

Clinical use of anti-TNF therapy and increased risk of infections

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Abstract: Biologics such as antitumor necrosis factor (anti-TNF) drugs have emerged as important agents in the treatment of many chronic inflammatory diseases, especially in cases refractory to conventional treatment modalities. However, opportunistic infections have become a major safety concern in patients on anti-TNF therapy, and physicians who utilize these agents must understand the increased risks of infection. A literature review of the published data on the risk of bacterial, viral, fungal, and parasitic infections associated with anti-TNF therapy was performed and the clinical presentation, diagnostic tests, management, and prevention of opportunistic infections in patients receiving anti-TNF therapy were reviewed. Awareness of the therapeutic potential and associated adverse events is necessary for maximizing therapeutic benefits while minimizing adverse effects from anti-TNF treatments. Patients should be adequately vaccinated when possible and closely monitored for early signs of infection. When serious infections occur, withdrawal of anti-TNF therapy may be necessary until the infection has been identified and properly treated.

Keywords: anti-TNF therapy, infections

Introduction

Tumor necrosis factor- α (TNF- α) is a 26 kDa homotrimeric transmembrane protein that is expressed on the surface of macrophages, T-lymphocytes, natural killer cells, smooth muscle cells, and fibroblasts.¹ TNF- α is an important proinflammatory cytokine and has been implicated in the pathogenesis of many inflammatory and autoimmune diseases including rheumatoid arthritis,² inflammatory bowel disease (IBD), and ankylosing spondylitis.³ The reduction of TNF- α levels by anti-TNF agents leads to reduced chronic pathologic inflammatory responses in these diseases.³ Currently available anti-TNF agents and their approved indications are listed in Table 1.

One of the major risks of using anti-TNF therapy is the small but significant risk of serious opportunistic infection.⁴⁻⁶ Opportunistic infection is defined as a usually serious and progressive infection by an organism that, under normal circumstances, possesses little or no pathologic capabilities. However, predisposing factors such as underlying disease or medical treatment can reduce a patient's immunity, permitting the organism to cause an infectious disease.⁷ Several risk factors place patients at higher risk for an opportunistic infection. Increased age leads to decreased innate immune function⁸ and increased risk of opportunistic infections.⁹ Malnutrition and micronutrient deficiency, which are common in patients with chronic disease, is associated with diminished immune function and increased risk of opportunistic infection.¹⁰ Exposure to opportunistic pathogens is also increased by living or traveling

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Table 1 Currently available anti-TNF agents, their mechanism of action, and approved indications

Drug name	Mechanism of action	Approved indications
Infliximab (Remicade; Centocor, Inc, Malvern, PA)	Chimeric mouse Fv1 human IgG1 TNF- α monoclonal antibody ^{4,175}	RA, PA, AS, UC, and CD ^{84,176}
Adalimumab (Humira; Abbott Laboratories, Abbott Park, IL)	Fully human recombinant IgG1 TNF- α monoclonal antibody	RA, PA, AS, UC and CD ⁴
Etanercept (Enbrel; Amgen, Thousand Oaks, CA)	Bivalent human TNFR2 receptor fused to the Fc portion of human IgG1 ¹⁷⁷	RA, P, PA, and AS ⁴
Certolizumab pegol (Cimzia; UCB, Belgium)	Fab' humanized fragment of an anti-TNF antibody attached to a polyethylene glycol moiety (PEGylated) ¹⁷⁷	RA and CD ¹⁷⁷
Golimumab (Simponi; Janssen Biotech, Inc, Horsham, PA)	Fully human IgG1 human TNF- α monoclonal antibody	RA, PA, and AS ¹⁷⁸

Abbreviations: RA, rheumatoid arthritis; PA, psoriatic arthritis; P, psoriasis; AS, ankylosing spondylitis; UC, ulcerative colitis; CD, Crohn's disease.

in endemic areas, through occupational exposure, or through contaminated food and water. Comorbid diseases, such as diabetes mellitus or alcoholism, also increase the risk of opportunistic infections.¹¹ Immunomodulatory therapy (eg, corticosteroids, methotrexate, azathioprine) and biologic therapy (eg, anti-TNF agents, other monoclonal antibodies), especially when used in combination, are associated with an increased risk of opportunistic infection.^{5,9} It must be noted, however, that the risk of opportunistic infection with combination therapy is low and each case should be evaluated to assess the risks and benefits of treatment options on disease activity.

Mechanism of immune deficiency

There are several proposed mechanisms of immune deficiency in patients receiving anti-TNF therapy. TNF- α is essential for the formation and maintenance of granulomas,^{5,6} therefore its inhibition can lead to increased risk of new tuberculosis infection, reactivation of latent tuberculosis, and can predispose to other granulomatous infections, such as *Histoplasma capsulatum*.¹² TNF- α plays a role in macrophage activation and differentiation and phagosome formation, and is critical for the clearance of intracellular pathogens (eg, *Listeria*, *Legionella*, *Salmonella*).⁵ Neutropenia can occur after anti-TNF administration, predisposing to opportunistic infections such as *Candida* or *Aspergillus*.⁹ TNF- α is also important for immune responses against viral pathogens, and its inhibition could cause complications in patients infected with hepatitis B virus (HBV)¹³ or varicella zoster virus (VZV),¹⁴ for example.

Bacterial infections

Anti-TNF therapy is associated with an increased risk of bacterial infections. Some common bacterial infections associated with the use of anti-TNF therapy are described below and summarized in Tables 2 and 3.

Mycobacterium tuberculosis

The problem of tuberculosis (TB), caused by *M. tuberculosis*, has been increasing with the development of both multidrug-resistant and extensively drug-resistant organisms. The incidence of TB in the US population is reported to be 3.4 cases per 100,000.¹⁵ Reactivation of granulomatous infections is a serious complication in patients taking anti-TNF therapy. The relative risk for TB increases 1.6–25 times with anti-TNF therapy depending on the clinical context, the drug used, and the patient's country of origin.¹⁶ Pulmonary TB usually manifests as cough, weight loss, fatigue, fever, night sweats, chest pain, dyspnea, hemoptysis, anorexia, wasting, and malaise. It is important to remember that >50% of reported TB cases associated with anti-TNF therapy are extrapulmonary,¹⁷ and can present as disseminated disease involving the lymph nodes, peritoneum, and pleura, or less commonly, it can cause meningeal, osteoarticular, or genitourinary tract disease.¹⁸ TB infection caused by inhalation of viable bacilli that persists in an inactive state is known as latent TB infection.

Tuberculin skin testing (TST) and interferon- γ (IFN- γ) release assay are the two available screening tests for latent TB, and the sensitivity of these tests is estimated to be 70%–90%, and the specificity for all tests is >95%; an exception is that the TST in patients vaccinated with Bacillus Calmette–Guerin has 60% specificity owing to cross-reactivity.¹⁹ The IFN- γ release assay measures the release of IFN- γ from a patient's T-cells when exposed to mycobacterial antigens, and may help overcome the confounding effect of Bacillus Calmette–Guerin vaccination because IFN- γ release assay is more specific than TST.²⁰ The sensitivity of TST may be enhanced by performing repeat examinations. For instance, a repeat TST after an initial negative test may enhance the sensitivity of detecting latent TB,²¹ and a second TST enhances the ability of achieving a reliable delayed-type

Table 2 A list of common opportunistic infections, their clinical presentation, diagnostic tests, and management in patients on anti-TNF therapy

Disease/pathogen	Clinical presentation	Diagnostic tests	Management
Bacterial infection			
Tuberculosis (<i>M. tuberculosis</i>)	Cough, weight loss, fatigue, fever, night sweats, chest pain, dyspnea, hemoptysis, anorexia, wasting, malaise	CXR, TST, IGRA	Active TB (either pulmonary or extra-pulmonary) prior to starting anti-TNF therapy: standard 4 drug therapy (INH, rifampicin, ethambutol, pyrazinamide) for at least 2 months before starting anti-TNF therapy. Active TB (either pulmonary or extra-pulmonary) while on anti-TNF therapy: standard 4 drug therapy, and anti-TNF therapy can be continued if clinically indicated. Abnormal CXR consistent with prior pulmonary or extra-pulmonary TB, with prior adequate treatment: start anti-TNF therapy, with monitoring of CXR every 3 months. Abnormal CXR consistent with prior pulmonary or extra-pulmonary TB, with no prior adequate treatment: if active TB has been excluded, chemoprophylaxis with INH for 6 months before initiating anti-TNF therapy. Normal CXR, negative test for latent TB: no chemoprophylaxis. Normal CXR and positive TST or IGRA: chemoprophylaxis with either INH for 6 months, or INH and rifampin for 3 months Withhold anti-TNF therapy while active infection is treated. Mild to moderate CDI: metronidazole for 10–14 days. Severe CDI: vancomycin for 10–14 days. Severe, complicated CDI: vancomycin with or without IV metronidazole. First recurrence: mild – Metronidazole for 10–14 days; Severe – Vancomycin for 10–14 days. Second recurrence: pulsed and prolonged tapering of oral vancomycin. Refractory and Severe CDI: surgery (subtotal colectomy with end-ileostomy); fecal bacteriotherapy. Withhold anti-TNF therapy while active infection is treated. Pneumonia: fluoroquinolones (moxifloxacin, gemifloxacin, or levofloxacin) or a beta-lactam (high-dose amoxicillin, amoxicillin-clavulanate, or ceftriaxone). Alternative agents: ceftiofloxime or cefuroxime, plus a macrolide (azithromycin or clarithromycin). Meningitis: empiric intravenous vancomycin for 10–14 days, and third generation cephalosporins (eg. ceftriaxone) with adjuvant therapy of dexamethasone. Withhold anti-TNF therapy while active infection is treated. Pontiac fever: self-resolving. Legionnaire's disease: mild – fluoroquinolones for 5 days; Severe form and immunosuppressed patients – fluoroquinolones for 21 days.
<i>Clostridium difficile</i> infections (CDI)	Usually: diarrhea, fever, nausea, vomiting, abdominal pain, leukocytosis. In severe cases: fulminant colitis, toxic megacolon	Stool studies: culture, EIA to detect toxins A and B, PCR to detect toxigenic DNA	
Pneumococcal infections – pneumonia, meningitis (<i>S. pneumoniae</i>)	Pneumonia: nonspecific – fever, productive cough with rusty colored sputum. Meningitis: fever, leukocytosis, neck stiffness, altered mental status	Pneumonia: sputum cultures, blood cultures, and urine streptococcal antigens Meningitis: lumbar puncture, blood cultures, and urine streptococcal antigens	
Legionnaire's disease, Pontiac fever (<i>L. pneumophila</i>)	Pontiac fever: fever, headache, and myalgia. Legionnaire's disease: severe pneumonia causing fever, productive cough	Urinary antigen testing, direct fluorescent antibody staining, PCR	

(Continued)

Table 2 (Continued)

Disease/pathogen	Clinical presentation	Diagnostic tests	Management
Listeriosis (<i>L. monocytogenes</i>)	Mild gastrointestinal symptoms like diarrhea and fever, myalgias, sepsis, meningitis	Blood, CSF cultures	Withhold anti-TNF therapy while active infection is treated. Ampicillin and penicillin G for 10–14 days for bacteremia and 2–4 weeks for CNS infections. If penicillin allergy, desensitize or use TMP-SMX. In immunocompromised patients: add gentamicin for synergy for 7–10 days. For bacteremia, treat for 3–6 week; for CNS infections, treat for 4–8 weeks Withhold anti-TNF therapy while active infection is treated.
Salmonellosis (<i>Salmonella enteritidis</i>)	Typhoid fever. Diarrhea, abdominal pain, bacteremia, sepsis, meningitis	Blood culture, urine culture, stool culture	Any one of the following for 14 days: quinolones (ciprofloxacin or levofloxacin); TMP-SMX; penicillins (amoxicillin; third generation cephalosporins such as ceftriaxone or cefotaxime)
Nocardiosis (<i>Nocardia spp.</i>)	Pulmonary infection: resembles TB with fever, cough, chest pain CNS: headache, lethargy, confusion, seizures, or sudden onset of neurologic deficit Cutaneous infection: ulcerations, pyoderma, cellulitis, nodules, and subcutaneous abscesses	Modified acid-fast stain of sputum or infected material, and culture of the infected tissue	Withhold anti-TNF therapy while active infection is treated. Induction therapy for severe infection without CNS involvement: IV TMP-SMX plus amikacin for 3–6 weeks followed by oral TMP-SMX. Severe infection with CNS involvement: IV TMP-SMX plus imipenem for 3–6 weeks followed by oral TMP-SMX. If sulfa allergy or refractory to sulfonamides: IV imipenem plus amikacin. Duration: 3–6 months for isolated cutaneous infection in immunocompetent patients, but for 6 to 12 months in immunocompromised patients. Serious pulmonary infection is treated for 6–12 months or longer. Immunosuppressed patients and CNS disease should receive at least 12 months of therapy.
Fungal infections			
Histoplasmosis (<i>Histoplasma capsulatum</i>)	Generally non-specific including cough, dyspnea, fever, malaise	CXR, urine or serum antigen testing BAL or pulmonary lesion biopsy	Withhold anti-TNF therapy while active infection is treated. Mild to moderate infections: itraconazole for 6–12 weeks. Severe infections: amphotericin B deoxycholate followed by itraconazole for 12 weeks; Methylprednisolone if patient is hypoxic (PaO ₂ < 70 mmHg).
Coccidiomycosis (<i>C. immitis</i> and <i>C. posadasii</i>)	Usually asymptomatic; common symptoms of chest pain, cough, and fever	CXR, serology (IgG and IgM), BAL and culture, biopsy and histopathology, and PCR for coccidioid DNA	Withhold anti-TNF therapy while active infection is treated. Mild to moderate infections: fluconazole for 3–6 months. Severe infections: amphotericin B deoxycholate until clinical improvement, followed by fluconazole for 12 months.
Candidiasis (<i>Candida spp.</i> , most commonly <i>Candida albicans</i>)	Wide spectrum, ranging from local mucocutaneous infection to disseminated with multi-organ failure	Gold standard: microscopic identification of organism from the infected site	Withhold anti-TNF agents for severe infections. Mucocutaneous candidiasis: topical antifungals such as nystatin applied 2–3 times daily.
Aspergillosis (<i>Aspergillus spp.</i>)	Can present with pulmonary infection, cutaneous infection or extra pulmonary dissemination. Common symptoms with pulmonary infection include chest pain, cough, and fever	CXR, BAL, serum antigen testing, and biopsy with culture	Disseminated/systemic infection: fluconazole or amphotericin B deoxycholate for at least 14 days after last positive blood culture. Withhold anti-TNF therapy while active infection is treated. Voriconazole with a loading dose followed by maintenance doses for at least 6 to 12 weeks, or after resolution of symptoms.

<p>Cryptococcosis (<i>C. neoformans</i> or <i>C. gattii</i>)</p>	<p>Commonly affects the respiratory tract but can present with fungemia, cutaneous infection, CNS infection especially meningitis and tenosynovitis</p>	<p>Cryptococcal antigen testing and cultures derived from involved tissues or fluid</p>	<p>Withhold anti-TNF therapy while active infection is treated. Mild to moderate infections: fluconazole for 6–12 months. Severe infections: liposomal amphotericin B or amphotericin B lipid complex, plus flucytosine for at least two weeks followed by fluconazole for 8 weeks.</p>
<p>Pneumocystis pneumonia (<i>Pneumocystis jirovecii</i>)</p>	<p>Fever, non-productive cough, and progressive dyspnea</p>	<p>CXR, CT scan; microscopy or PCR from BAL, induced sputum or biopsy of the lung lesions</p>	<p>TMP-SMX for at least 21 days. Add prednisone if hypoxic (PaO₂ < 70 mmHg).</p>
<p>Viral infections Hepatitis B</p>	<p>Ranges from asymptomatic infection to varying degree of acute hepatitis and hepatic failure. Chronic hepatitis, cirrhosis and hepatocellular carcinoma</p>	<p>Serology starting with HBsAg, HBcAb Viral DNA and liver biopsy may be indicated</p>	<p>HBV DNA < 2000 IU/mL: lamivudine beginning 2–4 weeks prior to the start of anti-TNF therapy and to be continued for 6 months after the cessation of the therapy HBV DNA > 2000 IU/mL: lamivudine until HBeAg seroconversion and HBV DNA becomes undetectable. Consider adding tenofovir or entecavir if anti-TNF treatment is needed for more than 1 year</p>
<p>Hepatitis C</p>	<p>Ranges from asymptomatic to chronic hepatitis, cirrhosis and hepatocellular carcinoma</p>	<p>Serology with anti-HCV</p>	<p>Anti-TNF therapy safe.</p>
<p>Human immunodeficiency virus (HIV)</p>	<p>Various stages starting with acute viremia, latent period to AIDS</p>	<p>Gold standard: serum antibodies against HIV antigens including p24, gp 120 and gp41 Viral load to monitor disease progress</p>	<p>Treatment with combination of pegylated-interferon and ribavirin Anti-TNF considered safe for HIV patients and HAART therapy can be used concomitantly.</p>
<p>Herpes simplex virus (HSV)</p>	<p>Primary infection: asymptomatic or mild self-limited oral-labial lesions Immunocompromised patients: severe dissemination including encephalitis, meningitis, esophagitis, colitis, and hepatitis</p>	<p>PCR detection from the infected tissue or body fluid</p>	<p>Withhold anti-TNF therapy for severe infections. Treatment by using acyclovir, valacyclovir or famciclovir for recurrent infection.</p>
<p>Varicella zoster virus (VZV)</p>	<p>Chickenpox: usually affects children. Latent infection. Reactivation (shingles): painful skin lesions in dermatomal distribution. Immunocompromised patients: severe disseminated disease such as hepatitis, pneumonia, encephalitis and hemorrhagic complications</p>	<p>VZV serology, PCR, and viral culture all can be used for the diagnosis of VZV infection</p>	<p>Withhold anti-TNF therapy in severe or disseminated infections. Treatment with acyclovir, valacyclovir or famciclovir. Alternative for resistant cases is foscarnet.</p>
<p>Ebstein-Barr virus (EBV)</p>	<p>Primary infection: asymptomatic or can lead to infectious mononucleosis. Latent infection: associated with lymphoproliferative diseases and different types of cancers</p>	<p>RT-PCR to detect virus, serology</p>	<p>Withhold anti-TNF therapy in severe cases. Usually no treatment indicated. Severe cases: acyclovir or ganciclovir.</p>

(Continued)

Table 2 (Continued)

Disease/pathogen	Clinical presentation	Diagnostic tests	Management
Cytomegalovirus (CMV)	Immunocompetent primary infection: ranges from asymptomatic to causing mononucleosis-like syndrome. Most infections will become latent Immunocompromised: reactivation, can involve nearly any organ with retinitis, colitis, hepatitis and pneumonia being the most common complications Cervical dysplasia and cancer	Serology, viral culture and PCR detection of the viral DNA	Withhold anti-TNF therapy in severe cases. Asymptomatic patients or those with mild disease: no treatment indicated For severe disease: IV ganciclovir for 2–3 weeks, can consider switching to oral valganciclovir after 3–5 days of IV therapy. Alternative for resistant cases: IV foscarnet for 2 weeks.
Human papilloma virus (HPV)	Cervical dysplasia and cancer	Screening for cervical cancer using a Pap smear	No antiviral therapy indicated for patients with HPV infection; treatment of the complications (dysplasia and neoplasia) include surgery, chemotherapy, and radiotherapy.
Parasitic infections			
Toxoplasmosis (<i>Toxoplasma spp.</i>)	Immunocompetent patients: asymptomatic Immunocompromised patients: chorioretinitis and cerebral toxoplasmosis	Serology using ELISA, or serum, CSF, or amniotic fluid PCR	Sulfadiazine with pyrimethamine in combination with folinic acid for 6 weeks. Sulfa allergy: atovaquone.
Strongyloidosis (<i>Strongyloides spp.</i>)	Immunocompetent patients: asymptomatic, or cutaneous, gastrointestinal and pulmonary manifestations Immunocompromised patients: possible accelerated autoinfection (dissemination or hyperinfection) which can be fatal	Direct identification of strongyloides rhabditiform larvae from sputum, serum/blood, bronchial aspirate, CSF, peritoneal or ascitic fluid samples	Withhold anti-TNF until infection treated. Ivermectin for 2 days. For severe hyperinfection or dissemination, treatment is extended for 7–10 days, or until clinical symptoms are resolved.
Leishmaniasis (<i>Leishmania spp.</i>)	Cutaneous form which is a disfiguring and stigmatizing disease Or visceral form also known as kala-azar which can affect any organ	Detection of the parasite in bone marrow smears, in the culture of blood or bone marrow, and with the PCR of blood and bone marrow	Sodium Stibogluconate for about 20 days. Amphotericin B for 30–40 days.

Abbreviations: CXR, Chest x-ray; TST, tuberculin skin test; IGRA, Interferon-gamma release assay; INH, isoniazid; EIA, enzyme immunoassay; PCR, polymerase chain reaction; CSF, cerebrospinal fluid; BAL, bronchoalveolar lavage; HbsAg, Hepatitis B surface antigen; HbcAb, Hepatitis B core antibody; HAART, highly active antiretroviral therapy; RT-PCR, real-time polymerase chain reaction; ELISA, enzyme-linked immunosorbent assay.

Table 3 Preventative measures for common opportunistic infections in patients on anti-TNF therapy

Pathogen/disease	Preventative measures
<i>Mycobacterium tuberculosis</i>	TB screening prior to initiation of anti TNF therapy and regular TB screening while on therapy.
<i>Clostridium difficile</i>	Minimize the use and duration of antibiotics and proton pump inhibitors Implement strict infection-control practices like contact precautions and washing hands with soap and water Educate health care workers and patients about CDI risk factors
<i>Streptococcus pneumoniae</i>	PPSV23 and PCV13 vaccination preferably before initiation of anti TNF therapy
<i>Legionella</i>	Avoid contaminated water sources
<i>Listeria</i>	Proper food handling techniques like washing cucumbers or melons before consuming, rinsing raw fruits and vegetables before cutting, cooking meat and poultry thoroughly Avoid unpasteurized milk, and properly store refrigerated foods Pregnant and immunosuppressed patients should avoid coleslaw, cheeses made of unpasteurized milk, deli meats, and refrigerated seafood
<i>Salmonella</i>	Safe food handling practices Improving food safety in restaurants and at home by properly cooking raw eggs, avoiding unpasteurized milk and improperly cooked meat, oysters, ground beef and poultry
<i>Pneumocystis jirovecii</i>	For patients on triple immunomodulator therapy with one of agents being anti-TNF therapy or calcineur inihibitor, chemoprophylaxis with TMP-SMX (80–400 mg daily) is recommended For patients on double immunomodulators, with one of these being a calcineurin inhibitor or anti-TNF therapy, prophylaxis can be considered but recommendations are still unclear
Hepatitis B virus	Screening with serology (HBsAg, HBcAb) and vaccination for those who are seronegative is strongly recommended for all patients who might be considered for anti-TNF therapy
Hepatitis C virus	No indication for screening or chemoprophylaxis
HIV	General measures including safe sex, avoiding shared needles
Herpes simplex virus	No indication for screening or chemoprophylaxis, no vaccination is available
Varicella zoster virus	Varicella vaccine if no immunity to varicella and Zoster vaccine in patient with 60 years or above age. Passive vaccination with VZV IgG is also recommended for seronegative patients with close contact to patients with active VZV infection
Ebstein-Barr virus	No indication for screening or chemoprophylaxis, no vaccination is available
Cytomegalovirus	No indication for screening or chemoprophylaxis, no vaccination is available
Human papilloma virus	Primary prevention with vaccination is recommended for all females aged 11 or more Screening with cervical Pap smear starting at age of 21 or within 3 years of becoming sexually active
Toxoplasma	Avoid eating under cooked meat, use gloves when cleaning cat filter boxes. Secondary prophylaxis in certain immunosuppressed patients (such as HIV)
Strongyloides	Screening of people coming from endemic areas Chemoprophylaxis with ivermectin (200 mcg/kg per day) for 2 days every 2 weeks for those with history of chronic infection to prevent hyperinfection/disseminated infection
Lishmania	Chemoprophylaxis may be indicated in certain immunosuppressed patients (such as HIV)

Abbreviations: BCG, Bacille Calmette–Guérin; TST, tuberculin skin test; CDI, *Clostridium difficile* infection; PPSV23, 23-valent pneumococcal vaccine; PCV13, 13-valent pneumococcal conjugate vaccine; TMP-SMX, Trimethoprim-Sulfamethoxazole; HBsAg, Hepatitis B surface antigen; HBcAb, Hepatitis B core antibody.

hypersensitivity reaction – this “booster phenomenon” results in fewer false-negative results.²²

Before starting anti-TNF therapy, a history of prior TB infection should be determined and a careful physical examination, chest radiograph, and TST or IFN- γ release assay should be performed. Patients who develop active TB (either pulmonary or extrapulmonary) prior to starting anti-TNF therapy are treated with standard four-drug therapy, which includes isoniazid, rifampicin, ethambutol, and pyrazinamide, and they should receive a minimum of 2 months of standard four-drug therapy supervised by an infectious diseases specialist before starting anti-TNF therapy. Ideally, anti-TNF therapy should be delayed until a full course of anti-TB treatment is

completed.²³ Patients who develop active TB (either pulmonary or extrapulmonary) while on anti-TNF therapy are treated with standard four-drug therapy, and the anti-TNF therapy can be continued if clinically indicated.²³ Patients with an abnormal chest radiograph consistent with prior pulmonary or extrapulmonary TB, who have received adequate treatment, can be started on anti-TNF therapy – these patients should be monitored with a chest radiograph every 3 months and should have sputum culture obtained if symptoms of TB develop.¹⁷ Patients with an abnormal chest radiograph consistent with prior pulmonary or extrapulmonary TB, who have not received adequate treatment, should be ruled out for active TB before initiating anti-TNF treatment. If active TB has been excluded,

chemoprophylaxis with isoniazid for 6 months is suggested before initiating anti-TNF therapy. If delaying anti-TNF therapy is not advisable, this should be discussed with the patient and an infectious disease specialist.^{17,23}

In patients with a normal chest radiograph in whom anti-TNF therapy is planned, the next step in management is based on the results of TST or IFN- γ release assay testing. For patients with negative tests for latent TB, no chemoprevention is recommended. Patients with a positive TST or IFN- γ release assay should receive chemoprophylaxis with either isoniazid for 6 months, or isoniazid and rifampin for 3 months.²³ All patients should be closely monitored. In patients receiving anti-TNF therapy, serial TB screening tests are indicated to identify patients with reactivation of latent TB or new TB exposure; however, the frequency and best screening methods have not been determined.²⁴

Clostridium difficile

C. difficile is a Gram-positive, spore-forming anaerobic bacillus. There has been a significant increase in the proportion of hospitalizations complicated by *C. difficile* infection (CDI) from 1998–2004 (7/1000 versus 11/1000; $P < 0.05$).²⁵ Acquisition of the infection occurs more frequently in those with recognized risk factors, including age > 65 years, prolonged hospitalization, solid organ transplantation, immunosuppression, use of high risk medications (eg, corticosteroids, anti-TNF therapy, antibiotics such as cephalosporin, clindamycin, and fluoroquinolones), and IBD (ulcerative colitis, Crohn's disease).²⁶ CDI is usually a nosocomial infection, but community-acquired infections are also reported and associated with significant mortality.^{26,27} Clinically, patients with CDI can present with nausea, vomiting, diarrhea, fever, leukocytosis, abdominal pain, and in severe cases with toxic megacolon and fulminant colitis. Hospitalized patients with unexplained leukocytosis, even in the absence of diarrhea, should be tested for *C. difficile*.²⁸ Hypervirulent strain NAP1/B1/027 of *C. difficile* is associated with severe disease and resistance to conventional medical therapy.²⁷

There are multiple modalities available for diagnosing CDI. Stool culture for *C. difficile* is highly sensitive but labor intensive. Enzyme immunoassay testing to detect toxins A and A+B is relatively simple and inexpensive. Recently, polymerase chain reaction (PCR) to detect toxigenic DNA has been adopted as the test of choice in many hospitals and health care facilities.²⁸ The sensitivity and specificity for PCR is better than enzyme immunoassay (93% and 97% versus 73% and 97%, respectively).²⁹

For all CDI infections, anti-TNF therapy should be withheld until the active infection is properly treated. An initial episode of mild to moderate CDI (white blood cell count of $< 15,000$ cells/ μL and a serum creatinine < 1.5 times the premorbid level) is treated with metronidazole (500 mg orally three times daily) for 10–14 days.³⁰ An initial episode of severe CDI (white blood cell count of $> 15,000$ cells/ μL and serum creatinine > 1.5 times the premorbid level) is treated with vancomycin (125 mg orally four times daily) for 10–14 days.³⁰ For severe, complicated CDI manifested by hypotension, ileus, toxic megacolon, colonic perforation, lack of response to therapy, or a need for intensive care unit admission or colectomy, vancomycin (500 mg orally four times daily) is administered with or without metronidazole (500 mg intravenously [IV] every 8 hours).³⁰ The first recurrence of CDI is treated similarly as an initial episode; metronidazole may be used for mild CDI relapse, and vancomycin for severe relapse.³⁰ A second recurrence is treated with pulsed and prolonged tapering of oral vancomycin (125 mg four times daily for 10–14 days, 125 mg twice daily for a week, 125 mg once daily for a week, and then 125 mg every 2–3 days for 2–8 weeks).³⁰ Two recent trials have compared the efficacy of vancomycin (125 mg four times daily) with fidaxomicin (200 mg twice daily) given over 10 days. The rate of clinical cure was similar in both treatment groups (88% fidaxomicin versus 86% vancomycin);³¹ however, the rate of recurrent CDI was significantly lower in the fidaxomicin arm (15%) compared to those treated with vancomycin. Rifaximin has also been used to successfully treat recurrent CDI, including in IBD patients.³² Early surgical consultation is recommended in refractory or severe CDI as a delay in surgery has been associated with substantial morbidity and mortality. Surgical candidates include those patients with leukocytosis ($> 15,000/\text{mm}^3$), elevated serum lactate, or underlying IBD.^{33,34} Subtotal colectomy with end ileostomy is preferred over hemicolectomy or segmental resection.²⁶ Recently, fecal bacteriotherapy has been used for severe and recurrent CDIs not responding to medical therapy.³⁵ A systematic review of 27 case series and reports of patients treated with fecal transplant for recurrent and severe CDI reported disease resolution in 92% of patients.³⁶ CDI preventive measures include minimizing the use and duration of antibiotics and proton pump inhibitors, implementing strict infection-control practices, washing hands with soap and water, and educating health care workers and patients about CDI risk factors. Alcohol-based hand disinfection is not effective in preventing CDI. Probiotics such as *Saccharomyces boulardii*, *Lactobacillus*, or brewer's yeast (*Saccharomyces cerevisiae*) are

also increasingly used for recurrent CDI, but their efficacy remains in question.²⁶

Streptococcus pneumoniae

S. pneumoniae is an encapsulated Gram-positive bacterium often referred to as pneumococcus. The organism is a leading bacterial cause of otitis media, sinusitis, and community-acquired pneumonia. In immunocompromised patients it can cause disseminated or invasive infections such as meningitis and bacteremia, and infections like necrotizing fasciitis and septic arthritis have also been reported.³⁷ Anti-TNF therapy diminishes humoral and cellular immunity, leaving patients more susceptible to invasive pneumococcal infections. Pneumococcal pneumonia can present clinically with fever and a productive cough with rusty-colored sputum. Pneumococcal meningitis presents with fever, leukocytosis, neck stiffness, and altered mental status. Sputum cultures, blood cultures, and urine streptococcal antigens are usually obtained from suspected patients prior to giving antibiotics.

Anti-TNF therapy should always be withheld until an active pneumococcal infection is treated. The choice of antibiotic depends on the resistance and local epidemiological data. Empirical treatment options for patients with community-acquired pneumonia include fluoroquinolones (moxifloxacin 400 mg daily, gemifloxacin 320 mg daily, or levofloxacin 750 mg once daily) or a β -lactam (first-line agents: high-dose amoxicillin 1 g three times daily, amoxicillin-clavulanate 2 g twice daily, or ceftriaxone 1 g daily; alternative agents: cefpodoxime 200 mg twice daily or cefuroxime 500 mg twice daily), plus a macrolide (azithromycin 500 mg on the first day followed by 250 mg/day for 4 days or clarithromycin 250 mg twice daily).³⁸ Empirical treatment of meningitis should be treated with IV vancomycin (15–20 mg/kg IV every 12 hours for 10–14 days) and a third-generation cephalosporin such as ceftriaxone (2 g IV every 12 hours) until antibiotic susceptibility is known. Adjunctive therapy with dexamethasone (10 mg IV every 6 hours for 4 days) should be considered in all cases of pneumococcal meningitis.³⁹

Prevention of pneumococcal infection is largely accomplished through vaccination. The 23-valent pneumococcal polysaccharide vaccine (PPSV23) should be administered to adults aged 19–64 years who are receiving immunosuppressive therapy. The Advisory Committee on Immunization Practices recommends routine use of 13-valent pneumococcal conjugate vaccine (PCV13) for adults with immunocompromised conditions aged \geq 19 years, followed by the PPSV23 vaccine.⁴⁰ Anti-TNF therapy may impair the response to pneumococcal vaccination, so the vaccine is

usually recommended \geq 2–3 weeks prior to starting anti-TNF therapy.⁴¹

Legionella

Legionella pneumophila is a Gram-negative, aerobic, intracellular coccobacillus. It has been identified from multiple environmental sources including surface water, mud, thermally polluted lakes or streams, whirlpool spas, cooling towers, air-conditioning units, and humidifiers.⁴² It is an important cause of hospital-acquired and community-acquired pneumonia. Legionnaire's disease is a severe form of pneumonia caused by *Legionella*, and it is difficult to clinically distinguish Legionnaire's disease from pneumococcal pneumonia. Pontiac fever is a milder form of *L. pneumophila* infection and manifests with fever, headache, and myalgia, and spontaneously resolves in 3–5 days.⁴³ Diagnosis is made with rapid diagnostic tests, such as urinary antigen testing, direct fluorescent antibody staining, or PCR. Less commonly, *Legionella* antibody tests such as indirect fluorescent antibody and enzyme-linked immunosorbent assay are used. Definitive diagnosis of Legionnaire's disease is based on isolation of *Legionella* from culture.

Fluoroquinolones, such as oral levofloxacin (750 mg once daily), are recommended for 5 days for mild forms of *Legionella* infection. In immunosuppressed patients who are severely ill from Legionnaire's disease, treatment should be extended to 21 days.⁴⁴ Macrolide antibiotics such as azithromycin (initial dose of 1 g on the first day followed by 500 mg daily for 7–10 days) are also effective. In 2011, the US Food and Drug Administration (FDA) added a boxed warning about the risk of *Legionella* infection for the entire class of anti-TNF agents.⁴⁵ Anti-TNF therapy should always be withheld until the active infection is resolved.

Listeria monocytogenes

L. monocytogenes is a small, aerobic, Gram-positive intracellular bacillus. Listeriosis most commonly affects newborns, pregnant women, older patients, and the immunocompromised, such as patients on immunomodulators, transplant patients, and patients with acquired immunodeficiency syndrome (AIDS). Listeriosis is a foodborne illness transmitted most commonly by melons, processed meats, hot dogs, soft cheeses, smoked seafood, and pâté. In non-neonatal forms, listeriosis presents with mild gastrointestinal symptoms like diarrhea, fever, and myalgia. Pregnant women may have a flu-like illness with fetal loss possible. In patients taking anti-TNF therapy, the infection is more invasive, causing sepsis and meningitis.

Diagnosis is usually made by isolation of the pathogen in the blood or cerebrospinal fluid (CSF). Negative cultures may not completely rule out *Listeria*, especially when there is a high clinical suspicion. The infection is associated with a high mortality rate – up to 30% die despite medical therapy.⁴⁶ In 2011, the FDA added a boxed warning about the risk of listeriosis for anti-TNF agents. In a report on granulomatous infectious diseases from the FDA Adverse Event Reporting System from 1998–2002, there were 38 cases of *Listeria* infection in patients taking anti-TNF agents.⁴⁷ A search of the medical literature in 2011 identified 26 published cases of listeriosis in patients who had received anti-TNF therapy, including seven deaths.⁴⁵

First-line agents to treat listeriosis are ampicillin (2 g IV every 4 hours) and penicillin G (4 million units IV every 4 hours). The role of adding an aminoglycoside to penicillin-based treatment is debated. Penicillin-allergic patients should be desensitized if necessary, or treated with trimethoprim–sulfamethoxazole (10–20 mg/kg/day IV of the trimethoprim component divided every 6–12 hours).⁴⁸ In immunocompromised patients, 3–6 weeks of treatment is preferred in cases of bacteremia and 4–8 weeks in cases of central nervous system (CNS) infections.^{48,49} While the data regarding management of anti-TNF therapy is lacking in literature, it is recommended to withhold anti-TNF therapy until the *Listeria* infection is resolved. Usually the decision to resume anti-TNF therapy is individualized, weighing the risks and benefits of the treatment. Patients should be counseled regarding proper food handling techniques, like washing cucumbers or melons before consumption, rinsing raw fruits and vegetables before cutting, cooking meat and poultry thoroughly, avoiding unpasteurized milk, and properly storing refrigerated foods. Pregnant patients should avoid coleslaw, cheese made of unpasteurized milk, deli meats, and refrigerated seafood.

Salmonella

Salmonella spp are aerobic Gram-negative bacilli. Salmonellosis caused by *Salmonella enteritidis* is the most common bacterial cause of foodborne disease in the US.⁵⁰ International travel and consuming raw eggs or undercooked meat are some common risk factors for *Salmonella* infection. Infection can result in several syndromes including gastroenteritis, typhoid fever, bacteremia, sepsis, or meningitis. Salmonellosis should be suspected in an immunocompromised patient presenting with diarrhea, fever, and abdominal cramps. Immunocompromised patients can also present with *Salmonella* bacteremia without gastroenteritis, resulting in a higher mortality rate than

similar infections in immunocompetent patients.⁵¹ Diagnosis is usually made by isolating *Salmonella* from blood, urine, or stool samples.

For active *Salmonella* infections, anti-TNF therapy should be withheld until the infection is properly treated. Antibiotics such as ciprofloxacin (500 mg orally twice daily) or levofloxacin (500 mg orally once daily), trimethoprim–sulfamethoxazole (160 mg/800 mg orally twice daily), amoxicillin (500 mg orally three times daily), a third-generation cephalosporin such as ceftriaxone (1–2 g IV once daily) or cefotaxime (2 g IV every 8 hours) for 14 days effectively treats salmonellosis.^{52–54} Attention to local antibiotic resistance patterns is required to aid empirical antibiotic choices. Patients with severe diarrhea should receive fluid rehydration. Safe food handling practices such as properly cooking raw eggs, avoiding unpasteurized milk, and avoiding improperly cooked meat, oysters, ground beef, and poultry should be practiced at home and in restaurants. No commercial vaccine is available other than for typhoid fever prevention.

Nocardia

Nocardia spp are filamentous, aerobic, Gram-positive, weakly acid-fast bacteria. Infection is acquired by inhalation, ingestion of contaminated food, and by direct inoculation. Immunocompromised persons are at greatest risk for *Nocardia* infection.⁵⁵ Nocardiosis can present as an invasive pulmonary infection resembling TB, manifested by fever, cough, and chest pain. Hematogenous dissemination to the CNS can cause symptoms of headache, lethargy, confusion, seizures, or sudden onset of neurologic deficit. Cutaneous infection is through direct inoculation of the organism through skin from trauma or penetrating injury and presents with ulcerations, pyoderma, cellulitis, nodules, and subcutaneous abscesses. Diagnosis is made by modified acid-fast stain of sputum or infected material, and culture of the infected tissue.

Trimethoprim–sulfamethoxazole (15 mg/kg/day IV of the trimethoprim component in two to four divided doses) plus amikacin (7.5 mg/kg IV every 12 hours) is the first line of therapy.⁵⁶ If the patient is allergic to sulfa drugs, desensitization should be performed when possible. Alternatively, imipenem (500 mg IV every 6 hours) plus amikacin (7.5 mg/kg IV every 12 hours) can be used. Combination drug therapy (sulfonamide, ceftriaxone, and amikacin) is recommended in patients not responding to standard antimicrobial treatment. Immunocompromised patients and those with CNS disease should receive induction

therapy with trimethoprim–sulfamethoxazole (15 mg/kg/day IV of the trimethoprim component in two to four divided doses) plus imipenem (500 mg IV every 6 hours) for 3–6 weeks, followed by oral trimethoprim–sulfamethoxazole (10 mg/kg/day of the trimethoprim component in two or three divided doses) for ≥ 12 months with close clinical monitoring.⁵⁶ Anti-TNF therapy should be withheld during active infection and can be resumed after successful treatment.⁵⁷

Fungal infections

TNF- α is an essential cytokine for the formation and maintenance of granulomas, thereby a key host defense mechanism against intracellular pathogens.⁶ Increased use of anti-TNF therapy has been accompanied by reports of fungal infections such as histoplasmosis and blastomycosis,⁴⁷ and anti-TNF therapy has been associated with both primary and reactivated fungal infections. In an attempt to increase awareness of this problem, in September 2008, the US FDA issued a “black box” warning alerting clinicians of the risks of certain endemic fungal infections in patients treated with anti-TNF therapy.⁵⁸ Some common fungal infections associated with the use of anti-TNF therapy are described below and summarized in Tables 2 and 3.

Histoplasmosis

Histoplasmosis is a common endemic mycosis caused by *H. capsulatum*. The infection is found worldwide, but is particularly common in North and Central America. In the US, the infection tends to occur more commonly in the Midwestern states, especially in the Ohio and Mississippi River valley regions.⁵⁹ Potential exposures include demolition of old buildings, cleaning chicken coops, and spelunking.⁵⁹ The infection primarily affects the lungs causing acute pneumonia. Disseminated disease occurs in approximately one in 2000 patients with acute infection and immunosuppression (eg, AIDS, solid organ transplantation, treatment with anti-TNF agents) has been identified as the most important risk factor for disseminated infection.⁶⁰ Among patients on anti-TNF therapy, histoplasmosis has been identified as the most common cause of invasive fungal infection.⁶¹ Signs and symptoms are generally nonspecific with cough, dyspnea, fever, malaise, and interstitial pneumonitis on chest radiographs being commonly reported.⁶¹ In patients suspected of having histoplasmosis, chest radiograph should be obtained, although they may be normal in 40%–70% of cases. Common chest radiograph findings include diffuse or localized infiltrates and/or hilar lymphadenopathy.⁶²

One test used to diagnose *Histoplasma* infection is urine or serum antigen test. This test is done using an enzyme immunoassay and is useful for rapid diagnosis in severe infections. Biopsy of pulmonary lesions and bronchoalveolar lavage (BAL) may be required in some cases.⁶³

Anti-TNF therapy needs to be discontinued in patients who develop histoplasmosis or other invasive fungal infections during therapy.⁶⁴ For mild to moderate infections limited to the lungs, without systemic compromise, itraconazole (200–400 mg daily) for 6–12 weeks is the preferred treatment. For severe pulmonary or disseminated infections, the general approach is 1–2 weeks of amphotericin B deoxycholate (0.7–1.0 mg/kg/day) followed by itraconazole (200 mg twice daily) for 12 weeks. Methylprednisolone can also be added for severe respiratory complications including hypoxemia (partial pressure of oxygen in arterial blood < 70 mmHg).^{65,66} Treatment response is monitored using *Histoplasma* antigen concentrations in the urine or serum.⁶⁷ Treatment is usually very effective, except in patients with CNS histoplasmosis owing to the poor penetration of most antifungal agents into the CSF. Only 60%–80% of patients with *Histoplasma* meningitis respond to treatment with amphotericin B, and up to one-half of responders relapse during subsequent years.⁶⁸ Resumption of anti-TNF therapy after successful treatment of histoplasmosis does not seem to increase the long-term risk of recurrence.⁶²

Coccidioidomycosis

Coccidioidomycosis is caused by the dimorphic fungi of the genus *Coccidioides* (*Coccidioides immitis* and *Coccidioides posadasii*). The infection is spread by inhalation of spores. The fungus tends to be endemic in the southwestern US and parts of Central and South America. More than half of the illnesses are asymptomatic; among symptomatic patients, chest pain, cough, and fever are the most common manifestations. A chest radiograph may show a diffuse bilateral reticulonodular pattern that sometimes is indistinguishable from *Pneumocystis* pneumonia (PCP). A high index of suspicion of coccidioidomycosis infection in patients from endemic areas is necessary. BAL and culture, serology, biopsy, and histopathology and PCR for coccidioidal DNA can facilitate diagnosis. However, anticoccidioidal antibodies (immunoglobulin G and immunoglobulin M) do not readily differentiate between new and old infection and can be falsely negative in immunocompromised patients. Coccidioidal antigen detection in urine may be helpful in diagnosis of severe infection.⁶⁹ Serology and antigen testing can also be used for following response to treatment. A real-time PCR for

coccidioidal DNA in respiratory secretions has recently been developed and initial testing shows 100% sensitivity and 98% specificity for the diagnosis of *Coccidioides* as compared to culture. Although not readily available everywhere, it may provide a rapid and safe way of diagnosis.⁷⁰ In endemic areas for *C. immitis*, a chest radiograph and coccidioidal serologic tests for immunoglobulin M and immunoglobulin G should be considered before starting anti-TNF therapy to establish baseline.⁷¹ However, most cases of infection are acute rather than a reactivation, and these tests may be of limited value.⁷¹

Anti-TNF therapy should be discontinued whenever an invasive coccidioidal infection is identified. Treatment for pulmonary coccidioidomycosis is fluconazole (400–800 mg/day) for a period of 3–6 months. For severe systemic infections, treatment usually consists of amphotericin B deoxycholate (0.5–1 mg/kg/day) until clinical improvement is achieved, followed by fluconazole (400–800 mg/day) for 12 months.⁷²

Candidiasis

Candida spp are considered part of the normal flora of the gastrointestinal and genitourinary tracts of humans. However, in certain conditions such as disruption of the normal flora, a breach of the mucocutaneous barrier, or a defect in host cellular immunity, *Candida* can invade and cause disease.⁷³ Candidiasis can present as a wide spectrum of disease ranging from local mucous membrane infections to widespread dissemination with multisystem organ failure. The gold standard for diagnosis is microscopic identification of the fungus from the infected site.

For mucocutaneous candidiasis topical antifungals such as nystatin applied two to three times daily is usually very effective. For disseminated or systemic infection, first-line treatment for *Candida albicans* is fluconazole (800 mg loading dose followed by 400 mg/day) for ≥ 14 days after last positive blood culture, or amphotericin B deoxycholate (0.5–1 mg/kg/day) for ≥ 14 days after last positive blood culture.⁶ Second-line treatment for resistant cases includes IV caspofungin, micafungin, or anidulafungin.⁶

Aspergillosis

Aspergillus spp are ubiquitous in nature and the spread of infection is usually by inhalation of infectious conidia, but rarely can occur through the gastrointestinal tract and direct skin inoculation. Aspergillosis can present in a variety of ways, causing respiratory tract diseases, cutaneous infection, or extrapulmonary dissemination. Pulmonary infection with cough, fever, dyspnea, and chest pain is the most common

presentation. Disseminated disease is most frequently associated with immunocompromised states, as seen in patients with hematologic malignancies, hematopoietic cell transplantation, solid organ transplantation, or anti-TNF therapy. Signs and symptoms can be varied depending upon the organs involved. Chest radiographs are generally the first test obtained and may show nodules with surrounding ground glass infiltrates (halo sign). Diagnosis can be established by microscopic examination of respiratory secretions or BAL, serum antigen testing, and biopsy with culture.

The drug of choice for invasive infection is voriconazole beginning with a loading dose (6 mg/kg every 12 hours for two doses) followed by maintenance doses (4 mg/kg every 12 hours) for ≥ 6 –12 weeks, or after resolution of symptoms. Alternatives include amphotericin B deoxycholate, posaconazole, itraconazole, and caspofungin.

Cryptococcus

Cryptococcus is an encapsulated fungus that has a worldwide distribution and is generally found in soil and in high concentrations near bird roosts. The organism is spread by inhalation after disruption of soil. Cryptococcosis is an invasive infection due to *Cryptococcus neoformans* or *Cryptococcus gattii*, and opportunistic infections by these pathogens have become increasingly more prevalent in immunocompromised patients. Although the presentation of cryptococcal infection can be varied, lung infection is most common. Other manifestations include fungemia, cutaneous infection, tenosynovitis, or CNS infection, especially meningitis.⁶¹ Diagnosis is established by antigen testing and cultures derived from involved tissues or fluid.

For mild to moderate pulmonary infections, treatment with fluconazole (400 mg/day) for 6–12 months is usually sufficient. For severe infections and CNS involvement, therapy consists of induction using liposomal amphotericin B (3–4 mg/kg/day IV) or amphotericin B lipid complex (5 mg/kg/day IV) plus flucytosine (100 mg/kg/day orally in four divided doses, adjusted for renal function) for ≥ 2 weeks followed by fluconazole (400 mg/day) for 8 weeks.⁷⁴

PCP

PCP is a nongranulomatous fungal infection caused by *Pneumocystis jirovecii*. The organism is spread via aerosol route and has the capacity to colonize the respiratory tract of asymptomatic individuals.⁷⁵ Patients with impaired cell-mediated immunity – as seen in AIDS, hematopoietic stem cell and solid organ transplant recipients, cancer patients (particularly hematologic malignancies), and patients on

immunosuppressive medications (eg, glucocorticoids, chemotherapeutic agents) – are a higher risk for developing this infection.⁷⁶ Patients contracting PCP in the absence of AIDS generally present with a more abrupt onset of respiratory insufficiency including fever, nonproductive cough, and progressive dyspnea. The rapid decline in respiratory status may correlate with a stronger inflammatory response, indicated by the presence of more neutrophils and lower numbers of *Pneumocystis* organisms in the lungs of such patients as compared to patients with AIDS.^{77,78} Typical radiographic findings include bilateral perihilar interstitial infiltrates that gradually become more homogenous. Other less common findings include nodules in the lungs, upper lobe infiltrates, and rarely pneumothorax. High resolution computed tomography scan is more sensitive than chest radiograph and may reveal extensive ground glass attenuation.⁷⁸

The gold standard for diagnosis is demonstration of the organism from BAL, induced sputum, or biopsy of the lung lesions. *Pneumocystis* cannot be cultured in vitro.⁷⁸ PCR for *Pneumocystis* nucleic acid from BAL, blood, or nasopharyngeal aspirates, or β -D-glucan assay (a cell wall component) from the serum can also be used for initial screening. These tests have high sensitivity and specificity and are useful for rapid diagnosis, with the PCR test being used more frequently.^{78,79}

The first-line treatment is trimethoprim–sulfamethoxazole (two double strength tablets three times daily) for ≥ 21 days. For acutely ill patients with partial pressure of oxygen in arterial blood < 70 mmHg, trimethoprim–sulfamethoxazole is given (dose based on the trimethoprim component at 15 mg/kg/day IV) with prednisone (40 mg twice daily) for 5 days, usually followed by a tapering dose.^{78,80} Second-line treatment is either IV pentamidine, atovaquone, trimethoprim, and dapsone or pentamidine and clindamycin plus primaquine for 14–21 days.⁷⁸ For those patients on triple immunomodulator therapy, with one of these being a calcineurin inhibitor or anti-TNF therapy, standard prophylaxis with trimethoprim–sulfamethoxazole (80–400 mg) is recommended, if tolerated. For those on double immunomodulators, with one of these being a calcineurin inhibitor or anti-TNF therapy, prophylaxis can be considered but recommendations are still unclear.⁸¹

Other fungal infections

Other fungal infections that have been reported with anti-TNF therapy include zygomycetes, blastomycosis, mucormycosis,⁸² and sporotrichosis.⁸³ These infections are rare among

patients on anti-TNF therapy and information about their management remains limited.

Viral infections

TNF- α , along with IFN- γ , plays a significant role in the immune response against viral infections. Inhibition of TNF- α can theoretically increase the risk of viral infections, but has only recently become an increased area of research.⁸⁴ Some common viral infections associated with the use of anti-TNF therapy are described below and summarized in Tables 2 and 3.

HBV

HBV is a member of the *Hepadnaviridae* family and has a worldwide prevalence of 350 million infected.⁸⁵ Transmission occurs by parenteral, sexual, and perinatal routes. TNF- α and IFN- γ synergistically inhibit the expression and replication of HBV genes,⁸⁶ and TNF- α is also important for viral clearance.⁸⁷ Anti-TNF therapy therefore carries a risk of viral reactivation, defined as either an increase of $> 1 \log_{10}$ viral load, or > 2000 copies/mL above the baseline HBV DNA load, or the appearance of serum HBV DNA above the standard cutoff values (> 300 copies/mL).⁸⁸ Reactivation has been observed in anti-TNF-treated patients who were hepatitis B surface antigen negative but hepatitis B core antibody positive;^{89–93} this is probably related to the persistence of HBV DNA in the hepatocytes.⁹⁴

The clinical manifestations of hepatitis B reactivation range from asymptomatic to varying degrees of acute hepatitis leading to hepatic failure.⁹⁵ Reactivation may occur during therapy or after the withdrawal of the anti-TNF therapy due to the reconstitution of the immune system.⁹⁶ Because of the risk of reactivation, it is strongly recommended that patients' HBV status be identified before starting therapy. Therefore, ascertainment of hepatitis B surface antigen, anti-hepatitis B core antibody, and anti-hepatitis B surface antibody status should be determined in all patients – regardless of previous HBV history – to assess their infection and vaccination status.⁹⁷ Viral DNA and liver biopsy may be indicated as well, depending on the serology results.

There is no standardized recommendation regarding chemoprophylaxis for HBV carriers planning to receive anti-TNF therapy. For patients with lower viral loads (< 2000 IU/mL), lamivudine beginning 2–4 weeks prior to the initiation of anti-TNF therapy and continued for ≥ 6 months after cessation of therapy is recommended.⁹⁸ This approach carries a high risk of development of lamivudine resistance if treatment is required for a longer course.⁹⁹ Patients with HBV

DNA levels > 2000 IU/mL should be treated for chronic hepatitis B as outlined by specific guidelines for HBV treatment.⁹⁸ If a longer course of anti-TNF therapy is anticipated (ie, >1 year), which is usually the case in chronic inflammatory diseases, other nucleotide/nucleoside analogs such as tenofovir or entecavir should be considered.^{88,95,98} No chemoprophylaxis is currently recommended in anti-hepatitis B core antibody positive patients. Careful monitoring with viral tests and transaminases level, however, should be done every 1–3 months while the patient is on anti-TNF therapy.⁸⁸ For those with active disease, HBV infection should be treated and controlled prior to the initiation of the anti-TNF therapy.⁸⁸ HBV vaccination is an effective way to prevent infections and should be offered to all HBV-negative patients considering the use of anti-TNF agents.¹⁰⁰

Hepatitis C virus (HCV)

HCV, estimated to infect more than 200 million worldwide,¹⁰¹ is the leading cause of liver-related death in the US.¹⁰² The use of anti-TNF agents is safe and not associated with any significant change in viremia or liver function in patients infected with HCV.^{103–110} Etanercept has a synergetic effect when used in combination with recombinant IFN- α -2b and ribavirin in a Phase II randomized double-blind placebo-controlled study, making the use of anti-TNF agents favorable when patients have a concomitant HCV infection.¹⁰⁷

Human immunodeficiency virus (HIV)

HIV affects nearly 1.1 million people in the US.¹¹¹ It is transmitted through parenteral, sexual, and perinatal routes. HIV-related mortality has declined dramatically since the introduction of antiretroviral therapy.¹¹² TNF- α has been implicated in the pathogenesis of HIV infection by contributing to HIV replication through activation of nuclear factor- κ B.¹¹³ Elevated levels of TNF- α are correlated to advanced stages of HIV infection and with opportunistic infections.¹¹⁴ Two small studies evaluating the safety of anti-TNF therapy in HIV patients failed to show any change in plasma HIV ribonucleic acid, cluster of differentiation-4+ lymphocyte count, or the occurrence of severe adverse effects.^{114,115} In conclusion, it appears the use of anti-TNF therapy in HIV patients is safe. Close monitoring of cluster of differentiation-4+ lymphocyte count and viral load with careful monitoring of clinical features of HIV and other infections is required.¹¹⁶

Herpes simplex virus (HSV)

HSV-1 and -2 are members of the *Herpesviridae* family. Primary infection with HSV in immunocompetent individuals

usually causes an asymptomatic or mild self-limited oral-labial (generally HSV-1) or genital (generally HSV-2) infection, followed by HSV persistence (latency) in nerve ganglia.^{117,118} HSV reactivation in immunocompromised patients can lead to disseminated disease including encephalitis, meningitis, esophagitis, colitis, and hepatitis.^{119–121} Anti-TNF therapy is associated with increased risk of HSV reactivation and dissemination.^{122,123} HSV colitis can mimic certain chronic inflammatory conditions such as acute exacerbation of IBD and has been associated with higher risk of colectomy.¹²⁴ The gold standard method for diagnosing the infection is to detect the virus using PCR from infected tissues or body fluid.¹²⁵

Acyclovir, valacyclovir, and famciclovir can be used for the treatment of acute or recurrent HSV infection. It is not recommended to use anti-TNF agents during the acute phase of HSV infection due to the increased risk of dissemination. Interruption of immunosuppression is recommended in patients with severe HSV infection.⁸⁶

VZV

VZV belongs to the *Herpesviridae* family of viruses. Worldwide, up to 90% of adults demonstrate serologic evidence of prior infection with VZV.¹²⁴ Infection is transmitted by close contact, most likely via the respiratory tract.⁹⁸ TNF- α plays a significant role in the immune response against VZV as it blocks antigen expression and virus replication. Anti-TNF agents inhibit this antiviral activity,¹²⁶ leading to severe viral infection.¹⁴ VZV infection, unlike the other herpes virus infections, is usually symptomatic.^{124,127} It causes chickenpox in children (primary varicella) which is a mild self-limited disease; the primary infection then becomes latent, and in adults reactivation can occur and can cause shingles, which is manifested by painful skin vesicular lesions following a dermatomal distribution pattern. In immunocompromised patients, primary or reactivated infection can lead to more severe disseminated disease, such as hepatitis, pneumonia, encephalitis, and hemorrhagic complications.^{124,127} History of prior exposure is often not reliable; therefore VZV serology may need to be obtained in patients undergoing anti-TNF therapy. Those who are seronegative can be offered the varicella vaccine.¹²⁸ Serology has a limited value in diagnosing acute VZV infection;¹²⁴ PCR, viral culture, and hybridization methods are more sensitive for confirming a diagnosis.

Several antiviral agents such as acyclovir, valacyclovir, and famciclovir can be used to treat acute VZV infection. Foscarnet as an alternative is recommended for resistant cases.¹²⁴ Varicella vaccination is recommended in all children

aged 12–18 months with a booster dose at 11–12 years of age.¹²⁹ Varicella vaccine can also be offered to all adults without evidence of immunity to varicella prior to the initiation of immunosuppression. Zoster vaccination has also been found to reduce the incidence of VZV by 50% and the risk of postherpetic neuralgia by 66% in people aged > 60 years.¹²⁷ It is recommended to administer the zoster vaccine to all of the immunocompetent persons aged \geq 60 years.¹³⁰ Live varicella vaccine is contraindicated during anti-TNF therapy and should be administered \geq 3 weeks prior to the initiation of any immunosuppressant agent including anti-TNF agents.

Epstein–Barr virus (EBV)

EBV is also a member of the *Herpesviridae* family. It is transmitted by close contact through oral secretions.¹³¹ By adulthood, 90%–95% of people worldwide have been expected to have been exposed to the virus.¹³² Primary infection can be asymptomatic or can cause infectious mononucleosis in children and adolescents.¹³¹ Latent infection can be associated with different types of cancers and lymphoproliferative diseases. In transplant recipients receiving immunosuppressive therapy, >80% of non-Hodgkin lymphomas are associated with EBV.¹³³ Reports of EBV-associated lymphoproliferative disorder in patients on anti-TNF therapy have also been published.^{134,135} Diagnosis of the primary infection is usually suggested by clinical findings of infectious mononucleosis associated with atypical lymphocytosis on peripheral blood smear.¹³² Serologic tests measuring antibodies against specific viral antigens are useful in diagnosis, but real-time PCR may be more sensitive and reliable, especially in the early period of the EBV infection.¹³⁶

Treatment is generally not required for infectious mononucleosis and supportive measures are adequate due to the self-limited nature of this illness.¹³² Antiviral therapy including acyclovir or ganciclovir can be used in more severe disease. Withdrawal of anti-TNF therapy should be considered in cases of severe EBV-associated disease. There is no commercially available vaccine for prevention and chemoprophylaxis is not recommended due to the insignificant risk imposed by anti-TNF therapy.

Cytomegalovirus (CMV)

CMV is a member of the *Herpesviridae* virus family, and is found and transmitted through body fluids.¹³⁷ Seroprevalence studies suggest that 10%–20% of prepubescent children have been exposed to CMV and that this increases to 40%–100% in adults.¹³⁸ Like other herpes viruses, the primary infection in immunocompetent patients is almost always asymptomatic, or

it can present as a mononucleosis-like syndrome.¹³⁹ Most CMV infections will become latent. In immunocompromised patients, there is a risk of reactivation of latent infection and the disease can involve nearly any organ.¹³⁸ There have been several case reports of CMV reactivation causing severe infections after the initiation of anti-TNF therapy including disseminated disease,¹⁴⁰ retinitis,¹⁴¹ colitis,^{142,143} hepatitis,¹⁴⁴ and pneumonia.¹⁴⁵

Although serology was found to be strongly associated with viremia,¹⁴⁶ it has limited value in the diagnosis of an active infection in immunocompromised patients.¹⁴⁷ Viral culture – although highly specific – has limitations due to the prolonged incubation period, lack of viral quantitation, high false negativity, and low sensitivity compared with the antigenemia.¹⁴⁷ PCR detection of viral DNA in blood is a fast and reliable method of early detection of viremia and has become widely used because of its high sensitivity and specificity. No screening is recommended for CMV in asymptomatic patients prior to starting anti-TNF therapy. A careful examination for end-organ manifestations of CMV infection prior to the initiation of the treatment is recommended. The CMV pp65 antigen level or the CMV DNA quantification should be performed in those who are symptomatic and suspected to have CMV infection.

For asymptomatic patients or those with mild disease, no therapy is indicated, and there is no contraindication to continuing the anti-TNF therapy. For patients with severe infection, immunomodulator therapy should be withheld and antiviral treatment instituted.¹⁴¹ Treatment options include ganciclovir (5 mg/kg IV twice daily) for 2–3 weeks; oral valganciclovir after 3–5 days can also be considered. Foscarnet (90 mg/kg IV twice daily or 60 mg/kg IV three times daily) is an available alternative in cases of ganciclovir resistance or intolerance. Cessation of anti-TNF therapy is advised and can be resumed after the infection is resolved.¹⁴⁸ CMV colitis should be considered in the differential diagnosis of IBD exacerbation. Diagnosis should be ruled out, usually by performing a tissue PCR, in the steroid refractory disease before starting another immunosuppressive agent or prior to performing a colectomy.

Human papillomavirus (HPV)

HPV, a member of the *Papillomaviridae* family, is the most common sexually transmitted disease in the US.¹⁴⁹ Several subtypes of HPV have been identified, but the most important subtypes are 16 and 18 which are associated with 70% of HPV-associated cervical cancers.¹⁵⁰ The risk of HPV-associated cancers increases with the use of immunosuppressant agents such as anti-TNF agents.^{151,152} Low-risk subtypes (eg, 1, 2, 4, 6, 11) cause skin warts, while the high-risk strains (eg, 16, 18, 30, 31) are associated with cervical

dysplasia, cervical cancer, rectal carcinoma, and penile, vulvar, vaginal, and oropharyngeal carcinomas.¹⁵³

The majority of HPV infections are silent and asymptomatic, and the virus is usually cleared as a result of cellular immune responses within 1 year.¹⁰² Multiple factors are associated with increased risk, such as age (with highest risk between 35–55 years), cigarette smoking, use of contraceptives, family history, and coexistence of other infections such as HIV.¹⁴² Cervical screening with Pap smears is recommended annually for younger women (<30 years) and every 2–3 years for older women (>30 years) who have had three consecutive annual negative Pap smears. Screening should begin at 21 years of age, or within 3 years of beginning sexual activity.

No systemic antiviral therapy is indicated for patients with HPV infection. Treatment of complications, including dysplasia and cancer, include surgery, chemotherapy and radiotherapy.¹⁵⁴ Primary prevention through vaccination is recommended for all females > 11 years old; secondary prevention is by regular cervical screening. Recent studies recommend the HPV vaccine for males to prevent HPV-associated penile carcinoma.

Parasitic infections

Parasitic infections often cause significant morbidity and mortality in immunocompromised patients.¹⁵³ Only a few case reports are available describing these infections in patients receiving anti-TNF therapy.¹⁵⁵ Some common parasitic infections associated with the use of anti-TNF therapy are described below and summarized in Tables 2 and 3.

Toxoplasma

Toxoplasma gondii, an intracellular protozoan that causes toxoplasmosis, is well described in HIV-positive patients.¹⁵⁶ Felines are the primary host of this protozoan and *T. gondii* oocytes pass with the animal's stool and cause toxoplasmosis if ingested by humans. TNF- α and IFN- γ synergistically inhibit the growth of *T. gondii*.¹⁵⁷ In an immunocompetent host, the primary infection is asymptomatic in 90% of cases. To date, only a few cases of toxoplasmosis in patients receiving anti-TNF agents have been reported, including cases of cerebral toxoplasmosis and chorioretinitis in patients who were treated with either etanercept or infliximab.^{158–160} Diagnosis of toxoplasmosis is usually accomplished by serologic assays, including enzyme-linked immunosorbent assay and detection of the organism's DNA using PCR from blood, CSF, or amniotic fluid.¹⁶¹

The first-line treatment consists of 6 weeks of sulfadiazine (1.0–1.5 g orally every 6 hours) with pyrimethamine (100–200 mg orally loading dose, then 50 mg orally once daily) and folinic acid (10–20 mg orally once daily).¹⁶² In patients allergic to sulfa drugs, the sulfadiazine may be substituted by atovaquone or clindamycin. Infection with toxoplasma can be prevented by consuming properly cooked meat, avoiding close contact with stray cats, avoiding contaminated soil and/or water, and avoiding unscreened blood transfusions. No preventive vaccine is commercially available.

Strongyloides

Strongyloidiasis, caused most commonly by *Strongyloides stercoralis*, is endemic in tropical and subtropical regions with prevalence rates reaching up to 25% in Central America, Latin America, Africa, and Southeast Asia.¹⁶³ Infection occurs either through the penetration of the skin or through an autoinfection by intestinal mucosa penetration in previously infected patients. *Strongyloides* infection, which can be asymptomatic in 30% of cases, usually presents with cutaneous, gastrointestinal, or pulmonary symptoms. In immunocompromised patients, it can also cause accelerated autoinfection called hyperinfection syndrome or disseminated infection. The diagnosis of disseminated infection is confirmed by direct identification of *Strongyloides* rhabditi-form larvae from different clinical specimens: stool, sputum, serum/blood smears, bronchial aspirates, CSF, peritoneal fluid, or ascitic fluid.¹⁶⁴ Serology with enzyme-linked immunosorbent assay can be performed if *Strongyloides* infection is suspected and larvae cannot be detected.¹⁶⁵

Ivermectin (200 μ g/kg/day) for 2 days is the treatment of choice for immunocompetent patients with chronic asymptomatic *Strongyloides* infection. If hyperinfection syndrome or disseminated infection develop, the same treatment should be continued for ≥ 7 –10 days, or until the clinical symptoms are resolved.¹⁶⁶ Chemoprophylaxis with ivermectin to prevent hyperinfection syndrome or disseminated infection is recommended in immunocompromised individuals who are a confirmed asymptomatic chronic carrier, including those receiving anti-TNF therapy.¹⁶⁷

Leishmania

Leishmaniasis is caused by heterogeneous group of *Leishmania* spp, which are intracellular protozoan parasites. Global epidemiological surveillance has shown that *Leishmania* infections affect more than 12 million people worldwide, and 2 million new cases are reported annually.¹⁶⁸ Clinically, two basic forms are recognized: cutaneous

leishmaniasis, a disfiguring and stigmatizing disease, and visceral leishmaniasis or kala-azar, a life-threatening but treatable condition if diagnosed early. TNF- α has a major role in mediating host protection against visceral leishmaniasis,¹⁶⁹ so the use of anti-TNF agents may potentially cause worsening or reactivation of latent infection.¹⁶⁹ Four case reports of visceral leishmaniasis occurring in rheumatoid arthritis patients treated with infliximab have been published.^{169–172} Diagnosis is made by the detection of the parasite in bone marrow or blood, or by PCR assays performed on blood and bone marrow.¹⁷¹

Antileishmanial therapy consists of antimonial compounds (sodium stibogluconate and meglumine antimoniate), miltefosine, and amphotericin B. Liposomal amphotericin B (3.0 mg/kg) is the drug of choice for treatment of visceral leishmaniasis.¹⁷³

Other parasitic infections

Giardia intestinalis is a common pathogenic intestinal parasite of humans that causes acute and chronic diarrhea. *Cryptosporidium* spp are also common parasites, causing significant mortality and morbidity worldwide, especially among immunocompromised patients.¹⁷⁴ However, no increased risk of these parasitic infections associated with use of anti-TNF therapy was found.

Conclusion

Biological therapies targeting TNF- α represent a revolution in the treatment of chronic inflammatory diseases, especially in cases refractory to conventional treatment modalities. They offer significant benefits in disease control and improving quality of life. As anti-TNF blockers are increasingly used in the management of these illnesses, their adverse effects, risk versus benefit analysis, and patient individualization of treatment options must be considered. Patients must be advised about the risk of infections, malignancies, and various other potential adverse effects of anti-TNF therapy.

Disclosure

The authors report no conflicts of interest in this work.

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