REMICADE® (infliximab) Serious Fungal Infection Education Guide

• Treatment with REMICADE® or other anti-TNFα agents puts patients at increased risk for serious infections including invasive fungal infections that can lead to hospitalization and death.

• Invasive fungal infections including histoplasmosis and coccidioidomycosis and other opportunistic fungal infections are frequently unrecognized.
  – Patients being treated with REMICADE® or other anti-TNFα agents are more susceptible to invasive fungal infections, especially when residing in, or visiting endemic areas of the world.

• Invasive fungal infections are frequently unrecognized and treatment is frequently delayed.
  – If these conditions are not considered in the differential diagnosis, appropriate therapy may be delayed with potentially life-threatening consequences.
  – Patients, including those being treated with REMICADE® or other anti-TNFα agents, may present with disseminated infection rather than local disease.
  – Antigen and antibody tests for these invasive fungi may be falsely negative in patients being treated with REMICADE® or other anti-TNFα agents. Patients should undergo a complete diagnostic workup, which may include fungal cultures, histopathological or cytological evaluations, as well as antigen detection and serum antibody titers.

• Patients have died when the initial physician who came in contact with the patient did not consider or recognize the invasive fungal infection (eg, histoplasmosis, coccidioidomycosis).
  – Invasive fungal infections must always be considered when a patient receiving REMICADE® or other anti-TNFα agents presents acutely ill, particularly with a history of residence in or travel to endemic areas. A high index of suspicion is key to appropriate management of this risk.
  – Urgent consultation with an infectious disease specialist and/or empiric antifungal therapy should be considered in patients at risk for invasive fungal infections, including those being treated with REMICADE® or other anti-TNFα agents who develop severe systemic illness.

Background: Systemic Fungal Infections

1. Exposure
   a. Result of airborne exposure to organisms that cause histoplasmosis or coccidioidomycosis or other fungal agents
   b. Increased in areas endemic for specific fungal agents
      1) Histoplasmosis - Ohio and Mississippi River valley (prevalence – up to 80%)
      2) Coccidioidomycosis - Southwestern US particularly Arizona and the San Joaquin Valley in California (prevalence – up to 50%)
2. **Other Risk Factors**
   a. Immunosuppression
   b. Chronic lung disease
   c. Elderly and Children less than 2 years old
   d. Occupation (farmers, construction workers, spelunkers)
   e. Exposure to a large inoculum (ie, dust storms)

3. **The role of tumor necrosis factor-alpha (TNF-α) in severe fungal infections**
   a. TNF-α may play a role in granuloma formation and containment of fungal infection
   b. Cases of severe fungal infections including histoplasmosis and coccidioidomycosis have been reported in patients treated with anti-TNF therapies and have resulted in death.

4. **Active Disease**
   a. Patients should be closely monitored during and after treatment with REMICADE® (infliximab) for the development of signs or symptoms of possible systemic fungal infection including fever, malaise, weight loss, sweats, cough, dyspnea, pulmonary infiltrates on X-ray, or serious systemic illness including shock.
   b. Patients who develop an infection should be discontinued from REMICADE® therapy and undergo a complete diagnostic workup, which may include fungal cultures, histopathological or cytological evaluations, antigen detection and serum antibody titers.

**Before initiating and during treatment with REMICADE®**

Manage the potential risk of severe fungal infection with proper evaluation, monitoring and treatment.

1. **Evaluate:** Make a thorough history (including history of residence in or travel to endemic areas), physical, and, if indicated, evaluation (eg, laboratory tests, chest x-ray) part of your regular examination.

2. **Monitor:** Continue to monitor patients for signs and symptoms of systemic fungal infection (eg, respiratory symptoms, a general ill feeling, fever, chest pains, and a dry or nonproductive cough).

3. **Treat:** While diagnostic workup is being performed, appropriate empiric anti-fungal therapy should be considered and/or consultation with an infectious disease specialist for patients with signs and symptoms of systemic fungal infection. Empiric treatment is not a substitute for thorough work-up to establish definitive diagnosis and therapy.