MAJOR ARTICLE

Risk Factors for Severe Pulmonary and Disseminated Coccidioidomycosis: Kern County, California, 1995–1996

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Surveillance for coccidioidomycosis (CM) and a case-control study for risk factors among adults were conducted in Kern County, California. From January 1995 through December 1996, 905 cases of CM were identified, for an annual incidence of 86 cases per 100,000 population. A total of 380 adults were enrolled in the case-control study: 77 had severe pulmonary disease, 33 had disseminated disease, and 270 control patients had mild disease. Independent risk factors for severe pulmonary disease included diabetes, recent history of cigarette smoking, income of <$15,000 per year, and older age. Oral antifungal therapy before hospitalization was associated with a reduced risk of CM pneumonia. Risk factors for disseminated disease were black race, income of <$15,000 per year, and pregnancy. Early treatment of CM with oral antifungal agents may prevent severe pulmonary disease in groups considered to be at high risk, such as elderly individuals, persons with diabetes, and smokers. Persons at risk for severe CM may benefit from vaccination once an effective CM vaccine is available.

Coccidioidomycosis (CM), an infection caused by inhalation of arthroconidia of the fungus *Coccidioides immitis,* results in symptomatic illness in approximately one-third of infected persons. CM most commonly presents as a mild influenza-like illness, but it also has a wide clinical spectrum that includes pneumonia and disseminated disease, with the latter developing in ~1% of infected persons [1–3]. *C. immitis* is endemic in the soil in the southwestern United States and in parts of Central and South America [4, 5]. Kern County, located in the San Joaquin Valley of California, has been recognized as a site for hyperendemic CM since the 1940s [6]. From 1991 through 1992, there was a dramatic increase in the number of cases of CM reported from Kern County, with 959 cases reported in 1991 and 3027 cases reported in 1992 [7, 8]. From a review of medical records in Kern County, it was estimated that CM accounted for ~$66 million in direct costs associated with hospitalization and outpatient care during 1991–1993, and that most of the medical care costs were for those individuals with advanced and disseminated disease [9]. Although this outbreak now appears to be waning, CM continues to be a source of morbidity and mortality as well as public health expenditure in Kern County and other parts of the southwestern United States.

Descriptive studies and clinical reports have identified risk factors for infection with *C. immitis,* including male sex, soil exposure, and migration into areas of

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endemicity [10, 11]. Risk factors for disseminated CM include black or Asian race, male sex, pregnancy, and HIV infection or AIDS and other immune deficiencies [11, 12]. In an outbreak setting, black and Asian race, male sex, and age >20 years have been found to be risk factors for "severe CM," which is defined as CM that results in hospitalization [13]. However, no systematic studies have assessed the incidence of the various clinical forms of CM among symptomatic persons and the risk factors for severe pulmonary and disseminated disease, which are responsible for much of the public health burden that results from CM. In 1995 and 1996, we conducted population-based surveillance for CM in Kern County, California, and performed a case-control study to determine potentially modifiable risk factors for severe pulmonary and disseminated disease.

METHODS

In collaboration with the California Department of Health Services and the Kern County Health Department, we conducted population-based surveillance for CM in Kern County (population, 624,000) from 1 January 1995 through 31 December 1996. An "incident case" was defined as laboratory findings indicative of active CM and clinically compatible illness diagnosed during the period from 1 January 1995 through 31 December 1996 in a resident of Kern County. Patients with evidence of previous CM were excluded. Laboratory criteria for the diagnosis of CM were similar to those adopted by the Council of State and Territorial Epidemiologists (Atlanta) for the CM surveillance case definition [14]. These criteria included the presence of cultural, histopathologic, or molecular evidence of *C. immitis*, or a serological test that is positive for coccidioidal antibodies in serum or CSF, as determined by (1) detection of coccidioidal IgM by immunodiffusion, EIA, latex agglutination, or tube precipitin, or (2) detection of a rising titer of coccidioidal IgG by immunodiffusion, EIA, or complement fixation. Not all cases were tested with use of all methods.

Cases were reported by the Kern County Health Department laboratory, which was the only laboratory in the county that performed diagnostic testing for CM in Kern County residents. A case-report form was completed for each case; it included information on age, sex, race, outcome, and the clinical syndrome of the patient, in addition to laboratory evidence of CM.

We conducted a case-control study to identify risk factors for severe pulmonary and disseminated disease in adults ≥18 years of age. For the purposes of the case-control study, "case patients with severe pulmonary disease" were defined as patients with CM who had radiologically confirmed pneumonia that resulted in hospitalization, whereas "case patients with disseminated disease" were defined as patients with extrapulmonary or miliary CM. "Control patients" were defined as patients with CM who had a mild flulike illness. Only case patients who received a laboratory diagnosis of CM during the period from 1 January 1995 through 30 September 1996 were eligible for inclusion in the case-control study.

We interviewed each case patient and control patient by telephone, by use of a standard questionnaire. Patients were asked to provide information about demographic characteristics, outdoor activities, dust exposures, past medical history, tobacco and alcohol use, duration of full-time residence in Kern County and in other states in which CM is endemic, occupation, and socioeconomic indicators. When a reference period was needed, we asked about the 2 months preceding laboratory confirmation of illness. To examine the usefulness of prophylactic medications, patients were asked if they had received therapy for CM while they were at home; if patients provided a positive response, they were asked to specify which medication they had received. Patients who had been hospitalized were told to include only medications that were prescribed before they were hospitalized. To evaluate the personal and public health burden of illness, patients were asked about the duration of their illness, the number of days missed from work or school because of illness, and the number of visits made to a doctor's office. The date of onset of symptoms, outcome, and laboratory results were confirmed by review of case-report forms and review of hospital records. History of skin rash and painful skin bumps was elicited from patients and was confirmed by hospital records, if available; insufficient data were available to more specifically define erythema multiforme or erythema nodosum. Immediate family members were interviewed as surrogates for deceased case patients, after consent was obtained. Interviews were conducted in either English or Spanish, as appropriate.

Patients who were excluded included (1) those who reported a history of a previous positive result of a CM skin test and (2) those who could not be interviewed either because they spoke only a language other than Spanish or English, or because they did not have a telephone (however, 94% of households in Kern County have telephones [source, Kern County Council of Governments]).

Epi Info, version 6.0 (Centers for Disease Control and Prevention [CDC]/World Health Organization), and SAS, release 6.12 (SAS Institute), were used for data entry and analysis. Univariate and multivariable analyses were done; the latter were performed with stepwise logistic regression to compare case patients who had severe pulmonary CM with control patients who had mild disease, and to compare case patients with disseminated CM with the same control patients. The multivariable model included variables that were significant on univariate analysis, in addition to known confounders, such as age and sex.

RESULTS

Surveillance. From 1 January 1995 through 31 December 1996, we identified 905 persons who met the surveillance case definition of CM. More cases were found in male patients (56%) than in female patients. The median patient age was 34 years (range, 1–92 years). Of the 826 patients for whom information was available, the majority were white non-Hispanic (45%) or Hispanic (39%). A smaller proportion were black (7%), Filipino (4%), or Asian (4%).

In 1995–1996 in Kern County, the average annual cumulative incidence of CM was 86 cases per 100,000 population. The incidence rate was higher in 1995 than in 1996 (100 cases per 100,000 population vs. 72 cases per 100,000 population; $P < .001$), and it was higher among males than among females (81 cases per 100,000 population vs. 65 cases per 100,000 population; $P < .001$). The incidence varied according to age group, with the highest incidence occurring among those persons who were 18–64 years of age (94 cases per 100,000 population) and the lowest incidence occurring among children <5 years of age (9 cases per 100,000 population). Incidence also varied according to race and ethnicity, with the highest rates occurring among those who were Filipino (196 cases per 100,000 population) and Asian (151 cases per 100,000 population). The rate of incidence was also elevated among Hispanics (85 cases per 100,000 population) and non-Hispanic blacks (87 cases per 100,000 population), compared with that among non-Hispanic whites (50 cases per 100,000 population).

The majority of cases of CM (85%) were classified as mild; 8% of cases were classified as severe pulmonary cases that required patient hospitalization, and 7% were classified as disseminated. Overall, 187 patients (20%) required hospitalization. The median duration of stay was 8 days (range, 0–122 days) for 154 hospitalized patients for whom admission and discharge data were available. Of the 63 patients with disseminated CM, most had infection of the skin or soft tissue (46%), the meninges (32%), or the bone or joints (28%); few patients (3%) had miliary disease. Fourteen patients died, for a case-fatality ratio of 2% and a cause-specific mortality rate of 1.3 deaths per 100,000 population.

Case-control study. A total of 682 patients with CM were identified by surveillance done from 1 January 1995 through 30 September 1996; 387 patients (57%) had onset in 1995, and 295 (43%) had onset in 1996. We were unable to contact 155 patients and were unable to interview an additional 10 because they were not English or Spanish speakers. We were unable to locate and interview the relatives of 4 deceased patients. In addition, 33 patients refused to participate, and 11 were excluded for other reasons. Therefore, a total of 380 patients (56%) were enrolled in the study, 242 from 1995 and 138 from 1996.

Patients enrolled in the case-control study were similar to the nonenrolled patients in terms of age, ethnicity, education, and income. Enrolled patients were more likely than nonenrolled patients to be female (45% vs. 36%; $P = .04$) and to be of white race rather than black race ($P = .02$). Because of an inability to locate relatives or because of relatives' refusal to be interviewed (for 3 of 14 deceased patients vs. 11 of 14 deceased patients, respectively), we were less likely to enroll deceased patients. However, the proportions of patients with mild, severe pulmonary, and disseminated disease were similar among enrolled and nonenrolled patients.

Of the 380 enrolled patients, 270 (71%) were classified as having mild CM, 77 (20%) were classified as having severe pulmonary CM, and 33 (9%) were classified as having disseminated CM. The clinical characteristics of patients differed according to the category of illness; in comparison with other patients, a higher proportion of patients with mild disease reported skin rash or skin lesions (table 1). Patients with disseminated CM were less likely to report fever or cough than were patients with mild CM. Of the 33 patients with disseminated CM, 14 (42%) had skin abscesses, 10 (30%) had meningitis, 4 (12%) had bone involvement, and 1 (3%) had miliary disease.

Patients with disseminated disease were more likely to have cultures that tested positive for CM than were patients with mild disease (table 1); culture was the only confirmatory test

Table 1. Clinical characteristics of and laboratory test results for patients with symptomatic coccidioidomycosis (CM) who were included in case-control study, Kern County, California, 1995–1996.

	No. (%) of patients with characteristic		
Finding	Mild CM[a] ($n = 270$)	Severe pulmonary CM ($n = 77$)	Disseminated CM ($n = 33$)
Clinical characteristic			
Fever	204 (77)	54 (72)	17 (57)[b]
Cough	190 (70)	63 (85)[b]	14 (45)[b]
Painful skin lesions	98 (38)	9 (12)[b]	7 (22)[b]
Skin rash	91 (34)	12 (16)[b]	5 (16)[b]
Laboratory positivity			
Complement fixation	255 (94)	70 (91)	31 (94)
EIA for IgM	194 (72)	50 (65)	22 (67)
Immunodiffusion for IgM	62 (23)	30 (39)[b]	7 (21)
Culture	3 (11)	5 (6)[b]	13 (39)[b]

NOTE. The denominator used to calculate percentages varies because information was missing for some patients.

[a] Control patients.

[b] Compared with mild disease, $P \leq .05$.

Table 2. Outcome or selected characteristics of patients with symptomatic coccidioidomycosis (CM), as evaluated in a case-control study in Kern County, California, 1995–1996.

Characteristic or outcome	No. (%) of patients with characteristic[a]		
	Mild CM[b] (n = 270)	Severe pulmonary CM (n = 77)	Disseminated CM (n = 33)
Age, median y	36	42[c]	38
Male sex	139 (52)	46 (60)	22 (67)[c]
Race			
Black	16 (6)	7 (9)	7 (22)[c]
Asian	19 (7)	5 (7)	1 (3)
Hispanic ethnicity	102 (38)	28 (36)	13 (39)
Pregnant, % of women	3 (2)	2 (6)	3 (27)[c]
Immunosuppressed	2 (1)	3 (4)	1 (3)
Agricultural worker	23 (9)	12 (16)[c]	2 (6)
Duration of residence in Kern County, median y	11	12	19
Duration of illness, median d	60	102[c]	109[c]
Time off work or school, median d	7	40	30
Doctor visits caused by this illness, no.			
≤5	123 (47)	22 (33)[c]	8 (6)[c]
6–14	114 (44)	24 (36)[c]	11 (37)[c]
≥15	23 (9)	20 (30)[c]	11 (37)[c]
Died	0	2 (3)	2 (6)[c]

NOTE. The denominator used to calculate percentages varies because information was missing for some patients.

[a] Data are no. (%) of patients, unless otherwise indicated.
[b] Control patients.
[c] Compared with mild disease, $P \leq .05$.

for 1 patient with disseminated disease and for 4 patients with severe pulmonary disease. No patients were given a diagnosis solely on the basis of histopathologic or molecular findings.

Table 2 summarizes the results of univariate analyses of case patients with severe pulmonary and disseminated CM, compared with results for control patients with mild CM. Patients with severe pulmonary CM were more likely to be older than patients with mild CM. Patients with disseminated CM were more likely to be black than were patients with mild CM. Only a small proportion of patients were Asian, and very few were immunosuppressed or had a history of HIV infection or AIDS. Female patients with disseminated CM were more likely to be pregnant than were female patients with mild CM. Of the 8 pregnant women, 3 were in the first trimester, 3 were in the second, and 2 were in the third. Patients with severe pulmonary or disseminated CM were significantly more likely to report a longer duration of illness than were patients with mild CM; these patients also reported more days taken off work or school, although this difference was not statistically significant. Of the 33 patients with disseminated CM, 21 (64%) were hospitalized. For patients with severe pulmonary CM, the median hospital stay was 7 days (range, 1–81 days). Overall, very few patients died (4 patients [1%]); patients with disseminated CM were more likely to die than were patients with mild CM.

In a multivariable model, compared with patients who had mild CM and excluding patients who had disseminated CM, patients who had severe pulmonary CM were more likely to be older, to have diabetes, and to be smokers (table 3). Although patients with severe pulmonary CM were more likely to be of low socioeconomic status (income, <$15,000) and to be male, these associations did not reach statistical significance. Black race was not significantly associated with severe pulmonary CM. Use of oral antifungal therapy for CM before hospitalization was protective against severe pulmonary CM.

In a separate multivariable model, compared with patients with mild CM and excluding patients with severe pulmonary CM, patients with disseminated CM were more likely to be pregnant, black, and of low socioeconomic status (table 4). Patients with disseminated CM were also more likely to have diabetes and to be smokers, although these differences were not statistically significant. Oral antifungal therapy was not significantly associated with a reduced risk of disseminated CM.

Ethnicity was not significantly associated with increased risk for either severe pulmonary or disseminated CM. Occupation, outdoor activities, and exposure to dust also were not associated with severe pulmonary or disseminated CM.

Table 3. Multivariable analysis of risk factors for severe pulmonary coccidioidomycosis (CM), compared with those for mild CM.

Risk factor	No. (%) of patients with characteristic		OR (95% CI)
	Severe pulmonary CM (n = 77)	Mild CM[a] (n = 270)	
Age	—	—	1.03/y[b] (1.0–1.1)
Diabetes	16 (21)	20 (7)	3.3 (1.3–8.1)
Smoked cigarettes in past 6 mo	20 (26)	30 (11)	2.4 (1.1–5.4)
Income of <$15,000	33 (46)	77 (31)	1.7 (0.9–3.3)
Oral antifungal therapy[c]	20 (27)	126 (52)	0.3 (0.1–0.5)
Male sex	47 (61)	139 (51)	1.7 (0.9–3.3)
Black race	7 (9)	16 (6)	1.4 (0.4–4.5

NOTE. The denominator used to calculate percentages varies because information was missing for some patients.

[a] Control patients.
[b] OR is 1.03 per year of age.
[c] Medication received for CM before hospitalization.

Table 4. Multivariable analysis of risk factors for disseminated coccidioidomycosis (CM), compared with those for mild CM.

Risk factor	No. (%) of patients with characteristic: Disseminated CM (n = 33)	Mild CM[a] (n = 270)	OR (95% CI)
Pregnant	3 (9)	3 (1)	7.3 (1.0–50)
Black race	7 (22)	16 (6)	4.6 (1.4–15)
Income of <$15,000	17 (57)	110 (35)	2.4 (1.1–5.7)
Diabetes	6 (17)	21 (8)	2.7 (0.8–8.9)
Smoked cigarettes in past 6 mo	6 (18)	30 (11)	2.3 (0.7–7.3)
Oral antifungal therapy[b]	13 (39)	126 (52)	0.7 (0.3–1.7)

NOTE. The denominator used to calculate percentages varies because information was missing for some patients.

[a] Control patients.

[b] Medication received for CM before hospitalization.

A separate analysis that compared disseminated CM with a combined category of mild and severe pulmonary CM resulted in findings similar to those that compared disseminated CM with mild CM (data not shown).

DISCUSSION

This study identified the population-based incidence of the various forms of symptomatic CM and identified risk factors for severe CM that are either potentially preventable or that may allow for the targeting of certain groups of high-risk individuals for preventive measures. As early as 1935, it was recognized that *C. immitis* caused both mild and fatal progressive forms of illness [11, 15, 16]. Of the patients with symptomatic CM that we detected by means of laboratory-based surveillance, most had a mild, influenza-like illness. Although mild illness can linger (median duration of reported illness, 60 days), most patients with mild CM do not take much time off from work, and their mortality rate is low. In contrast, severe pulmonary and disseminated CM, which accounted for 15% of cases of CM, led to hospitalization, more frequent visits to the doctor, and more time off from work. Immunologic studies have identified differences in response to *C. immitis* among persons with disseminated disease, which provides a possible biological explanation for disseminated CM as a separate clinical entity [17]; in contrast, pulmonary disease is likely to be part of the clinical spectrum of CM. We hypothesized that pulmonary CM and disseminated CM might have different predisposing risk factors, and we chose to examine risk factors for these 2 syndromes separately.

Previous epidemiologic studies have primarily examined the risk factors for severe CM in outbreak situations [18, 19]. Our study found that, in a nonoutbreak setting, older age and diabetes mellitus (both of which are associated with alterations in host immune response) were associated with severe pulmonary CM. In Arizona, the highest rates of CM were found among adults aged >64 years, and recent migration to Arizona was found to be the most important risk factor for CM in this age group [10, 20]. In Kern County, which has a stable population without frequent in-migration, older age was a risk factor, but duration of residence was not. Previous studies of the risk of diabetes mellitus have had conflicting results. One study showed no difference in skin test reactivity to coccidioidin among patients without diabetes and those with diabetes, which suggests a similar risk of infection, although fewer patients with diabetes reacted to spherulin [21]. Another study demonstrated an increased rate of CM-induced pulmonary cavitation among patients with diabetes, which suggests that patients with diabetes and older patients who are exposed to *C. immitis* are more likely to develop severe manifestations and could be targeted for preventive efforts [21, 22].

The increased risk of respiratory disease due to various fungal and bacterial pathogens associated with smoking has been attributed to its mechanical effects on the respiratory mucosa or its functional effects on the mucosal immune response. The association between smoking and an increased risk of severe pulmonary CM in this study, as well as the association between smoking and an increased risk of symptomatic CM in a study of older adults in Arizona [10], is likely to be due to similar mechanisms. Smoking cessation could decrease both the overall burden of CM and the public health costs associated with more severe CM.

Patients with both severe pulmonary and disseminated CM were more likely to be of low socioeconomic status. Difficulty gaining access to medical care may have played some role in the development of more severe CM among patients with lower income. Patients with an income of <$15,000 were more likely not to have insurance than were patients with higher incomes (33% vs. 11%; $P < .001$); however, patients with severe pulmonary or disseminated CM were likely to seek medical care more quickly after onset of their symptoms than were patients with mild CM (7.5 days vs. 10 days; $P = .0009$), which suggests that other unidentified factors contribute to the finding that low socioeconomic status was a risk factor. Although exposure to dust has been associated with an increased risk of CM [18], we were unable to identify environmental and occupational exposures that were significant risk factors for severe CM. The density of organisms inhaled is not likely to be the only factor that predisposes to CM; however, our finding may also be related to difficulty in quantitating exposure to dust in the arid climate of Kern County, California.

Although black race was a risk factor for disseminated CM, it was not a risk for severe pulmonary CM; Hispanic ethnicity

was not a risk factor for severe pulmonary or disseminated CM [12, 23, 24]. The numbers of individuals from other racial or ethnic groups were too limited for us to estimate risk among other groups in a case-control study; however, surveillance data found high rates of disease among Asians and Filipinos, consistent with previous studies [12]. We collected extensive information on underlying disease, environmental and occupational exposures, and migration patterns, which do not seem to account for the increased risk among black individuals. Racial differences in susceptibility to symptomatic CM may be due to differences in the major histocompatibility complex genes, which are important in the cell-mediated immune response and disease susceptibility [25]. Although they account for only a small number of patients ($n = 3$) with disseminated CM in our study, pregnant women were at higher risk for disseminated CM, as has been shown elsewhere [26, 27]. Studies have suggested that the apparent increase in the risk of CM during pregnancy may be due to the direct stimulation of growth of *C. immitis* resulting from the high serum levels of estradiol and progesterone in pregnant women, together with the depressed cell-mediated immunity of pregnancy [28].

Although it is impossible to completely rule out the influence of differential access to care, our study, similar to an earlier retrospective observational study [29], suggests that early use of antifungal therapy may prevent the development of severe pulmonary CM. Early therapy may be particularly important for severe pulmonary CM, because some of the risk factors, such as older age, are not modifiable. Because patients with disseminated CM may not present with flulike symptoms, it may be difficult to assess the role of oral antifungal therapy in the prevention of disseminated disease. Randomized, controlled clinical trials need to be conducted to better assess the benefit of early antifungal treatment [30], but patients with mild primary CM who are at higher risk for severe CM, such as those who are older, have diabetes mellitus, or smoke, may benefit from early oral antifungal therapy, initiated in response to primary mild CM.

With the aging of the US population and the increase in the number of immunosuppressed persons, severe pulmonary and disseminated CM threaten to become important public health problems in areas of endemicity. Because natural infection with *C. immitis* generally confers lifelong immunity, vaccination could be the ultimate prevention approach. A formalin-killed spherule vaccine, the only vaccine that has been tested in a double-blind human study, produced disappointing results [31]. New vaccines are currently being developed [5], and they may offer the best way to prevent CM in high-risk groups. In addition to the groups identified in this study, other persons who may benefit from vaccination include immunosuppressed persons and persons with intense exposure to soil in the desert of the southwestern United States, such as those with occupations that involve moving soil or participating in military training.

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