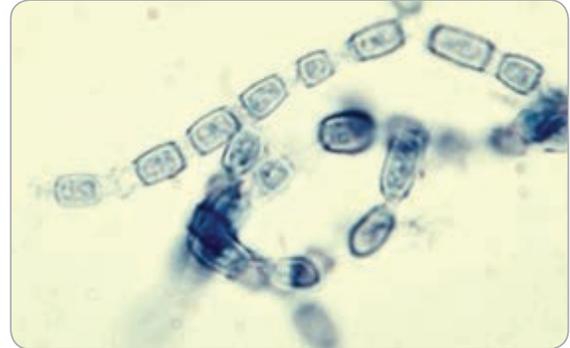
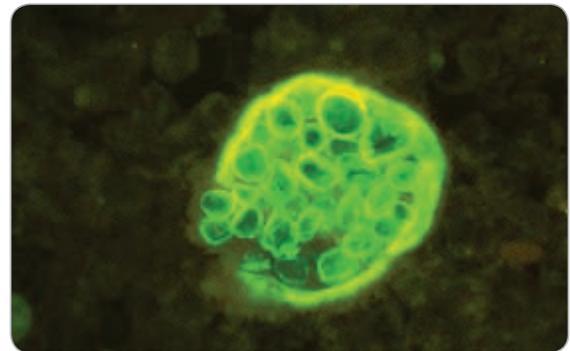


Coccidioidomycosis (Valley Fever): The Rise of a Life-altering Disease

- The causative agents, *Coccidioides immitis* and *C. posadasii*, are fungi found in the soil throughout desert areas of the western United States¹
- Infection with *Coccidioides* may occur after a spore from the fungus becomes airborne in dust and is inhaled. Symptoms typically appear between 1 and 3 weeks after exposure¹
- Diagnosis is often delayed for months as symptoms commonly present as an influenza-like illness, with symptoms that may include fever, cough, chest pain, headaches, rash, night sweats, myalgia, and arthralgia¹
- Occasionally, the lung infection may become severe or life-threatening, or may disseminate to any area of the body, most commonly skin, bone/joints, and the central nervous system, with potential deadly or lifelong consequences¹
- Serologic detection of coccidioidomycosis may require weeks to months, and 15-20% of patients will not develop diagnostic serology²
- The Infectious Diseases Society of America/American Thoracic Society Consensus Guidelines on the Management of Community-Acquired Pneumonia in Adults recommend diagnostic testing for endemic fungal diseases like Valley Fever at point of care³



Coccidioides immitis arthroconidia as would be observed in soil



Coccidioides immitis spherules as would be observed in tissue

Prevalence and burden

- 20,000 cases were reported in the United States in 2011, a 3-fold increase from 2002, and represents twice as many cases as tuberculosis⁴
- An estimated 150,000 cases go undiagnosed every year⁴
- 40% of all infections are symptomatic and lead to mild to severe illness⁵
- An average of 31 workdays will be missed by patients with Valley Fever⁶
- An average of 3 months of Activities of Daily Living will not be performed in patients due to Valley Fever⁶
- 40% of Valley Fever cases required hospitalization, with an average cost of nearly \$50,000 per hospital stay⁴
- A patient with disseminated coccidioidomycosis incurs an average lifetime cost of nearly \$875,000⁷



Cell-mediated Immune Response to Coccidioidomycosis

Cell-mediated immune response is a key factor in the body's defense of coccidioidomycosis

- T-cell dependent immune responses are the major determinant of defense against *Coccidioides*⁸
 - Protective immunity requires a strong T_H1 response and associated release of TNF- α ⁹
 - Delayed-type hypersensitivity to intradermal antigens demonstrates a cell-mediated immune response that is T-cell dependent¹⁰

Control of coccidioidomycosis depends on T lymphocytes¹¹

- Cell-mediated immunity is evident within 2 weeks of symptoms in 80% of patients² and persists for years¹²
- Anergy (absence of detectable cell-mediated immune response) often accompanies severe or disseminated infection⁸, and has been associated with the system being overwhelmed by fungal antigens¹³
- Intact cell-mediated immunity is a positive prognostic indicator, while anergy is a negative prognostic indicator in coccidioidomycosis⁸

Recovery of immune response was associated with a positive prognosis¹⁴

Antifungals aid in the cell-mediated immune response

- Severe disease, dissemination or spread, diffuse pneumonia, chronic progressive pneumonia, risk factors (eg, diabetes, preexisting cardiopulmonary disease, pregnancy, etc.), degrading patient condition, and immune suppression may indicate the need for antifungals in treatment of patients with coccidioidomycosis as described in the Infectious Disease Society of America Guidelines¹⁵
- Antifungals directly slow fungal growth or weaken the fungus
- Antifungals also enhance the effectiveness of the cellular immune response
 - Triazoles/azoles have also been shown to augment in vitro fungicidal activity of monocytes, macrophages, and neutrophils¹⁶
 - Amphotericin B has been shown to augment key cytokines in fungal immunity including TNF- α ¹⁶

Antifungals have indirect, immune system-mediated effects¹⁶

Understanding the role of cell-mediated immune response, monitoring the cell-mediated immune response, and aiding the cell-mediated immune response with antifungals are key elements in managing coccidioidomycosis.

References: 1. Valdivia L, Nix D, Wright M, et al. Coccidioidomycosis as a common cause of community-acquired pneumonia. *Emerg Infect Dis.* 2006;12(6):958-962. 2. Pappagianis D, Zimmer BL. Serology of coccidioidomycosis. *Clin Microbiol Rev.* 1990;3(3):247-268. 3. Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis.* 2007;44(suppl 2):S27-S72. 4. Fungal pneumonia: a silent epidemic. Coccidioidomycosis (valley fever). Center for Disease Control and Prevention website. <http://www.cdc.gov/fungal/pdf/cocci-fact-sheet-sw-us-508c.pdf>. Published December 2012. Accessed July 3, 2014. 5. Coccidioidomycosis. The Center for Food Security & Public Health and the Institute for International Cooperation in Animal Biologics Iowa State University website. <http://www.cfsph.iastate.edu/Factsheets/pdfs/coccidioidomycosis.pdf>. Accessed July 3, 2014. 6. Tsang CA, Anderson SM, Imholte SB, et al. Enhanced surveillance of coccidioidomycosis, Arizona, USA, 2007–2008. *Emerg Infect Dis.* 2010;16(11):1738–1744. 7. University of California San Francisco. The economic burden of valley fever in California: results and lessons learned. Presented at: 58th Annual Cocci Study Group; April 5, 2014, Phoenix, AZ. 8. Cox RA, Magee DM. Coccidioidomycosis: host response and vaccine development. *Clin Microbiol Rev.* 2004;17(4):804–839. 9. Johnson L, Gaab EM, Sanchez J, et al. Valley fever: danger lurking in a dust cloud. *Microbes Infect.* 2014;16(8):591–600. 10. Abbas AK, Lichtman AH, Pober JS. Effector cells of cell-mediated immunity. In: Abbas AK, Lichtman AH, Pober JS, eds. *Cellular and Molecular Immunology*. Philadelphia, PA: WB Saunders Co; 1991:245–252. 11. Galgiani JN. Coccidioides species. In: Mandell GL, Bennett JE, Dolin R, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*. 7th Ed. Philadelphia PA: Elsevier; 2010:3333–3344. 12. Wiant JR, Smith JW. Coccidioidin skin reactivity in pulmonary coccidioidomycosis. *Chest.* 1973;63(1):100–102. 13. Ibrahim AB, Pappagianis D. Experimental induction of anergy to coccidioidin by antigens of *Coccidioides immitis*. *Infect Immun.* 1973;7(5):786–794. 14. Stevens DA, Levine HB, Deresinski SC, Blaine LJ. Spherulin in clinical coccidioidomycosis. *Chest.* 1975;68(5):697–702. 15. Galgiani JN, Ampel NM, Blair JE, et al. Coccidioidomycosis. *Clin Infect Dis.* 2005; 41:1217–1223. 16. Ben-Ami R, Lewis RE, Kontoyiannis DP. Immunopharmacology of modern antifungals. *Clin Infect Dis.* 2008;47(2):226–235.