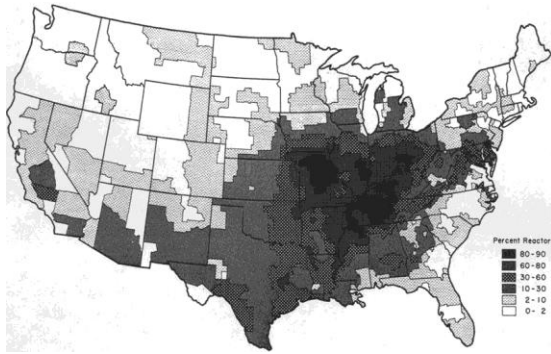


Histoplasmosis During Tumor Necrosis Factor Blocker Therapy

Introduction. Lee and colleagues noted that the incidence of histoplasmosis was about six cases per hundred thousand patients treated with tumor necrosis factor α blockers, and wrote "a discussion regarding avoidance of activities related to risk of HC (*Histoplasma capsulatum*) exposure, such as frequent exposure to soil... should be considered in patients receiving TNF- α antagonists who reside in HC endemic areas." [1]. Despite that advice, in a subsequent report of the same database, the incidence was reported at 16.7 cases per hundred thousand patients [2]. In the United States, especially in endemic areas, histoplasmosis appears to be more common than tuberculosis in patients receiving TNF blockers [3].



Endemic areas for histoplasmosis in the US [4]

lymphocytes; T_H1 cytokines (interferon- γ , TNF- α); interleukin 12 and 18; and activated macrophages [5]. If these elements are impaired, the yeast proliferates unchecked in the reticuloendothelial tissues, causing progressive disseminated histoplasmosis (PDH), and death if untreated [6]. TNF blockade prevented development of a protective immune response in experimental histoplasmosis [7-11], by impairment in activation of macrophages [12]. The risk appears to be higher with the monoclonal antibodies to TNF than with the soluble TNF receptor [11], but other factors, including age [6] may influence the risk for histoplasmosis.

Controversy exists as to the mode of acquisition of histoplasmosis in these patients. Histoplasmosis could represent 1). newly acquired primary infection, 2). reinfection caused by a loss of immunity during immunosuppression, 3). progression of undiagnosed "smoldering" histoplasmosis that was present when the TNF blocker was initiated, or 4). reactivation of "latent" histoplasmosis.

The [FDA](#) recently advised the makers of TNF blockers to add information about the risk of invasive fungal infections, including histoplasmosis, in the **Boxed Warning** and **Warnings sections** of the drug's prescribing information and the Medication Guide for patients, and encourages consultation with a physician experienced in the recognition and diagnosis of serious fungal infections.

Pathogenesis. Cell-mediated immunity plays a critical role in the host defense against *H. capsulatum*, and requires dendritic cells, which process antigens for stimulation of specific CD4 and CD8

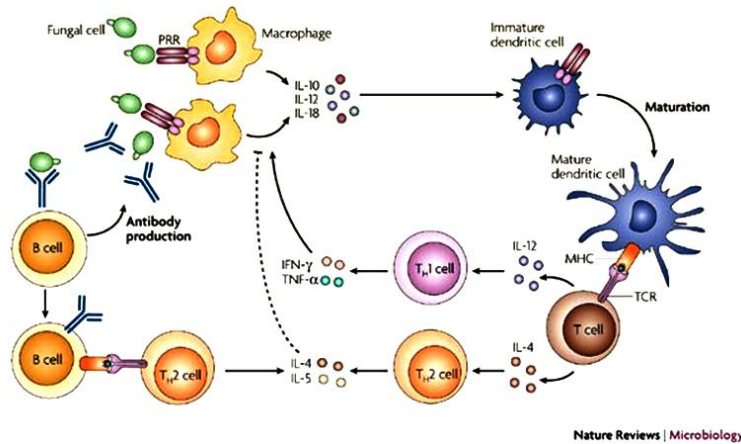


Figure 2. Cellular immune response in histoplasmosis. Reprinted by permission of Macmillan Publishers Ltd [5]

Since over half of residents from endemic areas have had histoplasmosis [4], if “latent” histoplasmosis was common, and reactivation occurred, the incidence in those receiving TNF blockers should be much higher than 1 to 2 cases/10,000 [2]. In fact, histoplasmosis remains rare in immunosuppressed patients in endemic areas. For example, not one case was diagnosed among nearly

600 transplant patients in Indianapolis during the year following transplantation [13], or among over 600 children given chemotherapy for malignancy in Memphis [14]. Reasons for the rarity of reactivation in histoplasmosis are unknown but probably include the effectiveness of acquired immunity at killing the organism. Earlier studies showed that organisms found in calcified lung lesions were not viable [15]. Progression of “smoldering” infection that existed when the TNF blocker was added to existing immunosuppressive therapy or newly-acquired infection appear to be more likely than reactivation of latent infection.

Screening for exposure or active infection. Patients who reside in areas endemic for histoplasmosis should be questioned about possible exposure or evidence for active or recent past pulmonary infection. Routine radiographs, serology or antigen testing are not recommended.

If there is a history of possible exposure or active infection, however, additional workup is appropriate, outlined below. Radiographic abnormalities associated with histoplasmosis may include diffuse reticulonodular or miliary infiltrates, focal or patchy infiltrates, non-calcified pulmonary nodules, and hilar lymphadenopathy. Some advice to patients is outlined in Appendix 1.

Clinical findings. Pneumonia and/or progressive disseminated disease (PDH) were present in 70-80% of reported cases [16-23] (Table 1). Most patients have exhibited progressive illnesses associated with fever and weight loss. Findings suggesting disseminated disease include hepatosplenomegaly, lymphadenopathy, mucocutaneous or gastrointestinal lesions, adrenal masses or insufficiency, anemia, leukopenia, thrombocytopenia, or hepatic enzyme elevation. Diffuse reticulonodular infiltrates also suggest dissemination in the absence of heavy exposure [24].

Immune reconstitution inflammatory syndrome (IRIS). A paradoxical worsening has been described after stopping TNF inhibitors in patients with tuberculosis [26], attributed to the inflammatory response to mycobacterial antigens. Similar findings might occur in patients with histoplasmosis, possibly resulting in inappropriate changes in antifungal therapy [25].

Findings of possible IRIS in histoplasmosis are summarized in table 2. One patient presented with respiratory failure refractory to amphotericin B therapy, and required prolonged mechanical ventilation [16]. Another presented with gastrointestinal histoplasmosis complicated by bowel perforation and abdominal compartment syndrome, both which required surgical therapy [19]. Two others developed skin and soft tissue necrosis, which required repeated débridement [17,18]. Itraconazole was added to amphotericin B lipid complex because of suspected treatment failure in one of these patients [17]. Of note is that these authors did not attribute their patients' worsening to IRIS, and the clinical details were inadequate to exclude progressive histoplasmosis.

Nevertheless, IRIS is possible and physicians should consider it in patients who deteriorate after starting treatment. Negative cultures or declining antigen concentration would favor IRIS rather than progressive infection. Differentiation of IRIS from progressive histoplasmosis is important, as IRIS would not respond to changes in antifungal therapy, but might improve in response to anti-inflammatory therapy, whereas progressive histoplasmosis would worsen if anti-inflammatory agents were given, and might require changes in antifungal therapy.

Diagnostic approach. A battery of tests is recommended, table 3 [27]. Both urine and serum should be tested to achieve the highest sensitivity for diagnosis by antigen testing [28], positive in over 90% of cases (Wheat, unpublished data). If BAL is performed, specimens should be tested for antigen [29]. Bone marrow examination may be helpful if tests for antigen are negative, and anemia, leukopenia or thrombocytopenia are present. Serologic tests also are positive in over 90% of cases, but are unable to distinguish active from past infection in some patients [27]. As none of the tests are positive in all cases, the diagnosis cannot be excluded by negative results. If the tests are negative, but the illness persists, repeat testing is recommended, as well as consideration of biopsy of any lesions.

Treatment. Treatment recommendations have been published ([IDSA guidelines](#)) [30]. The FDA alert indicated that empiric treatment should be considered in more ill patients with compatible epidemiologic and clinical features while awaiting results of diagnostic tests. Lipid formulations of amphotericin B are preferred for hospitalized patients, and itraconazole for those who are less ill [30]. Therapy probably should be continued for at least one year, and until antigenemia has resolved and antigenuria has fallen to low levels (< 5 ng/mL). While the IDSA guideline recommends a shorter duration of therapy for pulmonary histoplasmosis, undiagnosed disseminated disease is likely in immunosuppressed patients [6]. The need for chronic antifungal suppressive therapy is uncertain [30], but if treatment is stopped, antigen concentration should be monitored for evidence of relapse.

The FDA and manufacturers of the TNF blockers recommend discontinuation of the TNF blocker. Physicians should be alert to the possibility of IRIS after stopping TNF blockers. The optimal management of IRIS is uncertain, but usually includes corticosteroids. Additional information about the management of immunosuppression during the treatment for histoplasmosis in patients who are taking TNF blockers is needed.

Table 1. Key findings in published cases of histoplasmosis in patients treated with TNF inhibitors

Age	Sex	Dis	Drug	Pred	OIS	Pul	CXR/CT	PDH	Sev	Cul	HP	Ser	Ant	AmB	Itra	TNF	Fup	Ref #
50	M	RA	Inf	yes	MT	yes	Dif		yes	pos	pos	pos	pos	11 d	2 m			[16]
17	F	JRA	Inf	yes	AZ	yes	Nor	yes			pos	pos	pos	5 w	yes			[16]
50	F	RA	Eta	yes	MT	yes	Dif	yes			pos	pos	pos		yes			[16]
51	F	RA	Inf	yes	AZ	yes	Dif	yes		pos	pos	pos		9 m	12m		12m	[17]
56	R	CD	Inf				Dif	yes		neg	pos	pos	pos	4.5m	4.5 m		18m	[18]
20	M	CD	Inf	yes				yes			pos	pos	pos	yes	6 m		16m	[19]
19	M	CD	Inf		MP	yes		yes		pos				yes	yes			[20]
52	F	RA	Inf	yes		yes				pos	pos	pos	pos	yes	yes			[21]
40	M	CD	Inf	yes		yes	Dif			pos	neg			yes	yes	yes		[22]
75	F	RA	Inf	yes			Nor	yes			pos				yes	yes	4 m	[23]
61	M	RA	Inf			yes	Dif			pos				yes	yes			[1]
45	F	RA	Inf			yes	Ade	yes	yes	pos				yes	yes			[1]
78	F	RA	Inf			yes	Dif		died	pos				yes	yes			[1]
67	F	RA	Inf			yes		yes		pos				yes	yes			[1]
11	M	CD	Inf			yes	Dif		yes	pos				yes	yes			[1]
38	M	CD	Eta	yes	MT	yes	Nod	yes	yes	pos				yes	yes			[1]
42	M	CD	Inf			yes	Nod	yes	yes	pos				yes	yes			[1]
38	M	RA	Eta					yes				pos	pos	yes	yes			[1]
53	M	CD	Inf			yes	Dif			neg	neg	pos	pos	3d	6m	yes	12m	[31]
41	M	RA	Ada			yes	Dif	yes	yes	neg	pos	pos	pos	7d	6w			[32]

A blank indicates that no information was provided. Abbreviations used in the table are: Dis-inflammatory disease, Pred-prednisone, OIS-other immunosuppressant, Pul-pulmonary, CXR/CT-chest radiograph or CT scan, PDH-progressive disseminated histoplasmosis, Sev-severe manifestation (shock, respiratory failure, death), Cul-culture, HP-histopathology, Ser-serology, Ant-Histoplasma antigen, AmB-amphotericin B, Itra-itraconazole, TNF-resume TNF blocker, Fup-follow-up; RA-rheumatoid arthritis, JRA-juvenile rheumatoid arthritis, CD-Crohn's disease, Inf-infliximab, Eta-etanercept, Ada-adalimumab, MT-methotrexate, AZ-azathioprine, MP-mercaptopurine; Dif-diffuse, Nor-normal, Ade-adenopathy, Nod-nodular; pos-positive, neg-negative; d-day, w-week, m-month; Ref-reference.

Table 2. Findings of possible IRIS in histoplasmosis complicating TNF blocker therapy

Antifungal	Time on antifungal	Clinical findings suggestive of IRIS	Intervention	Ref
AmB	2 months	Respiratory failure	Mechanical ventilation	[16]
L-AmB, itraconazole	>3 months	Palmar abscess requiring multiple drainages, which didn't heal for 6 months	Multiple debridements, muscle flap	[18]
AmB, itraconazole	Not stated	Extensive bowel necrosis, abdominal compartment syndrome	Bowel resection, open decompression	[19]
ABLC	Not stated	New necrotic skin lesions	Débridement, addition of itraconazole to ABLC	[17]

Table 3. Diagnostic workup for histoplasmosis

Parameter	Testing	Finding
Pneumonia in past 2 years	Chest X ray or CT Serology Antigen	Infiltrate, mediastinal lymphadenopathy, cavity, non-calcified nodules Immunodiffusion (ID)-M or H precipitin Complement fixation (CF)-titer $\geq 1:8$ ($\geq 1:32$ more significant for recent exposure/active infection) Antigen present
Possible exposure	Serology	See above
Symptoms or physical findings	Antigen Blood culture Chest X ray/CT BAL if infiltrate Serology	Antigen present Growth of <i>H. capsulatum</i> Infiltrates as above Yeast microscopically or culture See above
X ray/CT findings	BAL	Antigen present Yeast microscopically or culture
Bone marrow suppression	Antigen Serology Blood culture Bone marrow biopsy	Antigen present As above Growth of <i>H. capsulatum</i> Yeast microscopically or culture
Hepatic enzyme elevation	Antigen Serology Blood culture Liver biopsy	Antigen present As above Growth of <i>H. capsulatum</i> Yeast microscopically or culture
Serology positive [M or H band, CF titer $\geq 1:8$	Antigen Blood culture	Antigen present Growth of <i>H. capsulatum</i>
Calcified lung or spleen lesions	Asymptomatic-none Symptomatic-as above	As above

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