

NASPGHAN Clinical Report: Surveillance, Diagnosis, and Prevention of Infectious Diseases in Pediatric Patients With Inflammatory Bowel Disease Receiving Tumor Necrosis Factor- α Inhibitors

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ABSTRACT

Children and adolescents with inflammatory bowel disease (IBD) receiving therapy with tumor necrosis factor α inhibitors (anti-TNF α) pose a unique challenge to health care providers in regard to the associated risk of infection. Published experience in adult populations with distinct autoinflammatory and autoimmune diseases treated with anti-TNF α therapies demonstrates an increased risk of serious infections with intracellular bacteria, mycobacteria, fungi, and some viruses; however, there is a paucity of robust pediatric data. With a rising incidence of pediatric IBD and increasing use of biologic therapies, heightened knowledge and awareness of infections in this population is important for primary care pediatricians, pediatric gastroenterologists, and infectious disease (ID) physicians. This clinical report is the result of a consensus review performed by pediatric ID and gastroenterology physicians detailing relevant published literature regarding infections in pediatric patients with IBD receiving anti-TNF α therapies. The objective of this document is to provide comprehensive information for prevention, surveillance, and diagnosis of infections based on current knowledge, until additional pediatric data are available to inform evidence-based recommendations.

Key Words: infections, pediatric inflammatory bowel disease, tumor necrosis factor α inhibitors

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Treatment of pediatric inflammatory bowel disease (IBD) has evolved considerably and increasingly includes the use of biologic therapies such as tumor necrosis factor α inhibitors (anti-TNF α). In patients with IBD, anti-TNF α therapies such as infliximab and adalimumab are effective in inducing and maintaining remission in patients with moderate to severe Crohn disease (CD) including fistulizing, perianal, and steroid-unresponsive disease and in patients with steroid-dependent, severe, or refractory ulcerative colitis (UC). The goals of therapy with anti-TNF α are mucosal healing and prevention of long-term end-organ damage and delay in growth and development.

The benefits of immunosuppressive treatment should be weighed against potential risks, including infectious complications, and adverse outcomes resulting from withholding biologic therapy for IBD treatment and progression of underlying disease. Factors predisposing patients with IBD to potential infectious complications include severity of underlying IBD, medical comorbidities, malnutrition, leukopenia, surgery, and immunosuppressive medications. Infections complicate any immunosuppressive therapy for IBD, most frequently with glucocorticoids but also other anti-inflammatory medications, anti-metabolites, alkylating agents, and anti-TNF α (1). This risk/benefit analysis should be assessed in each individual patient before starting anti-TNF α therapy; this is particularly important in patients with a history of chronic, recurrent, or opportunistic infections, known exposure to tuberculosis, identifiable risk factors, or with underlying comorbid conditions that may further predispose them to infections.

This clinical report will focus on available infection data associated with the use of infliximab and adalimumab in pediatric patients with IBD. The appraisal of the published literature was divided by infection type among the infectious disease (ID) group members who performed independent systematic reviews of both the adult and pediatric literature using the appropriate keywords in the PubMed database. A Delphi technique was then applied, resulting in an iterative process until full consensus was achieved among the ID physicians who wrote and reviewed each section. The draft report was then reviewed by the pediatric gastroenterology group members, and overall consensus was obtained. There was insufficient pediatric specific data to provide a grading of recommendations assessment, development, and evaluation (GRADE) system regarding the quality of the evidence and strength of recommendation.

Tumor necrosis factor- α (TNF- α) is central to macrophage and phagosome activation, recruitment of neutrophils and macrophages, differentiation of monocytes, formation and maintenance of granulomas, and modulation of the inflammatory process. It is

TABLE 1. Summary of pediatric inflammatory bowel registries evaluating infection events during therapy with TNF- α inhibitors

Registry	Population	N	Anti-TNF α	Infection events
REACH (10)	moderate to severe CD	112	I	Any infection, N = 61 (54.5%); Serious infection, N = 9 (8%)
DEVELOP (11)	CD, UC, IC	2586	I	Serious infection and anti-TNF α within 90 days: 5.82/100 PY; Time dependent I use: aHR 2.00 (95% CI 1.38–2.91)
IMAgINE (12)	moderate to severe CD	152	A	Infectious events in 129 patients (67%), 187.7 events/100 PY; Serious infections in 12 patients (6.3%), 8.6 events/100 pt year; Opportunistic infections in 2 patients, 1.3 events/100 pt year
RESEAT (13)	CD	115	A	No serious or opportunistic infections reported

A = adalimumab; aHR = adjusted hazard ratio; anti-TNF α = TNF- α inhibitor; CD = Crohn disease; CI = confidence interval; DEVELOP = A multicenter, prospective, long-term, observational registry of pediatric patients with inflammatory bowel disease; I = infliximab; IBD = inflammatory bowel disease; IC = indeterminate colitis; IMAgINE = a multicenter, double-blind study to evaluate the safety, efficacy, and pharmacokinetics of the human anti-TNF monoclonal antibody adalimumab in pediatric subjects with moderate to severe Crohn disease; N = number of IBD patients receiving anti-TNF α ; PY = patient-years; REACH = a randomized, multicenter, open-label study to evaluate the safety and efficacy of anti-TNF α chimeric monoclonal antibody in pediatric subjects with moderate-to-severe Crohn disease; RESEAT = retrospective evaluation of the safety and effect of adalimumab therapy; UC = ulcerative colitis.

proposed that anti-TNF α agents block both soluble and cell-associated TNF- α forward signaling and induce reverse signaling leading to cell activation, apoptosis, or cytokine suppression (2). The use of anti-TNF α can reduce IBD inflammation, while at the same time inhibiting the normal inflammatory responses against infectious agents, thus rendering the IBD patient immunosuppressed. Data from adults have linked targeted blockade of TNF- α to infections caused by bacteria, mycobacteria, fungi, viruses, and parasites. In particular, infections caused by pathogens that are intracellular or dependent on macrophages and granuloma formation for killing occur at higher rates in adults treated with anti-TNF α agents compared with adults treated with other immunosuppressive medications. A comprehensive review of infections described with anti-TNF α use across distinct populations is beyond the scope of this clinical report and has been published elsewhere (3–5). In a systematic review and meta-analysis of randomized controlled clinical trials in adults receiving infliximab or adalimumab therapy for rheumatoid arthritis, the pooled odds ratio for serious infection was 2.0 (95% CI 1.3–3.1), with a number needed to harm of 59 (95% CI 39–125); infections most commonly occurred within 3 to 6 months of starting anti-TNF α therapy (6). Similarly, a recent meta-analysis of randomized controlled trials performed in adults with IBD, who received any anti-TNF α compared with placebo, found the relative risk (RR) of developing an opportunistic infection to be significantly higher with anti-TNF α use (RR 2.05, 95% CI 1.1–3.85) (7). In summary, these studies indicate that therapy with anti-TNF α therapy independently increases the risk of infection.

The comparison of serious infections in patients receiving adalimumab for both rheumatologic and gastrointestinal (GI) indications noted infection rates of 1.4 to 6.6 events/100 person-years in adults versus 2 events/100 person-years in children (8). It is important to highlight some differences between pediatric and adult patients with IBD that could theoretically predispose the pediatric patient to infections when receiving anti-TNF α therapy. Compared with their adult counterparts, children with IBD have more extensive GI disease, are more likely to require systemic steroids, and may have a more severe disease course that leads to earlier development of complications (9). Robust pediatric specific data, however, are lacking.

Whether there is an absolute increased risk of infection, in particular of serious infections in children and adolescents with IBD, receiving anti-TNF α therapies is unknown. Lack of uniformity in case definitions and severity of infections, differences in study design, concomitant use of immunosuppressive therapy, and other comorbidities limit comparisons across studies. A serious (or

severe) infection has been defined in most studies as an infection that requires hospitalization or parenteral antimicrobial therapy. Given the lack of large population-based cohort studies, reports of infections in children receiving anti-TNF α therapies have been derived mainly from pharmacoepidemiological and registry studies evaluating the safety and efficacy of infliximab (REACH, DEVELOP) and adalimumab (IMAgINE, RESEAT) and are summarized in Table 1 (10–13). Case reports provide additional sources of pediatric data suggesting an association of anti-TNF α therapy and infection. A recent meta-analysis of 65 pediatric studies reported that the rate of serious infections among pediatric patients with IBD treated with anti-TNF α was significantly lower than adult rates (14). Of the 5528 children included, the rate of serious infections in pediatric patients with IBD receiving anti-TNF α therapy (352/10,000 patient-years of follow-up [PYF]) was similar to the expected rates in pediatric patients receiving immunomodulator monotherapy, but rates were significantly lower than the expected rate for children receiving corticosteroids (730/10,000 PYF). A systematic literature review of infections in children with IBD receiving anti-TNF α therapies reported serious infections occurring infrequently (incidence of 0%–10%) but were quite varied, including reports of disseminated varicella, *Listeria* meningitis, histoplasmosis, invasive pulmonary aspergillosis, systemic nontuberculous mycobacterial (NTM) infection, disseminated cytomegalovirus (CMV), bacterial sepsis, and *Pneumocystis jirovecii* pneumonia (15). Most frequently, children receiving anti-TNF α therapies most frequently had mild, viral upper respiratory infections (incidences ranging from 3%–77%).

Prevention is the foundation of pediatric medical practice. The National European and Canadian pediatric (16,17) and adult position statements (18,19) provide some ID screening guidance, summarized in supplementary Table 1 (<http://links.lww.com/MPG/A637>). In general, the adult literature, both in rheumatology and gastroenterology patients, recommends testing for *Mycobacterium tuberculosis*, hepatitis B, hepatitis C, and human immunodeficiency virus (HIV) before initiating anti-TNF α (19–21). There are, however, no US consensus statements to guide practices for the screening, monitoring, or prevention of infections before initiating anti-TNF α therapies in pediatric patients with IBD. This clinical report is a consensus document that resulted from reviews performed by pediatric ID and gastroenterology physicians of the relevant published literature regarding infections in adult and pediatric patients with IBD, receiving anti-TNF α therapies. Until additional pediatric data are available to inform evidence-based recommendations for children with IBD, this consensus document provides health care

professionals with information regarding the risk of serious infections and guidance for prevention, surveillance, and diagnosis of infections in pediatric patients with IBD who are or will be receiving anti-TNF α therapies.

In general, any pediatric patient with a new IBD diagnosis is a potential candidate for anti-TNF α therapy. Therefore, we recommend that screening evaluations with risk factor assessment be performed at the initial IBD diagnosis visit and before any immunosuppressive therapies are initiated. Heightened awareness, vigilant surveillance, routine and systematic preventive screening and counseling, and a high index of suspicion for infection leading to prompt diagnosis and institution of effective therapy are imperative for optimal outcomes in pediatric patients with IBD.

Summary of Findings Regarding Infection and anti-TNF α Therapy in Adult and Pediatric Patients With IBD

- (1) Underlying IBD activity and severity are independently associated with the risk of a serious infection in adults (22).
- (2) Patients receiving corticosteroid doses of $\geq 2 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$ or $\geq 20 \text{ mg/day}$ of prednisone or equivalent for ≥ 2 weeks, and higher doses of methotrexate ($>0.4 \text{ mg/kg/week}$), azathioprine ($>3 \text{ mg/kg/day}$), 6-mercaptopurine ($>1.5 \text{ mg/kg/day}$), or anti-TNF α therapy are considered to have a high level of immunosuppression (23). There is a trend to increased numbers of infections in infliximab-treated patients and in patients who received anti-TNF α therapy concomitantly with other immunosuppressive agents (most commonly methotrexate or corticosteroids) (12,24,25). For patients receiving ≥ 2 immunomodulatory medications, the risk of infection is almost 15-fold higher (OR 14.5, 95% CI 4.9–43) (24). The risk of infection may also vary with the type and duration of exposure to anti-TNF α therapy, with higher risk occurring shortly after starting anti-TNF α therapy (within 3–6 months).
- (3) Granulomatous infections caused by bacteria, mycobacteria, and fungi are the most frequently described infections in patients receiving anti-TNF α therapies. A total of 556 granulomatous infections were reported to the Food and Drug Administration (FDA) among 346,000 patients with distinct underlying conditions (eg, rheumatologic, IBD) treated with anti-TNF α therapy from June 1998 to September 2002, totaling rates of 239/100,000 patients treated with infliximab (26).
 - (a) More than 70% of these granulomatous infections occurred within 3 to 6 months of starting infliximab therapy, suggesting the possibility of reactivation of latent infection.
 - (b) *M tuberculosis* was the most frequent granulomatous infection reported in 54/100,000 infliximab-treated patients. Infections caused by NTM were reported with 10-fold lower frequency than *M tuberculosis* infections.
 - (c) Fungal infections were frequent, reported in 10 to 37/100,000 infliximab-treated patients and included histoplasmosis, candidiasis, aspergillosis, and coccidioidomycosis (26). Infections with dimorphic fungi should be considered in the differential diagnosis of pneumonia in patients receiving anti-TNF α therapies.
 - (d) Other granulomatous infections reported included those due to *Salmonella*, *Listeria*, *Brucella*, and *Bartonella* spp.
- (4) In general, anti-TNF α therapy should be discontinued during any severe infection. Uniform recommendations regarding resumption of anti-TNF α therapy after infections cannot be made. If and when anti-TNF α therapy can be restarted

following the resolution of an infection depends on multiple factors (eg, host factors, pathogen characteristics, and severity of infection and underlying disease); each situation should be evaluated case by case. When available, data from published reports are included in each section.

- (5) Updates regarding postmarket drug safety communications from the United States (US) FDA for providers can be found at: <http://www.fda.gov/drugs/drugsafety/postmarketdrugsafetyinformationforpatientsandproviders/ucm109340.htm>.

Invasive and Unusual Infections in Patients With IBD Receiving TNF- α Inhibitors

In the following sections, relevant information regarding infections occurring in patients with IBD who are receiving anti-TNF α inhibitors is presented and summarized in Table 2.

Bacterial Infections

IBD independently predisposes patients to bacterial infections. It is important to obtain a detailed history from the patient regarding previous bacterial infections. Perianal abscesses are a known complication of ongoing GI inflammation in patients with IBD. Data concerning an increased risk of postoperative bacterial infections after elective IBD surgery in patients receiving anti-TNF α therapies are inconclusive (27,28). Corticosteroid therapy carries a greater risk of bacterial infections in patients with IBD compared with anti-TNF α therapies. Sporadic cases of bacteremia and sepsis with *Staphylococcus aureus*, coagulase-negative staphylococci, and *Escherichia coli*, at times associated with the use of central venous catheters, however, have been described in pediatric patients with IBD receiving anti-TNF α therapy (15). Severe neutropenia associated with anti-TNF α therapy has been reported and is an additional risk factor for invasive bacterial and fungal infections. Data regarding overall increased risk of bacterial infections among patients with IBD who receive anti-TNF α therapies are conflicting, though there is an increased incidence of infections with intracellular bacteria in other groups of patients receiving anti-TNF α (6,29,30). It is recommended that the anti-TNF α therapy not be administered during severe bacterial infections requiring antibiotic therapy. TNF- α is integral in the T-cell-mediated immune destruction of intracellular pathogens; thus infections with specific intracellular bacteria are reviewed herein.

***Bartonella* spp. and *Brucella* spp.**

Background. Infections with *Bartonella* and *Brucella* spp. are potential zoonotic granulomatous infections that have been reported in adult patients receiving anti-TNF α therapies. *Bartonella* spp. and *Brucella* spp. infection rates of <1/100,000 patients have been associated with infliximab use (26). There have been no published cases of bartonellosis or brucellosis in children with IBD receiving anti-TNF α therapies.

Epidemiology. Cats are a natural reservoir for *Bartonella henselae*; contact with kittens (that are asymptomatic but more likely to have bacteremia) is associated with human infection resulting from inoculation of the bacteria through a scratch or bite, or via hands contaminated by flea feces touching an open wound or mucosal surface (eg, conjunctiva). Brucellosis is a zoonotic disease of wild and domestic animals transmissible to humans via exposure to animal tissues and infected fluids. Transmission can occur through inoculation of mucous membranes, cuts in the skin, inhalation of contaminated aerosols, or ingestion of infected foods (most commonly unpasteurized dairy products).

TABLE 2. Summary of infectious disease screening and diagnostics in candidates and recipients of anti-TNF α therapy with IBD

Infection/agent	Risk associated with anti-TNF α ?	Reported case in child with IBD, receiving anti-TNF α ?	Recommended interventions before starting anti-TNF α		Vaccination	Suggested diagnostics, if clinically indicated
			Screening	Vaccination		
Bacteria						
<i>Brucella</i> spp.	+	No	RF (eg, exposure to animals, unpasteurized dairy products)	N/A	Culture (blood, bone marrow, and body fluid); Serology	
<i>Bartonella</i> spp.	+	No	RF (eg, exposure to kittens)	N/A	Serology, histopathology and staining (tissue), PCR (tissue), and culture	
<i>Clostridium difficile</i>	-	Yes, not \dagger	No	N/A	Stool PCR	
<i>Legionella</i> spp.	++	No	RF (eg, dietary history, especially during outbreaks)	N/A	Urinary antigen, culture (respiratory specimens, tissue, sterile site), serology, PCR (BAL, urine)	
<i>Listeria</i> spp.	+	No	No	N/A	Culture (blood, tissue, CSF, sterile sites)	
<i>Nocardia</i> spp.	+	No	No	N/A	Culture (blood, respiratory specimens, tissue, body fluids)	
<i>Salmonella</i> spp.	++	No	RF (eg, exposure to reptiles, dietary history during outbreaks)	N/A	Culture (stool, blood, tissue, body fluids)	
Fungi						
<i>Aspergillus</i> spp.	++	Yes	RF (eg, exposure to construction)	N/A	Histopathology (tissue, sterile site), culture (respiratory specimens, tissue), BAL for galactomannan (BAL), PCR (BAL, tissue)	
<i>Candida</i> spp.	++	Yes	No	N/A	Culture, histopathology (tissue, sterile site), PCR (blood, sterile sites, tissue)	
Coccidioidomycosis	++	No	RF (eg, exposure to endemic area)	N/A	Culture (BAL, tissue, CSF), histopathology (tissue), PCR, serologies (blood, CSF)	
Cryptococcosis	++	No		N/A	Culture, antigen detection (blood, CSF), neuroimaging, lumbar puncture (with opening pressure), ophthalmological examination	
Histoplasmosis	+++	Yes	RF (refer to Table 3 and text)	N/A	Culture, histopathology (BAL, tissue), antigen detection (urine and blood), serology	
<i>Pneumocystis jirovecii</i> (formerly <i>P carinii</i>)	++	Yes	No	N/A	Microscopy with staining, PCR (sputum, BAL), histopathology, (1–3) β -D-glucan assay	
Mycobacteria	+++	Yes	RF and DT (TST and IGRA; refer to Table 1 and text for details)	N/A	AFB culture (sputum, BAL, gastric aspirate, CSF, sterile site), PCR (sputum, BAL, CSF, sterile site), TST, IGRA, imaging as clinically indicated	
NTM	+	Yes	No	N/A	Culture (respiratory specimens, wounds, tissue, sterile sites), PCR (tissue)	
Viruses						
Community respiratory viruses	-	Yes	DT in symptomatic individuals	Influenza vaccine	PCR (nasopharyngeal or respiratory specimen)	
CMV	+	Yes	No	N/A	Histopathology and immunohistochemistry (tissue), PCR (tissue, blood, vitreous), viral culture (tissue)	
EBV	-	Yes, not \dagger	No	N/A	Serology, PCR (tissue, blood), histopathology and immunohistochemistry (tissue)	
HBV	++	No	RF and DT	HBV vaccine	HBsAg, anti-HBs, anti-HBe, HBV DNA NAAT	
HCV	- \wedge	No	RF (if RF identified, then perform DT)	N/A	anti-HCV and HCV RNA NAAT	
HIV	-	No	DT \geq 13 years of age (if hospitalized) or \geq 15 years of age (with RF)	N/A	HIV antibody/antigen combination immunoassay, HIV RNA PCR	
VZV	+++	Yes	DT (VZV IgG)	VZV vaccine [#]	VZV PCR (scraping of base of vesicular lesion, blood, CSF)	

*No known increased risk of disease. ⁺ Increased risk of disease lowest. ⁺⁺ Intermediate risk. ⁺⁺⁺ Strong risk. ^{\dagger} No clear data for increased incidence related to anti-TNF α . ^aNo clear association but progression. AFB = acid fast bacilli; anti-HBs = hepatitis B core antibody; anti-HBs = hepatitis B surface antibody; BAL = bronchoalveolar lavage; CMV = cytomegalovirus; CSF = cerebrospinal fluid; DT = diagnostic testing for screening and guiding management strategies; EBV = Epstein-Barr virus; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; IGRa = interferon-gamma release assay; N/A = not applicable; NAAT = nucleic acid amplification test; NTM = nontuberculous mycobacteria; PCR = polymerase chain reaction; RF = risk factor assessment; TST = tuberculin skin test; VZV = varicella-zoster virus.

[#]Live virus vaccines (eg, varicella) should be provided to nonimmune patients, if not already immunosuppressed, and the vaccination can safely be dispensed \geq 4 weeks before starting immunosuppressive medications. Refer to Table 4 for additional vaccine information.

Clinical Data. *Bartonella* infections, or cat-scratch disease, may present with fever and regional lymphadenopathy and up to 25% may spread hematogenously to cause disseminated disease including granulomatous lesions in the liver, spleen, and bones, meningoencephalitis, neuroretinitis, and endocarditis.

Clinical manifestations of *Brucella* spp. infections are non-specific including fever, malaise, night sweats, and headache. In children, abdominal pain and arthralgia are common and may relate to physical examination findings of hepatosplenomegaly and arthritis. Brucellosis may also present with fever and pancytopenia. In immunocompromised patients, prolonged fevers without a source and complications such as osteomyelitis, endocarditis, and meningitis may occur.

Diagnostic Testing. *B henselae* is fastidious and thus recovery in routine bacterial cultures is difficult. Serologic testing and direct testing of tissue (lymph node) or body fluids (cerebrospinal fluid [CSF], pleural) by staining and *Bartonella* polymerase chain reaction (PCR) are useful for diagnosis. *Brucella* spp. can be isolated in culture of blood, bone marrow, or sterile tissue; however, the microbiology laboratory should be contacted and made aware of the clinical suspicion for optimal processing. Serologic testing (serum agglutination test) is also used with a 4-fold rise in antibody titers obtained 2 to 4 weeks apart confirming the diagnosis. Caution when interpreting serologic results in immunocompromised hosts is warranted because the ability to mount an antibody response may be attenuated.

Screening Before Anti-TNF α . No data to support routine laboratory screening. Consider screening for risk factors (eg, exposure to animals or consumption of unpasteurized dairy products).

Prevention/Isolation/Control Measures: Standard Precautions. Screening for a history of animal exposure before initiating immunosuppressive therapy is encouraged, with appropriate safe living guidance provided. Immunocompromised people should avoid contact with cats that scratch or bite, young cats (<12 months), and all strays. In addition, all of the household pets should receive appropriate veterinary care, be up-to-date with vaccinations, and receive appropriate flea control measures. Proper hand hygiene after exposure to animals and thoroughly washing any scratches or bites promptly with soap and water is imperative. Pasteurization of dairy products for consumption is recommended.

Legionella pneumophila

Background. In September 2011, the US FDA added a boxed warning based on 80 adult cases of *Legionella* infection in patients receiving anti-TNF α therapies reported to the FDA's Adverse Events Reporting System from 1999 to 2010, including 14 deaths (31). Most patients presented with pneumonia and had been receiving anti-TNF α therapies for a median of 10.4 months (range 1–73). Most important, the majority of patients were also receiving concomitant methotrexate, corticosteroids, or both. A second episode of confirmed legionellosis has been reported following reintroduction of anti-TNF α therapy; thus, caution is warranted if immunosuppressive therapies are resumed (32). Pediatric legionellosis has been reported in immunocompromised patients, those with underlying pulmonary disease, neonates, and children receiving systemic corticosteroids. No cases of legionellosis in children with IBD receiving anti-TNF α therapies were found in the literature.

Epidemiology. Infection is acquired through the inhalation of aerosolized water (shower, aerosol producing devices, and humidifiers) contaminated most commonly with *L pneumophila* in

hospital, home, and public settings. Methods of treatment of municipal water supplies affect the risk of disease within a geographic area. In the US, proven cases are reportable to local and state health departments.

Clinical Data. Legionellosis can manifest as Legionnaires disease or Pontiac fever. Legionnaires disease is characterized by high fever, GI symptoms, and mild-to-severe pneumonia. Hyponatremia and failure to respond to β -lactam antibiotics in a patient with pneumonia and diarrhea should increase the suspicion for *Legionella* infection. Complications include hepatic and renal dysfunction, and hematologic derangements (thrombocytopenia, DIC). Extrapulmonary disease with *Legionella* spp. is rare but occurs in immunocompromised patients and most commonly in a health care environment. Suppurative arthritis, sinusitis, and endocarditis have been reported and have higher mortality rates. Pontiac fever is a milder, self-limited influenza-like illness without lower respiratory disease.

Diagnostic Testing. A combination of bacterial culture and *Legionella* antigen detection is optimal for diagnosis. Isolation of *L pneumophila* from respiratory tract specimens, lung tissue or fluid, or from a normally sterile site confirms *Legionella* infection. Detection of urinary *Legionella* antigen is sensitive and highly specific for *L pneumophila* serotype 1 but will not detect other species and serotypes that can account for up to 10% of infections. Serology is available but may not be useful in immunocompromised patients. Chest X-ray findings are nonspecific, including unilobar airspace disease, interstitial infiltrates, and pleural effusions. In immunocompromised patients, nodular infiltrates may be seen and may cavitate.

Screening Before Anti-TNF α . No data to support routine laboratory screening.

Prevention/Isolation/Control Measures: Standard Precautions. Avoidance of known exposures to water sources that may not be completely treated according to recommended standards (eg, monochloramine treatment of municipal water supplies), especially in pediatric patients with IBD receiving anti-TNF α therapy and corticosteroids or with underlying lung disease, is prudent. Use of sterile water is recommended for the filling and terminal rinsing of nebulization devices used by immunocompromised individuals (33).

Listeria monocytogenes

Background. *L monocytogenes* is an intracellular bacterium for which TNF- α has a crucial role in host defense. In September 2011, the FDA released a drug safety communication updating the boxed warnings for the anti-TNF α class of biologics to include the risk of infections with *Listeria* species (spp.) (31). The report summarized the cases of serious infections due to *L monocytogenes*, including 7 deaths. Notably, the majority of patients were receiving combination therapy with anti-TNF α and another immunosuppressive drug (corticosteroids or methotrexate, most frequently). Cases of *Listeria* bacteremia and meningitis have been reported in pediatric patients with IBD (34–36). More important and similar to their adult counterparts, listeriosis occurred while receiving corticosteroid therapy and in 2 children, soon (3–7 days) after the addition of infliximab.

Epidemiology. Listeriosis is a relatively uncommon infection that can cause severe disease in immunocompromised hosts. Infection is caused by the intracellular Gram-positive diphtheroid

L. monocytogenes and is most commonly transmitted via ingestion of contaminated food products by immunocompetent and immunocompromised hosts (37). Foods implicated in transmission include soft cheeses, unpasteurized milk and milk products, raw produce, and ready-to-eat delicatessen products. Infection with *Listeria* carries a case fatality rate of 21%, among the highest of all food-borne pathogens per the Centers for Disease Control and Prevention (CDC) surveillance systems (38).

Clinical Data. The most common clinical syndromes of invasive listeriosis in immunocompromised patients are septicemia and central nervous system (CNS) infections including meningitis, encephalitis (rhombencephalitis), and parenchymal brain abscesses (37). Enteroinvasive GI disease, hepatic dysfunction, endophthalmitis, and endocarditis have also been described.

Diagnostic Testing. Identification of the organism by culture of the blood or other sterile sites, especially CSF confirms disease. Listeriosis is a notifiable disease to local and state public health departments in the US.

Screening Before Anti-TNF α . No data to support routine laboratory screening. Dietary history may be helpful in identifying patients at risk, especially during known outbreaks.

Prevention/Isolation/Control Measures: Standard Precautions. Food counseling advice was effective in decreasing the number of food-borne infections in a national cohort of patients receiving anti-TNF α therapies (39). Patients should be advised to avoid raw or unpasteurized milk and milk products (including soft cheeses), hot dogs, fermented and dry sausage, delicatessen meats, refrigerated smoked seafood, and other high-risk foods. Observe safe food preparation, consumption, and storage. Encourage appropriate washing and handling of foods and thoroughly cooking meats. Wash hands before and after handling any raw produce and promptly refrigerate and consume cut fruits and vegetables. Avoid prolonged storage of prepared ready-to-eat delicatessen foods such as meats and other prepackaged cold foods.

Nocardia species

Background. Ten cases of infection with *Nocardia* spp. were reported to the FDA among 233,000 adults with IBD receiving infliximab therapy, for a rate ratio of 4.85/100,000 treated patients (26). Most case reports in adults with IBD have occurred while receiving anti-TNF α therapy and corticosteroids or cyclosporine. One case of disseminated nocardiosis in an adolescent with CD receiving 6MP and corticosteroids was found in the literature, but there are no reported cases in pediatric patients with IBD receiving anti-TNF α (40).

Epidemiology. Nocardiosis is caused by multiple *Nocardia* spp., which are ubiquitous in soil, organic matter, and water. Invasive disease occurs in immunocompromised patients, most commonly via inhalation or via direct inoculation of traumatized skin with contaminated soil.

Clinical Data. Manifestations of nocardiosis include primary cutaneous, pulmonary, CNS, and disseminated disease. Pulmonary disease is the most common manifestation and may be acute, subacute, or chronic. Hematogenous dissemination from the lung to other organs may occur, including the liver, spleen, and skin, but with particular proclivity for the brain, leading to abscess formation.

Diagnostic Testing. *Nocardia* spp. are slow growing organisms; their isolation from bacterial cultures of blood, body fluids, or tissue specimens is diagnostic. The presence of beaded, branching Gram-positive rods that may be acid-fast in a relevant specimen, is suggestive of nocardial infection. The lab should be notified if *Nocardia* spp. are suspected. In immunocompromised patients with proven *Nocardia* pneumonia, neuroimaging is warranted to evaluate for CNS abscess formation, which may be asymptomatic.

Screening Before Anti-TNF α . No data to support routine laboratory screening.

Prevention/Isolation/Control Measures: Standard Precautions. *Nocardia* spp. are ubiquitous in the environment. Prompt and thorough cleaning of open wounds after contact with contaminated soil and avoiding inhalation of soil-contaminated dust are recommended.

Salmonella species

Background. *Salmonella* spp. are the most frequently reported cause of foodborne infection, with US rates of 15.9 cases/100,000 population in 2013 (41). There are sporadic reports of infections with *Salmonella* spp. in adults receiving anti-TNF α therapy; no cases were found in pediatric patients with IBD receiving anti-TNF α therapy (26,42).

Epidemiology. Principal reservoirs for *Salmonella* spp. include birds, mammals, reptiles, and amphibians. Contact with infected reptiles, amphibians, and rodents can result in transmission of *Salmonella* spp. and the development of the disease. Pet turtles and iguanas are notorious as the source of *Salmonella* infections in young children. Transmission to humans is primarily via foods, including poultry, eggs, beef, and dairy products or via fecal oral contamination of food products or water.

Clinical Data. Infection usually starts within the GI tract, primarily the distal small intestine and colon, but may disseminate hematogenously, causing osteomyelitis or meningitis as the most serious manifestations of infection. Clinical manifestations in adults receiving anti-TNF α therapies for both rheumatologic diseases and IBD clinical manifestations have included gastroenteritis, urinary tract infections, bacteremia, sepsis, acute cholecystitis, suppurative arthritis, and pyomyositis. Invasive infection is more likely in younger children and those who are immunocompromised.

Diagnostic Testing. Isolation of *Salmonella* spp. from cultures of stool, blood, biliary fluid, CSF, or other usually sterile body fluids confirms the diagnosis. Children, who present with severe colitis, should have stool specimens submitted for culture (43). *Salmonella* is a notifiable disease to local and state public health departments in the US.

Screening Before Anti-TNF α . No data to support routine laboratory screening. Assess risk by asking patients about contact with pets or other animals or consumption of foods involved in outbreaks.

Prevention/Isolation/Control Measures. Standard plus Contact Precautions for the duration of the GI illness. Prevention measures are similar to those provided for *Listeria* and *Nocardia* (above) and include good hand hygiene, proper food handling and preparation (avoidance of ingestion of raw eggs, undercooked meats, and unpasteurized dairy products), and avoiding exposure to reptiles,

rodents, and animals at petting zoos or farms. Patients should be advised against having pet turtles, iguanas, or other reptiles (44).

Fungal Infections

TNF- α is important in ensuring a robust cell-mediated immune response, including granuloma formation, in response to a fungal infection. Receipt of anti-TNF α therapies increases the risk of fungal infections regardless of underlying medical conditions or other concomitant immunosuppressive medication in adults. TNF- α inhibition leads to both a blunted immune response to new exposure and allows for reactivation of fungal infections that had been previously controlled (45). It is important to obtain a detailed history from the patient regarding previous fungal infections, past and current exposures, and potential high-risk activities. Patients with a history of previous mold infection or colonization with pathogenic fungi, who perform high-risk outdoor activities or travel to endemic areas, may be at increased risk of invasive fungal infections after anti-TNF α therapy (46).

Practitioners caring for patients with IBD receiving anti-TNF α therapies should have a high index of suspicion because many signs and symptoms of possible systemic fungal infection including fever, malaise, weight loss, sweats, and abdominal pain may overlap with IBD symptoms. Patients who live in or travel to endemic areas should be monitored closely for the development of signs and symptoms of histoplasmosis, coccidioidomycosis, and blastomycosis during and after anti-TNF α treatment (47). A timely and complete diagnostic evaluation and targeted antifungal therapy are needed in these patients for optimal outcomes. In general, anti-TNF α therapy should not be administered in the setting of an invasive fungal infection, and consultation with an ID specialist is recommended.

Aspergillosis spp.

Background. The first case report of *Aspergillus fumigatus* pneumonia following anti-TNF α therapy occurred in a 25-year-old man with CD who received the first dose of infliximab 5 days before the onset of infection (48). Delayed recognition of this mold as a potential pathogen in a patient with no other risk factors for invasive fungal disease and rapid disease progression likely contributed to his death. Since then, an additional 39 cases of invasive infections with *Aspergillus* spp. have been reported to the FDA, resulting in rates of 7 to 12.4 cases/100,000 patients receiving infliximab and resulting in a poor prognosis (26,49). A pediatric case of invasive pulmonary aspergillosis has been reported in a 15-year-old boy with panenteric CD, after receiving 20 doses of adalimumab and methotrexate, who died from sepsis and multiorgan failure (50).

Epidemiology. *Aspergillus* spp. are ubiquitous environmental fungi, found in soil and rotting vegetation. The most common route of transmission is via inhalation from environmental sources. Less commonly, direct inoculation of skin may cause disease in high-risk patients. Typical risk factors for invasive disease include prolonged and severe neutropenia and receipt of systemic corticosteroids. *Aspergillus* contamination of marijuana has also been implicated in pulmonary aspergillosis in immunocompromised hosts.

Clinical Data. Infection most commonly leads to pulmonary disease, though invasive sinusitis, rhinoorbital, and CNS disease, osteomyelitis, endocarditis, endophthalmitis, GI, and cutaneous manifestations may also occur. *Aspergillus* spp. have a proclivity for angioinvasion; thus, immunocompromised hosts should be evaluated for disseminated infection.

Diagnostic Testing. Proven disease is defined by isolation of the mold in culture or identification of septate, branching fungal hyphae

consistent with *Aspergillus* spp. invading diseased tissue on histopathology from a sterile site specimen.

Screening Before Anti-TNF α . No data to support routine laboratory screening. Assessing for construction or remodeling in the home and high-risk behaviors is prudent.

Prevention/Isolation/Control Measures. Standard precautions in health care settings. Avoidance of possible environmental exposures.

Candidiasis

Background. TNF- α enhances polymorphonuclear leukocyte recruitment, phagocytosis, and killing in response to systemic candidal infections. There have been reports of invasive candidal infections in patients with IBD receiving anti-TNF α therapy, most frequently associated with infliximab. Estimated rates of 5 to 20 cases/100,000 treated patients have been reported (26,46,49). Candidemia associated with central venous catheters and invasive systemic diseases, including osteomyelitis have been described in children receiving anti-TNF α therapies (15,50,51).

Epidemiology. *Candida* spp. can be present on mucosal surfaces, including mouth, and GI and genitourinary tracts, without causing disease. Most infections caused by *Candida* spp. result from endogenous invasion. Neutropenia, disruption of mucosal barriers, and receipt of systemic corticosteroids and other immunosuppressive agents increase the risk of invasive infection. Patients requiring long-term central venous catheters, abdominal surgeries, receipt of intravenous alimentation, or broad-spectrum antibiotics are at risk for *Candida* infections.

Clinical Data. Clinical manifestations vary from localized oropharyngeal and esophageal candidiasis to more invasive diseases including bloodstream infections (candidemia), osteomyelitis, endocarditis, and endophthalmitis. In patients with persistent candidemia, additional diagnostic evaluation for a deeper focus of infection is warranted, including a dilated ophthalmological examination to evaluate for endophthalmitis and a cardiac echocardiogram when candidemia is associated with a central venous catheter (52).

Diagnostic Testing. Proven disease requires isolation of *Candida* spp. from sterile body sites or demonstration of yeast-like organisms in tissue biopsies from sterile sites.

Screening Before Anti-TNF α . No data to support routine laboratory screening. In patients with known history of *Candida* colonization or infection, information regarding the *Candida* spp. and antifungal susceptibilities may guide empiric antifungal therapy, when clinically indicated.

Prevention/Isolation/Control Measures: Standard Precautions. Judicious antimicrobial usage, meticulous care of central venous catheters and other medical devices, and reduction of immunosuppression as soon as clinically feasible reduce the risk of candidemia. Prophylactic antifungal agents for the prevention of *Candida* infections are not recommended routinely.

Coccidioidomycosis spp.

Background. Most cases associated with anti-TNF α therapies in the literature occurred in patients from endemic areas or after intense exposure (53,54). The risk of coccidioidomycosis in these patients with inflammatory arthritis was higher when compared

with patients not receiving anti-TNF α therapies. Most patients were receiving concomitant immunomodulatory therapies and presented with pneumonia or disseminated disease. No cases in pediatric patients with IBD receiving anti-TNF α therapies were found in the literature.

Epidemiology. *Coccidioides immitis* and *Coccidioides posadasii* are dimorphic fungi endemic to the soil of the southwestern United States, Mexico, and Central and South America. Inhalation of *Coccidioides* spores results in acute, primary infection. Coccidioidomycosis may also result from the reactivation of previous infection.

Clinical Data. Initial inhalational exposure can result in asymptomatic, subclinical, or symptomatic infection. One half to two thirds of infections in immunocompetent hosts are subclinical; however, infections in immunocompromised hosts are more likely to progress to symptomatic disease, are frequently more severe, and carry a higher mortality rate. Pneumonia is the most common clinical presentation and is associated with dyspnea, pleurisy, or musculoskeletal pain. Constitutional symptoms including fever, fatigue, myalgia, arthralgia, and weight loss are frequent. The pneumonia is indistinguishable from other community-acquired bacterial, viral, or fungal infections, and, thus, specific diagnostic testing is required. In <10% of cases, residual pulmonary sequelae develop. Dermatologic manifestations (eg, erythema nodosum or multifforme) occur more commonly in children and may be associated with pulmonary infection or may be the sole manifestation of disease. Extrapulmonary disease may be more common in patients receiving anti-TNF α medications and other immunosuppressants (eg, high-dose corticosteroids). Disseminated disease involving bones and joints, CNS, and skin occurs more frequently in adults than in children.

Diagnostic Testing. Diagnostic yield is improved by using multiple testing methods, and the microbiology laboratory should be informed if there is clinical suspicion of coccidioidomycosis. Culture of infected tissue (sputum, bronchoalveolar lavage [BAL] fluid, or other tissue) using fungal media is the criterion standard for diagnosis. Blood, CSF, pleural, and peritoneal fluids, however, are less likely to have a positive culture result. Histopathology is less sensitive than culture, but direct visualization of the characteristic spherule containing endospores in infected fluid or tissue confirms infection with *Coccidioides* spp. Serologic testing may be helpful for diagnosis and monitoring of therapy but should be interpreted with caution in immunocompromised hosts with low or negative titers, as false-negative serologic testing has been described in immunocompromised patients with proven coccidioidomycosis (55). Enzyme-linked immunoassays for IgM and IgG antibodies are more sensitive, whereas detection by immunodiffusion or complement fixation is more specific for coccidioidomycosis. Serology can be detected as early as 1 to 2 weeks after primary infection but may lag weeks behind illness onset, especially in immunocompromised hosts; thus, repeat testing may be warranted. Persistent, high titers ($\geq 1:16$) are associated with severe and disseminated disease. As only 15% of CSF cultures are positive, CNS coccidioidomycosis is generally diagnosed by detecting complement fixing IgG antibody in CSF.

Screening Before Anti-TNF α . Not recommended routinely. Limited data regarding screening exist in solid organ transplant recipients living in endemic areas. In these transplant centers, *C. immitis* serologies (IgM and IgG) and chest radiographs were obtained before the institution of immunosuppressive therapies, and azole prophylaxis was offered to transplant patients at higher risk for

reactivation of coccidioidomycosis (56,57). It should be recognized, however, that the intensity of immunosuppression is different when comparing transplant recipients to patients receiving monotherapy with anti-TNF α agents. Furthermore, many cases of coccidioidomycosis after anti-TNF α therapy represent an acute infection and would not be detected with prescreening serology. Prophylaxis may be a consideration for certain patients receiving anti-TNF α therapy and higher doses of systemic corticosteroids, who live in endemic areas or have a history of a previous episode of coccidioidomycosis, but given the paucity of data, no firm recommendations can be provided (58). Although antifungal prophylaxis reduces the risk of infection, it does not eliminate it.

Prevention/Isolation/Control Measures: Standard Precautions. Patients should be advised to avoid endemic areas. For patients who live in endemic areas, avoidance of exposure to dust storms, construction, or other soil disrupting activities that aerosolize spores is prudent. It is unclear whether patients who are diagnosed with coccidioidomycosis can resume anti-TNF α therapy. Up to 89% of patients with a history of CNS coccidioidomycosis had relapse years after stopping antifungal therapy (56). Consultation with an ID expert is recommended.

Cryptococcosis spp.

Background. Immune responses to *Cryptococcus* spp. rely on effective T-cell host responses. Cryptococcosis has been reported most commonly in patients with rheumatologic conditions receiving anti-TNF α , with estimated rates of 4.7 to 7 cases/100,000 patients receiving anti-TNF α therapy (46,49). Most patients were also receiving additional immunosuppressive agents. No cases in children with IBD receiving anti-TNF α therapies have been reported.

Epidemiology. *C. neoformans* and *C. gattii* are encapsulated fungi that cause human disease. *Cryptococcus* spores are found in soil that is contaminated with bird guano. Although this fungus may be found worldwide, it is endemic in California, southwestern and pacific northwestern United States, and in British Columbia in Canada, Mexico, and Central and South America. Inhalation of the fungal spores occurs with activities causing soil disruption.

Clinical Data. Pulmonary cryptococcosis is the most common clinical manifestation of infection, presenting as fever, cough, and chest pain. Extrapulmonary disease may occur more commonly in immunocompromised hosts and includes disseminated disease, arthritis, cutaneous lesions (pyoderma gangrenosum), and meningitis. Manifestations of CNS disease include severe headache, enlarged ventricles or space-occupying lesions, and symptoms of elevated intracranial pressure. Meningitis, however, may also follow an indolent course. Disease results from a new acute infection or from reactivation of a previous exposure in an endemic region.

Diagnostic Testing. Isolation of the fungus from body fluids or tissue specimens using fungal media is diagnostic. Immunocompromised patients with cryptococcal pneumonia should be evaluated for disseminated disease, including performing blood and CSF cultures and cryptococcal antigen testing. A fundoscopic examination, neuroimaging, and measurement of CSF opening pressure are strongly recommended. Cryptococcal antigen detection in CSF has a diagnostic sensitivity of 94% for meningitis and if detected in serum, 90% for lung disease. Antigen detection is available in most clinical microbiology laboratories. False-negative results are uncommon but may be caused by a prozone effect or by a non-encapsulated strain. CSF cell count, protein, and glucose may be normal, despite a large organism load on CSF stains and isolation in

culture. Anti-TNF α therapy should be withheld during invasive infection; however, it is important not to completely withdraw all immunosuppressive therapies at once to minimize the risk of developing an immune reconstitution inflammatory syndrome (IRIS) (59). If and when anti-TNF α therapy can be resumed after cryptococcal infection is unclear. Consultation with an ID expert is recommended.

Screening Before anti-TNF α . No data to support routine laboratory screening. A history of past cryptococcal infection may be helpful in choosing empiric therapy for acute infection episodes after anti-TNF α therapy is begun and in certain patients, in considering secondary prophylaxis until immune reconstitution is achieved (60).

Prevention/Isolation/Control Measures: Standard Precautions. Avoidance of high-risk activities associated with aerosolization of soil is prudent. Routine antifungal prophylaxis is not generally recommended.

Histoplasmosis

Background. Histoplasmosis is the most common endemic mycosis in the US, prevalent in the Ohio and Mississippi River valleys, and in parts of Mexico and Central and South America. Rates of histoplasmosis in adult patients receiving anti-TNF α exceed the overall national rates of infection (26). Anti-TNF α agents blunt the host's T_H1 response resulting in impaired macrophage activation, lymphocyte proliferation, and inhibition of granuloma formation (61). Infection occurs either by reactivation, reexposure and reinfection, or as newly acquired infection (49). In 2008, the FDA issued a warning about the risk for pulmonary and disseminated histoplasmosis in patients receiving infliximab or other anti-TNF α based on 240 reports of histoplasmosis cases, with 12 fatal outcomes (FDA alert, September 4, 2008, <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm124185.htm>).

The largest case series describing histoplasmosis in pediatric patients with IBD receiving anti-TNF α therapies included 5 patients with a median age of 14 years (range 13–21) with CD (range of duration of disease 10 months to 10 years) who had received 2 to 13 doses of infliximab ($n=4$) or adalimumab ($n=1$) and a concomitant immunomodulator (6-MP or methotrexate) but had not been receiving systemic corticosteroids for ≥ 2 months (62). All of them presented with nonspecific complaints including intermittent fevers, malaise, decreased appetite, and abdominal pain, and 4 had mild respiratory symptoms. All of them received antifungal therapy and survived; anti-TNF α therapy was successfully reinstated in 2 patients a median of 2 years after the *Histoplasma* diagnosis.

Epidemiology

Histoplasmosis is the most common cause of invasive fungal infection in patients receiving anti-TNF α therapies, with a mortality rate of $\sim 20\%$ in adults (46,49). Infection is acquired primarily through inhalation; soil disruption especially of soil rich with bat or bird guano that results in aerosolization of microconidia is considered an important risk factor.

Clinical Data. Most cases of histoplasmosis are subclinical in immunocompetent hosts. When symptomatic, the most common clinical manifestation is acute pneumonia, indistinguishable from a community-acquired pneumonia. Larger inocula cause more severe disease leading to reticulonodular infiltrates and hypoxemia. Most important, symptoms of histoplasmosis may be indistinguishable from manifestations of IBD, including extraintestinal

manifestations. Patients may present with unexplained or prolonged fevers and nonspecific symptoms such as fatigue, weight loss, or night sweats, and some may develop skin or mouth lesions. Patients receiving anti-TNF α therapies are at higher risk of disseminated histoplasmosis, including hepatosplenomegaly, adenopathy, and bone marrow suppression reflected as pancytopenia. Dissemination may occur early in the illness and after instituting anti-TNF α therapy.

Anti-TNF α therapy should not be administered in the setting of proven or probable histoplasmosis. Clinicians, however, should also be aware of the possibility of paradoxical clinical worsening despite documented improvement in the fungal infection that may follow discontinuation of anti-TNF α therapy and is consistent with an IRIS (63). The optimal time to restart anti-TNF α therapy after the diagnosis of acute histoplasmosis is unknown; some experts recommend that anti-TNF α therapy not be resumed. In a small subset of 7 adult patients with histoplasmosis, anti-TNF α therapy was restarted after a mean of 10 months of antifungal therapy (range 6–12 months) with no relapse noted during ≥ 1 year of follow-up (63). In a larger retrospective review of 98 patients receiving anti-TNF α and diagnosed with histoplasmosis, 97% had anti-TNF α therapy initially discontinued, and 34% resumed anti-TNF α therapy after a median of 12 months (range 1–69 months) (64). There was recurrence in 3 patients, 2 of whom had restarted anti-TNF α therapy; mortality rate was 3.2%. Consultation with an ID specialist is recommended.

Diagnostic Testing. If histoplasmosis is suspected, diagnostic testing should include evaluation of histopathology, fungal blood and tissue cultures, antigen detection in both urine and blood, and serologic testing. The performance characteristics of each diagnostic test will depend on the clinical histoplasmosis syndrome, and the extent and timing of histoplasmosis infection. In general, multimodal testing will optimize diagnostic sensitivity. For example, the sensitivity of antigen detection varies by clinical manifestation (higher in disseminated vs local pulmonary disease), underlying immunosuppression, and disease severity (65). The highest diagnostic sensitivity is achieved when both urine and serum antigen testing are performed concomitantly. Antigen testing can also be performed on BAL fluid. Serologic testing should include antibody testing by both complement fixation (higher sensitivity) and immunodiffusion (higher specificity) methods. Of note, negative results do not eliminate histoplasmosis as a possible etiology, and both antigen and antibody testing may be negative in the setting of active infection.

Screening Before Anti-TNF α . At this time, there are no data to support routine screening with serologic testing or antigen detection, even in endemic areas given the low sensitivity when used in this scenario. Risk factor assessment, however, is encouraged before starting anti-TNF α therapy in all patients (Table 3). In particular, if significant recent exposure or symptoms of active or recent (in the previous 2 years) histoplasmosis are elicited, additional testing may be recommended, including a chest radiograph (63). Patients with history, clinical, or laboratory findings suggestive of active histoplasmosis should receive antifungal therapy with itraconazole for ≥ 3 months before starting anti-TNF α therapy, and antifungal therapy should be continued for ≥ 1 year if anti-TNF α therapy must be used (66). Continued surveillance of symptoms and urinary antigen level monitoring (every 3 months and as clinically indicated) should be performed.

Prevention/Isolation/Control Measures: Standard Precautions. As per the FDA, for patients who have resided or reside in regions where histoplasmosis is endemic, the benefits and risks of

TABLE 3. Risk factors for developing infection in patients with IBD living in a histoplasmosis endemic area

Before starting anti-TNF α blocker therapy	Assess for: Possible exposure to <i>Histoplasma</i> (may include, but not limited to, any of the following activities): Old buildings (remodeling, demolition); Chicken coops (demolition, feeding, fertilizing); Barns (cleaning, demolition, feeding); Bird roosts (excavation, wood cutting, camping); Wood piles (transporting or burning wood); Caves (spelunking); Bat exposure; Gardening or landscaping Past diagnosis of histoplasmosis (especially if in last 2 years); Evidence of recent histoplasmosis (history of pulmonary infection with radiographic findings showing infiltrates, nodules, or lymphadenopathy without a clear etiology; <i>Histoplasma</i> antigen in urine, or anti- <i>Histoplasma</i> complement fixation antibody titers $\geq 1:32$) Diagnosis of pneumonia in the last 2 years Symptoms compatible with histoplasmosis in the last 3 months Counsel regarding: Avoiding exposure to <i>Histoplasma</i> (see activities above) For exposures that are anticipated but absolutely unavoidable, wear a surgical mask Contacting the physician with symptoms of prolonged cough, prolonged/unexplained fevers, night sweats, skin or mouth lesions
During anti-TNF α blocker therapy	

Adapted from Hage et al (63). anti-TNF α = TNF- α inhibitor; IBD = inflammatory bowel disease.

anti-TNF α treatment should be carefully considered before initiation of therapy. Universal antifungal prophylaxis for patients living in endemic areas who are receiving anti-TNF α therapy is not routinely recommended. In outbreak situations and in patients who have recovered from active histoplasmosis in the 2 years before anti-TNF α therapy, itraconazole prophylaxis may be considered (66). The efficacy and optimal duration of antifungal prophylaxis are unknown. Providing advice to patients about avoiding exposure to *Histoplasma* is encouraged.

Pneumocystis jirovecii (Formerly *Pneumocystis carinii*)

Background. *Pneumocystis jirovecii* (formerly *Pneumocystis carinii*) is the species that infects humans. Because both cellular and humoral immune dysfunction are risk factors for *Pneumocystis* pneumonia (PCP), CD4 $^{+}$ lymphocyte counts alone are not reliable for PCP risk assessment in HIV-negative immunocompromised patients (67). Immunosuppressive therapies that increase the risk for PCP include high-dose steroids (even during the tapering phase), calcineurin inhibitors, and receipt of anti-TNF α .

Review of the FDA adverse event reporting system identified 84 cases of PCP in adults during infliximab therapy, of which 16 patients had IBD, most commonly CD ($n = 14$) (68). Concomitant immunosuppressive medications included methotrexate, prednisone, azathioprine, leflunomide, 6-mercaptopurine, and cyclosporine. The risk of PCP was highest early (≤ 6 months) in treatment; the mean time to PCP infection was 21 days (± 18 days) from infliximab infusion (mean of 2.1 infusions ± 1.3), and 23 (27%) patients died. PCP mortality rate is greater in the non-HIV population and may be owing to a more intense inflammatory response. The exact incidence of PCP in patients with IBD receiving immunomodulatory therapy is not known but is likely less than that observed in solid organ transplant recipients (5%–15%) and may be less than in patients with rheumatologic conditions who do not receive PCP prophylaxis (1%–6%) (69). The first pediatric case of PCP was described in an 8-year-old child with CD who had been receiving infliximab for 15 months (70). This case occurred together with disseminated histoplasmosis. An adolescent girl with CD developed PCP while receiving infliximab for 2 months and concomitant prednisone, methotrexate, and mycophenolate mofetil (25).

Epidemiology. No environmental reservoir outside of human colonization has been identified for *Pneumocystis* species. High rates of

detection have been demonstrated in healthy adults, and patients at risk for PCP may be asymptotically colonized before developing disease. Rare instances of patient-to-patient transmission have been reported; it is likely that the load of *Pneumocystis* organisms is so low in most non-HIV immunocompromised patients that patient-to-patient transmission would occur only under very unusual circumstances of a combination of host, strain, and environmental factors.

Clinical Data. HIV-negative immunocompromised patients present most often with an acute onset of respiratory symptoms including dry cough and fever that may progress to respiratory failure. Associated mortality is increased compared with HIV-infected patients who have a more insidious onset; mortality may be as high as 30% to 60%. The more abrupt clinical presentation in patients with IBD may be a reflection of a more exuberant inflammatory response to relatively few organisms. If steroids are used to treat IBD, they may mask the signs and symptoms of PCP. Despite respiratory distress and hypoxemia, auscultation of lung fields may be normal. Radiographic features seen most commonly are bilateral interstitial and/or alveolar infiltrates that involve the lower lobes more than the upper lobes. A diffuse reticulonodular pattern, however, may also develop.

Diagnostic Testing. Demonstration of the fungi in lung tissue with methenamine silver stain has been the criterion standard for diagnosis. Commercially available fluorescein-conjugated monoclonal antibody and PCR tests for detection of *P. jirovecii* DNA in expectorated or induced sputum, BAL fluid, or deep tracheal aspirate has decreased the need for lung biopsy.

Screening Before Anti-TNF α . No data to support routine laboratory screening. Assessment of degree of immunosuppression recommended.

Prevention/Isolation/Control Measures: Standard Precautions. Chemoprophylaxis using trimethoprim-sulfamethoxazole, aerosolized or intravenous pentamidine, dapsone, or atovaquone has been associated with a 91% reduction in occurrence of PCP in a meta-analysis of the experience in immunocompromised patients with hematologic cancers or solid organ transplants (71). Although the indication for chemoprophylaxis in HIV-infected patients can be determined by the CD4 $^{+}$ lymphocyte count, such data do not

exist for patients with IBD who are receiving immunosuppressive therapies. There are no published, evidence-based guidelines for PCP prophylaxis in the IBD literature, and the recommendation at present is to consider on a case-by-case decision (19,72).

In an analysis of the LifeLink Health Plan Claims Database 1997–2009, the crude incidence of PCP in patients with IBD was 10.6/100,000 (73). Patients with CD and those who were receiving steroids (with or without other immunosuppressive therapies) were at the greatest risk for PCP. In a meta-analysis of randomized trials of PCP prophylaxis in non-HIV immunocompromised patients, prophylaxis was warranted when the risk of PCP is $\geq 3.5\%$ in adults, with a number needed to treat 19 patients (95% CI 17–42) to prevent 1 case of PCP (71). In a review of the literature, Okafor and colleagues (74) identified the following risk factors for PCP:

- (1) Patients on high-dose corticosteroids (risk factor: daily dose of ≥ 6 mg).
- (2) Patients receiving multiple immunosuppressive agents, including corticosteroids plus anti-metabolites, a biologic agent, or a calcineurin inhibitor.
- (3) Lymphopenia (absolute lymphocyte count <600 cells/mm 3 , CD4 $^+$ count <300 cells/mm 3 , or leukopenia).
- (4) Patients with multiple comorbidities (especially adults with chronic obstructive pulmonary disease).
- (5) Patients >55 years.

European consensus guidelines recommend PCP prophylaxis for adult patients with IBD who are receiving an anti-TNF α agent as part of either a triple immunomodulation regimen or if anti-TNF α is given in conjunction with a calcineurin inhibitor (19,75). Similar recommendations for PCP prophylaxis in children are advised. Severity of disease and specific comorbidities may be an additional consideration in pediatric patients with IBD receiving combination immunosuppression. For example, PCP prophylaxis is advised for malnourished children receiving dual immunosuppression (that includes a combination of anti-TNF α and either a calcineurin inhibitor or high-dose corticosteroids) and in children <6 years of age with severe IBD manifestations in whom a primary immunodeficiency disorder is likely (17). Current consensus guidelines for the management of pediatric patients with severe, corticosteroid-refractory UC recommend that children receiving combination immunosuppressive regimens (anti-TNF α with calcineurin inhibitors or cyclosporine) also be considered for PCP prophylaxis (43).

Mycobacterial Infections

Soon after the FDA approval of infliximab in 1998, the role of TNF- α in preventing mycobacterial disease was further characterized and screening recommendations emerged (supplementary Table 1, <http://links.lww.com/MPG/A637>). It became evident that TNF- α plays a critical role in the host immune response against intracellular microorganisms. Murine and human studies have shown that TNF- α deficiency impairs granuloma organization leading to increased organism burden and premature death (76). We describe the presentation, epidemiology, diagnostics, and suggested screening for both *M. tuberculosis* and NTM infections in pediatric patients with IBD.

M. tuberculosis

Herein, “disease” refers to illness with *M. tuberculosis*, whereas “infection” refers to patients with latent tuberculosis infection (LTBI) who are asymptomatic.

Background. Adults with IBD are at increased risk for serious mycobacterial infections because of the severity and duration of

underlying IBD disease, advanced age, and use of corticosteroid therapy (24,77,78). In addition, adult data demonstrate increased rates of *M. tuberculosis* disease in patients with IBD treated with anti-TNF α agents (26,77,79–82). Treatment with anti-TNF α increases the risk of *M. tuberculosis* infections 4- to 5-fold higher in adult patients with IBD compared with an anti-TNF α unexposed cohort (77,78,83). The risk of developing *M. tuberculosis* disease is greatest in the initial 3 months after anti-TNF α exposure, most likely representing reactivation of LTBI and inability to maintain granulomas, with progression to disease; this appears to be greater with the use of infliximab compared with adalimumab (84). A recent systematic review evaluating the risk of *M. tuberculosis* reactivation in adult IBD and rheumatology patients found that whereas anti-TNF α use independently increased the risk of *M. tuberculosis* disease, the risk was further increased when an anti-TNF α was combined with either methotrexate or azathioprine (83). Less frequently, anti-TNF α therapy can also predispose to new TB infections that progress rapidly to active disease (26,79).

It is unknown to what extent anti-TNF α therapy increases the risk of mycobacterial infections in children and adolescents with IBD or whether they are predisposed to these infections because of the underlying IBD. Two cases of *M. tuberculosis* disease have been reported in pediatric patients with IBD during anti-TNF α therapy, and both presented with disseminated disease (85). The low incidence of TB disease in pediatric patients with IBD treated with anti-TNF α may be due in part to overall lower incidence of *M. tuberculosis* infection in children and to evolving screening recommendations before starting immunosuppressive therapies.

Epidemiology. In the US, foreign-born individuals have a higher rate of *M. tuberculosis* infection. Three-quarters of pediatric patients with tuberculosis in the US in 2008–2010 had potential TB exposures through foreign-born parents or residence outside of the US (86). Additional risk factors include exposure to a person with active pulmonary tuberculosis that has not been treated, travel to endemic regions, or medical conditions that increase the risk of progression to disease, such as immunosuppressive therapy (87). A review of tuberculosis in children with comorbidities demonstrates the importance of screening and the increased mortality associated with tuberculosis in this high-risk population (88).

Clinical Data. Children and adolescents with TB disease can present with fever, fatigue, weight loss, poor weight gain, night sweats, and persistent, unremitting cough (>2 weeks). Chest radiographs can demonstrate extensive involvement, sometimes with evidence of miliary disease. Cavitary lesions and pleural effusions are more likely to occur in teenagers. Receipt of anti-TNF α may also lead to atypical disease manifestations with mycobacterial infections. Pediatric and adult patients with IBD may be more likely to present with disseminated or extrapulmonary tuberculosis (15,79,85). Extrapulmonary disease may present with lymph node, spleen, CNS, or skeletal involvement. Improved awareness of the clinical presentation of *M. tuberculosis* disease will allow for optimal management.

Diagnostic Testing. Definitive diagnosis of TB disease relies on microbiological confirmation with a clinical scenario suggestive of tuberculosis as proposed by an expert panel (89). For *M. tuberculosis* disease, this includes isolating the organism by acid fast bacilli (AFB) culture of gastric aspirates, sputum, pleural fluid, BAL, bone marrow, lymph node, or CSF. In younger children, this requires 3 gastric aspirates collected in the early morning on separate days. Histologic evaluation for AFB or granulomas from tissue biopsy can be helpful in establishing the diagnosis. Isolates from cultures usually are identified within 6 to 8 weeks for *M. tuberculosis*.

Overall yield, however, can be as low as 30% to 50% in pediatric patients because of paucibacillary disease. Nucleic acid amplification tests (NAATs) performed on sputum and extrapulmonary specimens are more sensitive and rapid than culture techniques. Some pediatric patients may need to be treated for TB disease based on clinical scenario, radiographic imaging, immunodiagnostic test results, and risk factors, without definitive culture results, but every effort should be made to identify an isolate for resistance testing. The management of suspected or proven TB disease may benefit from input from a pediatric ID specialist.

Immunodiagnostics are adjuncts to diagnosis and include a tuberculin skin test (TST) or interferon- γ release assays (IGRAs) such as quantiferon-TB or T-SPOT.TB. A positive reaction of either immunodiagnostic helps establish a diagnosis of LTBI or *M. tuberculosis* disease; however, none can differentiate between active TB disease and LTBI. In addition, a negative test does not reliably exclude the possibility of TB disease.

Both TST and IGRAs have limitations in diagnosing TB disease and LTBI in children. TST reading can be compromised if not performed and read by experienced personnel within 48 to 72 hours after placement. Positive results can occur in a person with NTM infection or in persons who received the bacille Calmette-Guerin (BCG) vaccine; false-negative results may occur in immunocompromised hosts, patients receiving systemic corticosteroids, and in patients with severe TB disease. Administration of live virus vaccines can affect TST results. For example, measles vaccine can temporarily suppress tuberculin reactivity for 4 to 6 weeks; the effect of live-attenuated influenza, varicella, and yellow fever vaccines on TST reactivity is unknown. It is recommended that TST testing be performed on the same day as live virus immunization. If it cannot, then TST testing should be postponed for ≥ 4 to 6 weeks. Similarly, IGRAs are also susceptible to variable results if improperly collected or not promptly processed, when performed in immunocompromised hosts or in patients with leukopenia, and results may not always be reproducible (90). The effect of live virus vaccination on IGRA results is also not known. There have been conflicting results as to whether the TST or IGRA is more reliable in patients with IBD; each method can be negatively impacted by age, immune status, immunosuppressive therapy, and underlying IBD disease activity (87,91,92).

The diagnosis of LTBI requires a positive immunodiagnostic test in a patient who is asymptomatic and has a negative chest X-ray. The experience with IGRAs in children was recently reviewed and a strategy for testing recommended in a technical report from the American Academy of Pediatrics (AAP) (90). The choice of immunodiagnostic test used (TST or IGRA) depends on the presence of risk factors, age, and receipt of the BCG vaccine. Adult guidelines (from the US and Europe) reviewed in a consensus statement had varying recommendations using 1 or both modalities and different cutoffs for TST positivity (93). In children, TST and IGRAs have similar sensitivity rates; IGRAs are more specific in areas of low *M. tuberculosis* disease burden and in BCG-vaccinated persons at 90% to 100%, compared with 56% for the TST when evaluating for LTBI (90).

Screening Before and During Anti-TNF α . We recommend that all patients with IBD be routinely screened for TB risk factors before administering anti-TNF α agents, ideally at the time of initial IBD diagnosis before any immunosuppressive therapy is started, and annually during anti-TNF α therapy. Screening includes a thorough evaluation of TB risk factors such as birth place, travel to endemic regions, disease exposure, possible concerning symptoms (eg, >2 weeks of cough), and whether the person previously received BCG vaccine. Any symptomatic patient requires further diagnostics.

In addition, we also recommend immunodiagnostic screening of all pediatric patients with IBD with both a TST and an IGRA at the time of IBD diagnosis and before initiation of anti-TNF α therapy, to increase diagnostic sensitivity (87,90). A TST cutoff value of 5 mm of induration should be considered positive in all pediatric and adolescent patients with IBD. Patients with an indeterminate IGRA result should have the IGRA repeated, ensuring the specimens are processed correctly according to the manufacturer's directions. It is not uncommon for immunocompromised children to have discordant results of TST and IGRA testing; however, if either test is positive, further diagnostic evaluation is recommended. If either the TST or the IGRA is positive or the second IGRA remains indeterminate, we recommend that a chest radiograph be performed to assess for *M. tuberculosis* disease. If imaging is negative in an asymptomatic patient with a positive immunodiagnostic result, the patient should be treated for LTBI for ≥ 2 months before starting anti-TNF α therapy, with a total duration of 9 months of mycobacterial therapy (19,94). Adherence to anti-mycobacterial agent(s) should be ascertained before initiating anti-TNF α therapy.

Any symptomatic person requires additional diagnostic evaluation for possible *M. tuberculosis* disease, even if TST and IGRA results are both negative. In general, anti-TNF α therapy should not be administered in the setting of active *M. tuberculosis* infection. If there is concern for pulmonary or extrapulmonary TB disease, consultation with an ID expert is advised.

For patients diagnosed with TB disease, when to resume anti-TNF α therapy safely depends on the extent of TB disease, clinical response to TB therapy, and severity of underlying IBD. In a study of adults with rheumatologic conditions, 6 of the 13 patients who developed TB disease while receiving anti-TNF α therapy were able to restart biologic therapy: 4 within 2 months of starting TB therapy, and 2 after completion of TB therapy (95). None developed recurrence of *M. tuberculosis* disease after resuming anti-TNF α therapy, at a mean of 30.6 months of follow-up.

Annual screening of patients who continue anti-TNF α therapy should be performed by risk factor assessment as previously described. This includes reevaluation of travel and possible TB exposures in the past year. Repeat immunodiagnostics should also be considered; however, the optimal testing strategy (which test(s) and how often) for evaluation is not known. In patients receiving anti-TNF α with identification of new risk factors (especially known exposure to a case of pulmonary TB or travel to an TB endemic region) or in those receiving corticosteroids and negative prior immunodiagnostics, consideration should be given to performing both TST (if prior TST negative) and IGRA to increase sensitivity, with consideration of performing a chest X-ray. Screening pediatric patients with IBD who have no new concerning risk factors and are not receiving triple immunosuppression or corticosteroids, with a single immunodiagnostic assay may be sufficient, but data are lacking to guide further recommendations. If LTBI is diagnosed in an asymptomatic patient, anti-TNF α therapy should be withheld, and antimicrobial therapy for LTBI provided for ≥ 2 months before restarting anti-TNF α therapy. If a patient has already been diagnosed and treated for LTBI, then annual screening should include careful assessment of possible exposures, symptoms, and a chest X-ray, as clinically indicated.

Prevention/Isolation/Control Measures. Airborne isolation plus standard precautions are recommended for active *M. tuberculosis* disease, including those with cavitary pulmonary tuberculosis or extensive pulmonary disease, positive sputum AFB smears, and children undergoing procedures that cause aerosolization of respiratory secretions including intubation, bronchoscopy, or administration of nebulized therapies. In addition, all household contacts should be evaluated for TB disease. Visitors of hospitalized patients

with newly diagnosed TB disease should be screened before they are allowed to visit.

Non-TB Mycobacteria

Background. Adult patients with IBD treated with anti-TNF α agents are at increased risk of developing NTM infections (77). It is unknown if pediatric patients with IBD receiving anti-TNF α therapy are similarly at increased risk of NTM infections and whether risk is impacted by anti-TNF α therapy. One case of systemic *Mycobacterium avium complex* (MAC) infection was reported in an 11-year-old girl with CD who presented with generalized lymphadenopathy after receipt of infliximab followed by adalimumab (96).

Epidemiology. NTM are ubiquitous organisms in nature, found in soil, food, water, and animals. MAC, *M haemophilum*, *M fortuitum*, *M abscessus*, and *M marinum* are the most common species that cause disease in children. The portal of entry for NTM infection is varied and can occur if there is disruption of the skin barrier (skin abrasions, penetrating trauma, and the presence of central venous catheters), or through the oropharyngeal mucosa and the GI and respiratory tracts.

Clinical Data. Manifestations of NTM infection in children can include fever, rash, cough, generalized lymphadenopathy, anorexia, and weight loss. NTM infections in children are often localized and most commonly cause cervical lymphadenitis (especially in children <5 years of age), followed by soft tissue and pulmonary infections, and rarely skeletal infections (97). In immunocompromised pediatric patients, NTM infections can cause disseminated disease and catheter-associated bloodstream infections.

Diagnostic Testing. Definitive diagnosis of NTM infection requires isolation of the pathogen by culture or detection in tissue or body fluids by molecular methods. NTM isolates that grow rapidly on special culture media may be identified as early as 2 to 3 weeks. Sites of NTM culture depend on clinical presentation but may include BAL, sputum, wounds, peritoneal fluid, CSF, bone marrow, blood, or lymph node tissue. Multiple blood cultures may need to be obtained to isolate the pathogen in the setting of disseminated NTM disease because of intermittent bacteremia. If unable to isolate the pathogen in culture, a probable diagnosis relies on clinical presentation. Use of immunodiagnostic tests for the diagnosis of NTM infection have not been well studied and, when performed, are often inconclusive, and therefore not helpful in establishing the diagnosis.

Screening Before Anti-TNF α . There are no data to support routine laboratory testing, but screening for high-risk activities may be prudent.

Prevention/Isolation/Control Measures. Standard precautions are recommended for children who are hospitalized with NTM infections. Patients should be advised to avoid cleaning and changing water in aquariums and to avoid exposure to soil that may be aerosolized, including potting soil (98).

Viral Infections

Data derived primarily from the rheumatology literature indicate that ~30% of all infections and 11% of serious infections related to anti-TNF α therapy are caused by viruses (99,100). In general, anti-TNF α therapy should not be administered in the setting of severe, active viral infections.

Cytomegalovirus (CMV)

Background. Upon initial exposure to CMV, latent infection is established in hematopoietic cells, mainly lymphocytes. TNF- α is required for regulation of CMV replication and dissemination; therefore, recipients of anti-TNF α agents could have an increased risk of reactivation of CMV infection. The true incidence and burden of CMV disease in patients with IBD and those receiving anti-TNF α therapy is unknown. When CMV reactivation occurs in patients with IBD treated with immunomodulators, clinical manifestations can vary from asymptomatic or minimally symptomatic to severe disease. Prospective studies in patients with CD or rheumatoid arthritis have shown no evidence of significant CMV reactivation (measured by CMV PCR in plasma) following infliximab infusion. Similarly, infliximab treatment does not appear to affect colonic tissue CMV viral load (101). CMV reactivation has been detected most commonly in the GI tract of patients with steroid refractory UC, with a prevalence of 32% (102). It remains unclear, however, to what extent CMV detection contributes to IBD disease, posing a challenge for diagnosis and management (103–106). Proven cases of CMV disease, including enteritis, pneumonia, secondary hemophagocytic lymphohistiocytosis, and disseminated disease have been reported in patients with IBD receiving immunosuppressive therapies, including anti-TNF α agents (107–111). In children, primary CMV infection is more likely than in adults. Few pediatric cases have been reported, including a fatal case of disseminated CMV in a child with CD receiving infliximab and 6-mercaptopurine (112–114).

Epidemiology. CMV is common in all the socioeconomic groups from developed and developing countries. CMV may be transmitted from person to person through infected body fluids. Patients with compromised immune systems are the most likely to develop symptomatic disease upon exposure, especially if they are seronegative. Health care personnel working in children's hospitals do not have an increased rate of CMV seroconversion compared with the general population (115).

Clinical Data. CMV may cause infection (detection of CMV) or disease (evidence of end organ involvement). It is also important to note that CMV infection may represent a primary, symptomatic infection in children, as opposed to reactivation with asymptomatic or mild, self-limited symptoms in adults. Active CMV disease manifestations include retinitis, pneumonitis, hepatitis, colitis, and encephalitis. In patients with IBD who develop a severe colitis flare, it is recommended that biopsies be performed to evaluate for CMV disease, particularly in children with steroid-resistant UC (19,43,75). Discontinuation of anti-TNF α and other immunosuppressive therapies is recommended for proven CMV disease (19).

Diagnostic Testing. Tests to detect CMV that were formerly used (eg, tissue culture, shell vial centrifugation culture assay, and the detection of pp65 antigen) have been replaced by quantitative nucleic acid tests, usually PCR, to detect and quantify CMV DNA or RNA in blood or other body fluids (116). The detection of CMV in urine or the presence of CMV IgM antibodies is nonspecific and not helpful for diagnosing disease associated with an acute infection. Detection of CMV RNA in plasma is indicative of active replication, whereas detection of CMV DNA may indicate latent viral infection or, if rising, active replication. Although high CMV copy numbers in blood by PCR may increase the index of suspicion for CMV and has high sensitivity for systemic infection, it is not definitive and may be falsely negative in patients with CMV colitis. It is important to note that given the high sensitivity of the PCR assays, CMV detection in tissue by PCR methods alone does not have sufficient specificity to confirm disease (117). When tissue

biopsies are obtained, histologic examination may reveal characteristic cell types, and *in situ* hybridization can be used to confirm and quantify the amount of CMV in tissue. Mucosal viral loads of CMV have been reported to be useful for identifying viral colitis that responds to anti-CMV antivirals in refractory IBD in adults but are not standardized. In patients with evidence of CMV end organ disease, an ophthalmological examination to exclude the presence of CMV retinitis is also prudent (19,101,102). Discontinuation of immunosuppressive agents is recommended when systemic CMV disease (eg, colitis, hepatitis, and meningoencephalitis) is diagnosed.

Screening Before Anti-TNF α Therapy. Screening for CMV infection before beginning therapy with anti-TNF α agents is not recommended routinely; detection of CMV IgG is indicative of latent infection and does not reliably predict conditions that would require prophylaxis or therapy in this population. For those individuals with severe UC who are failing steroid therapy, transitioning to second line or augmented immunosuppressive therapies including anti-TNF α , and in whom there is a suspicion for CMV colitis, biopsies of colonic tissue should be examined by histopathology and immunohistochemistry to confirm the presence of CMV end organ disease that would warrant antiviral treatment (19,112).

Prevention/Isolation/Control Measures. No additional isolation measures beyond standard precautions are recommended in health care facilities for patients who have CMV infection with or without disease (118). The highest concentrations of CMV are found in urine, saliva, and blood; therefore, use of hand hygiene and gloves according to standard precautions when in contact with blood or body fluids will protect health care personnel and pregnant women from acquiring CMV. Following standard precautions with all patients is especially important because most patients who are shedding CMV are not identified. Outside of the health care environment, special care should be taken by immunocompromised and pregnant individuals when changing diapers, feeding a young child, wiping a young child's nose or saliva, and handling children's toys.

Hepatitis B Virus

Background. Hepatitis B virus (HBV) persists after infection and can be reactivated when patients receive immunosuppressive therapies. TNF- α is critically involved in the control of HBV replication and in stimulation of anti-HBV T-cell responses. Reactivation of hepatitis B infection in unimmunized adults with IBD receiving anti-TNF α has been reported since 2003 (101,119,120). No cases in children with IBD have been reported. Risk of reactivation was higher in patients who received infliximab concomitantly with other immunosuppressive therapies or had detection of HBV DNA but was lower in patients who received antiviral prophylaxis (120). In the absence of anti-viral therapy, patients with chronic HBV infection treated with anti-TNF α agents have experienced elevations in viral loads and serum transaminases with clinically apparent disease and even death. The time after receiving anti-TNF α agents and before reactivation is highly variable. Additionally, some children may not have received the complete HBV vaccine series before their IBD diagnosis or initiation of immunosuppressive therapy. In 1 published series, 75 of the 87 (86%) previously immunized children with IBD treated with anti-TNF α agents were considered immune against HBV infection based on hepatitis B surface antibodies (anti-HBs) levels \geq 10 μ JU/mL or an anamnestic response to a single HBV booster dose (121). Of note, the nonresponders received infliximab at an increased frequency than the responders.

Epidemiology. HBV is blood-borne and may be transmitted during the perinatal period, household contacts of an actively infected individual, exposure to blood, or during sexual contact with an individual who is a carrier or is actively infected. Patients may be at risk of HBV from being born in a country with high (>8%) HBV prevalence, local incidence rates, current or previous lifestyle practices, hemodialysis, or those with a history of hepatitis C infection, jaundice, or liver disease of uncertain etiology. Nonhospital health care-associated outbreaks of HBV infection associated with failure to use safe injection practices have occurred in long-term care facilities, assisted living facilities, and outpatient endoscopy centers (122). The overall prevalence of chronic HBV infection in children is much lower than in adults, likely owing to the introduction of universal administration of HBV vaccine to infants in 1990 in the US (refer to safe living section and Tables 4 and 5 for more information on hepatitis B vaccination).

Clinical Data. Infection with HBV may be asymptomatic, associated with acute or chronic hepatitis, liver failure resulting in liver transplantation or death, and in rare instances, may be associated with the development of hepatocellular carcinoma.

Diagnostic Testing and Screening Before Anti-TNF α . In general, anti-TNF α therapy is not recommended to be started in patients with active HBV infection, and caution is advised for patients with a known history of chronic or recurrent HBV infection with liver injury (defined as Child-Pugh classes B or C). Thus, medical and immunological status assessment before starting anti-TNF α therapy is recommended. Identification of patients at high risk for HBV reactivation by screening is important; however, the optimal screening, monitoring, and anti-viral strategies have not been established (19,123–125). Immunization records should be reviewed to determine whether a patient has received a 3-dose series of HBV vaccine, and seroresponse should be confirmed. The following tests should be performed to document immunity and to determine whether the patient is infected with HBV: hepatitis B surface antigen (HBsAg), anti-HBs, and hepatitis B core antibody (anti-HBc). If anti-HBc is the only antibody that is positive, a HBV DNA load should be measured. Patients may be found to have only anti-HBc for the following reasons:

- (1) False-positive reactivity attributed to nonspecific reactions with competitive anti-HBc enzyme immunoassays (EIAs) and cross-reactivity with interfering serum substances or with IgA- or IgM-related molecules produced from nonspecific HBV-activated B-lymphocytes;
- (2) Passive transfer of antibody from recently received immunoglobulin products; or
- (3) Low level of chronic carriage with loss of other markers of HBV infection.

In such patients, HBV DNA in the blood should be determined; if HBV DNA load is negative, a true infection with HBV is unlikely. Patients with chronic HBV infection should be screened by laboratory testing (eg, liver enzymes and HBV DNA) every 2 to 3 months during and after cessation of immunomodulator therapy (19,125). Antiviral prophylaxis or therapy may be required in some patients with chronic HBV infection or if there is viral reactivation (125). Patients who test positive for HBV should also be tested for HIV and hepatitis A and C viruses.

Prevention/Isolation/Control Measures. Because HBV is transmitted via blood and body fluids in health care settings, infected patients should be managed using standard precautions with special attention to safe injection procedures (118,126). The equipment

TABLE 4. Baseline evaluation of vaccine preventable infections in pediatric patients with IBD

Baseline evaluation*				
Pathogen or vaccine	Review risk factors, vaccine records, and prior infections	Check serologic status	Offer vaccine if not up to date, or nonimmune, and age-appropriate	Subsequent annual evaluation
<i>Haemophilus influenza</i> type b	Yes	No	Yes	No
Hepatitis A virus	Yes	Consider	Yes	No
HBV	Yes	Yes (HBsAg, anti-HBc, and anti-HBs)	Yes	Repeat series once if inadequate serologic response; recheck anti-HBs (2 months after 3rd dose)
HPV	Yes	Encourage gynecologic/anal examination if age appropriate	Yes, minimum age 9 years	Yes, if appropriate
Influenza, inactivated vaccine	Yes	NA	Yes, annually	Yes
Inactivated polio vaccine	Yes	NA	Yes	No
MMR	Yes	Yes	Yes ^{†,‡}	No
Meningococcal conjugate vaccine	Yes	No	Yes	Yes, if age appropriate or risk factors [§]
Pneumococcal conjugate vaccine (PCV13)	Yes	No	Yes	NA
PPSV23	Yes	No	Yes [¶]	Booster once 5 years after first dose of PPSV23 (max 2 lifetime PPSV23 doses)
Tetanus, diphtheria (Td), acellular pertussis (Tdap)	Yes	NA	Yes	After Tdap, Td booster every 10 years
Varicella-zoster virus	Yes	Yes [#]	Yes, if no evidence of immunity ^{†,‡}	NA

ACIP = Advisory Committee on Immunization Practices; anti-HBc = hepatitis B core antibody; anti-HBs = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HPV = human papillomavirus; IBD = inflammatory bowel disease; MMR = measles–mumps–rubella; NA = not applicable; PPSV23 = pneumococcal polysaccharide vaccine.

*Should include review of vaccine record and any prior testing/serologies.

[†]If not receiving immunosuppressive therapy (please refer to text, vaccine section for dosing) including prednisone in the past 30 days, or any of the following in the past 3 months: 6-mercaptopurine, methotrexate, azathioprine, or any biologic agent, including anti-TNF α therapy.

[‡]Dispense if live virus vaccine can be administered \geq 4 weeks before starting immunosuppressive therapy.

[§]Adolescents may require a booster dose in accordance with the ACIP vaccine schedule. Vaccine may also be needed if there are identified risk factors such as travel to a country where meningococcal disease is epidemic, or hyperendemic, or in patients with persistent complement deficiency, or functional or anatomic asplenia.

^{||}For children 6 to 18 years old, if no prior doses of PCV7 or PCV 13 then give 1 dose of PCV13, followed 8 weeks later by PPSV23.

[¶]If both PCV13 and PPSV23 are indicated, PCV13 should be given first, followed by PPSV23 given \geq 8 weeks afterward.

[#]Send serology if evidence of immunity unknown; evidence of immunity is defined as: health care provider diagnosis of varicella disease or herpes zoster, laboratory confirmation of disease, serologic evidence of past disease, or documentation of having received vaccine series.

used for invasive procedures (eg, endoscopes) must be processed according to the most recent multisociety guideline on reprocessing flexible GI endoscopes (127). Patients should be counseled to avoid high-risk behaviors.

Recently, the American Gastroenterological Association has drafted guidelines regarding the prevention and treatment of hepatitis B reactivation during immunosuppressive therapy (125). High- and moderate-risk patients who are HBsAg positive (or HBsAg negative, but anti-HBc positive), who do not have liver injury, and require anti-TNF α therapy may be candidates for antiviral prophylaxis and viral monitoring during anti-TNF α therapy; it is recommended that antiviral prophylaxis be continued for \geq 6 months after immunosuppressive therapy is discontinued. Pooled effect estimates demonstrated that antiviral prophylaxis was associated with an 87% RR reduction of HBV reactivation (95% CI

70–94) and RR reduction of 84% (95% CI 58–94) of HBV-associated hepatitis flares (125). Antiviral therapy does not eliminate the risk of hepatocellular carcinoma, as such surveillance should continue to be performed in at-risk individuals. An expert in the treatment of pediatric HBV infection should be consulted for the most up-to-date prevention and treatment strategies.

Hepatitis C Virus

Background. Routes of transmission and clinical manifestations of hepatitis C virus (HCV) infection are similar to those of HBV, but HCV may be associated with a more prolonged period of silent infection. Although effective chemotherapeutic regimens for HCV infections exist, no intervention has proved to prevent transmission either preexposure or postexposure. Acute HCV during anti-TNF α therapy has not been reported. HCV infection has been rarely

TABLE 5. Summary of recommendations for safe living in patients with IBD receiving anti-TNF α and other immunosuppressive agents

Category	Preventive practices	Infectious agent	Vaccines
Food, water safety	Boiled, filtered water; sealed bottled soda, water, sports drinks; carbonated drinks; Wash fresh produce before eating; Eat raw fruits only if you have peeled them yourself or know who has peeled; Raw poultry, meat, fish, and seafood should be handled separately from other foods; Cook poultry, meat according to recommendations; Avoid soft cheeses, smoked deli meats; Consume only pasteurized dairy products	<i>Cryptosporidium</i> and other waterborne pathogens, Hepatitis A, <i>Salmonella</i> , <i>Toxoplasma</i> , <i>E coli</i> 0157, <i>Listeria monocytogenes</i> , Norovirus, <i>Brucella</i> spp.	HAV
Environmental safety	Avoid construction sites and any other areas with large amount of dust in air; Avoid heavy exposure to soil; Avoid areas with heavy bird droppings	<i>Aspergillus</i> spp., NTM, <i>Cryptococcus</i> , <i>Histoplasma</i> , <i>Coccidioides</i> , <i>Blastomyces</i> , <i>Nocardia</i> spp.	None
Animal safety	Hand hygiene after contact with animals; Use soap and water if hands visibly soiled; Avoid changing litter box if possible or wear gloves if must change litter box; Avoid reptiles as pets; Avoid contact with water in aquariums or use hand hygiene if contact cannot be avoided	Influenza strains transmitted from animals, <i>E coli</i> 0157, <i>Toxoplasma</i> , <i>Salmonella</i> , <i>Mycobacterium marinum</i>	Influenza vaccine
Travel safety	Follow food and water safety practices above; Consult CDC travel page for current preventive measures by geographic area (wwwnc.cdc.gov/travel), with special attention to recommendations for those travelers who are immunocompromised; Chemoprophylaxis and mosquito protection by area	Examples by geographic area: <i>N meningitidis</i> (the Hajj, sub-Saharan Africa), Japanese encephalitis virus, Yellow fever virus; <i>Salmonella typhi</i> , malaria, chikungunya, dengue	HAV, HBV; Specific vaccines per geographic area
Person-to-person; respiratory tract; safe sex	Avoid crowded places during influenza season; Avoid or maintain 3 to 6 feet distance from people who are coughing or sneezing; Screening for TB: (a) At initial IBD diagnosis (Risk factor, PPD, TST, and IGRA); (b) Annually while receiving anti-TNF α (risk factors and immunodiagnostics, see text for details); Use latex condoms when not in a long-term monogamous relationship	Respiratory tract viruses, (eg, influenza, RSV); <i>Mycobacterium tuberculosis</i> ; CMV, HSV, HIV, HPV, HBV, HCV and other sexually transmitted agents	Influenza vaccine patients, contacts; HBV, HPV
Immunizations	Killed vaccines per annual ACIP/AAP recommendations and IDSA recommendations for immunocompromised hosts; Avoid live virus vaccines during periods of immunosuppression	See vaccination section and annual immunization recommendations	See vaccination section, annual immunization recommendations

AAP = American Academy of Pediatrics; ACIP = Advisory Committee on Immunization Practices; CDC = Centers for Disease Control and Prevention; CMV = cytomegalovirus; HBV = hepatitis B virus; HCV = hepatitis C virus; HPV = human papillomavirus; IBD = inflammatory bowel disease; IDSA = Infectious Diseases Society of America; IGRA = interferon γ release assay; NTM = Nontuberculous mycobacteria; RSV = respiratory syncytial virus; TST = tuberculin skin test.

reported in patients receiving anti-TNF α therapy but long-term data are lacking (101,128,129). Progression of liver disease in patients with chronic HCV and liver injury receiving anti-TNF α has been reported. HCV infection in children with IBD during treatment with anti-TNF α therapies has not been reported.

Epidemiology. Similar to HBV, HCV is a blood-borne pathogen that is acquired via blood or mucous membrane exposure to infected blood or body fluids. The most common route of HCV infection in young children is maternal-fetal transmission; the perinatal transmission rate is ~5%. Specific behavioral risk factors for HCV include the use of injectable illicit drugs and tattooing, HIV infection, and sexual activity. Increased use of nonhospital health care facilities, exposure to hemodialysis centers, endoscopy, and drug diversion by HCV-infected individuals also contribute to the risk of acquisition of HCV infection (122). Outbreaks in

nonhospital settings have highlighted the importance of observing safe injection practices (130).

Clinical Data. In contrast to HBV, TNF- α appears to contribute to the pathogenicity of HCV infection, triggering hepatocyte apoptosis and perpetuating liver inflammation (101). It is generally recommended to avoid anti-TNF α agents in patients with acute HCV infection or chronic HCV with significant liver injury (Child-Pugh classes B or C). To date, however, the use of anti-TNF α in patients with chronic HCV infection without liver disease appears to be safe; concomitant anti-HCV treatment is not recommended in this group during anti-TNF α treatment (131). It is worth noting that the majority of these data are derived from adult patients with rheumatoid arthritis and chronic HCV, receiving etanercept. Adult patients with IBD, particularly with CD, treated with interferon therapy for HCV may be at risk for exacerbation of intestinal inflammation and

the development of mixed cryoglobulinemia (101). An expert in the treatment of pediatric HCV infection should be consulted for the most up-to-date treatment strategies.

Diagnostic Testing. Updated guidance for diagnostic HCV testing is available (132,133). There are 2 groups of tests: IgG antibody EIAs for HCV and NAATs to detect HCV RNA. A rapid blood test has been approved for use in patients ≥ 15 years of age for the detection of antibody. Third generation EIAs are 97% sensitive and >99% specific. A reactive antibody test should be followed by NAAT testing. In immunocompromised patients in whom antibody testing may be falsely negative, both antibody and NAAT testing should be sent concomitantly. The detection of HCV RNA confirms infection. Consultation with an expert in pediatric HCV is recommended. New short-term therapeutic agents have been identified for the treatment of HCV infections, but there is no experience in children. Patients who test positive for HCV should also be tested for HIV, HBV, and hepatitis A.

Screening Before Anti-TNF α . In the presence of risk factors or elevated liver enzymes, screening for HCV antibody is recommended. If positive, HCV RNA testing should be performed. In patients already receiving immunosuppressive therapy, concomitant screening with HCV antibody and NAAT testing is recommended.

Prevention/Isolation/Control Measures. Because HCV is transmitted via blood in health care settings, infected patients should be managed using standard precautions with special attention to safe injection procedures (118,126). Equipment used for invasive procedures (eg, endoscopes) must be processed according to the most recent multisociety guideline on reprocessing flexible GI endoscopes (127). Patients should be counseled to avoid high-risk behaviors.

Varicella-Zoster Virus

Background. Following either immunization or natural primary infection, varicella-zoster virus (VZV) persists lifelong in dorsal root ganglia with the potential for clinical reactivation manifesting as shingles (zoster). The risk of zoster is lower in those who have received the vaccine than in those who have had natural primary infection. Overall, the incidence of primary varicella infection and associated morbidity and mortality in children has decreased since the licensure of the varicella-zoster vaccine in 1995 (134). Two doses of VZV vaccine are recommended.

Reviews of VZV infections in patients with IBD have reported both clinical primary varicella and zoster infections (15,99). Rates of 11.3/1000 patient-years have been reported for patients with IBD receiving anti-TNF α therapies (135). Anti-TNF α therapy may be a particular risk factor for severe primary infection, as TNF- α blockade allows for viral replication and dissemination of the virus in the early stages of infection. Corticosteroids (mean daily dose ≥ 10 mg), thiopurines, and anti-TNF α agents have been associated with an increased risk of VZV primary infection and reactivation; the risk is higher in those receiving combination immunosuppressive therapies.

Epidemiology. Primary varicella infection occurs more frequently in patients with CD than in those with UC, likely in part because of the increased immunosuppression in CD (99). The duration of time between starting immunosuppression and the development of either primary or reactivated VZV infection varies from a few days to years.

Clinical Data. Primary VZV infection may be more severe and may increase the risk of disseminated disease in patients receiving

immunosuppressive therapy. Patients with IBD treated with various immunosuppressive regimens who develop primary varicella have a case fatality rate of up to 25% (99). Disseminated VZV infection includes visceral involvement and may present with pneumonia, hepatitis, encephalitis, and disseminated intravascular coagulation (99). Reactivation of herpes zoster may have a prodrome of pain and tingling in a dermatomal distribution before the appearance of the vesicular rash. Depending on the location, a variety of neurologic syndromes have been described. Early diagnosis and initiation of antiviral therapy will decrease morbidity and mortality. In general, it is recommended that anti-TNF α therapy not be administered during an active herpes zoster infection. The decision to withhold immunosuppressive therapy during the VZV infection or to completely discontinue anti-TNF α agents, however, must be made individually based on the need for the immunosuppressive agents, severity of viral and underlying disease, and response to antiviral therapy, as data are lacking to make a single recommendation.

Diagnostic Testing. The appearance of VZV infections may be atypical in immunocompromised patients; therefore, diagnostic testing of skin lesions should always be performed. A scraping of the base of the vesicular lesion is the preferred specimen and should be sent for VZV PCR testing before initiating antiviral therapy. VZV PCR testing has improved diagnostic sensitivity compared with viral culture and Tzanck smear (136). VZV can be detected by PCR in whole blood during acute episodes of both primary varicella and herpes zoster but is less sensitive than testing of scrapings of skin lesions. VZV PCR may also be performed on CSF in the presence of encephalitis but is infrequently positive. Serology is not reliable in immunocompromised hosts to confirm acute infection but should be used for initial screening before immunosuppressive therapy is initiated (see below).

Screening Before Anti-TNF α therapy. The history of receipt of 2 doses of varicella vaccine should be obtained, and if the patient has not received 2 doses of varicella vaccine, immunity must be documented by measuring VZV IgG antibody in the blood before initiation of anti-TNF α therapy. A history of disease is not reliable unless confirmatory diagnostic testing was performed and results can be obtained. If the patient has protective antibody or confirmed prior history of VZV infection, primary varicella is unlikely to occur. In adults with IBD, the positive and negative predictive values for a reported history of VZV exposure were 93% and 0%, respectively (137).

Prevention/Isolation/Control Measures. Any patient with suspected VZV infection who is hospitalized should be placed in an airborne infection isolation room. Contact precautions are added until all skin lesions are dried and scabbed over and no new lesions are appearing. In ambulatory settings, the patient should be placed promptly in a negative pressure examination room or if such is not available, a mask is placed on the patient who is then escorted promptly into an examination room. Once it is clear that the lesions of herpes zoster are localized to a single dermatome, airborne precautions are no longer needed, but contact precautions are continued as described above.

Ideally, those who have not received the vaccine or are seronegative should receive 2 doses of vaccine (separated by >4 weeks for patients ≥ 13 years of age or ≥ 3 months if 1–12 years of age) ≥ 4 weeks before anti-TNF α blockers or any immunosuppressive regimen is initiated (23). With the prolonged interval recommended between the first and second doses and the frequent use of steroids or other immunosuppressive therapy in patients with IBD, this may, however, not be possible. Patients with IBD who are already receiving immunosuppression with high-dose

corticosteroids or anti-TNF α therapies should not receive VZV vaccine (23). Guidelines differ regarding the recommendation for administration of varicella vaccine in nonvaricella immune patients with chronic inflammatory diseases who are receiving long-term but low-dose immunosuppression; the strength of the recommendation and quality of the data to support this practice is weak and low, respectively. Receipt of varicella vaccine is not contraindicated in household or close contacts of immunocompromised patients. Refer to Table 3 for more information regarding immunizations in immunocompromised individuals and their close contacts.

Immunosuppressed individuals who are not immune to VZV should avoid exposure to people known to have primary varicella or reactivated herpes zoster that is not localized or cannot be covered completely. If a seronegative, immunosuppressed patient has been exposed to an individual with medically diagnosed chickenpox, VariZIG (Cangene Corporation, Winnipeg, Canada) should be administered according to the CDC recommendations (138). Antiviral prophylaxis should be considered if there has been a previous episode of shingles in patients at high risk for reactivation, including those requiring augmented immunosuppression (99).

Selected Infections Occurring in Pediatric Patients With IBD, No Confirmed Association With Anti-TNF α Use

Clostridium difficile

Background. Patients with IBD have a 3-fold increased susceptibility to *C difficile* infection compared with the general population and may be higher in patient with UC compared with patients with CD (139). A disproportionate increase in *C difficile*–associated hospitalizations is reported among pediatric patients with IBD in the US from 1997 to 2011 (140). Enteric infections may contribute to symptomatic relapses in patients with IBD, with *C difficile* being detected most frequently (141). Underlying disease activity was significantly greater in pediatric patients with IBD with *C difficile* infection than in uninfected patients (142).

Epidemiology. *C difficile* is acquired from the environment or via the fecal–oral route from direct contact with another colonized or infected patient or by indirect contact via carriage on the hands of health care personnel. Preceding antibiotic use, hospitalization, use of gastrostomy and jejunostomy tubes, and gastric acid suppression are established risk factors for *C difficile* infection. Data regarding the contribution of immunomodulatory therapies to increasing infection rates are scant. Corticosteroid therapy increases the risk for *C difficile* infections in patients with IBD; however, this association was not found with anti-TNF α therapies (143,144).

Clinical Data. *C difficile* asymptomatic colonization of the GI tract occurs soon after the neonatal period, in children <5 years of age, and is most frequent in infants <1 year of age. Asymptomatic *C difficile* colonization has also been described in patients with IBD without other identifiable risk factors (145). The spectrum of disease caused by *C difficile* varies from mild or moderate GI illness characterized by watery diarrhea and mild abdominal pain to severe colitis and toxic megacolon. Patients with IBD may not develop pseudomembranes but have a higher frequency of severe disease requiring colectomy (146).

Diagnostic Testing. Testing for *C difficile* toxin is prudent in patients with IBD > 2 years of age with risk factors, who present with worsening GI tract symptoms in an attempt to ascertain whether exacerbation is because of infection or underlying IBD

(43). If NAAT is used, 1 diarrheal stool specimen with a negative PCR result excludes *C difficile*–associated diarrheal infection with a sensitivity of 93% to 100% and a specificity of 100% (147). Optimally, a combination of a sensitive test (NAAT) with a specific test (cell cytotoxin immunoassay) may provide more accurate information to guide treatment decisions (148). A NAAT should not be performed for the test of cure given the persistence of positivity for weeks or months following the resolution of disease (149).

Screening Before Anti-TNF α . No data to support routine laboratory screening.

Prevention/Isolation/Control Measures. Standard plus contact precautions with bleach cleaning of surfaces must be followed. Practicing antimicrobial stewardship and proper isolation precautions, including meticulous hand washing are the most effective prevention methods. Because alcohol-based hand hygiene products do not inactivate *C difficile* spores, the use of soap and water for hand hygiene is recommended by most experts; however, there are no data that demonstrate a reduction in transmission associated with hand washing with soap and water versus waterless alcohol-based products.

Epstein–Barr Virus

Background. Primary infection with or reactivation of Epstein–Barr virus (EBV) is an important risk factor for the development of lymphoproliferative disease including lymphoma in transplant recipients. Increased risk of lymphoma has been reported in patients with IBD treated with thiopurines (19,150–152). Cases of EBV-associated lymphoma following primary disease have also been described with other immunosuppressive therapies, generally in combination (153–155). The data with anti-TNF α monotherapy are less clear, though no obvious signal for increased infection rates has been identified. Several studies of patients with IBD or rheumatoid arthritis treated with infliximab have not demonstrated EBV reactivation by infliximab therapy (156,157). There was no increased risk of development of EBV-associated lymphoma in patients with IBD treated with anti-TNF α agents who had high EBV viral loads; however, long-term clinical outcomes were not documented (158,159). In a recent systematic review, the risk of lymphoma was no greater among children with IBD who received anti-TNF α agents compared with those treated with other immunomodulator therapies (14). Primary EBV infection leading to lymphoproliferative disease in a teenager with CD has been reported (160).

Epidemiology. EBV is a ubiquitous virus. Primary infection in healthy individuals is asymptomatic or may be associated with an infectious mononucleosis syndrome that is most often mild. After primary infection, the virus remains latent in B lymphocytes in individuals with intact immune systems. EBV may be shed in saliva and only those with very close contact are at risk of acquiring infection.

Clinical Data. Data are lacking concerning the clinical presentation of EBV-associated lymphoma associated with anti-TNF α inhibitor therapy. Patients who have been treated with thiopurines may present with hemophagocytic lymphohistiocytosis (HLH) caused by primary EBV infection, lymphoproliferative syndromes, or lymphoma (161,162). Of note, 5 pediatric patients with IBD treated with systemic steroids, but not with anti-TNF α , developed HLH associated with primary EBV infection (163).

Diagnostic Testing. A serologic panel that includes IgM and IgG antibodies to the viral capsid antigen (VCA), antibodies to the early

antigen (EA) complex and to Epstein–Barr nucleic acid (EBNA) may be used to diagnose infection. Because EBNA antibody is not present in serum until several weeks to months after infection, its presence excludes a primary infection. EBV DNA can be detected in blood and quantitated by PCR and in situ hybridization for EBV RNA (EBER) is useful for detection of virus in tissue. Mucosal EBV viral loads were found to be useful for identifying viral colitis in adults with refractory IBD; however, there are too few data to make recommendations for diagnosis or treatment (116). EBV viral load surveillance in solid organ transplant recipients has been used to monitor for possible posttransplant lymphoproliferative disorder (PTLD) in high-risk patients; however, despite high sensitivity, it has poor specificity for PTLD (164). Furthermore, the detection and significance of a chronic, low-level EBV viral load is not completely understood in the IBD population. As such, currently there are no data to support this practice or guidelines for monitoring of EBV in patients with IBD receiving immunosuppressive therapy. Tissue histopathology in conjunction with EBER detection is the criterion standard for diagnosis of EBV-driven lymphoproliferative syndromes and lymphoma.

Screening Before Anti-TNF α Therapy. There is no definite indication to screen for EBV infection in children with IBD before the treatment with anti-TNF α agents. Performing an EBV panel that includes VCA IgM, VCA IgG, EA, and EBNA antibodies, however, may be useful to ascertain whether the patient has had a past infection, as primary EBV infection, if severe, may warrant antiviral therapy and is associated with higher risk for lymphoproliferative disease. Further research on this topic is needed in the IBD population.

Prevention/Isolation/Control Measures: Standard Precautions. The transmission of EBV is by intimate contact (eg, kissing), blood transfusion, and transplantation of stem cells, tissue, or solid organs; therefore, there are no specific isolation precautions beyond standard precautions that are recommended for health care facilities when caring for patients who have EBV infection.

Human Immunodeficiency Virus (HIV)

Background. Infection with HIV increases the risk of opportunistic infections, particularly if CD4 T cells are <200/mm³ (or CD4 percentage <15%) in individuals ≥6 years of age or if CD4 counts are <500 cells/mm³ (or CD4 percentage <15%) in children ages 1 to <6 years, and for all HIV-infected infants ages <12 months regardless of CD4 count or percentage (165,166). The risk of opportunistic infections is directly proportional to the viral load measured in blood and inversely proportional to the absolute CD4 count. The widespread use of highly active antiretroviral therapy (HAART) and prophylaxis has reduced the transmission, morbidity, and mortality associated with pediatric HIV. There are conflicting reports of the effect of anti-TNF α agents on the progression of HIV infection; therefore, these agents should not be withheld if needed but very close HIV load monitoring is required. Case reports describe the successful use of anti-TNF α therapies to treat inflammatory conditions in the setting of well-controlled HIV infection in adults receiving HAART (167).

Epidemiology. Modes of transmission of HIV include sexual contact, percutaneous blood exposure, mucous membrane exposure, perinatal transmission, including via breast-feeding or feeding of blood-tinged premasticated food, and transfusion of infected blood. Pediatric acquired immunodeficiency syndrome (AIDS) cases now account for <1% of all reported cases of AIDS in the US as a result of the implementation of comprehensive

programs to interrupt perinatal transmission. The rate of HIV acquisition during adolescence, however, has continued to increase in association with sexual exposures and illicit drug use.

Clinical Data. A total of 40% to 90% of newly diagnosed HIV infections may be associated with an acute retroviral syndrome (eg, fever, malaise, lethargy, myalgia, headache, adenopathy) that occurs 1 to 4 weeks following exposure and lasts <14 days. As individuals who are untreated become more immunosuppressed, they may present with general systemic deterioration, weight loss, unexplained fever, generalized lymphadenopathy, hepatosplenomegaly, pneumonia, and manifestations of the various opportunistic infections for which immunosuppressed individuals are at risk. Coinfection with HCV is present in 80% of HIV-infected patients who use intravenous illicit drugs and have hepatitis.

Diagnosis. The diagnosis of HIV infection is confirmed by following the testing algorithm approved by the FDA in 2014 that uses a fourth generation HIV 1/2 antigen/antibody combination immunoassay that allows for the detection of infection sooner than previous immunoassays (described below in the screening section). When clinical suspicion for recent HIV infection is high, testing by immunoassay and HIV-quantitative viral load testing can be performed simultaneously.

Initial Screening Before Anti-TNF α Therapy. The CDC recommends routine HIV screening of adolescents ≥13 years of age in health care settings in the US regardless of history or underlying medical conditions, unless the documented site-specific prevalence of undiagnosed HIV infection falls below 0.1% (168). In 2013, the US Preventive Services Task Force recommended routine HIV screening of all adolescents ≥15 years of age and of younger adolescents who are at increased risk (169). Repeat annual screening is recommended in those patients who are at high risk of acquiring HIV infection. Screening for HIV infection according to the most recent testing methodology described in the CDC/PHS recommendations (<http://www.cdc.gov/hiv/guidelines/testing.html>) is encouraged. Screening of patients <13 years of age may be considered, depending on risk factors and the degree of anticipated immunosuppression. Testing begins with a combination immunoassay that detects HIV-1 and HIV-2 antibodies and HIV-1 p24 antigen. All specimens reactive on this initial assay undergo supplemental testing with an immunoassay that differentiates HIV-1 from HIV-2 antibodies. Specimens that are reactive on the initial immunoassay and nonreactive or indeterminate on the antibody differentiation assay proceed to HIV-1 nucleic acid testing for resolution.

Prevention/Isolation/Control Measures. Because HIV may be transmitted via blood in health care settings, infected patients should be managed using standard precautions with special attention to safe injection practices (118,126). Adolescents with IBD who are or are likely to become sexually active should be counseled on effective preventive measures, availability, and limitations of postexposure and preexposure chemoprophylaxis, and the potential impact of HIV infection on the course of their IBD. Patients should be counseled to avoid high-risk behaviors.

Respiratory Viruses

Background. Respiratory viral infections in children are frequent and are more likely to occur as primary infections. Respiratory tract infections, presumably viral, were the most frequently reported type of mild and severe infections in pediatric patients with IBD receiving anti-TNF α therapies (15,170). Although viruses are

known to cause pneumonitis in immunocompromised hosts, no data are reported on the degree of risk of respiratory viral infections in children with IBD who are treated with anti-TNF α agents.

Epidemiology. Respiratory viruses generally cause seasonal community outbreaks which may vary by geographic location and year. Viral shedding may be prolonged (weeks to months) in the immunocompromised host.

Clinical Data. Clinical disease caused by respiratory viruses in patients treated with anti-TNF α blockers does not seem to be substantially different from disease in other patients.

Diagnostic Testing. The most sensitive diagnostic test for respiratory virus detection is a multiplex PCR panel that detects a variety of respiratory viruses. Because not all commercially available panels detect the same virus, it is important to know which test is used at one's own institution. Rapid diagnostic tests available for RSV are reliable but less sensitive than multiplex PCR panels. Diagnostic testing for influenza virus in symptomatic individuals is encouraged during the influenza season to identify patients who may benefit from antiviral therapy and to facilitate appropriate infection control measures.

Screening Before Anti-TNF α . Routine screening for respiratory viruses in asymptomatic individuals is not recommended.

Prevention/Isolation/Control Measures. Isolation precautions recommended by the Healthcare Infection Control and Practices Advisory Committee and the Centers for Diseases Control and Prevention for viral respiratory infections should be followed in health care facilities (118). For most respiratory tract viruses, contact plus standard precautions are recommended. Droplet precautions are added for influenza, adenovirus, and rhinovirus. Consistent hand hygiene and avoidance of crowds and individuals who have respiratory tract infections are general measures that will help reduce the risk of illness. Inactivated influenza vaccine is recommended for all immunocompromised patients during the influenza season. Inactivated or live attenuated influenza vaccine is recommended for all contacts of immunocompromised patients (23).

Parasitic Infections

There is no evidence that therapy with anti-TNF α agents increases the risk of parasitic infections. Parasitic infections with toxoplasmosis, strongyloides, malaria, and many cases of leishmaniasis, mostly in Europe and South America, have been reported in patients receiving anti-TNF α therapies, particularly in patients with underlying rheumatologic disease (111,171–175). No cases of parasitic infections have been published in children with IBD. These sporadic reports have epidemiological risk factors identified, highlighting the importance of a high index of suspicion and thorough history.

Safe Living

Vaccination

Background. Pediatric and adolescent patients with IBD are at increased risk for vaccine preventable illnesses (VPIs) and more fulminant disease associated with these infections than immunocompetent individuals. This risk can be exacerbated by disease severity and immunosuppressive therapies, including immunomodulators, corticosteroids, or biologics. Attention should be paid to vaccination status and attempts made to optimize vaccination at the time of diagnosis, especially because patients with IBD

are increasingly receiving immunosuppressive medications earlier in their disease course. Several gastroenterology publications highlight the need to review immunizations at the time of the first GI visit (176,177). The evaluation and vaccination strategy described in Tables 2 and 4 should be incorporated into the initial visits. These recommendations are in line with recent reviews, guidelines, and position statements in the gastroenterology and infectious disease literature but provide additional detail on other aspects important in the primary evaluation to optimize health (eg, HIV and serologies) (23,178). Parents may be reluctant to have their children receive vaccines, such as influenza vaccine, because of inadequate knowledge, concern for adverse effects, or incorrect fear of causing an IBD flare. Studies evaluating the immunogenicity and safety of vaccines in children with IBD, however, have not found an increased risk of serious adverse effects or disease flares after vaccination (179–183).

All inactivated vaccinations should be updated according to the current AAP and Advisory Committee on Immunization Practices (ACIP) vaccine schedule and as clinically indicated, using an accelerated catch-up schedule as long as the minimum window between doses has elapsed (184). Reasons to give a vaccine on an earlier schedule include the risk of more severe illness in patients with IBD who develop a VPI and impaired vaccine immunogenicity once immunosuppressive therapy is introduced. For newly diagnosed pediatric patients with IBD, inactivated vaccines should optimally be given ≥ 2 weeks before immunosuppressive therapy is started. Although there are no safety concerns if given later, this time interval may allow for a more robust seroresponse before immunosuppression. Patients with established IBD already receiving anti-TNF α and other immunosuppressive therapies should receive inactivated vaccines in accordance with the ACIP vaccine schedule. Diminished immune responses may occur in some patients, but inactivated vaccines can be given safely.

Studies evaluating the immunogenicity of inactivated vaccines in children with IBD are limited. Generally, most studies have shown that they respond adequately to inactivated vaccines, though response may vary by vaccine type and be impaired if administered while receiving immunosuppressive therapies. Pediatric patients with IBD have demonstrated adequate response to the 13-valent pneumococcal conjugate vaccine and hepatitis A vaccine when compared with healthy controls (182,185). Receipt of human papillomavirus vaccine was found to be safe and highly immunogenic in pediatric patients with IBD, even while immunosuppressed (181). Other studies, however, found that immune responses to influenza and the pneumococcal polysaccharide vaccine may be impaired in patients with IBD while on concurrent immunosuppressive medications (179,186). The HBV series may need to be repeated in this population because they may be at risk for higher rates of waning antibodies. One study of mostly adolescent patients with IBD found that only 56% (49/87) had protective levels against HBV infection despite completing the 3-dose vaccine series. In the group of 38 patients who were nonimmune despite receiving a full HBV series, 34 received a single booster dose; 26 of these 34 patients (76%) had an adequate response noted 4 weeks later (121). Patients receiving infliximab therapy were at increased risk for inadequate response. Pediatric patients with IBD with inadequate HBV antibody levels after the primary vaccine series should repeat the 3-dose series. The immune response should be rechecked 2 months after completion of the third dose to ensure the concentration of anti-HBs is ≥ 10 μ IU/mL. The combined hepatitis A and hepatitis B (Twinrix, GlaxoSmithKline Biologicals, Rixensart, Belgium) vaccine may be more immunogenic than the monovalent HBV vaccine and may offer an advantage. No recommendations are available on how to proceed if a patient continues to have inadequate response after HBV revaccination. Table 4

provides a summary of vaccination strategies in pediatric patients with IBD.

We encourage completion of the live vaccine series for varicella and measles–mumps–rubella (MMR) soon after the patient is diagnosed with IBD and before any (low or high level) immunosuppressive therapy is started. Pediatric and adolescent patients with IBD should have VZV serologies obtained as defined in Table 4. A retrospective review of newly diagnosed pediatric patients with IBD found that only 77% had serologic evidence of varicella immunity, highlighting the importance of checking for both vaccine administration and serologic confirmation (187). Obtaining serologies should also be considered for patients who were only able to receive 1 dose of either VZV or MMR. Results of serologic testing can guide vaccination practices, and in nonimmune patients with IBD who have significant exposure to varicella or measles, this serologic information can help guide postexposure measures, including passive immunoprophylaxis.

We strongly encourage providing live virus vaccines at IBD diagnosis in nonimmune patients because it may take 2 to 3 weeks to establish a postvaccine immunogenic response and because live virus vaccines should ideally be administered ≥ 4 weeks before initiation of any immunosuppressive therapy (23,176). Initiation of immunosuppression should not be delayed to provide live vaccines if immediate treatment is needed for the underlying IBD. Thus, providing live virus vaccine at IBD diagnosis provides a window period to optimize the immune response to vaccination and safely escalate immunosuppressive therapies later in the IBD course in a timely fashion, if clinically needed.

Once immunosuppressive therapies are started, live vaccines are generally contraindicated currently. In the US, live vaccines include MMR, VZV, live attenuated influenza vaccine, oral typhoid, and yellow fever vaccines. The degree of immunosuppression that is considered high level and may hamper immune response to vaccination or compromise safety includes patients receiving any anti-TNF α agent (at any dosage) or other biologic agent (eg, rituximab), corticosteroid therapy with a daily dose of ≥ 20 mg (or in patients weighing <10 kg, >2 mg/kg/day), methotrexate (>0.4 mg/kg/wk), azathioprine (>3 mg/kg/day), or 6-mercaptopurine (>1.5 mg/kg/day) (23,176). For similar safety and efficacy reasons, live virus vaccines should not be given after discontinuation of high-level immunosuppression, unless 3 months have elapsed since the last dose.

The Infectious Diseases Society of America guidelines state that VZV vaccine is the only live vaccine that can be considered in patients with chronic inflammatory diseases without evidence of varicella immunity who are receiving chronic, low-level immunosuppression (strength of recommendation, weak; quality of evidence, very low) (23). This consideration, however, deviates from recommendations by the ACIP and Centers for Disease Control and Prevention. Concern for severe illness after exposure to varicella or measles and experience of safe administration of live vaccines in other significantly immunocompromised pediatric patients suggest that the benefit of vaccination may outweigh potential risks, depending on the extent of immunosuppression. Six patients (ages 6–20 years, 2 receiving anti-TNF α agents) with IBD received VZV vaccine while immunosuppressed without adverse events; 5 demonstrated seroconversion and immunogenicity (188). No prospective studies, however, have been conducted and additional data are needed to evaluate the immunogenicity and safety of MMR and VZV vaccinations in pediatric patients with IBD receiving immunosuppressive therapy.

Close household contacts of patients with IBD should be encouraged to be fully immunized according to the adult immunization schedule to minimize the risk of transmitting a VPI to a pediatric IBD patient (23,189). All of the live virus vaccines (with

the exception of oral polio vaccine that is no longer used in the US) and smallpox vaccine may be given safely to household contacts of patients with IBD receiving immunosuppressive therapies.

Screening. All patients should be evaluated for history of viral, bacterial, and mycobacterial infections as detailed in Tables 2 and 4. This includes a review of vaccine records, prior illnesses, risk factors, and immunodiagnoses and serologies, if available.

Strategies for Safe Living and Infection Prevention in Patients With IBD

Since 2009, several documents have been published that provide guidance for safe living to patients with immunocompromising conditions that lead them to be vulnerable to certain types of infections (190–192). Pathogen-specific safe living recommendations are incorporated into the prevention section of the discussion for each pathogen in this document. Because every possible situation encountered cannot be anticipated, the principals of safe living for individuals with underlying medical conditions receiving immunosuppressive agents are summarized in Table 5. It is important to note that although vaccines are available for protection against some agents encountered in areas outside of the US, response to those vaccines may not be optimal, or those vaccines may be contraindicated during periods of treatment with potent immunosuppressive agents, including anti-TNF α therapy. For more details about unusual situations, ID and travel medicine experts should be consulted.

Refer to the following CDC websites for additional materials:

- (1) <http://wwwnc.cdc.gov/travel>
- (2) www.cdc.gov/mrsa
- (3) www.cdc.gov/features/animalexhibits/

Opportunities for Research

Given limited pediatric data, multiinstitutional studies assessing incidence, microbiology, and severity of infections in pediatric patients with IBD receiving anti-TNF α therapies are necessary to understand the burden of disease and better assess whether laboratory screening has a role for certain infections. Additional data regarding optimal vaccination strategies are also needed. These efforts would provide data for evidence-based recommendations, optimize preventive strategies, including identification of a subset of patients who may benefit from prophylaxis, and how best to monitor for infections during anti-TNF α treatment.

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Pyloric Stenosis

When we recall Harald Hirschsprung (1830–1916), we think of primarily his eponymous hypertrophy of the colon, yet he was a extraordinarily keen observer who published 4 case histories of esophageal atresia with tracheoesophageal fistula (1861), elaborated on controlled hydrostatic reduction of ileocecal intussusception (1876) using enema therapy, and meticulously described 2 postmortem cases of pyloric stenosis in 1888. Thereafter, the treatment of pyloric stenosis was primarily via dilatation and gastroenterostomy, until Conrad Ramstedt (1867–1963) introduced his method of pylorotomy. In an address to the 5th annual meeting of the British Association of Paediatric Surgeons (1958), Selwyn Taylor quoted Ramstedt:

At the laparotomy on August 23, 1911, I was astonished at the pyloric tumour as thick as my thumb. After I had split the tumour down to the mucosa for a distance of about 2 cm. I had the impression that the stenosis had been relieved. I still tried, however, to accomplish the plastic procedure by transverse suture of the muscle edges. However, the tension on the sutures was so very strong that the first one cut through immediately. Then the thought shot through my head, “A plastic alteration of the cut edges is completely unnecessary; the stenosis seems to be already relieved by a simple splitting. . . .” [I] left the cut gaping, covering it with a tab of omentum for safety sake and ended the operation.

Taylor S. *Arch Dis Child* 1959;34:20–23



Conrad Ramstedt (1867–1963)

—Contributed by Angel R. Colón, MD