Recent Advances in Our Understanding of the Environmental, Epidemiological, Immunological, and Clinical Dimensions of Coccidioidomycosis

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SUMMARY

Coccidioidomycosis is the endemic mycosis caused by the fungal pathogens *Coccidioides immitis* and *C. posadasii*. This review is a summary of the recent advances that have been made in the understanding of this pathogen, including its mycology, genetics, and niche in the environment. Updates on the epidemiology of the organism emphasize that it is a continuing, significant problem in areas of endemicity. For a variety of reasons, the number of reported coccidioidal infections has increased dramatically over the past decade. While continual improvements in the fields of organ transplantation and management of autoimmune disorders and patients with HIV have led to dilemmas with concurrent infection with coccidioidomycosis, they have also led to advances in the understanding of the human immune response to infection. There have been some advances in therapeutics with the increased use of newer azoles. Lastly, there is an overview of the ongoing search for a preventative vaccine.

INTRODUCTION

This review summarizes the population biology, epidemiology, immunology, and clinical management of two understudied but increasingly important fungal pathogens of humans: *Coccidioides immitis* and *Coccidioides posadasii*, the etiologic agents of coccidioidomycosis (San Joaquin Valley fever, or simply “valley fever”). These fungi occur in the soil of certain desert regions in the Western Hemisphere. When airborne spores are inhaled by humans or many other species of mammals, infection develops in the lungs. The consequences of infection range from an inconsequential illness with resulting lifelong resistance to reinfection to severe and potentially life-threatening pneumonia or tissue destruction throughout the body.

Several reviews have summarized the historical evolution of our understanding of coccidioidomycosis (1–3). Others have dealt with immunologic studies of experimental infections, primarily in mice (4, 5). Since then, there has been a renewed interest in the mycology and population biology of *Coccidioides* spp. in the environment. There is also a growing appreciation of the impact of coccidioidomycosis in the United States, as regions of endemicity are increasingly becoming urbanized and destinations for tourists. This review focuses on recent development in these areas and also updates approaches to patient management.

MYCOLOGY AND POPULATION STRUCTURE

Coccidioides immitis and *C. posadasii* (Ascomycota, Pezizomycotina, Eurotiomycetes, Onygenales, Onygenaceae) are the only two species recognized within the genus. Their closest relative for which a genome sequence is currently published, determined by both phylogenetic analysis and morphology, is *Uncinocarpus reesii* (Onygenaceae), a keratinophilic saprotroph (6, 7). Whereas *U. reesii* has a known sexual life cycle (7, 8), the sexual cycle of *Coccidioides* remains undescribed. No other dimorphic pathogens of humans have been

described in the Onygenaceae family (7, 9, 10). The Onygenales order, however, contains other dimorphic pathogens, such as *Paracoccidioides brasiliensis*, *Ajellomyces* (*Histoplasma*) *capsulatus*, and *Ajellomyces* (*Blastomyces*) *dermatitidis* (10, 11).

Both species of *Coccidioides* are dimorphic fungi that grow saprotrophically as hyphae. Spores (arthroconidia) differentiate as alternating segments which separate and ultimately undergo autolysis. This process produces single, barrel-shaped cells which are approximately 3 to 5 μm in size and are the infectious propagules for mammals (Fig. 1). Under dry conditions, arthroconidia are very stable spores, remaining viable for up to many years. When they are inhaled into the lungs (likely to the level of the terminal bronchiole), the fungus initiates isotropic growth, remodeling its cell wall into a specialized structure called a spherule, which is unique to the *Coccidioides* genus. The spherule expands in size over a 4-day period and undergoes nuclear division, producing a cellular structure which, at maturity, may be up to 100 μm in diameter and contains 100 to 300 asexual, singled-celled propagules (endospores). When spherules rupture, the endospores are released, and each is capable of developing into new spherules until the host's immune system (or medical intervention) represses the growth of the fungus. Though the primary route of infection is pulmonary, the organism can disseminate hematogenously to any organ (12–14).

Sexual structures have never been observed in either species of *Coccidioides*, unlike the aforementioned relative *U. reesii*. However, molecular data do suggest the existence of a sexual phase. Analysis of different strains indicates that recombination, not clonal growth, occurs (15, 16). Mating type alleles (*MAT*) identified in *Coccidioides* are typical of a heterothallic ascomycete with alternate idiomorphs at a single locus (8, 17), with one idiomorph containing a high-mobility-group (HMG) box characteristic of the mating type *MAT1-2* allele and the other containing an α -box gene that defines the *MAT1-1* allele. In both species, a 1:1 ratio of mating type alleles was seen by PCR analysis of a collection of more than 400 clinical and environmental isolates, which would be expected only for a sexually recombining species (8). All mating type genes in both loci were expressed, which suggests that they are functional. In addition, analysis of *Coccidioides* genomes for a set of core meiotic genes necessary for sexual reproduction indicated that most are present and expressed in *Coccidioides* (B. M. Barker, M. A. Mandel, and M. J. Orbach, unpublished data). These findings are congruent with population genetic data suggesting that *Coccidioides* undergoes sexual recombination and are supported by the fact that the majority of isolates examined to date, whether from human patients, veterinary diagnostic laboratories, or soil samples, have a unique genotype (15, 18–22).

POPULATION GENETICS AND GENOMICS

Because disease severity is highly variable—ranging from asymptomatic to lethal infections—understanding the distribution of

FIG 1 Life cycle of *Coccidioides* spp. Both *C. immitis* and *C. posadasii* share the same asexual life cycle, which is represented here. The parasitic phase occurs in the host. The saprophytic life cycle occurs in the soil environment.

genotypes among pathogen populations, as well as human host variation, is important for monitoring outbreaks, correlating genotypic variance with virulence, and predicting potential disease progression and outbreaks. Correlating disease spectrum and severity with pathogen genotype may assist in identifying genes associated with differential virulence, as well as potentially influencing patient management.

To begin to explore genetic variation, *C. immitis* and *C. posadasii* were chosen for comparative genomics at the species and population levels. In 2002, the previously monotypic genus was formally recognized as two closely related species (23). Additionally, both species were divided into at least two populations: northern and southern California for *C. immitis* and Arizona/Mexico and Texas/South America for *C. posadasii* (24). In 2010, genome sequencing was completed for 20 *Coccidioides* strains (25). The sequenced strains represent both species, with variations in biogeography, virulence, and isolate source. The availability of these sequences has facilitated investigation of the frequency of hybridization and introgression between species.

Based on previous observations, the genomes of *C. immitis* and *C. posadasii* were assessed for indications of hybridization. The results suggest that hybridization has indeed occurred between species, and at least one fragment appears to have undergone introgression in *C. immitis*, in a population-specific manner (25). This discovery was enabled by previous studies that recognized phylogenetic species and populations and by the availability of *Coccidioides* reference genomes for both species (16, 19, 26). The analysis identified regions from each genome that had higher sequence identity to the opposite species.

The genomic analyses of *Coccidioides* spp. that are now possible are only beginning to be explored. Recent RNA sequencing data show a number of differentially expressed transcripts between the two species and morphological states (27). These data will provide the necessary scaffold for future studies to understand the genetic basis of coccidioidomycosis.

COCCIDIOIDES IN THE ENVIRONMENT

Improving the limited understanding of ecological factors that influence the growth and reproduction of the organism in the

environment could assist in predicting and preventing exposure to the pathogen. It is believed that the distribution of *Coccidioides* is limited to the Americas, since it has never been isolated from soil outside the Western Hemisphere. *C. immitis* is proposed to be restricted to central and southern California, although its range may extend south into Baja California (23–25). *C. posadasii* is present throughout southern and western Arizona, with the highest incidence in Pima, Pinal, and Maricopa Counties, extending eastward into Texas, north into isolated areas of Utah, and south into Mexico. Additionally, there are isolated populations of *C. posadasii* in Central and South America. The recent discovery of hybrid strains of the organism suggests that there is gene flow between the species and among populations (25).

It is unknown how long *Coccidioides* has been in the Americas. Genomic comparisons suggest that *C. immitis* and *C. posadasii* split around 5 million years ago (26). *Coccidioides* as a genus has existed longer—possibly as long as 40 to 50 million years (22, 23, 28). *Coccidioides* spp. are proposed to have emerged in the early Cenozoic period, corresponding to a point in time where there was rapid diversification of mammalian orders, with the first fossils of Rodentia appearing (29). Development of the Sierra Madres and the Rocky Mountains also corresponds with the fossil record for early North American mammals (29). At that time, South America was still a separate continent, which would support a more recent introduction of *C. posadasii* to South America and the origin of *Coccidioides* in North America (24).

Skin test surveys of humans, livestock, and domestic animals in regions where the disease is thought to be endemic were used extensively to map the geographic distribution of the fungus in the environment (30). Since coccidioid infection confers very long-lived dermal hypersensitivity to antigen extracts of *Coccidioides*, these surveys measured the prevalence of prior exposure. These surveys thus provided estimates of the distribution of *Coccidioides* in the southwestern portion of the United States (31, 32). Additionally, some counties in the Southwest had much higher proportions of skin reactivity: skin testing of long-term residents of single counties showed that in Arizona, Maricopa County (Phoenix), Pima County (Tucson), and Pinal County had over 70% positive skin test rates, compared to 10 to 40% in surrounding

counties (33, 34). In California, 50 to 70% of skin tests were positive in Kern (Bakersfield), Tulare, and Kings Counties, whereas the rate of positive skin tests dropped to 10% in areas a few hundred miles away (33). However, these data were not analyzed at a local level and were unable to provide the level of mapping detail (township or neighborhood) that would be more applicable to precise mapping of exposure. For sparsely populated areas, these data provide even less of an indication of where the pathogen exists in the environment. Furthermore, movement of humans easily confounds such data over long and short distances. As such, skin tests were also performed in cattle in parts of Arizona (34). Analysis of these data found a close correlation between positive cattle skin tests and the Lower Sonoran Life Zone. These results prompted researchers to attempt to define ecological factors associated with the presence of *Coccidioides*, as well as to determine directly the distribution of the fungus in the soil at local sites (35–38).

Stewart and Meyer were the first to show that *Coccidioides* could be isolated from soil (39). Extensive soil mapping indicated that the distribution of the fungus was sporadic and localized (40). Additionally, early work at sites known to be positive for *Coccidioides* included surveys of infection rates in trapped animals, primarily rodents (41). Finally, skin testing confirmed that the distribution of the fungus extended into Mexico, Central America, and South America (42, 43).

More recently, efforts to isolate *Coccidioides* from the soil for niche identification and population analyses have focused on sites of historical human exposure (44), recent exposure of humans or dogs (18), or associations with rodents (45) or armadillos (46). PCR using *Coccidioides*-specific ribosomal DNA (rDNA) primers in a nested reaction protocol has allowed detection in some cases (45, 46), although the sensitivity of detection is not clear. This approach, while useful for identifying positive sites, does not allow for molecular or phenotypic analysis. Recovery of environmental isolates by use of semiselective plating has had a low rate of success, due at least partially to overgrowth of *Coccidioides* by other soil fungi (44). The most efficient way of isolating the organism from the soil involves using mice as biosensors; injecting susceptible animals with soil extracts results in purification of *Coccidioides* from soil microbes and allows recovery of pure cultures (18, 37, 39, 47). Unfortunately, this approach is cost-prohibitive, requires fungal virulence, and, as such, is a biased method for isolating environmental strains.

The potential role of rodents in the life cycle of *Coccidioides* is debated. Early researchers noticed a correlation of infections with people and animals digging in and around rodent burrows (48), leading Ashburn and Emmons to suggest that desert rodents may be a reservoir for *Coccidioides* in the environment (41). However, infection rates in trapped wild rodents are low (49). Additional work showed susceptibility of wild-caught rodents; however, the extremely high dosage of arthroconidia used to induce infections exceeds that expected in natural environments, and the use of the intraperitoneal rather than intranasal route of infection may complicate the interpretation of the study (50).

There is no evidence that *Coccidioides* will pass through the guts of common predators of desert rodents, including foxes, coyotes, and owls: a number of fecal samples from kit fox (*Vulpes macrotis*), badger (*Taxidea taxus*), bobcat (*Lynx rufus*), coyote (*Canis latrans*), and owl (*Otus asio* and *Speotyto cunicularia*) pellets were collected over a 5-year period near known *Coccidioides*-

positive sites and then tested, but the organism was never recovered (51). However, arthroconidia and spherules will pass through the guts of laboratory and wild mice (51, 52), which would allow for the fungus to survive even in the case of rodent cannibalism. Additionally, in these studies, fecal samples were taken from lizards (*Uta stansburiana*, *Gerrhonotus* spp., *Sceloporus occidentalis*, *Crotaphytus wislizeni*, and *Cnemidophorus tigris*), skunks (*Spilogale gracilis*), black-tailed deer (*Dama hemionus*), goats (*Capra* spp.), sheep (*Ovis* spp.), and burros (*Equus assinus*). Again, no samples produced *Coccidioides*. In one interesting report, the organism was cultured from bat guano (53).

The observed association of *Coccidioides* with rodent burrows could be due to infection of rodents that recover but retain quiescent, viable spherules. When the rodent ages and dies, the fungus reactivates to colonize the carcass, creating a new source of inoculum. By this model, *Coccidioides* would recognize the immunocompetent host as a hostile environment and go dormant in a fungistatic manner to survive. When the host dies, the environment will be conducive to growth, allowing spherules to convert back to active growth. As conditions would no longer be favorable for spherulation (high CO₂, 37°C), reversion to hyphal growth and arthroconidia would occur. This is supported by experiments in which infected animals were buried in an area that had previously been sampled thoroughly and found to be negative for *Coccidioides*. Subsequent resampling recovered the organism (54).

Alternatively, the fungus could infect a rodent, from which it could be shed passively or released upon the death of the animal. Such burrows may be conducive to *Coccidioides* growth, providing moisture, a relatively stable temperature, and nutrients in the form of nitrogenous wastes, feces, and other rodent proteins. As members of the Onygenales are known to degrade keratin (10, 26), *Coccidioides* may thus be associated with hair and skin in rodent burrows rather than with direct infection of the animal. Support for the adaptation of *Coccidioides* to mammalian tissue for nutrients comes from genomic analyses where gene family losses were found in the Onygenales for plant-digestive enzymes, including a total absence of proteins containing the cellulose binding domain CBM1, as well as tannases, melibases, pectate lyases, and pectinesterases, and dramatic reductions in cellulases and cutinases (26). Gene family expansions in the *Coccidioides/Uncinocarpus* lineage are seen for proteinases, including subtilisin N domain-containing proteins that have been shown to be associated with pathogenicity in some fungi and prokaryotes (26). Expansions were also seen in the peptidase S8 family and the deuterolysin metalloprotease (M35) family, in which one gene member, *MEP1*, is a *Coccidioides* virulence determinant (222).

Other ecological factors that might be associated with the success of *Coccidioides* in the environment remain largely unexplored. In California, the fungus appears more frequently in saline and alkaline soils (37, 55), whereas, in Arizona, it appears to be associated with sandy, porous soil and rodent burrows (18, 38, 41, 56). However, these results are based on a few studies and therefore cannot be considered conclusive. In fact, the majority of soil samples tested in previous studies were negative, and recovery rates in a randomized collection study were below 1% (57). Investigation of other soil microbes present at positive sites has also provided little information about antagonistic or cooperative relationships among organisms (36, 58). *Coccidioides* has been reported to be a poor competitor with other fungi, as plating experiments have reported overgrowth of *Coccidioides* colonies by other

FIG 2 New cases of coccidioidomycosis reported to the Arizona and California Departments of Public Health. Provisional 2012 statistics for Arizona were supplied by C. Tsang, Arizona Department of Health Services (personal communication), and those for California are from reference 221. (Adapted from reference 75.)

rapidly growing fungi (18, 38, 44). However, in the environment, *Coccidioides* may persist for many years in the same location, and therefore it must be competitive under certain circumstances (18, 44).

Another factor influencing the incidence of disease in areas of endemicity is weather patterns. Analysis of reports from doctors following new recruits at Williams Air Force Base in Maricopa County and from cases diagnosed in University of Arizona students in Pima County showed two seasonal spikes in infection rates, associated with dry periods after winter and summer precipitation in Arizona (59, 60). Over the past 2 decades, there has been considerable variation in the number of reported cases for Arizona and California from year to year. For example, in California, there was a very large increase in the early 1990s (61, 62), while another was seen in Arizona from 1998 to 2001 (63). The case for windy conditions was clearly evident following one very severe Santa Ana windstorm in California's central valley (64). However, neither average wind velocity nor wind velocity in the previous 2 months was positively correlated with the Arizona increases (63). As shown in Fig. 2, there was a 39% increase in Arizona infections in 2011 compared to 2010. Surprisingly, this increase was evenly distributed throughout the year and was not associated specifically with the July dust storms in Maricopa County, which were so severe that they received national media attention (Fig. 3). In contrast, rainfall does appear to be a significant weather variable. A recently developed mathematical model has shown a strong correlation between seasonal precipitation variation and the annual number of cases of coccidioidomycosis reported to Arizona Public Health for Pima and Maricopa County residents (65, 66). Data from Kern County in California show a single peak of infection associated with dry periods after the winter rainy season, with relatively equal rates during the rest of the year (67, 68). There is a general lack of information about climatic factors affecting rates of disease in the remainder of the area of endemicity, specifically in Mexico and South America (45, 69).

To what extent the areas of endemicity or the intensity of exposure will remain stable cannot be predicted from our current understanding of *Coccidioides* in the environment. The fungus has been found sporadically as far north as the Dinosaur National Monument in Utah, which suggests that it is possible that a suit-

able habitat exists in the Great Basin Desert (70). Also, spherules were identified histologically in the jaw of a bison, excavated in Nebraska, which was thought to have died about 8,500 years ago (71). The fact that Nebraska is far from the current region of endemicity raises the possibility of other factors rearranging the boundaries of endemicity. As discussed above, Arizona has experienced increasing numbers of reported coccidioidal infections (Fig. 2). This trend was factored out of the weather model referred to above (66). Analysis of *Coccidioides* isolates recovered from patients does not support the concept that this rise was caused by a single pathogenic clone (20). In fact, it is still unclear if any environmental change plays a role, since the increase could also be explained by improved recognition by physicians, increasingly susceptible patient populations, or more complete reporting to the state. Clearly, a better understanding of the ecology of *Coccidioides* in the environment could improve our ability to assess the public health risk of endemic exposure, and potentially its mitigation, in the future.

FIG 3 The July 2011 dust storms in Maricopa County, AZ, were so severe that they garnered national attention. (Courtesy of Mike Olbinsky.)

FIG 4 Dermal hypersensitivity mapping of the endemic intensity of coccidioidomycosis. (Adapted from reference 220 [edited by Libero Ajello] with permission of the University of Arizona Press. © 1967 The Arizona Board of Regents.)

CURRENT EPIDEMIOLOGY OF HUMAN COCCIDIOIDOMYCOSIS

Regions of Endemicity and Reported Numbers of Infections

The dermal hypersensitivity mapping of the endemic intensity for acquiring coccidioidomycosis referred to above was conducted on over 88,000 U.S. Navy personnel from 1948 to 1950 (33) (Fig. 4). Although nothing of this scale has been repeated, coccidioidomycosis is a reportable disease in California and Arizona, and recent case rates for these states (72, 73) by county (Fig. 5) show a similar distribution at the county level to the prior prevalence of infection found half a century ago (33). Presumably, other states, including Texas, New Mexico, Utah, and Nevada, also continue to have the same endemic geography. Other regions of endemicity within the Western Hemisphere include portions of Mexico, Guatemala, Honduras, Argentina, Brazil, Paraguay, Bolivia, Venezuela, and probably Columbia (74).

Of the 117,717 cases of coccidioidomycosis reported to the CDC between 1998 and 2011, 97% were from Arizona and California (75). Arizona reporting uses a case definition in which patients with a single coccidioidal antibody test are considered positive and has been clinical laboratory based since 1997, whereas California, until recently, required rising antibody titers in paired sera and received reported cases from the treating physicians. As a result, Arizona's statistics may more completely reflect the actual numbers of cases that are diagnosed annually than the California statistics. Even so, it would appear that Arizona's number of reported cases is at least twice that of California. As can be seen in Fig. 5, nearly all of Arizona's infections occur in three counties: Maricopa, Pinal, and Pima Counties. Primarily because of the

concentration of the state's population, over 80% of all Arizona coccidioidal infections are reported in Maricopa residents.

A striking increase in Arizona case numbers occurred in 2009, when annual numbers rose from just under 5,000 to over 10,000 (72). This increase was due to an administrative change by a major Arizona laboratory to report patients who were positive only by the more sensitive enzyme immunoassay (EIA) and not to require confirmation by immunodiffusion tests (76). The differences between EIA and immunodiffusion tests are discussed in greater detail in a later section, but the higher reported numbers since 2009 more accurately reflect the true disease burden in the state.

In Arizona, approximately equal numbers of men and women were reported to have new infections, although after the change in case identification in 2009, women were a slight majority (55%) rather than a slight minority (46%). One possible reason for this may relate to the greater sensitivity of EIAs. In an earlier study from the University of Arizona Campus Health, the male/female ratio of coccidioidal infection was proportional to the ratio of enrolled students, but male patients had significantly higher antibody titers, suggesting that with more sensitive testing methods the number of females might be higher (77). Also, Arizona state statistics show a striking increase in case rates with age. For example, in 2006, the case rate for persons aged 75 to 79 years was 225/100,000, in contrast to that for children under 15 years of age, where it was less than 25/100,000. Although age and/or associated comorbidities may increase the severity of coccidioidal infections (78, 79), other evidence suggests that the relatively low case rates in young adults may be due to less diligent attempts to identify coccidioidal infection as the specific etiology in younger patients

FIG 5 Map of case rates of coccidioidomycosis by county in Arizona in 2006 and in California from 2001 to 2009.

with community-acquired pneumonia. For example, in young adults at the University of Arizona from 1998 to 2006, the overall case rate was 91.4/100,000, and in scholarship athletes, it was 374/100,000 (80). These high rates in the University of Arizona program are likely due to the medical group's routine evaluation for valley fever in otherwise unexplained respiratory illnesses.

The demographics of California and Arizona differ significantly in that most Arizona residents live within the regions where coccidioidomycosis is endemic, whereas most California residents do not. For example, the 2010 populations for the three California counties (Kern, San Luis Obispo, and Tulare) where coccidioidomycosis is most intensely endemic total only 1.5 million (4%) of the 37.3 million for the state as a whole, whereas in Arizona the populations of the counties of endemicity, i.e., Maricopa, Pinal, and Pima, account for 5.2 million (81%) of the state's 6.4 million total.

Estimates of Disease Impact

Flaherman et al. (81) used hospital discharge data to estimate the incidence of coccidioidomycosis-associated hospitalizations in California. For 1997 to 2002, the average annual rate of hospitalization was 3.67 per 100,000 population, and deaths averaged about 70 per year. By way of comparison, the authors suggest that these statistics for coccidioidomycosis are similar to those for severe disease and death from varicella in the state before availability of the varicella vaccine (82).

Because of the statewide rising incidence of coccidioidomycosis, the Arizona Department of Health Services and the CDC undertook an enhanced surveillance program (83). From January 2007 through February 2008, 5,664 patients were reported to the state as newly diagnosed cases of coccidioidomycosis. Of those who could be contacted, 493 agreed to be interviewed, while only 41 declined. Some of the findings from this survey were as follows: 85% had infection limited to the lungs, the median time to diagnosis was 23 days, the median duration of illness was 120 days, the median number of days lost from work was 14 days, and the median time until activities of daily living were resumed was 47 days. Forty-one percent of respondents were hospitalized, and from Arizona hospital records, the calculated yearly inpatient cost of coccidioidomycosis was \$86 million (approximately \$30,000 per patient). Additional costs for outpatient care and time lost from work were not included in this study. Even so, it is clear from this enhanced surveillance report that coccidioidomycosis has a very significant medical and economic impact on populations within the area of endemicity.

In a follow-up study, 324 medical records from the same 493 patients that were interviewed were available for chart review. Of these, 26 (8%) contained documentation of extrapulmonary dissemination (84). By extrapolation, this suggests that there were approximately 400 newly diagnosed disseminated infections that year in Arizona. Since it is likely that most, if not all, cases of

disseminated infection would eventually be identified and reported to the state, this number is the most reliable estimate to date of how many patients have these complications annually.

THE HUMAN IMMUNE RESPONSE TO *COCCIDIOIDES* AND ITS INFLUENCE ON THE SEVERITY OF ILLNESS

The number of studies that directly examine the human immune response in coccidioidomycosis is limited, but these studies suggest that cellular immunity is a critical element of control. A comprehensive review of past publications that focus on the immune response in animal and human coccidioidomycosis was recently published (85). In addition, and germane to this discussion, there are numerous clinical reports that give a clear picture of those at risk for infection. These reports can be divided into two categories. In the first, specific defects in the human immune response have been noted to result in an increased risk for symptomatic and severe disease. In the second, certain groups have been observed to be at risk, but the precise defect in the immune response has not been found. Each of these is explored here in turn. Except in instances where background explanation is warranted, citations are limited to the last 5 years.

Specific Immune Deficits Associated with Coccidioidomycosis

HIV infection. Within a few years of the identification of the epidemic of the AIDS due to HIV-1 infection, it was clear that patients with CD4 T cell depletion were at high risk for developing active coccidioidomycosis. In a prospective study in a clinic for HIV-1-infected patients living in the region of endemicity, nearly 25% of the cohort developed clinically symptomatic infection by 41 months of follow-up (86). The risks for the development of coccidioidomycosis included a peripheral blood CD4 T cell count of $<250/\mu\text{l}$ and the diagnosis of AIDS. A history of coccidioidomycosis was not a risk factor, suggesting that new rather than reactivated infections accounted for most cases. Among the 13 subjects who developed infection, 6 had either diffuse pulmonary or extrapulmonary disease, and 5 died.

Subsequently, in another cohort of HIV-infected subjects, it was confirmed that a peripheral blood CD4 T cell count of $<250/\mu\text{l}$ was a major factor associated with the development of active coccidioidomycosis, as well as a lack of an *in vitro* cellular immune response to coccidioidal antigen (87).

The importance of reconstituting the immune response in preventing coccidioidomycosis in HIV-infected persons taking potent antiretroviral therapy was established when another cohort of HIV-infected patients was retrospectively reviewed in the same clinic as that in the previously cited prospective study. Between 2003 and 2008, there were only 29 (11.3%) instances of active disease among 257 subjects, with an annual incidence of 0.9%. Patients with symptomatic infection had a significantly lower mean CD4 T lymphocyte count ($285/\mu\text{l}$) than that of control subjects ($487/\mu\text{l}$). Moreover, both a higher HIV RNA concentration and a lower CD4 T cell count were significantly associated with more severe disease among those with coccidioidomycosis, suggesting that treatment of HIV infection has a markedly salutary effect (88).

An excessive reaction of the immune system after the initiation of potent antiretroviral therapy has been termed immune reconstitution inflammatory syndrome (IRIS) (89) and is manifested by either an unmasking of a subclinical infection or the paradoxical

worsening of a treated infection (90). Mycobacterial diseases and cryptococcal meningitis are the most common infections associated with IRIS. There are only three reports of IRIS associated with coccidioidomycosis among HIV-infected patients (91–93), and these are not compelling. Whether coccidioidomycosis can result in IRIS remains unclear, but if it does, it appears to be uncommon.

Allogeneic transplantation. Transplantation is increasingly available at centers located within the region of endemicity, leading to concern that patients receiving transplants will either reactivate a prior coccidioidal infection or develop severe symptoms from a new infection. Blair and colleagues have published extensively on coccidioidomycosis in patients with solid organ transplantations. As they note (94), prevention of allograft rejection requires suppression of the cellular immune response, thus placing patients at risk for the development of symptomatic disease.

Among donors receiving allogeneic solid organ transplants within the region of endemicity, the incidence of active coccidioidomycosis currently appears to be below 5% (95–98). It is presumed that 70% of cases are due to reactivation of a previously acquired infection (95, 99), based on the observation that more than 50% of cases occur within 3 months of transplantation and 70% occur during the first year, a time of maximum immunosuppression (95). However, patients without prior infection living in the region of endemicity remain at risk for infection. In a study of 41 patients with liver transplants outside the area of endemicity who then moved to Arizona, 37 were monitored for at least 1 year. One of these (2.7%) developed acute pulmonary coccidioidomycosis approximately 2 years after receiving the transplant, at a time when the patient was receiving methylprednisolone for acute rejection (100).

Donor-derived coccidioidomycosis has emerged as a vexing problem for allogeneic transplantation. The first case was reported in 2002 (101). A 21-year-old man without evidence of prior coccidioidomycosis developed pulmonary disease approximately 1 week after transplantation. He received a double lung transplant from a woman from Arizona. A hilar lymph node from the transplant was later found to harbor the organism. The recipient was treated with fluconazole and clinically improved. Since then, two cases of disseminated coccidioidomycosis from a single donor were reported in 2003 (102). Another fatal case was reported in 2004 (103), as well as one in France that occurred at nearly 1 year posttransplantation (104). Three other patients developed coccidioidomycosis from one donor within 3 weeks of transplantation (105), and three of five patients who received organs from a single donor developed active infection, two of which disseminated (106).

Anticytokine therapy. Antibodies directed against proinflammatory cytokines have emerged as potent therapeutic tools in the management of a variety of autoimmune diseases. Tumor necrosis factor alpha (TNF- α) is a proinflammatory cytokine that helps to generate a competent cellular immune response to a variety of pathogens but also appears to play a role in promoting the pathogenesis of chronic inflammatory diseases such as rheumatoid arthritis and Crohn's disease. Monoclonal antibodies directed against TNF- α include infliximab, adalimumab, and golimumab (26). Certolizumab is a humanized antibody lacking an Fc portion, so it does not induce apoptosis of T cells (107). Etanercept is a fusion protein that blocks TNF- α from binding its receptor (107, 108).

Smith and Kauffman reviewed the role of anti-TNF- α therapy

of fungal diseases and noted that, like the case for tuberculosis, patients receiving these agents were at increased risk for developing severe symptomatic disease, particularly histoplasmosis. Whether such cases represented reactivation of previously acquired infection or were severe manifestations of new infections was not clear, but the authors favored the former hypothesis (107). Bergstrom and colleagues (109) reviewed cases of coccidioidomycosis occurring in patients receiving TNF- α inhibitor therapy in five rheumatology practices located within the region of endemicity. Of the 13 patients identified, 12 received infliximab and 1 was treated with etanercept. Among these, nine had pulmonary disease and four had extrathoracic dissemination. While two patients died, only one death was attributed to coccidioidomycosis. Though some cases of coccidioidomycosis appeared to be due to reactivation, others seemed to represent recent infections. The authors calculated that the relative risk of developing coccidioidomycosis was >5-fold higher in those receiving infliximab than in those not receiving the therapy.

In a single case report, the rapidity and severity of primary infection are illustrated by the description of a patient in Iowa receiving methotrexate and infliximab for rheumatoid arthritis who developed a slowly expanding cheek lesion followed by rapidly progressive respiratory failure and death. Coccidioidal spherules were found in samples obtained by bronchoalveolar lavage. Although the patient had lived all his life in the Midwest, he had visited Phoenix, AZ, 6 months previously (110).

Cytokine therapy. *In vitro* studies of peripheral blood mononuclear cells have suggested that there is a diminished cytokine response to incubation with coccidioidal antigens in patients with disseminated coccidioidomycosis. In particular, there is a lack of release of interleukin-2 (IL-2) and gamma interferon (IFN- γ) (111). To this end, Kuberski and colleagues (112) treated a 57-year-old African-American woman who had severe pulmonary and disseminated coccidioidomycosis with adjunctive IFN- γ (50 $\mu\text{g}/\text{m}^2$ subcutaneously three times weekly) in addition to liposomal amphotericin B, after she failed to improve during 10 weeks of antifungal therapy alone. After initiation of IFN- γ , she demonstrated clinical improvement and was eventually discharged from the hospital on oral fluconazole. Subsequently, two additional patients with refractory coccidioidomycosis were treated with the same dose of IFN- γ and demonstrated prompt improvement (113). Immunological study of these patients revealed essentially normal cytokine responses, except for diminished release of TNF- α in response to lipopolysaccharide. However, no coccidioidal antigen stimulation was tested to determine if the two patients had an abnormal response to specific antigen stimulation.

Specific genetic mutations. Until recently, genetic mutations had not been associated with an increased susceptibility to coccidioidomycosis. However, in 2009, Vinh and colleagues reported a case of a man with widespread *Mycobacterium kansasii* infection and disseminated coccidioidomycosis who was found to be heterozygous for the 818del4 mutation in the gene encoding IFN- γ receptor 1 (114), which is known to predispose individuals to more severe mycobacterial disease. Subsequently, two siblings, both with disseminated coccidioidomycosis, were found to be homozygous for a mutation encoding the interleukin-12 receptor B1 (115). The addition of IL-12 to activated T cells from the first patient failed to show an increase in the phosphorylation of signal transducer and activator of transcription 4 (STAT4), demonstrating a functional defect in the IFN- γ /IL-12 axis, a critical element

of the cellular immune response. Very recently, two patients were identified as having a gain-of-function mutation in STAT1 (116). In contrast to the patients with the IFN- γ /IL-12 receptor mutations, these two patients had progressive noncavitary pulmonary involvement, which is distinctly different from the fibrocavitary lesions that are normally seen (117).

Characteristics Associated with Symptomatic Coccidioidomycosis without a Defined Immune Deficit

Ethnicity. It has long been asserted that certain ethnic groups are at higher risk for symptomatic and severe disease than others. In a work published in 1946, Smith and Beard noted a 10-fold higher rate of disseminated coccidioidomycosis among African-American men than among white men (118). After exposure of individuals due to a dust storm in California in 1977, Flynn and coworkers similarly demonstrated a 10-fold increased risk of disseminated disease among African-American men compared to white men (119). During the early 1990's, when the southern San Joaquin Valley was experiencing a dramatic increase in the number of cases of symptomatic coccidioidomycosis, Rosenstein and colleagues calculated an odds ratio of 4.6 for the risk for disseminated disease among African-Americans by using multivariable analysis (79, 120). In a very recent analysis of hospitalized patients with coccidioidomycosis in Arizona and California from 2000 to 2009 (121), Seitz and colleagues found that the rate of hospitalization for disseminated coccidioidomycosis in Arizona was 12-fold higher among African-Americans than among whites, and 21-fold higher than among Hispanics. Similar differences were seen in California. These data suggest an underlying immune defect among some African-Americans that places them at risk for dissemination, but the nature of that defect has not been defined.

Gender and pregnancy. In the same studies on race, men were consistently found to have a higher incidence of symptomatic and severe coccidioidomycosis than women, regardless of exposure history (79, 118, 119). One exception to this observation is in women during pregnancy, where the risk of severe, symptomatic coccidioidomycosis is high and increases the later during pregnancy that infection occurs (122). While it has been presumed that suppression of cellular immunity associated with pregnancy is the major cause for this increased risk, Drutz and coworkers have suggested that hormonal changes that occur during gestation may increase the growth of the fungus and lead to more severe clinical illness (123, 124).

Azole antifungal therapy and outcomes. While most evidence indicates that antifungal therapy leads to markedly improved outcomes in patients with symptomatic coccidioidomycosis, a risk of relapse after therapy is stopped occurs in 15 to 30% of patients with progressive nonmeningeal coccidioidomycosis among those treated with itraconazole or fluconazole (125). The risk of relapse is even higher for those with meningeal disease (126). A recent retrospective study found that among 54 patients with primary pulmonary coccidioidomycosis who received azole antifungal therapy, subsequent relapse of illness occurred in 8, compared to no patients who were less ill and did not receive antifungal treatment (127). This has led some to postulate that azole antifungal therapy may lead to a lack of an appropriate immune response. Thompson and colleagues (128) offered indirect evidence of this. In a retrospective, case-control study, they found that treatment with an azole antifungal within 2 weeks of the diagnosis of coccid-

oidomycosis was associated with the lack of development of an anticoccidioidal IgG response. *In vitro* assessment found that fluconazole diminished the expression of RNA encoding the chitinase antigen. The question of whether fluconazole therapy might also blunt the cellular immune response in coccidioidomycosis remains unexplored.

Newer concepts of the immune response and host resistance to *Coccidioides*. As our understanding of the immune response has increased, the interplay of the innate and adaptive immune response has become better appreciated (129). Critical links include production of proinflammatory cytokines such as IL-12 and IFN- γ . These T cell helper type 1 (Th1) responses have been found to be associated with a protective immune response in coccidioidal infection in animal models (130) and appear to be operative in humans (131). It had been felt that Th2 responses played no role, but data from a murine model suggest that B cell activity is operative in inducing host protection (132). In addition, chemoattractants for eosinophils, such as IL-5 and eotaxin (CCL11), which also represent the Th2 response (133), may work to amplify initial host responses. These could be pertinent given the observation that both peripheral blood and tissue eosinophilia occurs in human coccidioidomycosis (134).

IL-17 has been shown to be important in many bacterial and viral lung infections (135). Recently, Hung and colleagues investigated the immune response in mice vaccinated with a genetically engineered live attenuated strain of *Coccidioides posadasii* (136). The vaccinated mice produced a complex immune response with Th1, Th2, and Th17 components, with the Th17 cell response being the most important. Mice whose lymphocytes lacked the IL-17 receptor were highly susceptible to lethal challenge, even when vaccinated with an attenuated strain of *Coccidioides*. On the other hand, there was no difference in mice that were deficient in IFN- γ or IL-4. In addition, Wüthrich and colleagues (137) also demonstrated the importance of an initial Th17 reaction in inducing protection in a murine model of coccidioidal infection.

While specific immune responses in humans are difficult to evaluate beyond the *ex vivo* expression of cytokines (138), exploration of tissue responses (139), and *in vivo* skin test reactivity (140), a new alternative has recently become available. Mice that can be reconstituted with human immune systems have become available and can be employed to demonstrate the effector phase of the immune response (141), including autoimmunity (142). Using this model to study *in vivo* coccidioidal infection will provide the opportunity to examine the entire panoply of human immune responses in a convenient experimental animal model and to further determine the effectiveness of different fungal proteins in stimulating protective immune responses.

DIAGNOSTIC TESTING

Serology

A definitive diagnosis of coccidioidomycosis can be made by identification of the fungus in culture or by histological examination of tissue or body fluid specimens. The mature spherule containing endospores (Fig. 1) is pathognomonic and easily recognized by pathologists familiar with this infection. Specimens with rare intact spherules but numerous free endospores can be a diagnostic challenge: because endospores vary in size during their maturation, they can be mistaken for *Histoplasma*, *Cryptococcus*, or *Blasotomycetes*. This is especially true when the endospores about each

other, giving the false appearance of budding yeast (143). In lung tissue, especially when cavities are present, the hyphal form may occur and cannot be distinguished in histologic sections from the septate hyphae of other molds. Diagnosis using these methods can be challenging, because appropriate specimens for culture or pathology are not always easy to obtain. Many patients with coccidioidal pneumonia have a nonproductive cough, and obtaining tissue specimens requires invasive procedures. Therefore, serologic testing is the most common means of making the diagnosis. Several tests for anticoccidioidal antibodies are in current use, and they vary in sensitivity and specificity.

The classical tests included tube precipitin (TP), which used an antigen that reacts with IgM, and complement fixation (CF) using an antigen that reacts with IgG. TP antibodies were noted to develop earlier in the course of illness than CF antibodies (144). Immunodiffusion (ID) tests that used the same two antigen preparations were subsequently developed. These are referred to as the IDTP and IDCF assays. The TP antigen is now known to consist of a fungal cell wall polysaccharide, while the CF antigen consists of fungal chitinase. The newest serologic tests are commercial EIA kits, which use proprietary coccidioidal antigens. These assays are more sensitive than the traditional CF, TP, IDCF, and IDTP assays (145–147) and may detect antibodies earlier in infection (145–148).

With greater sensitivity has come a concern for possible reduced specificity, and experts in the field have long held the belief that the EIA IgM test in particular carries a significant false-positive rate. Two recent publications and an unpublished study have specifically addressed this question.

Blair and coworkers examined 706 positive EIAs for 405 patients (149). Chart review was conducted, and patients were defined as having coccidioidomycosis based on symptoms, serology, and radiographic findings. There were 28 patients with a positive EIA IgM test and negative EIA IgG. Twenty-four of the patients had either a concurrent positive TP or CF test or a subsequent positive EIA IgG test. The four remaining patients had a positive culture or biopsy specimen. The authors concluded that the false-positive EIA IgM rate was 0%.

In contrast, Kuberski et al. identified 17 patients with positive EIA IgM and negative EIA IgG tests and determined that only 3 of them “may have had coccidioidomycosis,” giving a false-positive rate of 82% (150). The inclusion/exclusion criteria were not specified, nor was it stated whether there was any additional serologic testing. It was the authors’ opinion that “in general, serology for *Coccidioides* was not indicated in the group of patients with false-positive results, reflecting the diverse levels of expertise of physicians ordering an EIA serology test for coccidioidomycosis in a community hospital.”

Petein and coworkers at the Arizona Department of Health Services analyzed all coccidioidomycosis serologic test results from a commercial laboratory in 2008 to 2009 (151). They identified 94 of 1,445 test sets in which the EIA IgM and/or IgG test was positive and the complement fixation and/or immunodiffusion test was negative. Chart review revealed that 97% of these cases were associated with “coccidioidomycosis symptoms.” Forty of the 94 cases had a positive IgM test only, but the prevalence of symptoms for this group specifically is not given.

Taken together, these studies confirm that the positive predictive value of the EIA IgM test depends on the pretest probability of coccidioidomycosis.

Fungal Antigen Detection

Serologic tests may not be positive during very early infection and have reduced sensitivity for use on immunosuppressed persons (152). Testing for coccidioidal antigens is therefore an attractive potential method of diagnosis.

The sera of patients with early coccidioidomycosis, as demonstrated by positive serum antibody or positive respiratory culture, contain an antigen reactive with antibodies to spherulin, a complex antigen preparation which is derived from the fungus in its endospore-producing phase. Antigen levels were seen to be highest early in the course of infection (147, 153, 154).

Another antigen test was developed after the observation that some patients with severe coccidioidomycosis have cross-reactive positive tests in an assay for *Histoplasma* antigen (155). The *Histoplasma* assay uses an antibody raised in rabbits against *Histoplasma* yeast cells to detect antigen in the serum or urine of patients. The reference standard is galactomannan purified from *Histoplasma capsulatum*. A specific assay for *Coccidioides* antigen was developed using the same methods (156). It is important that patients with positive results in this assay had severe coccidioidomycosis. The majority were immunosuppressed, and the performance of this assay for use on nonimmunosuppressed patients with primary pulmonary coccidioidomycosis has not been assessed.

Nucleic Acid Detection

PCR has been used to detect DNA of *Coccidioides* in patient serum (157) and respiratory specimens (158). Based on a small number of positive specimens, DNA detection in serum appeared to precede the development of antibody and then disappear when antibody developed. Real-time PCR testing of respiratory specimens yielded 100% sensitivity and 98.4% specificity compared with culture. Sensitivity and specificity for use on fresh tissue were 92.9% and 98.1%, respectively, while with paraffin-embedded tissue, the values were 73.4% and 100%, respectively (158). One institution has implemented an experimental PCR test for routine clinical use. Over a 12-month period, 5/153 respiratory specimens were noted to be PCR positive, of which 3 were also culture positive. Two specimens were PCR positive and culture negative, one of which was from a patient with a culture-positive specimen on the previous day. One specimen was PCR negative and culture positive (159). More validation is needed before PCR becomes a standard clinical diagnostic test for coccidioidomycosis.

APPROACHES TO MANAGEMENT

Guidelines for the management of coccidioidomycosis have been published (160). Each entity is described briefly here, followed by a summary of any recent developments in management.

Uncomplicated Pneumonia

Once a diagnosis of coccidioidal infection is established in a low-risk patient whose pulmonary involvement is not extensive, and in whom there are no evident extrapulmonary lesions, a rational management strategy can be formulated. Generally speaking, uncomplicated infection can be managed without antifungal treatment; however, periodic follow-up visits are recommended. The management of uncomplicated primary pulmonary involvement has been reviewed extensively elsewhere (160).

Complicated Pulmonary Coccidioidomycosis

Nodules and cavities. Approximately 2 to 5% of coccidioidal lung infiltrates evolve into a nodule. Nodules are noncalcified, and the chief problem they present is distinguishing them from malignancy, especially when the clinical and radiographic history is not known. As many as 30% of lung nodules biopsied in the area of endemicity are due to coccidioidomycosis (161). Histologic examination is more sensitive than culture for detection of coccidioidal lung nodules (162, 163). Patients with asymptomatic lung nodules do not benefit from antifungal therapy (160). Pulmonary cavities as a complication of an infiltrate or nodule develop in a small percentage of patients. Cavitory disease appears to be more common in diabetic patients, especially those with poor glucose control (164). Cavities may be asymptomatic or symptomatic and may close spontaneously over time, with or without antifungal therapy (160). Indications for surgical treatment include increasing size, proximity to the pleura raising concern for rupture, and persistent symptoms such as hemoptysis, pain, or cough.

The increasing availability of video-assisted thoracoscopic surgery (VATS) has altered surgical practice and outcomes for pulmonary coccidioidomycosis. Jaroszewski and colleagues recently reviewed surgical cases at a single center in the area of endemicity from 1998 to 2008 (165). Of 1,496 patients diagnosed with coccidioidomycosis during this period, 86 (6%) underwent surgery. Although the most common indication was for diagnostic purposes in patients with nodules, 18 patients (21%) required surgery for cavitory lesions. Fourteen of these patients had symptoms, and 10 had cavities that were increasing in size despite therapy. Overall, VATS was employed in 34% of patients, with increasing use over time (22% prior to 2004 and 45% after 2005). Four of 29 (14%) patients with VATS developed complications, compared to 14/57 (25%) patients with open thoracotomy. Length of hospital stay was also significantly shorter following VATS. To improve outcomes, patients should be evaluated by a surgeon with experience in treating coccidioidomycosis, with careful attention to whether lesions cross the lung fissures.

Pleural effusion. Pleural effusion may be associated with acute pulmonary infection or may be a consequence of rupture of a peripheral cavity into the pleural space. A recent review of 22 inpatient cases in an area of endemicity indicated that the majority were associated with pulmonary rather than disseminated coccidioidomycosis (166).

Progressive pneumonia. Chronic or progressive lung infection occurs in a small percentage of patients. Relapsing infection may be more common in diabetics (164). Oral azole antifungal therapy for at least 1 year is the recommended treatment (160).

Disseminated coccidioidomycosis. Disseminated coccidioidomycosis is the term used to indicate disease outside the chest. Clinical manifestations vary from minor skin abscesses to life-threatening and treatment-refractory meningitis. The most common sites of dissemination are the skin, joints, bones, and meninges, but other sites are uncommonly reported, such as the larynx, abdomen, adnexa, and pericardium. In contrast to uncomplicated pneumonia, disseminated infection always requires antifungal therapy, for durations ranging from several months to lifelong. Long-term therapy has most commonly been performed with fluconazole or itraconazole. There is limited experience with the newer azoles in the management of disseminated disease, which is reviewed in further detail later.

Meningitis. Comprehensive reviews of the manifestations and treatment of coccidioid meningitis have been published recently (167, 168). Intravenous amphotericin B did not control this disease, so until the introduction of azole antifungal drugs, intrathecal amphotericin B was the only available treatment. Currently, azoles are the first-line therapy, generally starting with fluconazole at doses of 400 to 800 mg daily. Two articles describe the recent management of consecutive patients with coccidioid meningitis at tertiary medical centers, one with a comparison to a cohort of patients treated in the 1960s and 1970s (169, 170). The overwhelming majority of patients in both series were treated with fluconazole, with the most common dose being 800 mg daily. Eleven of 33 patients in one series received concurrent intravenous amphotericin B, compared with only 3/71 patients in the other series. Cerebrospinal fluid (CSF) shunting procedures were required in one-third to one-half of patients. Mortality was as high as 40%, without much change from the earlier to later cohorts (170).

Fungemia. *Coccidioides* fungemia is rare and is highly associated with immunosuppression. Several case series containing many patients who did not receive any antifungal therapy (due to occurrence before the development of amphotericin B or to rapid death before diagnosis was established) or had advanced HIV infection have been published. A recent review by Keckich and colleagues (171) identified 6 new cases from their institution between 1998 and 2009, as well as summarizing 107 previously reviewed cases. Among the new patients, none had HIV infection, but all had at least one comorbidity, such as diabetes mellitus, malignancy, or autoimmune disease. Two of the six died. Three of the four survivors received fluconazole only, and one received amphotericin B and fluconazole. Among the historical cases, only 39/107 patients received antifungal therapy. Of those who did receive therapy, there was no difference in mortality between those who received an azole alone and those who received other treatment.

Special Considerations for Immunocompromised Hosts

HIV infection. As described above, the outlook for patients with HIV and coccidioidomycosis has improved significantly in the era of highly active antiretroviral therapy (88, 172). For patients with preserved CD4 counts and mild illness, it has been proposed that treatment can follow the guidelines established for patients without HIV infection. The current U.S. Public Health Service guidelines for the treatment of opportunistic infections in HIV-infected adults recommend continuing antifungal therapy for 1 year in patients with focal coccidioid pneumonia who have responded promptly to therapy and have CD4 counts above 250 cells/ μ l. This recommendation is based on expert opinion (173).

Organ transplantation. Excellent data summaries and recommendations for management of coccidioidomycosis in transplant patients have been published (94, 174). Screening through serology, culture of organs, and chest radiography are recommended for donors residing in the region of endemicity. Universal screening is not recommended outside the area of endemicity.

Clinically active coccidioidomycosis at the time of transplantation predicts difficulty in controlling the infection afterwards, so the essential task is to determine whether a patient who is being considered for a transplant has active disease. Patients with active disease or a recent history (1 to 2 years) of disease are treated with antifungal therapy, with the dose and duration depending on the

severity and timing of the infection. However, reactivation of pre-transplant coccidioidomycosis has occurred despite antifungal therapy (175). Coccidioid infection can also be acquired *de novo* after transplantation. The spectrum of illness in transplant patients resembles that in immunocompetent hosts, but disseminated infection appears to be more common (174). At one center in the area of endemicity, transplant patients with asymptomatic seroconversion are carefully monitored but are not always treated with antifungal therapy (94).

Targeted antifungal prophylaxis at the time of transplantation has been advocated to prevent the emergence of clinically active coccidioidomycosis after solid organ transplantation in the region of endemicity (99). This approach is based on a study from 1999 to 2001 in which 4 of 76 patients undergoing liver transplantation in the region of endemicity received prophylactic fluconazole based on evidence of prior coccidioidomycosis. None subsequently developed active disease (176). Among another 44 patients with quiescent coccidioidomycosis at the time of solid organ transplantation who received antifungal prophylaxis, none developed later active infection (177). In another review from the same program (175), 100 patients with evidence of previous coccidioidomycosis underwent solid organ transplantation, and 94 received antifungal prophylaxis. Subsequently, five patients, all receiving antifungal prophylaxis, developed active coccidioidomycosis. None of the six who did not receive prophylaxis developed clinically active infection. Possible nonadherence to the antifungals was posited as a reason for those on therapy who developed disease.

Immunosuppressive medications. Corticosteroid use is a recognized risk factor for severe coccidioidomycosis (175), as is the administration of tumor necrosis factor inhibitors as described above. The incidence of infection may not be greater than that in the general population of the area of endemicity, but the risk of dissemination seems to be greater. The management of coccidioidomycosis in patients who require immunosuppressive medication for the ongoing treatment of other conditions poses a problem. A recent retrospective study from the area of endemicity examined 44 patients who developed coccidioidomycosis while taking disease-modifying antirheumatic drugs (methotrexate, azathioprine, or leflunomide) and/or biologic response modifiers (infliximab, etanercept, adalimumab, or abatacept) for rheumatologic disease. Twenty-nine patients had pulmonary coccidioidomycosis, nine had disseminated disease, and six had asymptomatic positive serologies. Most patients had their immunosuppressive medication discontinued at least temporarily, and almost all were treated with antifungal therapy for a median of 12 months. After a median of 30 months of follow-up, 33 patients had continued or resumed their immunosuppressive therapy, and half of them were no longer taking antifungal therapy. There were no cases of subsequent dissemination or development of severe coccidioidomycosis. These results suggest that continuing or resuming immunosuppressive therapy for underlying conditions such as rheumatologic disease may be feasible in some patients (178).

Advances in Antifungal Therapy for Coccidioidomycosis

Lipid preparations of amphotericin B. Amphotericin B remains an important option for treatment after more than 50 years of use; however, due to toxicity, it is reserved for the most severe cases or for cases where azole therapy is failing or not tolerated. Due to the lack of randomized clinical trials, the relative efficacy of ampho-

tericin B compared to fluconazole and other azoles is debatable. In the past decade or so, the initial selection of lipid formulations over conventional amphotericin B (CAB; deoxycholate) has evolved to become most common. There is no evidence that lipid formulations are more effective than CAB; however, the available formulations provide various improvements in infusion-related toxicities and in nephrotoxicity. In terms of infusion-related toxicity, the order of efficacy is amphotericin B colloidal dispersion > amphotericin B lipid complex > liposomal amphotericin B. All three lipid formulations offer improved renal tolerance compared to that with CAB, although relative differences among the agents are controversial.

With lipid formulations, nephrotoxicity occurs later into therapy and is less severe. Select patients can receive acetaminophen and diphenhydramine prior to each polyene dose to minimize infusion-related reactions, including fevers, chills, and headache. Adequate hydration is essential, and administration of 0.5 to 1 liter of normal 0.9% sodium chloride solution prior to each dose provides some renal protective effects for patients who can tolerate fluids. Serum creatinine should be monitored every 1 to 2 days early in therapy, and perhaps less often (twice weekly) once tolerance is established. Renal wasting of potassium and magnesium is common, and monitoring the serum concentrations of these electrolytes is important. Amphotericin B may occasionally cause severe anaphylactic reactions, heart arrhythmias, and chest pain/tightness.

Antifungal azoles. (i) Voriconazole. Voriconazole was approved in 2002, and reports of its use for salvage therapy in coccidioid meningitis appeared over the next 2 years. The oral formulation is well absorbed, and penetration into the cerebrospinal fluid is good. Efficacy was demonstrated in a few cases that failed therapy with high-dose fluconazole and amphotericin B (179, 180). In the latter case, the patient suffered renal failure from CAB and then received amphotericin B lipid complex at 5 mg/kg of body weight/day, and eventually liposomal amphotericin B at up to 10 mg/kg/day. After placement of an Ommaya reservoir, intraventricular amphotericin B at up to 1 mg/day was administered. Neurotoxicity developed and did not resolve with a reduced dose and frequency of intraventricular administration. After initiation of voriconazole at 400 mg twice daily, improvement was apparent; however, the patient required ventroperitoneal (VP) shunt placement and drainage of a thoracic intradural abscess (180). Subsequent reports support the use of voriconazole for salvage therapy of nonmeningeal coccidioidomycosis (181). From 2009 to 2011, there were two case series published that claimed a response in 6/7 and 14/21 patients treated with voriconazole (182, 183). Most of the patients had refractory disease or were intolerant of other treatments. Cases of chronic lung infection and disseminated nonmeningeal and meningeal infections were included. Based on observations and calls to the Valley Fever Center for Excellence, some physicians in Arizona have considerable experience with using voriconazole for coccidioidomycosis.

Voriconazole shares some of the problems seen with fluconazole and itraconazole, including dose-related nausea, anorexia, and, occasionally, vomiting. Uniquely, visual disturbances are commonly seen in a 2- to 4-h time window coinciding with the peak concentration (184–187). There are reports of hallucinations and other psychiatric events. Voriconazole may cause elevations in serum transaminases, an effect that is positively associated with plasma concentrations (188). As with other azoles, there have

been a few reports of serious hepatotoxicity. Skin rashes have been reported, with distribution over sun-exposed areas, consistent with phototoxic reactions (186). Chronic skin inflammation associated with this exposure appears to promote skin cancer, including squamous cell carcinoma and melanoma (189–191). Skin cancer surveillance is recommended when long-term voriconazole is used (192). In addition, patients who are undergoing long-term voriconazole treatment should use a physical sunscreen lotion and protective clothing to minimize exposed skin.

Voriconazole tablets and intravenous solution are formulated with sulfobutyl ether β -cyclodextrin as a solubilizer. Oral bioavailability is >95% and is not influenced by gastric pH. Administration with food is associated with a small (22%) reduction in bioavailability. For treatment of coccidioidomycosis, dosing has ranged from 200 mg every 12 h (q12h) to 4 mg/kg q12h. The drug undergoes extensive metabolism via CYP-3A4, CYP-2C9, and CYP-2C19. CYP-2C19 is a polymorphic genotype that is responsible for much of the wide variation in drug clearance and exposure (193). Voriconazole clearance averages 932 ml/min in ultra-rapid metabolizers, 522 ml/min in extensive metabolizers, and 147 ml/min in poor metabolizers (194). Both CYP-2C19 genotyping and therapeutic drug monitoring have been suggested as approaches to guide therapy and control pharmacokinetic variability (195–197). The voriconazole half-life averages 7 to 14 h, depending on the genotype.

Managing drug interactions with voriconazole can be difficult. Enzyme inducers can lead to subtherapeutic serum voriconazole concentrations. Voriconazole is a potent inhibitor of CYP-2C9 and CYP-2C19 enzymes. CYP-3A4 enzymes are also inhibited to a moderate degree. Comparatively, the inhibition of the 2C subtypes is greater than that with fluconazole, and inhibition of 3A4 enzymes is less than that with itraconazole. Nonetheless, some interactions are critically important, such as those with tacrolimus and sirolimus.

(ii) Posaconazole. The potential efficacy of posaconazole for coccidioidomycosis was reported from a murine model in 2002 (198). Treatment with posaconazole at doses ranging from 0.5 to 10 mg/kg/day for 20 days, beginning at 2 days postinfection, resulted in 100% survival, compared to 0% with placebo. Survival was also complete with itraconazole given at 90 mg/kg/day (divided into three doses). Lung, liver, and spleen fungal burdens were similar after treatment with itraconazole at 90 mg/kg/day and posaconazole at 0.5 mg/kg/day, but doubling the posaconazole dose to 1 mg/kg/day resulted in a >1-log decrease in fungal burden. Interestingly, increasing the dose of posaconazole to 10 mg/kg/day resulted in a paradoxical effect, with organ fungal burdens being >3 log greater than those seen with the dose of 1 mg/kg/day. Pharmacokinetics were not reported in this study. In 2005, a case series of six patients in whom posaconazole was used for salvage therapy was reported, and a response was seen in five (199). Posaconazole dosing was omitted in most cases, but relatively high doses of 400 mg every 8 h to 400 mg every 6 h were mentioned for one patient. Another patient was given 400 mg twice daily via a feeding tube. In another series, posaconazole treatment for 1 to 12 months was considered successful for 11/15 patients (200). Seven of the patients in that study had disease limited to the lungs, and the other eight had disseminated nonmeningeal infections. Posaconazole dosing was described as 800 mg/day in divided doses; however, the report was not clear on whether this meant 400 mg every 12 h or 200 mg every 6 h. A

similar open-label study was reported for patients without failed prior therapy (201). Patients with chronic pulmonary or nonmeningeal disseminated coccidioidomycosis were treated with 400 mg of posaconazole once daily or 800 mg once daily (two patients) for a median of 173 days. Eighty-five percent of the patients had satisfactory responses to treatment. A more recent publication supported the use of either posaconazole or voriconazole for salvage therapy, and responses were seen in cases where posaconazole was used after voriconazole failure and vice versa (183). Overall, 75% of 16 patients responded to posaconazole given at 400 mg twice daily or 600 mg twice daily ($n = 1$) for a median of 17 months.

Posaconazole is available only as an oral suspension. Absorption appears to be adequate in most cases, and serum concentrations were fairly consistent during treatment of coccidioidomycosis with doses of 400 to 800 mg once daily (201). However, there have been cases reported where adequate serum concentrations were difficult to achieve in patients with prolonged neutropenia or with graft-versus-host disease. As with itraconazole capsules, absorption is improved when the dose is given with fatty food. Absorption is also improved when the dose is given with an acidic carbonated beverage but is reduced in the presence of gastric acid suppression.

Posaconazole is metabolized by glucuronidation by the UDP glucuronosyltransferase UGT1A4. Drugs that induce this enzyme subtype include phenytoin, efavirenz, and rifabutin, and concomitant administration of these drugs may lead to lower posaconazole concentrations. Posaconazole is a substrate for p-glycoprotein, and agents that induce or inhibit this transport protein may affect the absorption of the drug, although the clinical relevance of such interactions has not been explored. With regard to other drugs, posaconazole is a potent inhibitor of CYP-3A4.

Future prospects. Nikkomycin Z is a novel orphan antifungal drug that inhibits chitin synthase and offers a different mechanism of action from those of currently available antifungal drugs. Based on studies in mice, nikkomycin Z exhibits fungicidal activity and greater efficacy than that of fluconazole (202). In phase I studies, nikkomycin Z achieved clinically relevant concentrations after oral administration, and thus far it has shown no safety concerns (203, 204). However, phase II or III clinical trials have not yet been reported.

Combination therapy with an antifungal azole and amphotericin B is sometimes used in clinical practice; however, the merits of this approach are unclear. There is a theoretical interaction where prior azole exposure decreases the ergosterol content of the cell membrane. Since amphotericin B binds to and disrupts ergosterol, depletion of ergosterol could impair the action of amphotericin B. The practical relevance of this theory has never been determined or demonstrated. There are no clinical studies comparing combination therapy to single drug therapy, and since amphotericin B adds considerable potential for toxicity, the benefits of combination therapy would need to be substantial to justify combination therapy. However, if nikkomycin Z becomes available in the future, combination therapy with azoles should be explored given the synergy or additive effects demonstrated in animal models (205, 206).

Current Status of Clinical Vaccines To Prevent Coccidioidomycosis

Because so many persons develop durable, lifelong immunity to second infections following natural coccidioidal infection, it has

long been a research goal to develop a preventative vaccine for clinical use (207). Several thorough reviews on progress toward a candidate vaccine have been published previously (4, 5, 208). Since then, additional studies, particularly in mice vaccinated with a variety of recombinant antigens and administered a Th1-biased adjuvant, have resulted in various degrees of protection and an increasing understanding of how protection is induced (14, 120, 132, 136, 209–218). This work continues to support the possibility that a vaccine candidate could be identified as suitable for clinical trials.

On the other hand, for clinical trials to actually be initiated, several challenges will need to be overcome (219). One will be the technical obstacles to making a recombinant vaccine antigen suitable for use in human experimentation. There are numerous problems in increasing the production scale and engineering quality control manufacturing processes that would meet acceptable standards for clinical use. Another challenge will be to develop a formulation that includes an adjuvant that, like the recombinant antigen or antigens, will meet safety standards for use in a preventative vaccine. These hurdles are no different from those for any vaccine development program for a vaccine that would be based on a recombinant antigen and adjuvant formulation but are more significant for a coccidioidal vaccine, whose anticipated market is very small in comparison to that for vaccines addressing worldwide problems such as viral hepatitis, tuberculosis, or AIDS. Even though the impact of coccidioidomycosis leads to health and economic tolls that support a persuasive public health argument to develop a preventative coccidioidal vaccine (73), the limited market size severely constrains a business model for such a vaccine's development.

This is not to say that the difficulties ahead for moving vaccine candidates to clinical trials should slow work on a coccidioidal vaccine. The research community involved with vaccine discovery has moved the field to a stage where all of the current molecular and genetic technologies in play today are in use in the study of coccidioidomycosis. As a result, advances that might occur in nearly any area of vaccinology are accessible to be applied quickly to a new coccidioidal vaccine candidate. Clearly, if the cost of formulating a vaccine is reduced, the likelihood of clinical trials of a coccidioidal vaccine candidate will increase. Furthermore, to the extent that vaccine development is increasingly aligned with public health needs, funds for vaccines that benefit smaller groups may increase. A vaccine to prevent coccidioidomycosis remains a very worthwhile goal.

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Chinh Nguyen received his M.D. at Georgetown University School of Medicine in 2002, completed his residency in internal medicine at Virginia Commonwealth University Health Systems in 2005, and completed a fellowship in infectious diseases at the University of Maryland in 2007. Afterwards, he did research on endothelial cell biology and the pathogenesis of anthrax infections at the Mucosal Biology Research Center at the University of Maryland. He accepted a position as Staff Physician at the Southern Arizona Veterans Affairs Health Care Systems in the fall of 2011. As a newcomer to the southwestern United States, he found that this paper presented an excellent opportunity to review the latest updates on the biology, genomics, epidemiology, and clinical management of coccidioidomycosis.

Bridget Marie Barker received her Ph.D. from the University of Arizona in 2009, working on the population genomics of *Coccidioides*. She completed her postdoctoral training in the lab of Robert Cramer, working with *Aspergillus fumigatus* at Montana State University. She has been a Research Assistant Professor at Montana State since 2012, returning to work on *Coccidioides*. She has been working on the population genetics and ecological niche of *Coccidioides* for about 10 years.

Susan Hoover received her medical and postgraduate education at the University of Colorado, Case Western Reserve University, and the National Institute of Allergy and Infectious Diseases. She served as Associate Professor of Medicine in the Section of Infectious Diseases and Valley Fever Center for Excellence at the University of Arizona College of Medicine, Tucson, AZ, from 2006 to 2013. Her clinical and research interests in coccidioidomycosis include its epidemiology and natural history, management of the disease in immunosuppressed patients, and clinical trials of a novel antifungal agent. She is currently Associate Professor of Medicine at the University of South Dakota Sanford School of Medicine and a Scientist at Sanford Research in Sioux Falls, SD.

David E. Nix received his B.S. (Pharmacy) in 1982 and his Pharm.D. in 1984, from The University of Georgia. From 1984 to 1986, he completed a postdoctoral fellowship in infectious disease pharmacotherapy at The State University of New York at Buffalo. From 1986 to 1996, he held several positions at the Clinical Pharmacokinetics Laboratory of Millard Fillmore Hospital in Buffalo, ending as Associate Director. Dr. Nix joined The University of Arizona Faculty in 1996 and is now a Professor of Pharmacy Practice and Science and of Medicine. Current responsibilities include teaching (infectious diseases), a post as an Infectious Disease Clinical Pharmacist (University Medical Center, Tucson, AZ), and research. His current research involves a collaboration to develop an orphan drug (nikkomycin Z) for treatment of coccidioidomycosis. Dr. Nix has authored or contributed to over 90 research papers. Dr. Nix is board certified in pharmacotherapy (BCPS) and applied pharmacology (American Board of Clinical Pharmacology).

Neil M. Ampel is a Professor of Medicine at the University of Arizona and a Staff Physician at the Southern Arizona Veterans Affairs Health Care System. He has a long interest in the clinical management of coccidioidomycosis as well as in the relationship between the cellular immune response and outcomes in human coccidioidomycosis.

Jeffrey A. Frelinger received his B.A. in biology from UCSD in 1969 and his Ph.D. from Caltech in 1973, under the direction of Ray Owen. Following a Jane Coffin Childs Postdoctoral Fellowship at the University of Michigan, he accepted an Assistant Professorship at the University of Southern California. In 1980, Dr. Frelinger spent a sabbatical at the MRC Radiobiology Unit at Harwell in the United Kingdom, with Mary Lyon. In 1983, he moved to the University of North Carolina. While there, he was appointed a Sarah Graham Kenan Professor and spent sabbatical leaves at the Institute of Molecular Medicine in Oxford University with Sir Andrew McMichael and at the NIH with Jon Yewdell and Jack Bennick. He served as Chair of the Department of Microbiology and Immunology for 17 years, until 2007. In 2010, Dr. Frelinger moved to the Department of Immunobiology at the University of Arizona, where he now collaborates on studies of the immune response to coccidioid infection.

Marc J. Orbach received his B.S. in biological sciences at the University of Michigan and his Ph.D. at Stanford University, where he studied the molecular genetics of fungi. He did postdoctoral research on fungal plant pathogenesis at the Dupont Experimental Station prior to joining the University of Arizona faculty in 1991. He is currently a Professor of Plant Pathology and Microbiology at the University of Arizona. He started working on *Coccidioides* in 1994 and has developed a program to study the molecular genetics and genomics of *Coccidioides* pathogenesis. His interests focus on the analysis of parallels in pathogenesis between fungal pathogens of plants and animals. His research also examines the ecological aspects of the distribution of the valley fever fungus in soil.

John N. Galgiani received his B.S. from Stanford University and an M.D. from Northwestern Medical School. He was then a fellow in infectious diseases at Santa Clara Valley Medical Center/Stanford University. Since 1978, he has been a faculty member of the University of Arizona College of Medicine, where he is currently a tenured Professor. During this time, he has been clinically active in the field of infectious diseases, and his research has focused on several aspects of coccidioidomycosis, including its epidemiology, clinical diagnostics, drug therapy, and potential preventative vaccines. Dr. Galgiani founded the Valley Fever Center for Excellence, which was approved by the Arizona Board of Regents in 1996. This has helped to expand the interest and understanding of this disease throughout Arizona, as evidenced by this review.