Coccidioidomycosis

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On completion of this article, you should be able to (1) describe the geographic areas that have a high risk of coccidioidal infection and recognize the different clinical presentations of infection with Coccidioides *species and the risk factors for disseminated disease, (2) interpret the different types of coccidioidal serologies and recognize their use in diagnosis and follow-up of patients with coccidioidomycosis, and (3) recognize different treatment options for coccidioidomycosis.*

Coccidioidomycosis is a common infectious disease in the southwestern United States. Although *Coccidioides* species are not endemic in other areas of the country, the rapid population growth in the southwestern United States in recent decades and the increase in tourism mean that many people travel to the Southwest and return home before developing the clinical syndrome of coccidioidomycosis. In this respect, coccidioidomycosis is a disease of national importance. It can occur in various manifestations: acute pneumonia, chronic progressive pneumonia, pulmonary nodules and cavities, extrapulmonary nonmeningeal disease, and meningitis. The diagnosis is often made on the basis of serologic findings. Treatment is usually with an azole or amphotericin B, depending on the clinical manifestations and the immune status of the host. We discuss the most common clinical manifestations, the best way to make the diagnosis, and the treatment of common infections.

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CF = complement fixation; EIA = enzyme immunoassay; HIV = human immunodeficiency virus

The first cases of coccidioidomycosis were recognized in the 1890s in central California agricultural workers as a diffuse, progressive, disfiguring skin disease that involved primarily the head and neck and was uniformly fatal.[1] As the population in California increased dramatically in the early 20th century, an acute respiratory illness known as *valley fever* was observed, named for the San Joaquin Valley of central California. It was not until 1937 that the cause of this acute respiratory syndrome was recognized to be the same organism that caused the progressive chronic skin disease.[2] The organism was identified and named *Coccidioides immitis*.[3] Valley fever occurred frequently during World War II among the thousands of military troops who trained in the southwestern United States for desert warfare.

Coccidioidal infection has primarily affected the rapidly growing populations in the US Southwest, especially California and Arizona, its occurrence punctuated with intermittent major epidemics in the past 30 years.[3] Notable epidemics occurred in the San Joaquin Valley in the 1990s and after the 1994 Northridge earthquake north of Los Angeles. Additionally, a surge of new cases developed in southern and central Arizona, especially in the Phoenix area.[4] In the past 10 years, the incidence of coccidioidal infections in Arizona has increased from approximately 12 new cases per 100,000 population in 1995 to 58.2 new cases per 100,000 population in 2005 (Figure 1). Several likely factors for this increasing incidence include a greater number of nonimmune persons moving into endemic areas, a growing immunosuppressed population, and new construction in previously undeveloped desert areas that results in more dust and arthrospores in the air. Additionally, as awareness of this infection increases within the endemic area, both physicians and patients are more likely to request serologic testing.[5] A recent study also indicates that the incidence increases when rainy summers are followed by dry winters and windstorms, resulting in enhanced growth and dispersion of arthrospores.[6]

EPIDEMIOLOGY AND ECOLOGY

Coccidioides species are found only in the western hemisphere and are endemic to the US Southwest and adjacent areas in northern Mexico. The disease is also seen in several areas of South America, primarily Argentina and Paraguay, which have a climate similar to that of the Southwest. A second species, *Coccidioides posadasii*, has been identified recently as the predominant organism outside California.[7] *Coccidioides* species are found primarily in the soil of the arid lower Sonoran Desert, although they can exist in other similarly warm, dry climates. They live in warm, sandy soil in a climate characterized by hot summers, mild winters, and fewer than 20 inches of rainfall per year.[8] The organism does not grow at altitudes greater than 3700 feet.

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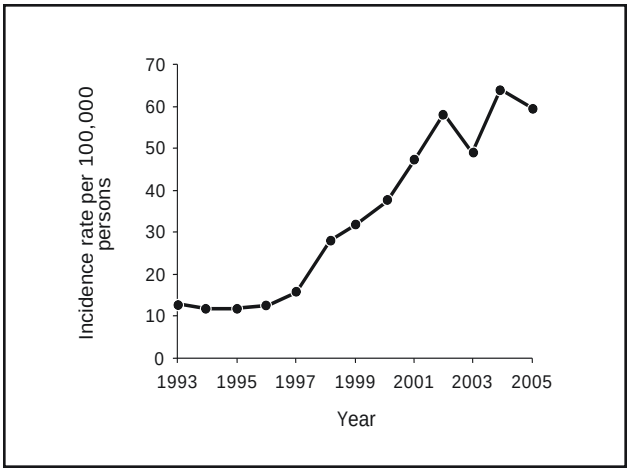

FIGURE 1. The incidence of coccidioidal infection in Arizona, 1993-2005. Data from reference 5.

Coccidioides sp exist in 2 phases: the mycelial phase, which is a mold in the soil growing in branching, septate hyphae; and the spherule phase. The mycelial phase is extremely hardy and can remain viable in the dry desert soil for months to years. After a rain, it multiplies rapidly, forming arthroconidia. Wind disperses these arthroconidia into the air, and they may be inhaled by an animal or a human, who becomes an accidental host. Within the lung, the arthroconidia transform into new, multinucleated spherical structures called spherules (Figure 2, left). The spherules then grow larger and contain hundreds to thousands of endospores. The spherules eventually break open, releasing the endospores (Figure 2, right), which grow to form new spherules, and the cycle continues.[9]

With the large increase in population in California, Arizona, and other areas of the southwestern United States, a large number of cases of coccidioidal infection has been seen in the past 20 years.

CLINICAL MANIFESTATIONS

Coccidioidal infection has 5 main manifestations: acute pneumonia, chronic progressive pneumonia, pulmonary nodules and cavities, extrapulmonary nonmeningeal disease, and meningitis.[10]

Acute Pneumonia

The primary clinical manifestation is an acute respiratory infection that occurs approximately 1 to 3 weeks after inhalation of arthroconidia.[11] The symptoms are usually indistinguishable from those of any type of community-acquired respiratory illness and include fever, headache, sore throat, cough, profound fatigue, and pleuritic chest pain. In an acute respiratory illness, symptoms that strongly suggest coccidioidal infection are severe headache and severe pleuritic chest pain. Profound fatigue that lasts for several weeks to months is observed frequently in association with coccidioidal pneumonia. In 1 study of community-acquired pneumonia in Tucson, AZ, 16 (29%) of 55 cases were serologically positive for coccidioidal infection, supporting the concept that *Coccidioides* sp are a common cause of community-acquired pneumonia in endemic areas.[12]

Radiographic findings of acute respiratory infection (ie, lobar, segmental, or subsegmental infiltrates) are similar to those of other community-acquired pneumonias (Figure 3). Hilar or paratracheal adenopathy is uncommon in bacterial pneumonia but occurs in approximately 25% of coccidioidal infections. In acute community-acquired pneumonia in a patient who has been in an endemic area, the finding of lobar infiltrates and adenopathy is strongly suggestive of

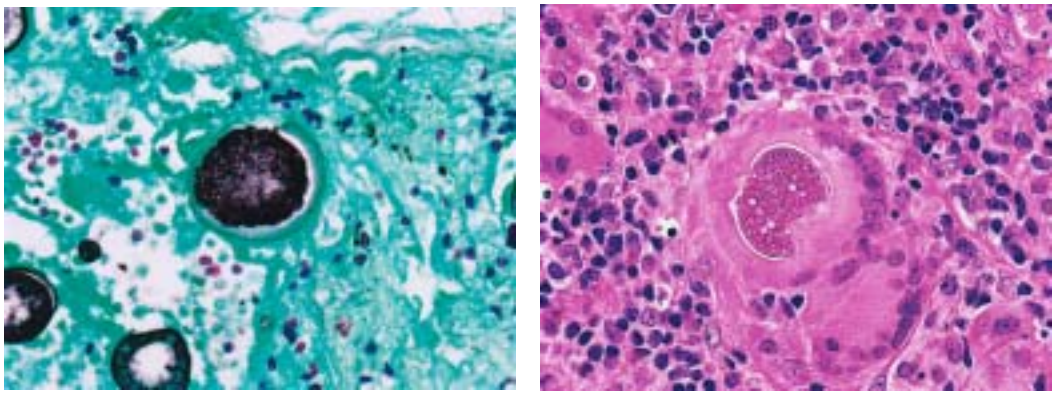

FIGURE 2. Left, Spherule of *Coccidioides* species in lung tissue (Grocott-Gomori methenamine-silver, original magnification ×400). Right, Coccidioidal spherule rupturing and spilling endospores into surrounding tissue (hematoxylin-eosin, original magnification ×400). Photograph provided by Kevin O. Leslie, MD, Division of Anatomic Pathology, Mayo Clinic, Scottsdale, AZ.

coccidioidal pneumonia.[13] Pleural effusion occurs in approximately 5% to 10% of cases. The pleural fluid is usually exudative and may contain a high percentage of eosinophils.[11]

Acute pneumonia due to coccidioidomycosis can be associated with several cutaneous abnormalities. Erythema multiforme, erythema nodosum, and toxic erythema reflect a brisk immune response rather than dissemination. Erythema nodosum is associated with a favorable prognosis.

Diffuse pneumonia, an uncommon presentation of acute coccidioidal pneumonia, is thought to result either from inhalation of a large number of coccidioidal arthrospores or from hematogenous spread. This type of pneumonia often occurs in patients with some immunologic deficiency (ie, those with human immunodeficiency virus [HIV] or a hematologic malignancy or those receiving immunosuppressive therapy). Typically, patients are severely ill, with high fever, dyspnea, and hypoxemia. Chest radiographs or computed tomograms show diffuse, small, fluffy nodules in all lobes of both lungs. The diagnosis can be made by bronchoscopy, bronchoalveolar lavage that recovers organisms, or, if necessary, surgical lung biopsy. Diffuse disease can progress into acute respiratory distress syndrome and could necessitate mechanical ventilation.[10]

Chronic Progressive Pneumonia

Although most cases of acute pneumonia resolve spontaneously or with treatment, a small percentage of cases cause persistent illness that lasts longer than 3 months. This condition is termed *chronic progressive pneumonia*. Patients with chronic progressive pneumonia have persistent coughing, sputum production, hemoptysis, and weight loss. Serologic testing is almost always positive for *Coccidioides* sp.[10] Various radiographic findings indicate chronic progressive pneumonia, but the most common findings are dense unifocal or multifocal consolidations, which could include many areas of cavitation.

Pulmonary Nodules and Cavities

Acute coccidioidal pneumonia may resolve, and the pulmonary infiltrate may contract into a solitary nodule or cavity. Such nodules and cavities are the residual effect of the primary coccidioidal infection and can occur in immunocompetent hosts. Often, the pneumonic infiltrate resolves by developing into a 1-cm to 2-cm nodule or a thick-walled or thin-walled cavity (Figure 4). The cavity may wax and wane over time and may develop air-fluid levels that disappear on subsequent radiographs.

Initial presentation of a primary coccidioidal infection could be a solitary pulmonary nodule or cavity found on chest radiographs or computed tomograms. Although a new solitary pulmonary nodule must be distinguished from a malignant nodule, a respiratory infection that develops after travel to an endemic area is strongly suggestive of a coccidioidal nodule. Most cavities and nodules are benign and usually do not cause symptoms, although cough, chest pain, or hemoptysis can occur. Serologic testing is positive for *Coccidioides* sp in 30% to 60% of cases.[14] Infrequently, a pulmonary cavity near the pleural surface ruptures and causes hydropneumothorax. If a surgically resected nodule or cavity is identified as a coccidioidal nodule, the prognosis is very favorable and antifungal therapy is unnecessary.

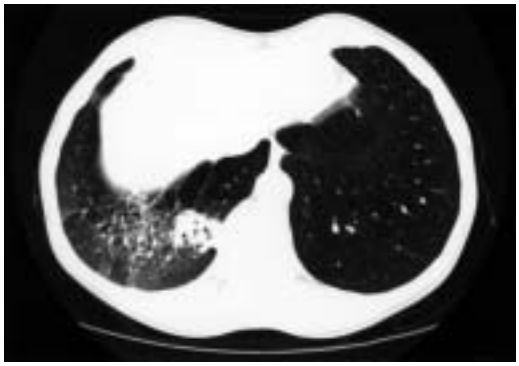

FIGURE 3. Computed tomogram showing coccidioidal consolidation in right lower lobe.

Extrapulmonary Nonmeningeal Disease

In fewer than 5% of immunocompetent patients, coccidioidal infection evolves into progressive pulmonary infection or disseminated extrapulmonary disease. At increased risk are people who are of African or Filipino ancestry; those younger than 1 year; women in the third trimester of pregnancy; and people who are immunocompromised, especially from HIV infection. Patients receiving immunosuppressive therapy after an organ transplant are at increased risk of disseminated disease, as are patients who have hematologic malignancies or who take tumor necrosis fac-

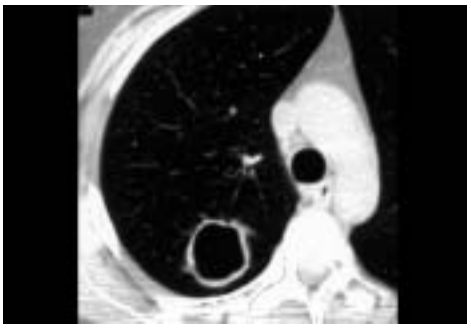

FIGURE 4. Computed tomogram showing a pulmonary cavity due to coccidioidomycosis.

tor inhibitors for inflammatory disease. Patients with diabetes mellitus are also at risk for problematic infection that could respond poorly to therapy.

Extrapulmonary coccidioidomycosis can affect any area of the body, but the most common sites of dissemination are the skin, lymph nodes, bones, and joints. Involvement of regional lymph nodes is common. The most severe extrapulmonary manifestation is meningitis.[10] In immunocompetent patients, extrapulmonary coccidioidomycosis is typically associated with a complement fixation (CF) titer of 1:16 or greater. Dissemination is often diagnosed several months after the onset of pulmonary symptoms. Extrapulmonary disease almost always requires treatment with antifungal medications and may require surgical excision, depending on its anatomic location.

Meningitis

Meningitis, the most feared complication of coccidioidal infection, is often a catastrophic illness that results in long-term morbidity. Before the introduction of amphotericin B, coccidioidal meningitis was frequently fatal. Outcomes have improved with the use of amphotericin B and the azoles, but meningitis is still associated with substantial morbidity.[15]

The most common presentation of coccidioidal meningitis is headache. The condition is often associated with mental status changes and neurologic deficits, particularly cranial nerve deficits. Computed tomography or magnetic resonance imaging scans often show meningeal enhancement characteristic of meningitis; these findings may be evident either early or late in the process.[16] Cerebral infarction can also occur with coccidioidal meningitis. The finding of hydrocephalus or cerebral infarction is associated with the highest mortality rate.[17] The diagnosis of meningitis is based on a positive finding on serologic testing of cerebrospinal fluid that typically shows an elevated white blood cell count, a high level of protein, and a low level of glucose. Culture for *Coccidioides* sp is usually negative, so serologic testing from serum and cerebrospinal fluid should be requested for a patient with meningitis who has traveled to or resided in an endemic area.

DIAGNOSIS

The diagnosis of coccidioidal infection can be made in 3 ways: (1) identification of coccidioidal spherules in a cytology or biopsy specimen, (2) culture from any body fluid that is positive for *Coccidioides* sp, or (3) a serologic test that is positive for the organism. The finding of spherules in tissue, sputum, bronchoalveolar lavage fluid, or other body fluid or a positive culture from any location in the body is diagnostic of coccidioidal infection, because *Coccidioides* is not a colonizing species. The sensitivity and specificity of serologic testing make it helpful in diagnosis and management. It can also provide useful information to the clinician for assessing progression or improvement in disease status.[18]

Because diagnosis and management of coccidioidomycosis rely heavily on serologic testing, the use of reference laboratories that perform a high volume of these tests is strongly encouraged. Serologic testing is based on identification of IgM or IgG antibodies to a coccidioidal-related antigen. Early immune response to infection is characterized by the presence of IgM, which can be detected by a tube precipitin method, immunodiffusion, latex agglutination, or enzyme immunoassay (EIA). Latex agglutination and EIA are highly sensitive but are associated with false-positive results; findings should be confirmed by immunodiffusion.[18] In approximately 50% of primary coccidioidal infections, IgM is detected in the first week; in 90%, by week 3.

Appearing after the initial IgM response, the IgG antibody can be detected by several testing methods. Qualitative tests, such as immunodiffusion, EIA, or counterimmunoelectrophoresis, provide positive or negative results but no quantitative information. By comparison, CF provides a quantitative titer that reflects the intensity of the immune response.[19] In an immunocompetent patient, serial testing with CF provides a useful correlation with response to treatment. A CF titer also provides important prognostic information: a CF titer of 1:2 or 1:4 is associated with a favorable outcome; a CF titer of 1:16 or greater, with disseminated disease. A CF titer might not be as reliable in an immunosuppressed patient, who is unable to mount the same antibody response as an immunocompetent patient. However, even in the immunocompetent patient, overwhelming and life-threatening disease may be associated with a low CF titer.

Antibodies cannot be detected in approximately 5% of patients, most of whom have some degree of immunosuppresion but a few of whom are immunocompetent. The role of newer diagnostic studies, such as nucleic acid amplification of coccidioidal DNA (polymerase chain reaction) or antigen detection, in clinical evaluation has not yet been determined.[20]

TREATMENT

Guidelines for treatment of coccidioidal infection have been published.[21] Coccidioidal infection can be treated by an antifungal agent (eg, fluconazole, itraconazole, voriconazole, amphotericin B, or the lipid-soluble preparations of amphotericin B), with itraconazole and fluconazole used the most frequently. Each agent is taken orally and typically is well tolerated.

The usual dose of fluconazole is 400 mg/d; however, a dose of up to 1200 mg/d can be used. The usual dose of itraconazole is 400 to 600 mg/d. Itraconazole requires an acidic gastric pH for optimal oral bioavailability, and absorption is impaired by medications that reduce gastric acid, such as proton pump inhibitors. A study comparing itraconazole with fluconazole in nonmeningeal disease suggested that the former is more effective than the latter, but the difference was not statistically significant.[22] Recently introduced, voriconazole has been found to be useful in some patients whose coccidioidal infection does not resolve with fluconazole; however, data on its use are limited at this time. The exact role of another newer azole, posaconazole, in the treatment of coccidioidomycosis remains unclear. A trial comparing posaconazole with fluconazole is under way.

No studies have directly compared amphotericin B treatment with azole therapy. However, amphotericin B should be considered when patients are rapidly progressing in their clinical course and are hospitalized because of coccidioidal infection. An azole can be used for less severe illness and for prolonged maintenance therapy.

Most patients with primary coccidioidal pneumonia will improve without specific therapy. However, concurrent risk factors such as HIV infection, organ transplant, or hematologic malignancy are an indication for treatment with an azole. Treatment is warranted for those at higher risk, such as people of African or Filipino ancestry. Treatment is also indicated if a patient is severely ill, with symptoms of weight loss, intense night sweats, extensive pulmonary infiltrates, or a CF titer of 1:16 or greater.

Diffuse pneumonia is usually associated with immune deficiency or some form of impairment. Treatment is usually initiated with an azole or amphotericin B and followed by maintenance azole therapy for a year or longer. If a patient is immunocompromised, indefinite azole therapy is indicated. For symptomatic chronic or progressive pneumonia, prolonged azole therapy is given at the highest dose the patient can tolerate. If no improvement occurs after several months, a change to a different azole or to amphotericin B is indicated.

Most nodules and cavities due to *Coccidioides* sp have a benign course and do not require therapy. Treatment of asymptomatic pulmonary nodules or cavities is not necessary in the absence of evidence of coccidioidal infection at other sites. If coccidioidal organisms are identified in a solitary pulmonary nodule by use of needle biopsy or surgical resection, no specific therapy is needed. If a cavity is near the pleural surface, it could enlarge, rupture into the pleural space, and cause hydropneumothorax. Fortunately, such an event is uncommon. A ruptured cavity that causes hydropneumothorax requires chest-tube drainage and possibly resection of the cavity and decortication. Although no controlled studies have examined the use of an antifungal medication in conjunction with resection, antifungal therapy typically is given before and after surgical resection.

Extrapulmonary nonmeningeal infection is most commonly treated with an azole. Therapy is given until clinical manifestations resolve and serologic testing shows a decrease to a negative finding or a titer of 1:2. Careful follow-up is always indicated because the infection could recur after therapy is discontinued. In some patients, therapy could last a year or longer; in certain circumstances, it could be lifelong. Amphotericin B is used if the infection appears to be worsening rapidly or is located in vital areas, such as the pericardium or a vertebral body adjacent to the spinal cord. Few studies have evaluated the utility of surgery for coccidioidal infection; in general, surgical débridement is used sparingly. If the abscess is located in an area where the infection can be associated with substantial morbidity, such as a paravertebral abscess with risk of impingement on the spinal cord, then débridement might be warranted.

Before the introduction of the azoles, coccidioidal meningitis was treated with a combination of intravenous and intrathecal amphotericin B. However, several studies have shown that fluconazole is effective in treating coccidioidal meningitis. A high relapse rate occurs if the medication is stopped, and therapy is lifelong for this condition. Typically, coccidioidal meningitis should be treated with the highest tolerated dose of fluconazole—between 400 and 1000 mg/d. Sometimes, coccidioidal meningitis is treated with both oral azole therapy and intrathecal amphotericin B therapy. Hydrocephalus can develop despite adequate treatment and should be treated with a shunt for decompression.

How does a physican outside the endemic area approach the patient returning from the desert Southwest who has persistent respiratory symptoms? Coccidioidal serologic testing can be obtained from a reference medical laboratory that does a large volume of such testing. A qualitative test (EIA or immunodiffusion) positive for *Coccidioides* sp should be followed with a quantitative test (CF or quantitative immunodiffusion). Sputum or bronchoscopy lavage can be evaluated by cytologic analysis and culture. A specimen from a skin lesion, lung mass, or soft-tissue abscess should be obtained by biopsy for pathologic evaluation and culture.

Although treatment guidelines have been published,[21] no consensus exists regarding the treatment (if any) of acute coccidioidal pneumonia in a patient without risk factors for dissemination. Although data are lacking to confirm an improved outcome, patients with severe symptoms from primary pneumonia are generally treated. Pa-

tients with persistent coccidioidal pneumonia should be treated with an azole. Evidence-based studies recommending intervals for serologic testing are lacking; however, depending on the severity of illness, the testing can be done every 2 to 4 months. Patients should be monitored clinically, radiographically (as indicated), and serologically over time. The duration of treatment is variable; it could be as short as 1 month in some uncomplicated cases or as long as a lifetime in severely ill patients. Patients who have risk factors for dissemination or who do not respond appropriately to treatment should be referred to a specialist.

CONCLUSION

The incidence of coccidioidomycosis will continue to increase as the population of the southwestern United States continues to grow. Because patients travel to the Southwest during the winter and return home to the Midwest or East or elsewhere, physicians outside the southwestern United States will likely see an increasing number of cases of coccidioidal infection and should be familiar with its clinical presentation and treatment.

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CME Questions About Coccidioidomycosis

1. In which <u>one</u> of the following geographic areas is infection due to *Coccidioides* species <u>most commonly</u> seen?
   a. Any desert area worldwide
   b. The Mississippi River Valley
   c. The Sonoran Desert of the southwestern United States, including central California, Arizona, and northern Mexico
   d. The Rocky Mountains
   e. The Sierra Nevada Mountains of California

2. Which <u>one</u> of the following population groups is <u>not</u> at higher risk of disseminated coccidioidal infection?
   a. People of Filipino ancestry
   b. People of African ancestry
   c. People with human immunodeficiency virus–related disease
   d. People of Mediterranean ancestry
   e. People receiving tumor necrosis factor inhibitor therapy

3. Which <u>one</u> of the following is the <u>best</u> test for diagnosing possible meningitis due to coccidioidal infection?
   a. Computed tomography of the brain
   b. Electroencephalography
   c. Magnetic resonance imaging of the brain
   d. Serologic testing of cerebrospinal fluid for *Coccidioides* sp
   e. Staining and culture of cerebrospinal fluid for fungal organisms

4. Which *one* of the following agents is *not* a treatment option for coccidioidomycosis?

   a. Caspofungin acetate
   b. Fluconazole
   c. Amphotericin B
   d. Voriconazole
   e. Itraconazole

5. Which *one* of the following serologic tests is *most frequently* used to obtain a quantitative titer for assessing coccidioidomycosis disease severity and response to treatment?

   a. IgG by complement fixation
   b. IgM by tube precipitin method
   c. IgG by counterimmunoelectrophoresis
   d. IgM by latex agglutination
   e. IgG by latex agglutination

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