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## Host–Pathogen Interactions in Coccidioidomycosis: Prognostic Clues and Opportunities for Novel Therapies

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### Abstract

**Purpose:** Coccidioidomycosis (CM) is a systemic fungal disease caused by the dimorphic fungi *Coccidioides immitis* and *Coccidioides posadasii*. In its endemic areas of the United States, CM is growing as a public health challenge with a marked increase in incidence in the last 15 years. Although *Coccidioides* infection is asymptomatic in most cases, symptomatic pulmonary disease occurs in ~40% and disseminated coccidioidomycosis (DCM) occurs in ~1% of previously healthy children and adults. DCM is markedly more common in immunocompromised people, who often experience life-threatening disease despite use of antifungal medications. Although options for antifungal therapy have improved, lifelong therapy is needed for those who develop coccidioidal meningitis. The purpose of this article was to review the state of antifungal therapy and recent studies of host–pathogen interactions in CM in light of advances in immunomodulatory therapy.

**Methods:** The study included a review of PubMed and abstracts of the Coccidioidomycosis Study Group (years 2000–2019).

**Findings:** Current therapy for CM relies upon azole and polyene antifungal agents. Murine models and studies of DCM in patients with monogenic primary immunodeficiency states and acquired immunodeficiency have revealed the importance of both innate and adaptive immune responses in the control of infections with *Coccidioides* species. In particular, defects in sensing of fungi and induction of cellular immune responses have been frequently reported. More recently,

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#### DISCLOSURES

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polymorphisms in key signaling pathways and in the generation of Th17 and Th1 immune responses have been linked with DCM.

**Implications:** Antifungal therapy is sufficient to control disease in most cases of CM, but treatment failure occurs in cases of severe pulmonary disease and nonmeningeal disseminated disease. Lifelong therapy is recommended for meningitis in view of the very high risk of recurrence. Corticosteroid therapy is advised by some experts for severe pulmonary disease and for some neurologic complications of DCM. DCM is only rarely the result of a severe monogenic immunodeficiency. Case studies suggest that reorienting cellular immune responses or augmenting effector immune responses may help resolve DCM. Systematic investigation of immunotherapy for coccidioidomycosis is advisable and may help to address the recent marked increase in reports of the disease in endemic areas.

### Keywords

Antifungal; *Coccidioides*; Coccidioidomycosis; Genomics; Immunology; Valley fever

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## INTRODUCTION

Coccidioidomycosis (CM) is a systemic disease caused by infection by the closely related dimorphic fungi *Coccidioides immitis* and *Coccidioides posadasii*, found only in the semi-arid areas of North America, Central America, and South America (Figure 1). In California, most cases occur in the central San Joaquin Valley, giving rise to the term “valley fever,” which is often used as a synonym for systemic disease due to *Coccidioides* infection. In the United States, most cases (95%) occur in California and Arizona.<sup>1</sup> A marked increase in incident cases from these 2 states has occurred in the last decade, particularly in California, where the annual rate increased in 2017 to 18.8 per 100,000 population with 7466 reported cases, the highest annual number of cases ever recorded. In 2017, more than 14,000 cases were reported from all states to the Centers for Disease Control and Prevention, but this figure may represent as few as 6% of the true number of new infections. For example, in one prospective study in Arizona, 16% of individuals presenting with prolonged chest symptoms or community-acquired pneumonia between 2003 and 2004 were found to have serologic evidence of CM. Similar results were obtained in a retrospective analysis of data from 30 outpatient clinics in the city of Phoenix.<sup>2,3</sup>

CM was first described in Argentina in 1892 followed by the recognition of 2 additional cases in 1894 in California; all 3 subjects died of similar disease that included granulomatous lesions of the skin.<sup>4</sup> In the mid-20th century, Charles Smith and others developed serologic methods and skin test reagents used in seminal epidemiologic and clinical studies of CM. These studies clarified that respiratory acquisition of infection may be followed by severe pulmonary disease, osteomyelitis, meningitis, and other life-threatening complications, leading Smith to note “its notorious clinical and pathological mimicry of tuberculosis.”<sup>5-7</sup> These studies and others also revealed that Filipino subjects and people of African ancestry are at greater risk of disseminated CM (DCM).<sup>6,8,9</sup> Although this fraction remains small (~3.4% among African-American subjects in the seminal study by Smith and Beard<sup>6</sup>), DCM can have devastating consequences in previously healthy

individuals. Studies in the late 20th century revealed that diabetes, HIV infection, and iatrogenic immunosuppression increase the risk of DCM.<sup>10–13</sup>

Fortunately, the antifungal medications developed in the mid-to late-20th century have reduced the morbidity and mortality of CM, including DCM. Amphotericin B (AmB) deoxycholate, a polyene antifungal agent, was developed in the 1950s and immediately shown to have utility in the treatment of coccidioidal meningitis.<sup>14</sup> Although often poorly tolerated, intravenous AmB deoxycholate remained the mainstay of antifungal therapy for severe CM and DCM until the development and licensure of antifungal azole medications. Newer lipid formulations (eg, liposomal AmB and amphotericin lipid complex) of AmB are less toxic than the original AmB deoxycholate preparation and are often used in the initial treatment of nonmeningeal DCM in immunocompromised hosts. Ketoconazole, an imidazole, was modestly effective but has been supplanted by the more effective and less toxic triazoles (eg, fluconazole, itraconazole, posaconazole, isavuconazole).<sup>15–17</sup> One prospective study was performed comparing the relative activity of triazoles; itraconazole appeared marginally more effective than low daily dose (400 mg/d) oral fluconazole in a multicenter comparison of the 2 drugs as treatment for progressive, nonmeningeal CM.<sup>18</sup> Current antifungal therapy for severe pulmonary CM or DCM generally consists of oral triazole antifungal medications or intravenous lipid formulations of AmB.<sup>19,20</sup> Unfortunately, the triazoles and polyenes are poorly fungicidal, and neither class produces a sterilizing cure of meningitis; relapse of meningitis is very common if triazole therapy is stopped,<sup>21</sup> and lifelong, continuous antifungal therapy is recommended.<sup>19,20</sup> These and other limitations of current antifungal therapy for CM have recently been reviewed in detail.<sup>19</sup>

Overall, CM is a disease that is unrecognized in most cases and may not require antifungal therapy if limited to minor pulmonary disease. At the opposite end of the spectrum, extrapulmonary disease occurs in ~1%, in whom antifungal therapy is not always successful. The current review analyzes recent data revealing host–pathogen interactions that may be determinants of dissemination of CM and which suggest possible therapeutic approaches. We postulate that genomic evaluation of individuals with DCM is advisable and that immunomodulatory therapy to augment or reorient immune responses is a therapeutic avenue that should be subjected to investigation.

## MATERIALS AND METHODS

The PubMed and [Clinical Trials.gov](https://clinicaltrials.gov) databases were searched for related titles published until December 2019, using the following key words alone and in combination: *Valley Fever*, *Coccidioides*, *coccidioidomycosis*, and *disseminated coccidioidomycosis*. These were reviewed alone and in combination with at least one of the following terms: *genetic*, *pathogenesis*, *meningitis*, *mortality*, *predisposition*, and *host*. In addition, references listed in relevant articles were reviewed for other references related to the theme of host–pathogen interactions in human infections caused by *Coccidioides* species. Abstracts for Coccidioidomycosis Study Group were also reviewed, as available online.

## OVERVIEW OF HOST–PATHOGEN INTERACTIONS IN CM

### ***Coccidioides* life cycle and biology**

As noted earlier, 2 distinct species of *Coccidioides* are now recognized: *C immitis* (largely confined to California) and *C posadasii* (found in all other endemic areas in the Americas). Although the 2 species exhibit minor differences in their growth characteristics in vitro, their life cycle and clinical manifestations are indistinguishable.<sup>22,23</sup> The fungus grows in filamentous form within the upper several centimeters of soil. Septation of the hyphae occurs during fungal growth, and alternate cells undergo autolysis, liberating spores (arthroconidia). Dispersal of these infectious arthroconidia occurs when the soil is disturbed by wind, excavation, recreational activities, and other phenomena<sup>24</sup> (Figure 2). Once inhaled into the lung, the arthroconidia germinate and form spherules, which can enlarge to as much as 150  $\mu\text{m}$  in diameter. Internal segmentation of these spherules produces multiple minute endospores (each 2–3  $\mu\text{m}$  in diameter) within a shell composed of a variety of macromolecules, including chitin, a long-chain polysaccharide polymer. Eventually, the spherules rupture and release hundreds of endospores that may disseminate widely throughout the host, forming new spherules, with the potential to repeat the process. This form of exponential amplification is unique among endemic mycoses and is analogous to the reproduction of viruses that produce hundreds or thousands of progeny in parasitized cells in a single replicative cycle.<sup>9,25</sup>

This morphological transition of the fungus from its hyphal form to infectious endospores via spherule formation involves substantial transcriptional reprogramming. Coccidioidal arthroconidia can be induced to form spherules in vitro by an increase in environmental temperature and ambient carbon dioxide concentration. Two studies<sup>26,27</sup> have shown that spherule formation under these conditions is associated with changes in a number of metabolic pathways, particularly those involved in the metabolism of complex carbohydrates.<sup>22,27,28</sup> Among other findings, these in vitro studies showed that the fungal chitinase 2 and chitinase 3 genes are transcriptionally upregulated in spherules compared with mycelia, presumably due to the remodeling of the cell wall involved in spherule maturation and during the release of endospores. Interestingly, the presence of human neutrophils induces spherule differentiation during in vitro culture and also inhibits the formation of hyphae.<sup>29</sup> Because spherules seem to promote persistence of *Coccidioides*, this observation suggests that specific adaptations occurred during the evolution of *Coccidioides* that promote survival in the face of innate and adaptive immune responses mounted by animals.<sup>22,23,27,30,31</sup>

### **Innate immunity**

Our understanding of innate immune responses to *Coccidioides* is largely derived from murine models and the characterization of immune dysfunction in a handful of human cases.<sup>23,26,32–35</sup> Immune responses to fungi are generally initiated by sensing of cell wall components, fungal DNA, and other fungal elements by pattern recognition receptors. Detection of pathogen-associated molecular patterns expressed by pathogenic fungi has been most clearly shown by examination of the phenotype of mice lacking Dectin-1. Dectin-1, a lectin expressed on neutrophils, macrophages, and dendritic cells, recognizes  $\beta$ -1,3-glucan,

a key polysaccharide cell wall component of *Coccidioides*, *Histoplasma*, *Candida*, and other pathogenic fungi.<sup>36</sup> Dectin-1 has an extracellular carbohydrate recognition domain linked via a long stalk to a transmembrane domain and a cytoplasmic tail containing a tyrosine-rich immunoreceptor tyrosine-based activation domain. Clustering of Dectin-1 molecules by contact with poly- $\beta$ -1,3-glucan is followed by phosphorylation of tyrosine residues in the immunoreceptor tyrosine-based activation domain; this action triggers Syk tyrosine kinase activity that promotes downstream signaling through CARD9, leading to the elaboration of key cytokines that promote the activation and differentiation of T cells (Figure 3).

Mice that lack Dectin-1 are more susceptible to experimental coccidioidal infection, as shown by greater and more rapid mortality compared with control mice.<sup>26,34,37</sup> In addition, inbred mice differ in their susceptibility to *Coccidioides* infection, which maps to the differential splicing of *Clec7a*, the gene that encodes Dectin-1. Kirkland and Fierer<sup>38</sup> found that the estimated lethal dose of a patient-derived *Coccidioides* isolate differs by up to 10,000-fold among commonly used strains of mice. C57BL/6 mice are far more sensitive to infection than DBA/2 mice and produce a truncated splice variant of the *Clec7a* encoding a Dectin-1 protein lacking most of the extracellular stalk. By contrast, DBA/2 mice produce a full-length Dectin-1 protein. Cytokine expression profiles also differ between the strains: C57BL/6 mice produce more interleukin (IL)-10 and IL-4 and less interferon gamma (IFN- $\gamma$ ) in their lungs compared with DBA/2 mice. Moreover, dendritic cells from C57BL/6 mice produce more IL-10 and IL-23 and less IL-12 than cells from DBA/2 mice in response to exposure to spherules or purified  $\beta$ -glucan.<sup>37</sup> Finally, CARD9-deficient mice are highly susceptible to coccidioidal infection and cannot form protective immunity in response to inoculation with spores of a mutant *C posadasii* strain that lacks the ability to form spherules due to the deletion of chitinase 2 and chitinase 3.<sup>30,39</sup> These and other animal data<sup>33</sup> show that the innate immune responses set the stage for the successful control of *Coccidioides* infection. In contrast to other fungal pathogens (eg, *Blastomyces dermatitidis*, *Candida albicans*, *Aspergillus* species), murine models also indicate that mannose receptors, Dectin-2, Toll-like receptor 2 (TLR2), and Toll-like receptor 4 do not play a significant role in detection of coccidioidal infection.<sup>30,33,40–42</sup>

Interestingly, no cases of DCM in humans have as yet been attributed to Dectin-1 deficiency, even though polymorphisms in the *Clec7a* gene are known to exist and have been linked to mucocutaneous candidiasis,<sup>43</sup> and loss-of-function in CARD9 is strongly linked to invasive infections by *Candida* species.<sup>44</sup>

### Adaptive immunity

As noted previously, infection with *Coccidioides* species is often clinically inapparent.<sup>33,35</sup> This was shown by Smith and Beard<sup>6</sup> who found that 60% of servicemen stationed at airfields in the San Joaquin Valley developed skin test reactivity (ie, antigen-specific T-cell responses) to coccidioidal antigens without symptoms. Most of those who develop symptomatic coccidioidal disease have self-limited infection and low titers of complement-fixing antibodies to coccidioidal antigens. By contrast, the small fraction of people with extrapulmonary dissemination of coccidioidal infection typically have a high titer of

complement-fixing antibodies and lack delayed-type hypersensitivity, evincing a Th2 bias in cellular immune response.<sup>7,45</sup>

This type 2 immunity represents the presence of helper T cells producing the cytokines IL-4, IL-13, and IL-5. IL-4 stimulates B cells to boost immunoglobulin E (IgE) production to high levels, which has been correlated with the severity of *Coccidioides* disease.<sup>46</sup> Murine data suggest that IL-4 itself directly reduces the antifungal activity of innate immune cells as it promotes expression of arginase-1 and blocks nitric oxide production,<sup>47</sup> which is required for fungicidal activity.<sup>48</sup> Murine studies of cryptococcal infection indicate that IL-13 works in a similar fashion<sup>49</sup> in promoting high expression of IL-4.

Polymorphisms in an intron of the IL-4 gene have been associated with high serum levels of the cytokine in those who develop paracoccidioidomycosis, another endemic mycosis found in South America.<sup>50</sup> IL-5 promotes eosinophil development in the bone marrow, and peripheral eosinophilia has been correlated with disseminated disease, but it is not clear if there is a mechanistic relationship.<sup>51,52</sup> Thus, there is substantial evidence that type 2 immunity attenuates antifungal immune responses. To date, only one primary immune dysregulatory disorder of type 2 immunity has been identified that promotes CM: dominant negative signal transducer and activator of transcription (STAT) 3 disease.<sup>35</sup> However, we would expect increased susceptibility to severe CM or DCM in patients with mutations in phosphoglucomutase 3, IL-21R, and other primary atopic disorders.<sup>53,54</sup>

The main adaptive immune cells of type 1 immunity are the CD4<sup>+</sup> T cells that produce IFN- $\gamma$  (ie, Th1 cells). Vaccine models in mice have suggested that Th1 (and Th17) responses are essential for protection against DCM.<sup>31,55</sup> Patients who have diminished type 1 immunity because of monogenic defects in either chain of the heterodimeric IL-12 receptor (IL-12R $\beta$ 1 and IL-12R $\beta$ 2) have an elevated risk of DCM<sup>35,55–57</sup>, which reflects the central role of IL-12 in the development of Th1 helper T cells. Activated Th1 cells produce IFN- $\gamma$ , but individuals bearing loss-of-function defects in either of the IFN- $\gamma$  receptor chains (IFN-GR1 or IFN-GR2) cannot sense this cytokine and have impaired antifungal immunity. Downstream of the IFN- $\gamma$  receptor lies STAT1, and subjects with both dominant loss-of-function and dominant gain-of-function variants in STAT1 have an increased susceptibility to fungal infection.

Surprisingly, monogenic defects in the IFN- $\gamma$  cytokine itself have not been identified, but individuals bearing these defects would be expected to have a profound susceptibility to fungal infections, including CM. Peripheral blood cells from patients with DCM produce less IFN- $\gamma$  in response to *Coccidioides* antigen than cells from those with milder disease.<sup>58,59</sup> Treatment of mice with IFN- $\gamma$  was able to protect mice from systemic infection.<sup>60</sup> A few human patients with extrapulmonary disease have been treated successfully with IFN- $\gamma$  as well (as discussed later), supporting the importance of this cytokine in fighting CM. In these disorders of the IL-12/IFN- $\gamma$  axis, Th1 cell development or effector function is diminished. However, broader risk factors for DCM include pregnancy, HIV infection, and the use of immunosuppressive medications, in which Th1 immunity is suppressed in favor of Th2.<sup>35</sup>

Evidence in mice and humans also supports the importance of a third program of immune responses, called Th17 immunity, for fighting fungal infections. These helper T cells produce the cytokines IL-17A, IL-17F, and IL-22 upon stimulation. Th17 cells were noted in the development of synthetic candidate vaccines to *Coccidioides*.<sup>31,33</sup> The fact that depletion of Th17 cells after successful vaccination in mice removes the vaccine-induced protection supports the importance of these helper T cells in protective memory against *Coccidioides*.<sup>61</sup> A major role of IL-17A is to recruit neutrophils to the site of infection, which may be critical for preventing extrapulmonary dissemination of CM. IL-17A also directs natural killer cells to produce granulocyte-macrophage colony-stimulating factor, which recruits neutrophils and enhances their fungicidal activity.<sup>62</sup> Humans deficient in IL-17F are highly susceptible to mucocutaneous *Candida*, supporting the notion that this cytokine also plays a protective role in fungal immunity. IL-22 is also protective, preventing dissemination by recruitment of inflammatory innate cells and in augmenting barrier functions of infected tissues<sup>63</sup>; autoantibodies against IL-22 lead to a susceptibility to chronic infections with *Candida* in humans.<sup>64</sup> IL-17A and IL-17F bind to heterodimeric receptors that comprise subunits of IL-17RA and IL-17RC. Homozygous deficiency of IL-17RA has been shown in humans to incur susceptibility to yeast infections.<sup>65,66</sup> Notably, variants in IL-17RA are more commonly found in African-American subjects, who have a higher susceptibility to DCM.<sup>33</sup> Together, these clinical and experimental data strongly indicate the importance of Th17 immunity in fungal infections.

The development of Th17 cells in vitro and in vivo is driven by priming naive T cells in the presence of transforming growth factor- $\beta$  and an inflammatory cytokine such as IL-6. When IL-6 amounts are limiting, transforming growth factor- $\beta$  instead drives the development of induced regulatory T cells. Thus, induced regulatory T cells and Th17 cells form a balance of protective and repressive immunity based on the inflammatory context at the time of priming. This balance seems to be clinically important in determining dissemination of coccidioidal infection in humans,<sup>67</sup> although the data are limited, and it is unclear if regulatory T cells are purely suppressive of protective immunity. The complex relationship between Th17 cells and regulatory T cells offers some evidence that these cell types can, in fact, work cooperatively to promote adaptive immunity toward fungi.<sup>68</sup> More research is needed to illuminate the immunological crosstalk in cases of infection that are controlled compared with cases of DCM.<sup>69</sup>

### Evaluation of human cohorts with DCM: initial experience

Investigators at the National Institute of Allergy and Infectious Diseases (A. Hsu and S. Holland) recently reported initial results of systematic whole-exome or focused gene sequencing in 58 individuals with DCM.<sup>33</sup> The data from this analysis were examined by filtering for rare genetic variants (defined as a frequency of  $\leq 1\%$  in the Exome Aggregation Consortium database<sup>70</sup>) with a high probability of having deleterious effects on protein function and likely to be associated with disseminated fungal infections. More than 100 polymorphisms were identified in genes involved in innate immune responses, including innate immune sensing and signaling pathways. These genes included elements of IL-12/IFN- $\gamma$  signaling, intracytoplasmic nucleic acid sensing molecules (RIG-I), and both components of the heterodimeric IL-17 receptor (IL-17RA and IL-17RC). In vitro validation



of several variants has been completed by introducing the novel permutations into cell lines. Of particular interest is the finding of polymorphisms in STAT3 and STAT4 among African-American subjects with DCM, as these participate in IL-23 signal transduction involved in differentiation of naive CD4 T cells into Th17 cells.

Similarly, we have described whole-exome sequencing analysis involving a convenience sample of ethnically and racially diverse cohort of 22 adults living in California with extrapulmonary dissemination of CM.<sup>71</sup> Among these, 16 were men, 8 were African American, 2 were Filipino, and 2 were of Middle Eastern ancestry. In contrast to the analytic approach used by Hsu and Holland, we hypothesized that polymorphisms which predispose to dissemination of *Coccidioides* infection could be relatively common alleles among populations with Asian and African ancestry, yet be rare among those of European ancestry, in whom DCM is substantially less common. We identified a mean of 246,708 variants from the human reference genome per sample; of these, a mean of 6336 per sample passed quality controls, affected protein sequence or splicing, and had a frequency of 10% in the Exome Aggregation Consortium database (Table I). We identified 3 African-American individuals with alterations in the gene (CHIT1) encoding the human chitinase protein known to reduce or abrogate enzymatic activity.<sup>72</sup> This finding included 1 person who was homozygous for alleles for the single amino acid changes Ala442Val and Gly354Arg, either of which abrogate chitinase activity. In addition, 2 other individuals (K09 and K11) were compound heterozygous for the Gly354Arg allele along with a deletion that activates a cryptic splice site in exon 10 leading to production of a truncated and inactive chitinase protein. Thus, 5 (27%) of 22 individuals with DCM possessed genetic variants of CHIT1 predicted to abrogate chitinase. The impact of these genetic variants on chitinase activity and the outcome of coccidioidal infection require verification, but it is conceivable that chitinase release by neutrophils and macrophages interferes with spherule formation and extensive dissemination of *Coccidioides*.

Two African-American subjects (K09 and K11) were also found to have missense variants in CLEC7A that encode Ser161Leu (heterozygous) and Ile223Ser (homozygous), respectively. Both of these changes are rare in European subjects (~0.01%) but common in African-American subjects (3%–5%). The homozygous Ile223Ser change is computationally predicted as probably damaging to protein function (Combined Annotation Dependent Depletion [CADD] score, 24.5), and the Ser161Leu variant is estimated to possibly interfere with the function of Dectin-1 (CADD score, 11.9).<sup>73</sup>

We also identified an individual with a polymorphism in the cytoplasmic tail in IL17-RA encoding a missense mutation predicted to be deleterious (Pro562Gln) (CADD score, 26.6). This variant is known to be common with an allele frequency of 7.3% across all individuals and enriched to 31% among East Asian individuals. The presence of the missense mutation was confirmed by using Sanger sequence analysis, and flow cytometric analysis revealed low expression of IL-17RA on monocytes of this individual (Figure 4). Interestingly, IL-17RA was significantly lower on the monocytes of all 5 people with DCM compared with the healthy control subjects.

Confirmation of the significance of the chitinase, IL-17RA, and Dectin-1 polymorphisms described here has yet to be subjected to clinical study or laboratory studies of their impact on antifungal activity or signal transduction. However, these 2 studies clearly show that DCM is not usually a monogenic disorder. Instead, a number of possible mechanisms may determine the severity of pulmonary CM and the risk of extrapulmonary dissemination. Table II contains a list of established and putative risk factors for DCM.

## IMMUNE-BASED ADJUNCTIVE THERAPIES

### Systemic corticosteroids

The use of high-dose systemic corticosteroid medications, as well as disease-modifying antirheumatic drugs and antineoplastic chemotherapy, represents a risk factor for exacerbation or dissemination of unrecognized CM.<sup>20,74</sup> However, this does not mean that the systemic corticosteroids are unequivocally contraindicated by CM. Azadeh et al<sup>75</sup> performed a retrospective study of 74 individuals treated with a short course of corticosteroid therapy for rash, wheezing, or cough associated with primary pulmonary CM. No increase in complications, clinical relapses, or extrapulmonary dissemination occurred among those treated for a median of 6 days with typical doses of prednisone or its equivalent (median total dose, 150 mg prednisone equivalents). Most of these patients, and control subjects without corticosteroid treatment, received antifungal therapy. It should also be noted that it was unclear if corticosteroid treatment was uniformly beneficial.

In contrast to this outcome, a number of reports show that systemic corticosteroids may represent an important adjunct to antifungal medications in the treatment of some cases of severe or complicated CM. Improvement has been described in severe acute pulmonary CM, including cases of adult respiratory distress syndrome.<sup>76,77</sup> The indications for this therapy and the duration of therapy have yet to be defined; however, some experts recommend a tapering corticosteroid regimen similar to that used in cases of moderate to severe *Pneumocystis jirovecii* pneumonia for primary pulmonary CM with adult respiratory distress syndrome.<sup>78</sup>

Similarly, corticosteroids have been advocated as an adjunctive therapy during treatment of central nervous system complications of coccidioidal meningitis, including cranial neuropathy, arachnoiditis, vasculitic infarction, encephalitis, and the development of a syrinx, or to ameliorate symptoms.<sup>20,79,80</sup> Intrathecal corticosteroids are also given along with intrathecal injection of AmB deoxycholate to address the headache, fever, and vomiting of this treatment.<sup>80,81</sup>

### IFN- $\gamma$ therapy

Systemic IFN- $\gamma$  treatment has been described as an adjunctive therapy in several reports of intractable cases of DCM. Duplessis et al<sup>82</sup> administered subcutaneous IFN- $\gamma$  to 2 previously healthy African-American men who developed extensive, destructive, polyostotic coccidioidal osteomyelitis involving the axial skeleton. In both cases, DCM was clinically and radiographically refractory to prolonged therapy (5–8 months) with both azole antifungal medications (itraconazole and posaconazole) and liposomal AmB. Stimulation of

peripheral blood mononuclear cells with the mitogen phytohemagglutinin along with IL-12 yielded IFN- $\gamma$  release that was lower than expected. DNA sequencing of IFN- $\gamma$  receptor-1, IFN- $\gamma$  receptor-2, and STAT1 genes revealed no abnormalities, and the T lymphocyte subset analysis was unremarkable. After months without clear improvement with antifungal therapy alone, IFN- $\gamma$  1b injections were given 3 times weekly, with marked clinical improvement. Kuberski et al<sup>83</sup> described similar clinical improvement and eventual survival of an African-American woman after addition of IFN- $\gamma$  to antifungal therapy. The underlying mechanism by which IFN- $\gamma$  appeared beneficial in these cases is unclear, but enhancing the antifungal activity of macrophages might be involved. Expression of chitinase, which is upregulated by IFN- $\gamma$ , may be among these effector molecules.<sup>84</sup> This possibility is intriguing because it exhibits antifungal activity, and recombinant human chitinase has been shown to reduce mortality in experimental fungal infections in mice.<sup>85</sup>

### Refocusing of cellular immunity

As noted earlier, several types of data suggest that severe CM and DCM are associated with a Th2-biased cellular immune response.

Dupilumab is a monoclonal antibody that binds to the alpha subunit of the IL-4 receptor, antagonizing IL-4 and IL-13 signaling.<sup>86</sup> Dupilumab is approved by the US Food and Drug Administration for the treatment of patients with moderate to severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies; it is also approved as an add-on therapy for uncontrolled eosinophilic asthma or in patients with a dependence on oral glucocorticoids for asthma control.<sup>87,88</sup> In 2 recent trials, subcutaneous dupilumab given every 2 weeks was associated with a reduction in severe exacerbations of asthma and decreased corticosteroid usage. This therapy was tolerated over periods of 24–52 weeks; transient eosinophilia was noted in both trials and hypothesized to be the result of the blockade of effects of IL-4 on eosinophil activation and egress from peripheral blood.<sup>89,90</sup>

In view of the type 2 inflammatory state that often accompanies DCM, we recently tested the idea that dupilumab might bring about improvement in cases of DCM found to be refractory to antifungal therapy alone (Tsai et al, submitted for publication). A healthy 4-year-old boy presented with fevers and a 3-week history of enlarging subcutaneous nodules on his forehead that proved to be foci of coccidioidal osteomyelitis. Bony involvement was also identified in vertebral bodies, the right tibia and fibula and the right radius. He had no history of recurrent or severe infections but was found to have a polymorphism in the IL-12R $\beta$ 1 (IL-12 receptor subunit  $\beta$ 1) gene. Treatment with antifungal therapy (posaconazole and liposomal AmB) and IFN- $\gamma$  failed to stop the progression of bony disease. Weekly administration of dupilumab was begun and was associated with resolution of the patient's polyostotic osteomyelitis. Further experience is needed, but the current availability of immunomodulatory agents that refocus cellular immunity away from the type 2 pathway and toward IFN- $\gamma$ -focused T-cell responses suggest novel therapeutic approaches to refractory DCM, including coccidioidal meningitis. Targeting IL-5, IL-13, and IgE may also be fruitful in this regard. Clinical trials might preferentially involve individuals with eosinophilia, elevated IgE levels, and other markers of Th2 activity at the time of presentation with severe CM or DCM.

## CONCLUSIONS

We have far to go before we fully understand the unique pathogenicity of *Coccidioides* fungi, including their ability to disseminate widely, produce marked bony destruction, and to persist indefinitely. Moreover, apart from rare cases of monogenic defects in immunity, we do not yet know what factors permit dissemination of CM in the ~1% of those who become infected. The long-standing evidence that DCM occurs more frequently among otherwise healthy people of African and Filipino ancestry indicates that *Coccidioides* species exploit an otherwise benign difference in immune function to escape immune recognition and control. Although most cases of CM are self-limited, DCM is life-threatening and often responds poorly to antifungal therapy. Corticosteroid therapy may be beneficial in severe pulmonary and central nervous system disease to reduce inflammation as therapy is initiated, but augmenting or refocusing immune responses may be needed to induce remission or cure of coccidioidomycosis in some individuals. Systematic study of immune responses in acute CM and cases of DCM, and genetic evaluation of both those who control coccidioidal infection and those with severe disease, may help us distinguish those most likely to benefit from immunomodulatory therapy.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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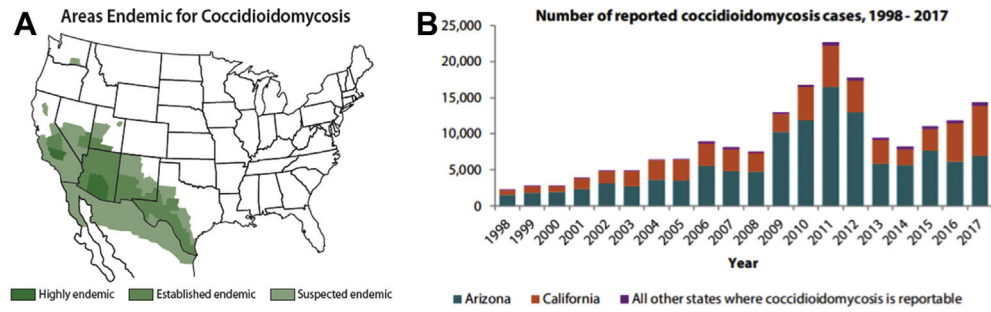
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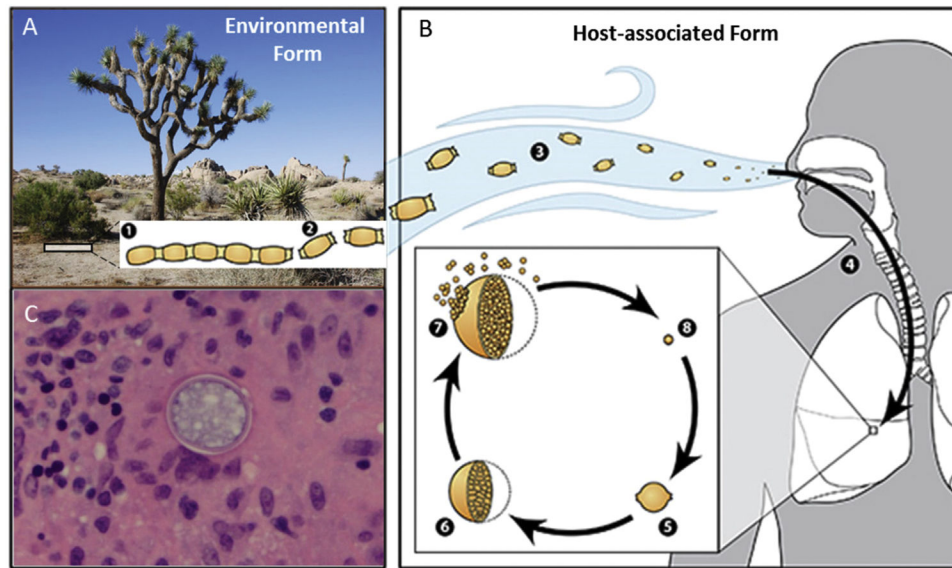
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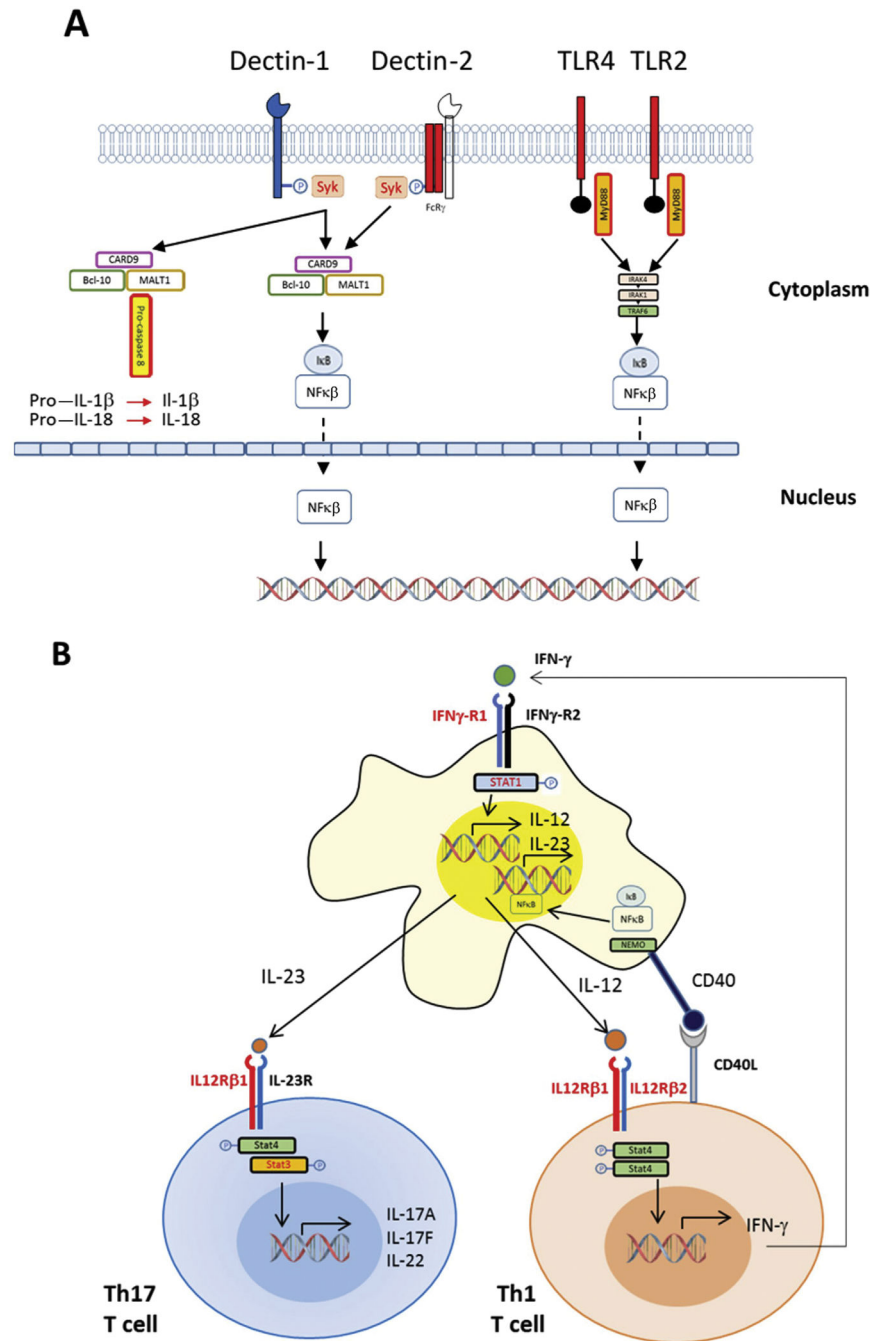
**Figure 1.**

Epidemiology of *Coccidioides* infection. (A) Areas in which human infection and autochthonous transmission to animals have been described. Reprinted from <https://www.cdc.gov/fungal/diseases/coccidioidomycosis/causes.html>. (B) Cases of coccidioidomycosis reported to the Centers for Disease Control and Prevention (1998–2017). Note the predominance of case reports from California and Arizona. Reprinted from <https://www.cdc.gov/fungal/pdf/valley-fever-expanding-cocci-P.pdf>.



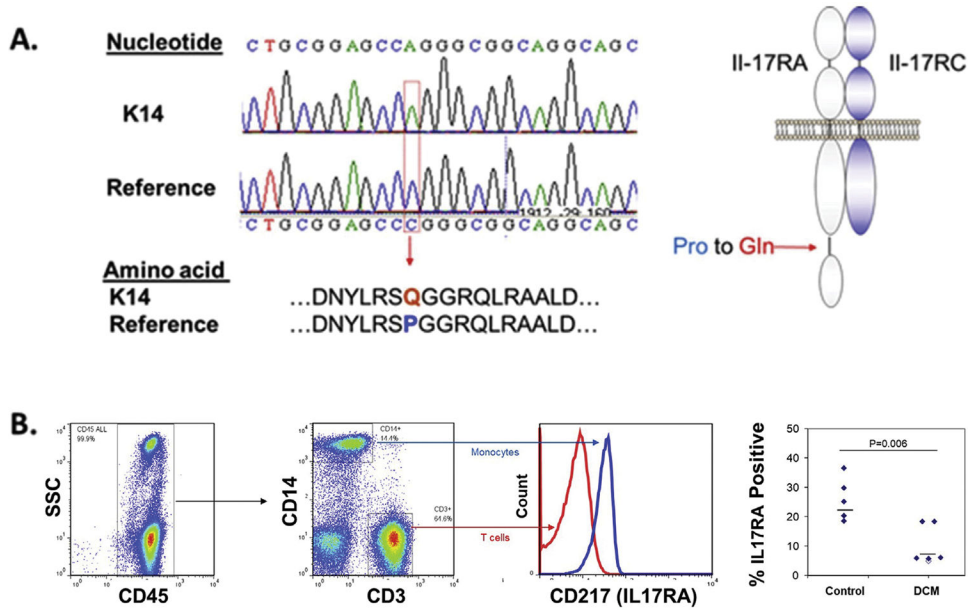
**Figure 2.**

*Coccidioides* biology. (A) *Coccidioides* grows as a mold with septate hyphae near the surface of the soil (1). The hyphae fragment into arthroconidia (2) and become aerosolized when the soil is disturbed by human activity or the wind (3). (B) These arthroconidia are inhaled and settle into the lungs, where signals from the environment promote the formation of spherules (5). Spherules divide internally until they are filled with endospores (6). When spherules rupture (7), the endospores are released. Endospores are then able to disseminate and develop into new spherules and to repeat the cycle. (C) Spherule in a soft tissue scalp lesion of a boy with disseminated coccidioidomycosis. Figure modified from <https://www.cdc.gov/fungal/diseases/coccidioidomycosis/causes.html#wastate>.



**Figure 3.** Immunobiology of coccidioidomycosis. (A) This simplified diagram outlines the recognition of fungal pathogen-associated molecular patterns by pattern recognition receptors that trigger activation of macrophages, neutrophils, and dendritic cells. Dectin-1 and Dectin-2 are examples of C-type lectin receptors involved in recognition of fungal cell wall components. Aggregation of Dectin-1 molecules in the presence of fungal polysaccharide ligands triggers phosphorylation of its cytoplasmic tail, leading to activation of Syk kinase, which induces formation of the CARD9-Bcl10-Malt1 complex, which mediates activation of nuclear factor

kappa  $\beta$  (NF- $\kappa$  $\beta$ ) and the production of cytokines, including interleukin (IL)-2, IL-6, IL-10, and IL-12, that activate and promote differentiation of T cells. Malt-1 can also engage and proteolytically cleave pro-caspase 8, activating the proinflammatory cytokines IL-1 $\beta$  and IL-18. Recognition of coccoidioidal molecules by Toll-like receptor 2 (TLR2) is essential for vaccine-induced protection in murine models of coccoidioidomycosis. Homodimers or heterodimers containing TLR2 are linked by an adaptor molecule to MyD88, activating IRAK4; subsequent downstream signaling leads to degradation of the I $\kappa$ B complex, releasing NF- $\kappa$ B complexes and allowing their nuclear entry and activation of cytokine transcription. Toll-like receptor 4 (TLR4) and Dectin-2 have not been confirmed to play a role in coccoidioidomycosis but are important in other mycoses. (B) Differentiation of CD4 T cells and their polarization into Th1 or Th17 cells and crosstalk with macrophages and other antigen-presenting cells. As outlined in panel A, recognition of fungal cellular components leads to activation of macrophages and other phagocytes, which release IL-2, IL-6, IL-10, IL-23, and other cytokines that promote the expansion and differentiation of naive CD4 T cells. Those that become Th17 cells express IL-17A, IL-17F, and IL-22, which promote production of antimicrobial peptides in epithelial cells. CD4 T cells that differentiate along the Th1 pathway in response to IL-12 release interferon gamma (IFN- $\gamma$ ), which enhances phagocytosis by macrophages and other phagocytes and the release of antimicrobial molecules. Red lettering reveals receptor and signaling molecules in which deleterious mutations have been found in cases of disseminated coccoidioidomycosis.<sup>33,35,91</sup> STAT = signal transducer and activator of transcription.



**Figure 4.** Detection and analysis of expression of an interleukin (IL)-17RA variant in coccidioidomycosis University of California Los Angeles (UCLA) Exome data. With approval from local ethics committees, DNA was extracted from peripheral blood (n = 20) and formalin-fixed tissue specimens (n = 2) of patients with extrapulmonary dissemination of coccidioidomycosis and submitted for whole-exome sequence analysis on a HiSeq 2500 instrument (Illumina, San Diego, California). The resulting data were filtered for variants in genes known or suspected to be in pathways relating to responses to fungal infections (see Supplemental Table S1). A potentially damaging homozygous variant was found in IL17-RA, an element of the heterodimeric IL-17 receptor. (A) Sanger sequencing confirmed a missense mutation in codon 562, producing a Pro562Gln change in the cytoplasmic tail of IL17-RA. (B) IL-17RA expression on monocytes of healthy control subjects and adults with disseminated coccidioidomycosis. Viable cryopreserved peripheral blood mononuclear cells from healthy young adults and 5 individuals with disseminated coccidioidomycosis (DCM) (K12, K13, K14, K17, and K18 in Table I) were thawed and analyzed by flow cytometry using fluorochrome-conjugated antibodies to CD3, CD14, CD45, and CD217 (IL-17RA). The median cell surface expression of IL-17RA (horizontal bars) was significantly reduced on monocytes from patients with DCM (Wilcoxon rank sum test) and was lowest in the cells from the individual with the Pro562Gln mutation (open symbol).

**Table 1.**

Clinical manifestations of coccidioidomycosis in study participants.

Patient Identifier	Sex	Population	Sites of Coccidioidal Disease
K03	Male	AFR	OM at 1 site with epidural abscess
K06	Male	AFR	Cavitary pneumonia. OM to multiple axial skeletal locations with soft tissue involvement
K08	Female	AFR	Miliary pneumonia. OM to multiple axial skeletal locations. Coccidioidal meningitis
K09	Male	AFR	OM at 12 axial skeletal locations
K11	Male	AFR	Pulmonary disease with dissemination to 2 soft tissue sites
K12	Male	AFR	OM at 3 axial skeletal locations
K13	Male	AFR	Pulmonary. OM at 3 axial skeleton locations with paraspinal abscess
K15	Male	AFR	Miliary pneumonia, coccidioidal meningitis, and OM with 2 axial skeletal locations
K14	Male	FIL	Pulmonary disease, coccidioidal meningitis complicated by arachnoiditis. OM at 1 axial skeleton location
U22	Female	FIL	OM of L4-S1 spine and right psoas muscle abscess
K01	Male	LAT	Pulmonary disease with OM at 2 axial skeletal locations. Soft tissue abscess
K02	Male	LAT	Miliary pneumonia. OM at 5 axial skeletal locations. Two soft tissue abscesses. Multiple cutaneous skin lesions
K05	Male	LAT	Severe fibrocavitary pulmonary. OM at 2 axial skeletal locations. Prostatic abscess
K07	Male	LAT	Pulmonary disease and coccidioidal meningitis. OM at 1 axial skeleton location
K10	Male	LAT	Miliary pneumonia with OM at 5 different axial skeletal locations
K16	Male	LAT	Pulmonary. Disseminated to skin, liver, and multiple axial skeletal foci of OM
K18	Female	LAT	Coccidioidal meningitis. OM at 5 axial skeleton locations
K19	Male	LAT	Pulmonary disease. Coccidioidal meningitis and OM at 2 axial skeletal locations
K20	Female	LAT	OM at 12 axial skeletal locations
U21	Female	LAT	Coccidioidal meningitis with hydrocephalus. Skin lesions
K04	Male	ME	OM at 6 axial skeletal locations. Six soft tissue abscesses
K17	Female	ME	Pulmonary disease. OM at 3 axial skeletal locations

AFR = African American; FIL = Filipino; ME = Middle Eastern; LAT = Latino; OM = osteomyelitis.

**Table II.**

Risk factors for disseminated coccidioidomycosis,<sup>1,6,10,12,20,34,35,55–57</sup>

<b>Older Age</b>	<b>Primary Immunodeficiency</b>
<b>Male Gender</b>	Hyper IgE syndrome (STAT3 mutations)
<b>Pregnancy</b>	IFN- $\gamma$ R1 polymorphisms
<b>Black race and Filipino ancestry</b>	IL12-R $\beta$ 1 or IL12-R $\beta$ 2 mutations
	STAT1 gain of function polymorphisms
<b>Immunosuppression</b>	<b>Other suspected deleterious genetic lesions</b>
HIV	Innate immune sensing <sup>*</sup>
Cancer/Chemotherapy	Signaling from innate sensing <sup>*</sup>
Solid Organ Transplantation	NF $\kappa$ B signaling <sup>*</sup>
Anti-inflammatory biological medications	IL-17 signaling <sup>*,**</sup>
	Human chitinase (CHIT1) <sup>**</sup>

<sup>\*</sup> Reference Hardison and Brown.<sup>36</sup>

<sup>\*\*</sup> This report.