces the immunogenicity of anti–TNF-α agents, especially when the latter are
administered episodically.\textsuperscript{45,46} Although combination therapy with biologic therapy and concomitant immunomodulators may be more effective, this increased efficacy may come at the cost of increased infectious complications.

A randomized trial of infliximab with concomitant MTX in more than 1000 RA patients was designed specifically to assess safety end points.\textsuperscript{47} Patients in the study were randomized to placebo infusion to week 22, then 3 mg/kg every 8 weeks to week 54; 3 mg/kg infliximab infusions to week 22 with escalation by 1.5 mg/kg as needed to control symptoms; and lastly to 10 mg/kg infliximab infusions for the length of the study. There was greater than a threefold increased risk of serious infections in the 10 mg/kg group at week 22 compared with those patients who received MTX alone ($P = 0.013$), but not in those who received 3 mg/kg on infliximab.

In patients with IBD, the evidence of increased risk with concomitant therapy is unclear. In one study, data from four prospective randomized phase 3 trials in IBD patients were used to assess the efficacy of concomitant immunomodulators with infliximab.\textsuperscript{46} In the pooled safety analysis of 1007 infliximab-treated patients, similar proportions of patients with and without combination therapy had infections (44.1% and 44.5) or serious infections (3.7% and 3.2%). In the earlier referenced population-based study out of British Columbia, an increased risk of serious infections was not found in patients receiving concomitant therapy with infliximab and an immunomodulator.\textsuperscript{43} In the study by Fidder and colleagues,\textsuperscript{41} only the concomitant use of steroids (and not immunomodulators) was associated with an increased risk of serious infection (OR, 2.7; 95% CI, 1.2–6.1). Throwing caution to these results, the case-control study by Toruner and colleagues\textsuperscript{4} demonstrated the OR for opportunistic infections in patients on two or more immunosuppressive medications simultaneously was 14.5 (95% CI, 4.9–43) and was “infinite” in patients with three immunosuppressive medications (CS, immunomodulators, and anti–TNF-\textgreek{a} agent). Further examination of this study suggests, however, that much of the increased risk was driven by the use of CS.

Although concomitant therapy may increase the risk of infection, it seems that it is the use of that CS plays the largest role in the development of serious or opportunistic infections.

**CYCLOSPORINE**

The use of cyclosporine in IBD is at present limited to rescue therapy for patients with fulminant UC. There are limited data on the safety of cyclosporine in this setting, and underlying disease severity complicates the assessment of safety.

In patients receiving cyclosporine for the prevention of liver allograft rejection, therapy was associated with a risk of infection of approximately 40%, sepsis in 20%, and cytomegalovirus in 15% to 25%.\textsuperscript{48} A study assessing the long-term outcome of treatment with intravenous cyclosporine in patients with severe UC demonstrated that in 86 patients treated with cyclosporine between 1992 and 2000, five (5.8%) patients had opportunistic infections, and three patients (3.5%) died (one from \textit{Pneumocystis jiroveci (carinii)} pneumonia [PCP] and two from \textit{Aspergillus} pneumonia).\textsuperscript{49} In addition, there were catheter-related infections in eight patients (9.3%). In a separate retrospective study, 19 patients with CS-refractory UC who received cyclosporine after infliximab or infliximab after cyclosporine were assessed.\textsuperscript{50} In total, three patients (15.8%) developed severe complications and one patient died (gram-negative bacterial sepsis with death, herpetic esophagitis, and pancreatitis with \textit{Enterococcus} and \textit{Klebsiella} bacteremia). Overall, these limited
data suggest that treatment with cyclosporine leads to an increased risk of serious infections.

**NATALIZUMAB**

Natalizumab (Tysabri, Biogen Idec, Cambridge, Massachusetts, and Elan Pharmaceuticals, South San Francisco, California), a humanized IgG4 monoclonal antibody against \( \alpha_4 \) integrin–mediated leukocyte migration, was approved by the FDA in 2008 for use in patients with Crohn disease with evidence of active inflammation who have had an inadequate response to or cannot tolerate anti–TNF therapy.\(^{51} \) In the ENACT-1 and ENACT-2 trials of natalizumab in Crohn disease, subjects in the treatment arm had a significantly increased risk of developing influenza or an influenza-like illness (12% vs 5%; \( P < .05 \)).\(^{52} \) One case of varicella pneumonia and cytomegalovirus hepatitis was also reported in the natalizumab group. In two earlier trials with natalizumab in Crohn disease and in one smaller trial in patients with UC, an increased risk of serious infections was not found.\(^{53–55} \)

After publication of the ENACT trials, a fatal case of JC virus–induced progressive multifocal leukoencephalopathy was reported in one patient who had been enrolled in this trial.\(^{56} \) Two further cases were identified in patients receiving natalizumab for multiple sclerosis, and the drug was withdrawn temporarily from commercial use.\(^{57,58} \) Natalizumab was reintroduced under restrictive rules prohibiting concurrent therapy with an immunomodulator or long-term CS therapy. Since being reintroduced to the market, of the 52,000 patients who have taken the drug, there are, as of early June 2009, six additional cases of progressive multifocal leukoencephalopathy (four cases occurred in patients not on any concurrent therapy) resulting in an incidence of approximately 1.2 cases per 10,000 patients treated.\(^{59} \)

**POSTOPERATIVE COMPLICATIONS**

Several studies have examined the risk of preoperative CS in patients undergoing abdominal surgery. A recent meta-analysis of five observational studies involving 1714 patients assessed the risk of postsurgical infectious complications.\(^{60} \) Pooled analysis showed an increased risk of postoperative infectious complications in patients on CS (OR, 1.68; 95% CI, 1.24–2.28), with an increased risk in patients on higher perioperative oral CS (>40 mg) (OR, 2.04; 95% CI, 1.28–3.26).

A retrospective cohort study that was included in this meta-analysis assessed 159 postoperative IBD patients and assessed the risk of infectious complications with AZA and 6-MP.\(^{61} \) Both univariate and multivariate analysis failed to demonstrate an increased risk of postsurgical complications in patients receiving AZA and 6-MP. In addition, studies assessing postoperative complications in 270 patients with Crohn disease and 151 patients with UC did not demonstrate an increased risk of postoperative complications in patients taking AZA, 6-MP, and MTX.\(^{52,63} \)

In terms of anti–TNF-\( \alpha \) medications, a retrospective cohort study of 141 UC patients compared preoperative infliximab exposure with those not previously exposed.\(^{64} \) The use of infliximab did not play a role in the development of postoperative complications but a moderate to high dose of CS (\( \geq 20 \) mg methylprednisone for \( \geq 2 \) months) was associated with an increased risk of short-term postoperative complications (OR, 5.19; 95% CI, 2.12–19.64; \( P = .001 \)). In addition, four other studies have failed to show an increase in postoperative infectious complications in patients treated with anti–TNF agents preoperatively.\(^{62,65–67} \) One of these studies assessed a total of 413 patients with both UC and Crohn disease undergoing abdominal surgery. One hundred twenty-one (24.5%) received preoperative infliximab and no increased risk
of infectious complication was identified compared with patients who had not received prior infliximab.65

Three separate studies, however, have demonstrated an increased risk of infection in patients with UC who were exposed to infliximab preoperatively. One small study, which assessed 47 postoperative UC patients, suggested that anti-TNF agents may increase infectious complications (adjusted OR, 2.7; 95% CI, 1.1–6.7).68 Another retrospective case-control study assessed 523 patients who underwent restorative proctocolectomy and found that preoperative infliximab use was associated with an increased risk of early complications (adjusted OR, 3.5; 95% CI, 1.51–8.31) and sepsis (adjusted OR, 13.8; 95% CI, 1.82–105).69 In a recently published abstract of a retrospective study of 436 patients who underwent ileal pouch–anal anastomosis (IPAA), infliximab use (within 12 weeks of surgery) was associated with a significant increase in early (<30 days) infectious complications (adjusted OR, 2.5; 95% CI, 1–6.1), but not overall early or late complications.70 In addition, these studies demonstrated that in patients on infliximab, a two-stage IPAA (proctocolectomy with formation of IPAA and protecting loop ileostomy, followed by ileostomy closure) resulted in increased infectious complications compared with those who underwent a three-stage IPAA (subtotal colectomy with Hartmann pouch and end ileostomy, followed by completion proctectomy and formation of IPAA with protecting loop ileostomy, followed by ileostomy closure).69,70

Given the conflicting results of these studies, the postoperative infectious risk of prior anti–TNF-α treatment remains unclear and further studies are needed to clarify the risk of these agents.

Overall, it seems that CS increases the risk of postoperative infectious complications and should generally be tapered to the lowest possible dose before surgery. Immunomodulators do not seem to confer an increased risk in the postoperative setting and can be continued perioperatively. Preoperative infliximab use may independently increase the risk of early infectious complications in patients with UC (no evidence in Crohn disease), and these patients should be considered for a three-stage IPAA rather than a two-stage surgical procedure.

BACTERIAL INFECTIONS

Tuberculosis

CS seems to play a role in the development of active TB. A retrospective study using the General Practice Research Database from the United Kingdom assessed 16,213 IBD patients and 66,512 controls for the development of active TB.71 The annual incidence of active TB was 20 cases per 100,000 person-years in IBD patients and 9 per 100,000 in control subjects, leading to an unadjusted relative risk for active TB of 2.36 (95% CI, 1.17–4.74). Exposure to CS was found to be a significant independent risk factor for active TB. In this study, no increased risk was found in patients on immunomodulatory medications.

The risk of reactivation of TB is significantly elevated in patients receiving anti–TNF-α medications. Mycobacteria (and other granulomatous infections) are sequestered within granulomas, and because TNF-α is required for the continued maintenance of granuloma structure, it is thought that anti–TNF-α agents may predispose to TB reactivation.72

A Spanish safety registry of over 1500 patients treated with anti–TNF-α drugs noted a TB incidence rate approximately 50 to 90 times higher than expected in the general Spanish population.75 A Swedish study of RA patients showed that those on anti–TNF-α agents were four times more likely than those not on anti–TNF-α agents to
develop TB.74 A United States study including more than 10,000 RA patients demonstrated an eightfold elevation in TB risk among infliximab-treated patients.75 

In 70 cases reported by the Food and Drug Administration (FDA) among 147,000 patients treated with infliximab (both IBD and RA), most cases of TB were extrapulmonary, and 24% presented with disseminated disease.76 Most of these cases occurred within 2 to 4 months of starting therapy in regions with a low prevalence of TB, and in patients with a limited recent exposure to TB. These findings suggest that these patients had reactivation of latent infection rather than newly acquired infection. In patients who have developed active TB while on anti–TNF-\(\alpha\) therapy, mortality has been reported to be as high as 13%.77 

This increased risk of TB is now incorporated into the black-box warning section on the prescribing information for all commercially available anti–TNF-\(\alpha\) agents. Recommendations indicate that latent TB should be assessed with a tuberculin skin test and chest radiograph before initiating anti–TNF-\(\alpha\) treatment.15 There are no prospective data on when anti-TNF therapy can be safely started (or restarted) once TB treatment is initiated. Patients with latent TB should ideally receive chemoprophylaxis with isoniazid for 9 months before anti-TNF therapy and should be supervised by a thoracic or infectious disease physician.78 At the minimum, if anti-TNF therapy needs to be started, patients should be receiving at least 1 to 2 months of TB treatment.15,72,79,80

**Other Granulomatous Infections**

*Listeria monocytogenes* has been described in patients receiving anti–TNF-\(\alpha\) therapy. The FDA reported 38 cases of *Listeria* infections in patients receiving anti-TNF therapy from 1998 to 2002 (15.5 cases [versus 1.8 expected] per 100,000 patients).81 *Listeria* infections of the bloodstream and central nervous system usually occurred in patients who were on concomitant immunosuppression.82–84 Other granulomatous infections, such as nocardiosis and nontuberculous mycobacteria, have also been reported in patients on anti-TNF agents.81,85

**Clostridium Difficile**

In the population-based study by Schneeweiss and colleagues43 the incidence of *Clostridium difficile* was 14 cases per 1000 person-years (95% CI, 10.6–18.2) in patients on CS. This risk of infection was triple that of other immunosuppressive agents (RR, 3.4; 95% CI, 1.9–6.1). Anti–TNF-\(\alpha\) therapy did not seem to increase the risk of *C difficile* infection. There are no prospective data on the use of immunomodulators or biologics in the setting of active *C difficile* infection. Given the association between immunomodulators and *C difficile* infection, the risk/benefit of continuing these medications should be carefully considered, especially in the setting of recurrent-resistant infections.78

**Fungal Infections**

**PCP**

Several case series and reports of IBD patients developing PCP after being treated with AZA and 6-MP have been published.86–88 PCP has also been reported in patients receiving cyclosporine for severe UC49,89,90 and in patients receiving anti–TNF-\(\alpha\) agents for Crohn disease or RA.42,86,91–93 A review of the FDA Adverse Event Reporting System found 84 cases of infliximab-associated PCP between 1998 and 2003 and 23 deaths (27%).86 In a case-control study, older age, pulmonary disease, and high doses of CS were risk factors for the development of PCP in patients taking anti–TNF-\(\alpha\) agents.94
Granulomatous Fungal Infections

Histoplasmosis and coccidioidomycosis infections have been reported in patients on anti–TNF-\(\alpha\) therapy.\(^9\) In 2008, the FDA issued a black-box warning with regards to the risk of pulmonary and disseminated fungal granulomatous infections (including blastomycosis) in patients who are being treated with anti–TNF-\(\alpha\) agents.\(^9\) This warning stems from the fact that as of September 2008, 240 cases of anti–TNF-\(\alpha\) associated histoplasmosis were reported (17 cases per 100,000 patients in infliximab-treated groups), whereas the number of cases from the late 1990s through July 2001 was only 10.\(^9\)

Among cases of anti–TNF-\(\alpha\) associated histoplasmosis in the United States, most patients had resided in areas endemic for the infection (Ohio and Mississippi River valleys), and virtually all were receiving other immunosuppressive agents.\(^9\) Similarly, symptomatic coccidioidomycosis following anti–TNF-\(\alpha\) therapy has been reported in the endemic areas of Arizona, California, and Nevada, and virtually all patients were on concomitant immunosuppression.\(^9\)

Other Fungal Infections

The FDA Adverse Event Reporting System listed 11 Cryptococcus neoformans infections in patents receiving infliximab therapy from 1998 to 2002 (4.7 per 100,000 patients).\(^8\) Most reports indicate that patients were on concomitant medications. In the same database, aspergillosis was reported in 39 patients on infliximab therapy (12.4 per 100,000 patients).\(^8\) There have been reports of invasive pulmonary aspergillosis, systemic candidiasis, and disseminated sporotrichosis in patients receiving anti–TNF-\(\alpha\) therapy.\(^9\)–\(^12\)

VIRAL INFECTIONS

Hepatitis B and C

The impact of CS, immunomodulators, or anti–TNF-\(\alpha\) therapy on the course of hepatitis B virus (HBV) infection or hepatitis C virus (HCV) infection has not been studied prospectively.\(^7\) Recently published guidelines suggest that all IBD patients should be tested for HBV infection and that vaccination should be recommended to all patients who are seronegative.\(^7\) Immunomodulator and anti–TNF-\(\alpha\) therapy may negatively affect the efficacy of vaccination and higher doses of HBV vaccine may be required to achieve immunity. In addition, serologic response should be measured after vaccination. There are case reports of patients with stable HBV infection who have had reactivation (both asymptomatic and severe) during treatment with infliximab.\(^10\)–\(^11\) Of note, reactivation of HBV is more commonly seen in patients on chemotherapeutic regimens containing CS who are being treated for lymphoma.\(^10\) Data from patients being treated with immunosuppressive chemotherapy have shown that HBV replication and reactivation can occur in up to 20% to 50% of cases.\(^11\) Patients with chronic HBV (HBsAg\(^+\)) should receive prophylaxis with antiviral agents (nucleoside–nucleotide analogues) to avoid a HBV flare of disease.\(^7\) Immunomodulator and anti–TNF-\(\alpha\) therapy should be delayed in patients with acute HBV infections.

There is no consensus with regards to HCV screening before starting immunomodulator or anti–TNF-\(\alpha\) therapy in patients with IBD.\(^7\) There are no data to suggest that treatment with any IBD therapeutic medication increases the risk of developing HCV or exacerbates existing HCV infection.\(^7\)
There are no data to suggest a role for CS, immunomodulator, or anti–TNF-α therapy in the development or progression of HIV infection in patients with IBD. Several case reports and small studies have shown no detrimental effects when using anti–TNF-α therapy in patients with established HIV.

**Human Papillomavirus**

There is an increased incidence of HPV-associated warts or condylomata in patients receiving immunomodulator therapy. Current or previous infection with HPV is not a contraindication to patients receiving immunomodulator or biologic therapy. Routine prophylactic immunization has been recommended in all females greater that 11 years of age and vaccination is most effective before onset of sexual activity. There are no specific guidelines for the use of HPV vaccine in patients with IBD, but it is a nonlive vaccine and can safely be used in female patients on immunomodulator or anti–TNF-α therapy.

**Other Viral Infections**

Viral infections, including herpes simplex virus, primary varicella infection, herpes zoster, Epstein-Barr virus, and cytomegalovirus, have been reported following CS, immunomodulatory, or anti–TNF-α therapy in both Crohn disease and RA. In cases of disseminated cytomegalovirus or varicella, these infections have been life-threatening. In a small prospective study of RA patients who were tested serially for viral loads for cytomegalovirus, Epstein-Barr virus, and human herpesvirus-6, infliximab did not result in reactivation.

**RECOMMENDED VACCINATIONS**

In addition to the vaccinations recommended to the general population, recently published European guidelines suggest that patients with IBD should be considered for five additional vaccines. Vaccinations for HBV-seronegative patients and HPV in young women have been discussed previously. In addition, vaccinations should be considered for influenza, pneumococcus, and varicella (specifically in those who are seronegative). Given the potential for decreased seroconversion in immunosuppressed patients, vaccination should be considered before therapy is instituted (at diagnosis) and patients on immunomodulatory-biologic agents should only receive inactivated vaccines.

**REFERENCES**


